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Association of the Sweet-Liking Phenotype and Craving for Alcohol With the Response to Naltrexone Treatment in Alcohol Dependence
A Randomized Clinical Trial

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IMPORTANCE Identification of moderators of the response to naltrexone hydrochloride treatment for alcohol dependence could improve clinical care for patients with alcohol use disorders.

OBJECTIVE To investigate the preliminary finding that the sweet-liking (SL) phenotype interacts with a high level of craving for alcohol and is associated with an improved response to naltrexone in alcohol dependence.

DESIGN, SETTING, AND PARTICIPANTS This 12-week double-blind, randomized, placebo-controlled clinical trial was conducted from February 1, 2010, to April 30, 2012, in an academic outpatient medical center. Eighty actively drinking patients were randomized by the SL (n = 22) or the sweet-disliking (SDL) (n = 58) phenotype and by pretreatment high (n = 40) or low (n = 40) craving for alcohol, with high craving defined as greater than the median. Patients and staff were blinded to categorization. Patients were excluded for unstable medical or psychiatric illness, including dependence on drugs other than nicotine. Four patients (2 in the placebo arm and 2 in the naltrexone arm) stopped medication therapy because of adverse effects. Data were analyzed from January 15, 2013, to May 15, 2016, based on intention to treat.

INTERVENTIONS Oral naltrexone hydrochloride, 50 mg/d, or daily placebo with weekly to biweekly brief counseling.

MAIN OUTCOMES AND MEASURES The a priori hypothesis tested SL/SDL phenotype, pretreatment craving, and their interaction as moderators of frequency of abstinent and heavy drinking days during treatment, assessed with the timeline follow-back method.

RESULTS Eighty patients were randomized (57 men [71%]; 23 women [29%]; mean [SD] age, 47.0 [8.6] years). A nonsignificant effect of naltrexone on heavy drinking was noted (4.8 fewer heavy drinking days; Cohen d = 0.45; 95% CI, −0.01 to 0.90; $F_{1,67}$ = 3.52; P = .07). The SL phenotype moderated the effect of naltrexone on heavy drinking (6.1 fewer heavy drinking days; Cohen d = 0.58; 95% CI, 0.12-1.03; $F_{1,67}$ = 5.65; P = .02) and abstinence (10.0 more abstinent days; Cohen d = 0.57; 95% CI, 0.11-1.02; $F_{1,67}$ = 5.36; P = .02), and high craving moderated heavy drinking (7.1 fewer heavy drinking days; Cohen d = 0.66; 95% CI, 0.20-1.11; $F_{1,67}$ = 7.37; P = .008). The combination of the SL phenotype and high craving was associated with a strong response to naltrexone, with 17.1 fewer heavy drinking days (Cohen d = 1.07; 95% CI, 0.58-1.54; $F_{1,67}$ = 19.33; P < .001) and 28.8 more abstinent days (Cohen d = 0.72; 95% CI, 0.25-1.17; $F_{1,67}$ = 8.73; P = .004) compared with placebo.

CONCLUSIONS AND RELEVANCE The SL phenotype and a high craving for alcohol independently and particularly in combination are associated with a positive response to naltrexone. The SL/SDL phenotype and a high craving for alcohol merit further investigation as factors to identify patients with alcohol dependence who are responsive to naltrexone.

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Alcohol dependence is a prevalent and damaging illness with significant economic and personal costs to families and society, yet only about 25% of individuals with alcohol dependence receive treatment.[1] Medications to treat alcohol dependence have been developed, but their effectiveness has been modest, with generally low to medium effect sizes seen in unselected populations.[2] A challenge for clinical research is to identify moderators of response.

Several moderators have been tentatively identified in the literature as positively associated with the response to the US Food and Drug Administration–approved medication naltrexone hydrochloride: high baseline craving for alcohol,[3-5] increased density of familial alcohol problems,[3,6-8] and the Asn40Asp polymorphism in the μ-opioid receptor gene (*OPRM1* [rs1799971]).[9,10] However, none of these factors has been clearly demonstrated in prospective trials to moderate naltrexone response.[11] The first published prospective trial of the Asn40Asp polymorphism reported negative findings.[12]

Evidence indicates that the hedonic response to sweet taste reflects activity of the endogenous opioid system, particularly the μ-opioid system.[13-15] In humans, hedonic response to sweet taste generally yields 2 broad types: those who like sweet taste (SL phenotype) and those who dislike sweet taste (SDL phenotype).[16,17] The SL/SDL phenotype has been shown to be stable and heritable[18,19] and to be associated with the familial risk for alcohol use disorders.[20,21]

We hypothesized that hedonic response to sweet taste might be associated with naltrexone response in individuals with alcohol dependence. An open-label trial of naltrexone, 50 mg/d, in 40 patients with alcohol dependence categorized as having the SL (n = 15) or the SDL (n = 25) phenotype[22] showed that the SL group demonstrated significantly greater abstinence with higher craving, whereas the SDL group had less abstinence with higher craving. In 2011, Laaksonen et al[23] performed a placebo-controlled trial in patients with alcohol dependence in which the SL phenotype was assessed after completion of the trial; the investigators found that higher sweet preference was associated with a naltrexone response, in keeping with our hypothesis. The present randomized clinical trial of naltrexone was designed to prospectively test this hypothesis and to examine for an interaction between the SL/SDL phenotype and the craving for alcohol.

Methods

Participants and Screening

The study sample consisted of 80 participants with alcohol dependence (none from the pilot study[22]) who met inclusion and exclusion criteria and were randomized to placebo or naltrexone (**Table** and **Figure 1**). The sample size of 80 was calculated to yield 78.3% power to test a 3-way interaction based on the pilot study.[22] The study was conducted in outpatient offices at the University of North Carolina, Chapel Hill, from February 1, 2010, to April 30, 2012. Men and nonpregnant women aged 18 to 65 years who wished to change their drinking behavior were recruited from the community. Three hundred patients were prescreened by telephone. The trial protocol (available in the

Key Points

Question Do the sweet-liking (SL) phenotype and high level of craving for alcohol moderate the response to naltrexone in patients with alcohol dependence?

Findings In this randomized clinical trial of 80 patients who were randomized to naltrexone hydrochloride, 50 mg/d, or placebo, the combination of SL phenotype and a high level of craving for alcohol was associated with a strong response to naltrexone, with 17.1 fewer heavy drinking days and 28.8 more abstinent days compared with placebo treatment. Patients without the SL phenotype or a high level of craving did not have a significant response to naltrexone.

Meaning The SL phenotype and high level of craving for alcohol may represent practical tools clinicians could use when deciding whether to prescribe naltrexone for alcohol dependence.

Supplement) was approved by the Committee on the Protection of the Rights of Human Subjects, School of Medicine, University of North Carolina, Chapel Hill. All participants provided written informed consent.

At the screening visit, participants received a breath alcohol test (0.0-g/dL result needed to proceed with the screening visit). Participants underwent medical evaluation, including blood levels of aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, bilirubin, and alkaline phosphatase and a serum pregnancy test. A urine toxicology screen was completed. Individuals also completed a 90-day timeline follow-back interview[24] and the Penn Alcohol Craving Scale (PACS).[25] Trained interviewers administered the Mini International Neuropsychiatric Interview[26] to determine psychiatric diagnoses. Participants were required to meet *DSM-IV* criteria for alcohol dependence and to consume more than 14 (for women) or 21 (for men) standard alcoholic drinks (defined as 360 mL of beer, 150 mL of wine, or 45 mL of liquor) per week, including a mean of at least 2 heavy drinking days per week (men, ≥5 standard drinks per day; women, ≥4 standard drinks per day) during a consecutive 30-day period within the 90 days before screening. Individuals were excluded if they had a history of drug dependence other than nicotine or alcohol in the past year or if they had a positive urine toxicology test result at screening. Participants were allowed to have a positive finding of a urine cannabinoid test in the absence of evidence of cannabinoid dependence. Exclusion criteria consisted of (1) a clinically significant medical illness; (2) a significant psychiatric disorder, including depression with suicidal ideation, bipolar disorder, or schizophrenia; (3) current use of a psychotropic medication, including medication for alcohol dependence, with the exception of a stable dose of an antidepressant except mirtazapine for at least 8 weeks; and (4) elevated bilirubin levels, documented cirrhosis, or an alanine aminotransferase or aspartate aminotransferase level greater than 3.0 times the upper limit of normal.

Overall Study Design

The study was a randomized, double-blind, placebo-controlled clinical trial with 12 weeks of medication therapy.

Table. Demographics of Study Population

| Characteristic | Study Group | | | | | | | | |
| | All Participants | | | SDL Phenotype | | | SL Phenotype | | |
	Placebo (n = 40)	Naltrexone (n = 40)	P Value	Placebo (n = 29)	Naltrexone (n = 29)	P Value	Placebo (n = 11)	Naltrexone (n = 11)	P Value
Age, mean (SD), y	48.28 (8.39)	45.78 (8.64)	.19	47.72 (8.41)	48.07 (7.92)	.87	49.73 (8.58)	39.73 (7.56)	.009
Male sex, No. (%)	28 (70)	29 (72.5)	.80	19 (65.5)	20 (69)	.78	9 (81.8)	9 (81.8)	>.99
Married, No. (%)	25 (62.5)	22 (55)	.50	19 (65.5)	15 (51.7)	.29	6 (54.5)	7 (63.6)	.66
Smoker, No. (%)	12 (30)	7 (17.5)	.19	7 (24.1)	4 (13.8)	.32	5 (45.5)	3 (27.3)	.38
Baseline days, mean (SD), %									
Heavy drinking[a]	0.66 (0.29)	0.64 (0.30)	.80	0.65 (0.29)	0.68 (0.30)	.71	0.67 (0.31)	0.54 (0.31)	.32
Abstinence	0.19 (0.24)	0.14 (0.16)	.26	0.17 (0.24)	0.13 (0.17)	.47	0.23 (0.25)	0.14 (0.14)	.33
PACS score at screening, mean (SD)	17.28 (5.86)	16.81 (6.22)	.73	17.07 (6.28)	17.10 (6.84)	.98	17.82 (4.79)	16.00 (4.36)	.36
Goal of abstinence, No. (%)	13 (32.5)	11 (28.2)	.68	6 (20.7)	8 (28.6)	.49	7 (63.6)	3 (27.3)	.09
White race, No. (%)	38 (95)	36 (90)	.39	28 (96.6)	26 (89.7)	.61	10 (90.9)	10 (90.9)	>.99
No family history of alcohol dependence, No. (%)	13 (32.5)	13 (32.5)	>.99	11 (37.9)	11 (37.9)	>.99	2 (18.2)	2 (18.2)	>.99
Age at onset, mean (SD), y	32.13 (11.76)	34.31 (11.30)	.41	34.07 (11.26)	37.45 (11.16)	.26	27.00 (12.02)	25.91 (6.52)	.79
ADS total score, mean (SD)[b]	14.23 (7.04)	14.75 (6.01)	.73	13.34 (6.16)	14.90 (6.67)	.36	16.80 (9.03)	14.36 (4.03)	.43
CIWA score, mean (SD)[c]	1.88 (2.11)	2.33 (2.45)	.38	1.59 (1.64)	2.52 (2.65)	.11	2.64 (3.01)	1.82 (1.83)	.45
DRINC total score, mean (SD)[d]	25.28 (9.47)	29.35 (8.13)	.04	23.90 (7.78)	29.52 (8.11)	.009	28.90 (12.66)	28.91 (8.51)	>.99

Abbreviations: ADS, Alcohol Dependence Scale; CIWA, Clinical Institute Withdrawal Assessment; DRINC, Drinker Inventory of Consequences; PACS, Penn Alcohol Craving Scale; SDL, sweet disliking; SL, sweet liking.

[a] Defined as at least 5 standard drinks per day for men and at least 4 standard drinks per day for women.

[b] Scores range from 0 to 47, with greater scores indicating a higher level of alcohol dependence.

[c] Scores range from 0 to 67, with greater scores indicating more withdrawal symptoms.

[d] Scores range from 0 to 50, with greater scores indicating more consequences due to drinking.

Figure 1. CONSORT Diagram
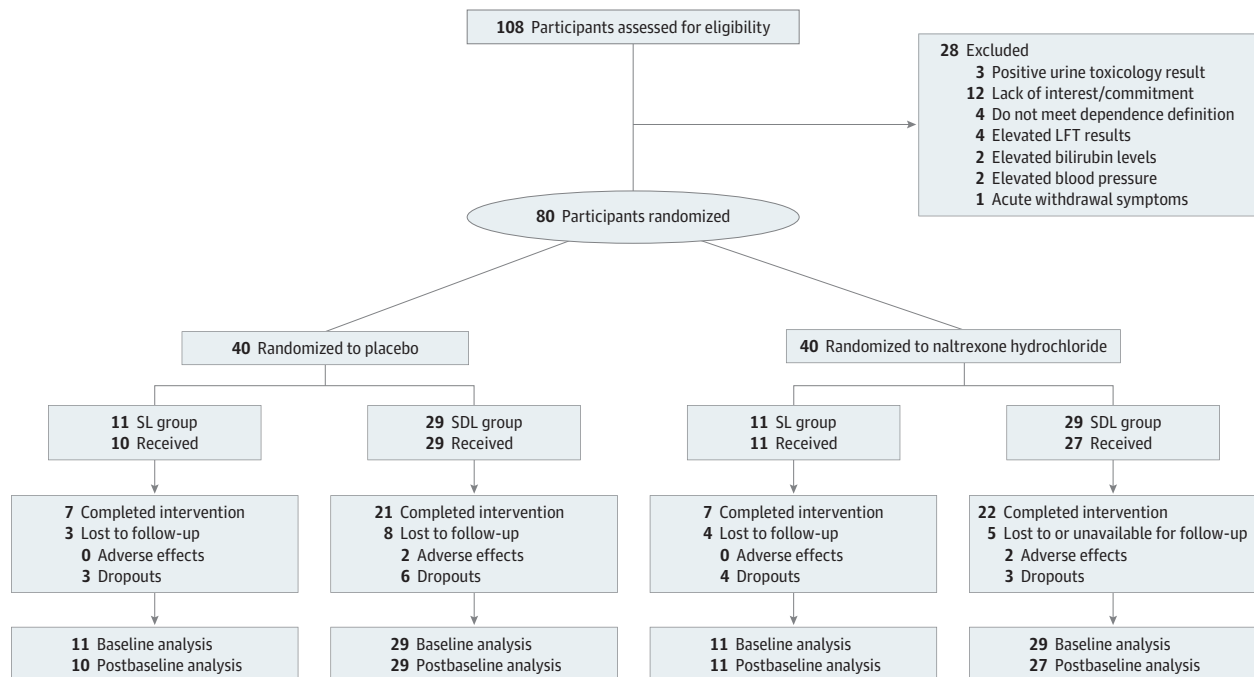
Active treatment consisted of naltrexone hydrochloride, 50 mg/d. LFT indicates liver function tests; SDL, sweet-disliking phenotype; and SL, sweet-liking phenotype.

After screening, individuals were encouraged, but not required, to achieve 3 days of sobriety before randomization. Participants were randomized to oral naltrexone hydrochloride, 50 mg/d, or to matching placebo, with randomization balanced by SL vs SDL status and high vs low levels of craving (dichotomized for randomization only on median PACS scores from prior trials[22]) based on a 1:1 algorithm assignment (SAS software; SAS Institute Inc) within the 4 respective blocks provided by one of us (R.J.G.) The University of North Carolina Investigational Drug Service assigned participants to interventions based on the randomization schedule. Participants were seen weekly for 3 weeks and then biweekly until week 12. We used BRENDA,[27] a low-intensity counseling method, for psychosocial treatment.

Study Procedures

At the initial treatment visit (week 0) and all subsequent study visits (weeks 1, 2, 3, 4, 6, 8, 10, and 12), a breath alcohol test was administered and vital signs were recorded. The revised Clinical Institute Withdrawal Assessment for Alcohol Scale[28] was administered to assess for symptoms of alcohol withdrawal. No one required referral for medical detoxification. Naltrexone hydrochloride dosing was titrated from 25 mg/d for the first 3 days to 50 mg/d for the remainder of treatment and provided in blister packs. Calendars were provided to record the number of pills taken, the number of drinks consumed, and any adverse effects of treatment. At weeks 4 and 12 or early termination, blood was drawn to assess aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, and bilirubin values. Pregnancy testing was conducted monthly.

Sweet-Taste Test

At the initial study visit, participants' sensitivity and hedonic response to sweet taste was tested by a research assistant who was not involved in any other assessments. Five concentrations of sucrose (0.05, 0.10, 0.21, 0.42, and 0.83M) were presented in 5 separate blocks for a total of 25 tastings in a pseudorandom order. Participants coded the intensity with "How strong was the taste?" and the pleasurableness with "How much do you like the taste?" of each tasting on 200-mm analog line scales.[20] The participant and staff involved in assessing and managing the participant were kept blind to the sweet-taste test results and craving scores until the entire study was completed. Participants were categorized as having an SL phenotype if they rated the highest concentration of sucrose (0.83M) as the most pleasurable; otherwise they were categorized as having an SDL phenotype.[20]

Outcome Measures

Two coprimary drinking outcome measures were selected: percentage of heavy drinking days and percentage of days abstinent. Tolerability was assessed by records of adverse effects, dropouts due to adverse effects, laboratory values, and serious adverse events.

Statistical Analysis

All values are given as the mean (SD) or, for model-based estimates, as the estimate followed by the SE, as noted. Model-based estimates allow for adjustments for variables associated with outcomes, covariates, and complex designs, such as repeated measures. Baseline drinking was defined as drinking during the period that included the 90 days before the screening visit plus the period between the screening and initial study visits minus the recommended 3 days of abstinence. The mean duration of this period was 102 (5) days. Baseline differences in demographic variables and level of baseline drinking between the naltrexone and placebo groups were investigated using 2-tailed t tests for continuous variables and χ^2 tests for categorical variables.

The timeline follow-back interview provides weekly scores of abstinence and heavy drinking for each participant during the 12 weeks of medication administration, resulting in hierarchical levels of clustering (multiple observations within each participant) present in these data. When the within-participant correlation is properly incorporated, the statistical framework results in an increase of statistical power over methods that compare groups cross-sectionally.[29] We implemented a general mixed-model analysis of variance (MMANOVA) framework that models the means per group over time and the covariance between the repeated measures and has been implemented in substance abuse research.[30] The terms in the MMANOVA model included treatment, craving, and the patient's SL/SDL status with the following 3 aims: (1) assessment of the treatment effect; (2) assessment of the dependency of the treatment effect on patients craving, as measured by the continuous PACS, and SL/SDL status, assessed separately; and (3) assessment of the dependency of the treatment effect on the combination of patients' craving and SL/SDL status. The first aim is assessed through the main effects. The second aim is assessed through separate 2-way interaction of treatment within craving and SL/SDL status. The third aim is assessed through the 3-way interaction of treatment × craving × SL/SDL status. Warnings have been issued about interpreting analysis results when continuous predictor variables are dichotomized.[31] All analyses involving craving used the continuous scale; for simplicity of displaying of higher-order interaction terms, we used a median split on the observed PACS score from our sample. Sensitivity analyses of daily abstinence and daily heavy alcohol use during the medication period analyzed through generalized estimating equations were used to examine the stability of the significant findings from MMANOVA.[32,33] We performed goodness-of-fit approaches for longitudinal data with assessment for influential observations and outliers. All analyses were conducted using SAS software (version 9.4; SAS Institute Inc). Statistical significance was set at $P < .05$ (2-tailed) for all tests based on intention to treat.

Results

Participant Recruitment and Characteristics

Eighty participants (57 men [71%]; 23 women [29%]; mean [SD] age, 47.0 [8.6] years) were randomized to study treatments. Figure 1 shows the CONSORT diagram for the trial with 77 of 80 participants for whom we have primary outcome measures. The demographic characteristics of the participants are shown in the Table (for race, individuals self-identified as white

Figure 2. Effect of Naltrexone Hydrochloride or Placebo on Percentage of Heavy Drinking Days
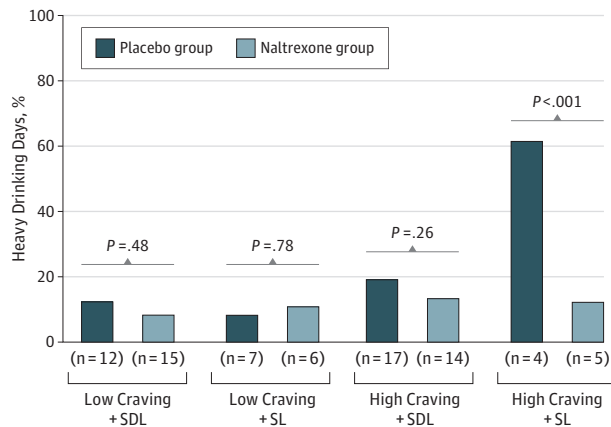
Heavy drinking days are defined as at least 5 standard drinks (defined as 360 mL of beer, 150 mL of wine, or 45 mL of liquor) per day for men and at least 4 standard drinks per day for women. Results are stratified by the sweet-liking (SL) phenotype and high alcohol craving status. Individuals with the SL phenotype and high craving for alcohol demonstrate a robust reduction in heavy drinking with naltrexone compared with placebo treatment in this analysis using weekly drinking measures. SDL indicates sweet-disliking phenotype.

Figure 3. Effect of Naltrexone Hydrochloride or Placebo on Percentage of Abstinent Days

Results are stratified by the sweet-liking (SL) phenotype and high alcohol craving status. Individuals with the SL phenotype and high craving for alcohol demonstrate a robust increase in abstinent days with naltrexone compared with placebo in this analysis using weekly drinking measures. SDL indicates sweet-disliking phenotype.

or African American). Although we found several baseline differences across groups, secondary analyses with these variables as covariates yielded the same pattern of results as those without these covariates. Thus, these variables were not included as covariates in the analyses reported herein. In addition, to maximize statistical power, other variables (eg, severity of dependence, family history, and smoking) were not included as covariates owing to the limited sample size.

Primary Outcomes

Percentage of Heavy Drinking Days

We found a nonsignificant overall naltrexone effect (4.8 fewer heavy drinking days; Cohen d = 0.45; 95% CI, −0.01 to 0.90; $F_{1,67}$ = 3.52; P = .07) on heavy drinking based on weekly summary scales; a significant interaction of treatment and continuous craving among participants with higher levels of craving responding best to naltrexone (7.1 fewer heavy drinking days; Cohen d = 0.66; 95% CI, 0.20-1.11; $F_{1,67}$ = 7.37; P = .008); a significant interaction of treatment and SL/SDL status, with the SL group responding best to naltrexone (6.1 fewer heavy drinking days; Cohen d = 0.58; 95% CI, 0.12-1.03; $F_{1,67}$ = 5.65; P = .02); and a significant 3-way interaction (Cohen d = 0.69; 95% CI, 0.22-1.14; $F_{1,67}$ = 7.91; P = .006). **Figure 2** presents the estimated proportion of heavy drinking days per week for the naltrexone and placebo arms across SL/SDL status. For presentation purposes, the continuous PACS score is dichotomized, yielding 4 combinations of craving and SL/SDL status. The SL subgroup with high craving demonstrated a marked response to naltrexone compared with placebo (17.1 fewer heavy drinking days; Cohen d = 1.07; 95% CI, 0.58-1.54; $F_{1,67}$ = 19.33; P < .001), whereas no significant differences were noted in the other groups. Goodness-of-fit as-

sessments on our MMANOVA did not indicate that these findings were driven by 1 or 2 outliers or influential observations. Sensitivity analysis with the generalized estimating equation replicated the MMANOVA results, which produced a marginal treatment × SL/SDL status interaction, with the SL group responding best to naltrexone (χ^2 = 3.21; P = .07); a significant interaction of treatment × craving, with participants with higher craving responding best to naltrexone (χ^2 = 4.59; P = .03); and a significant 3-way interaction of treatment × craving × SL status (χ^2 = 4.57; P = .03).

Percentage of Days Abstinent

We found a nonsignificant treatment (naltrexone) effect on abstinent days (Cohen d = 0.14; 95% CI, −0.31 to 0.59; $F_{1,67}$ = 0.33; P = .56); a nonsignificant interaction of treatment and continuous craving (Cohen d = 0.28; 95% CI, −0.17 to 0.73; $F_{1,67}$ = 1.29; P = .26); a significant interaction of treatment and SL status, with the SL group responding best to naltrexone (10.0 more abstinent days; Cohen d = 0.57; 95% CI, 0.11-1.02; $F_{1,67}$ = 5.36; P = .02); and a significant 3-way interaction (Cohen d = 0.68; 95% CI, 0.21-1.13; $F_{1,67}$ = 7.68; P = .007). Similar to these findings, **Figure 3** presents the estimated abstinence rates for the naltrexone and placebo arms across the 4 combinations of craving and SL status, where continuous craving was dichotomized. The SL subgroup with high craving demonstrated a marked response to naltrexone compared with placebo (28.8 more abstinent days; Cohen d = 0.72; 95% CI, 0.25-1.17; $F_{1,67}$ = 8.73; P = .004), whereas no significant differences were noted in the other groups. Goodness-of-fit assessments on our MMANOVA did not indicate that these findings were driven by 1 or 2 outlier or influential observations. Sensitivity analysis with generalized estimating equations yielded results similar to our MMANOVA model, with a

significant treatment × SL status interaction, the SL group responding best to naltrexone (χ^2 = 4.60; P = .03), and a significant 3-way interaction of treatment × craving × SL status (χ^2 = 5.13; P = .02).

To assess for evidence that the SL subgroup with high craving had more robust reduction in craving with naltrexone, we fit the MMANOVA structure on our repeated assessments of craving. We did not find evidence to support this hypothesis; rather, participants with SDL and high craving had the most rapid reduction of craving (t_{75} = 2.26; P = .03; Cohen d = 0.522), whereas participants with SL and high craving had the slowest. The patterns of change in craving were similar for naltrexone and placebo.

Association Between Treatment Adherence and SL Status

The χ^2 test of association indicated no significant difference between the naltrexone and placebo arms with respect to medication adherence, with 28 of 40 participants (70%) in the naltrexone arm and 33 of 40 participants (82%) in the placebo arm reporting no missed doses (χ^2 = 1.73; P = .19). Similar patterns are found for the SDL group, with 20 of 29 participants (69%) in the naltrexone arm and 23 of 29 participants (79%) in the placebo arm reporting no missed doses (χ^2 = 0.81; P = .37). Among the SL group, 8 of 11 participants (73%) in the naltrexone arm and 10 of 11 participants (91%) in the placebo arm reported no missed doses (χ^2 = 1.22; P = .27).

Adverse Events

One serious adverse event, a myocardial infarction, was not attributed to naltrexone treatment. Six participants in each group reported 1 or more adverse effects, with 4 patients withdrawing attributable to the adverse effects (2 participants in each treatment arm).

Discussion

The present randomized clinical trial found evidence that the SL phenotype moderates the response to naltrexone in alcohol dependence such that individuals with the SL phenotype show a significant response to naltrexone and those with the SDL phenotype show minimal evidence of response. Furthermore, and similar to some prior reports,[11] high craving for alcohol is associated with a response to naltrexone and, when combined with the SL phenotype, is associated with a particularly robust response to naltrexone, leading to a clinically meaningful reduction of 17.1 heavy drinking days and an increase of 28.8 abstinent days compared with placebo. The population was fairly typical for a US-based clinical trial in alcohol dependence, with the median age in the 40s and about 65% baseline heavy drinking days and being predominately male and white. Nevertheless, because recruitment was based on community advertising, generalizability to clinical populations is not ensured.

The present results are consistent with the pilot study data[22] and that reported by Laaksonen et al.[23] Thus, our study represents the third clinical study indicating that the SL phenotype may be a moderator of naltrexone response in alcohol

dependence and the second trial indicating an interaction between craving for alcohol and the SL phenotype. These data require replication and extension, but the combined results suggest that the SL/SDL phenotype can provide information as to which patients respond best to naltrexone and what neurobiological mechanisms may underlie naltrexone response. If these findings are confirmed, an assessment of the SL/SDL phenotype could be clinically useful. The phenotype shows good stability and reproducibility[34]; is simple, safe, and inexpensive to assess; and could evolve as a simple tool to help clinicians with medication decisions.

The genetic and neurobiological underpinnings of the SL/SDL phenotype are not well understood. Evidence suggests that a preference for stronger sweet solutions may be indicative of a relative opioid deficiency with an accompanying motivation to seek greater opioid stimulation (eg, higher concentrations of sucrose).[13,15] Given that alcohol actively releases β-endorphin[35] and activates the μ-opioid receptor, individuals with the SL phenotype may be more susceptible to this rewarding action of alcohol and most sensitive to pharmacologic agents (eg, naltrexone) that block this action. Although twin studies[18] have demonstrated that about 50% of the variance in preference for sweets is genetic, the specific genes involved in sweet preference are not well understood. Variants in the genes coding for the sweet-taste receptor (*TAS1R2* and *TAS1R3* [taste receptor type 1, members 2 and 3, respectively]) affect sweet-taste perception, as do other genetic variations,[36] and evidence suggests that variations in the taste receptor genes affect alcohol intake.[36] However, an association of these gene variants with naltrexone effects on alcohol intake has not been studied. How individuals with the SL vs the SDL phenotype may differ in activation of classic reward pathways in response to stimuli, such as sucrose or ethanol, is unclear. Kareken et al[37] found that greater activation of orbitofrontal cortical reward pathways in response to a strong sucrose solution and greater liking of a strong sucrose solution was significantly related to higher alcohol consumption; this finding suggests linkage between reward response to sweets and alcohol use. Phenotypic variation in reward response pathways to various stimuli should be investigated further vis-á-vis understanding the response to naltrexone.

The present study also found that a high craving for alcohol moderated reduction in heavy drinking by naltrexone. This finding is consistent with several but not all retrospective reports of craving as a moderator of naltrexone response[11] and a recent analysis of the COMBINE (Combining Medications and Behavioral Interventions for Alcoholism) Study.[38] In the present trial, we found evidence that the most robust responses to naltrexone occurred in individuals who had the SL phenotype and high craving, whereas those with the SDL phenotype or low craving did not respond. This association was similar to findings in the pilot study.[22] Craving for alcohol is a complex construct but one that may also index aspects of the endogenous μ-opioid system.[39-42] Therefore, a combination of these 2 variables—SL phenotype and high craving—may identify an endogenous opioid system particularly responsive to naltrexone.

Our study has limitations. The distribution of individuals with the SL/SDL phenotype was uneven, with an SL:SDL ratio of about 1:3. Therefore, the total number of participants in the SL group (n = 22) is small. However, because craving was analyzed as a continuous measure, the smallest cell size was 11 for the SL placebo and naltrexone groups, which is considered adequate for our analyses. Nevertheless, the total number of participants in the present study and the 2 prior studies[22,23] is 198, so replication of the finding in larger samples is essential.

Conclusions

The results of the present trial support the hypothesis that the SL phenotype is a moderator of the response to naltrexone in alcohol dependence and that this effect is most apparent in the presence of a high subjective craving for alcohol. Larger clinical trials in diverse populations of individuals with alcohol dependence will be necessary to confirm these findings.

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