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SYSTEMATIC REVIEW

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Naltrexone effects on subjective responses to alcohol in the human laboratory: A systematic review and meta-analysis

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Abstract

Naltrexone (NTX) has been widely studied for the treatment of alcohol use disorder with overall support for its efficacy. The mechanisms of action of naltrexone are thought to involve attenuation of the hedonic effects of alcohol and potentiation of its aversive effects. In order to provide a quantitative estimate of the effects of naltrexone on subjective response to alcohol, the aims of this meta-analytic review are to examine the effects of naltrexone across four domains of subjective response. Meta-analyses of naltrexone effects on alcohol craving (k = 16, N = 686), stimulation (k = 15, N = 675), sedation (k = 18, N = 777), and negative mood (k = 9, N = 281) suggested that under laboratory conditions and compared with placebo, naltrexone reduces craving (Hedges g = −0.252; SE = 0.054; 95% CI, −0.375 to −0.130; P < 0.01), reduces stimulation (g = −0.223; SE = 0.067; 95% CI, −0.372 to −0.074; P < 0.01), increases sedation (g = 0.251; SE = 0.064; 95% CI, 0.112-0.389; P < 0.01), and increases negative mood (g = 0.227; SE = 0.047; 95% CI, 0.100-0.354; P < 0.01). Results were robust when drinks per month and alcohol dose were added to the models as covariates. The effects of naltrexone varied by severity of alcohol use with medication effects on craving and stimulation being observed in sample of both heavy drinkers and AUD individuals. These results are consistent with the hypothesized mechanisms of action of NTX, although the effects are of small magnitude. This meta-analysis aggregates across multiple human laboratory studies of NTX's effects on subjective response to alcohol, providing a comprehensive summary of a key mechanism of NTX efficacy, namely, alteration of the subjective experience of alcohol.

KEYWORDS

craving, effect size, human laboratory, meta-analysis, naltrexone, subjective response

1 | INTRODUCTION

Alcohol use disorders (AUDs) are among the most common and costly psychiatric disorders with relatively few established treatment options.[1-4] The opioid receptor antagonist naltrexone has garnered considerable empirical support for the treatment of both alcohol[5-8] and opioid[9] use disorders.

Though naltrexone appears to promote alcohol abstinence, greater effect sizes are typically observed for reductions in heavy drinking on naltrexone compared with placebo. Specifically, meta-analytic results of randomized controlled trials observed a risk ratio (RR) for the outcome "return to any drinking" of 0.96 (95% CI, 0.92-1.00), whereas the RR for "return to heavy drinking" was 0.83 (95% CI, 0.76-0.90).[8] This same pattern of results was then replicated in a later meta-

analysis[10] with greater effect sizes observed for heavy drinking outcomes as compared with abstinence outcomes. Furthermore, secondary analysis of the large, multisite COMBINE trial[5] suggested that individuals who drank more regularly during the trial showed greater benefits of naltrexone.[11] These results suggest that naltrexone's clinical efficacy is partially a result of its interaction with the pharmacodynamics effects of alcohol.

Alcohol's pharmacodynamic interactions are complex, affecting a host of neurotransmitter systems including GABA, glutamate, dopamine, and endogenous opioids.[12] The reinforcing effects of alcohol are in part a consequence of β-endorphin release in mesolimbic reward systems.[13,14] Further, animal studies have demonstrated that naltrexone reduces ethanol self-administration by interfering with the dopamine-mediated effects of ethanol in the nucleus accumbens.[15] Multiple candidate gene studies of the μ-opioid receptor gene (OPRM1) have shown genetic variation in this opioidergic receptor to affect level of alcohol reward and reinforcement in terms of subjective responses to alcohol,[16-18] alcohol self-administration,[19] and striatal activity in the PET environment.[20] As a competitive opioid antagonist with primary affinity for μ-opioid receptors, one proposed mechanism of action for naltrexone is the suppression of alcohol's rewarding subjective effects.[21,22] In support, a PET study found that naltrexone at the 50-mg dose produced near complete inhibition of the μ-opioid receptor in a sample of individuals with AUD in early abstinence.[23]

The human behavioral pharmacology laboratory is ideal for testing this biobehavioral mechanism of action via controlled alcohol administration paradigms.[24-26] A systematic review of the alcoholism medication development literature identified 15 different pharmacological compounds that have been tested for their effects on laboratory outcomes,[27] and naltrexone is by far the most widely studied medication in the human laboratory (eg,[28-33]). Furthermore, while these studies appear to provide a consistent picture wherein naltrexone reduces the rewarding effects of alcohol and alcohol craving, only one systematic review and meta-analysis has been published addressing a subset of human laboratory outcomes, namely, alcohol craving and self-administration.[34] Hendershot et al.[34] analyzed data from 20 placebo-controlled studies on the effects of naltrexone on craving in response to alcohol administration and/or cue presentation, as well as the effects of naltrexone on alcohol self-administration. Hendershot and colleagues observed significant, though relatively small effect sizes for naltrexone on craving (Hedges g = −0.29; 95% CI, −0.42 to −0.16) and self-administration (Hedges g = −0.28; 95% CI, −0.42 to −0.13) in the human laboratory.

While Hendershot et al.[34] is the first study to quantify the magnitude of naltrexone effects on measures of alcohol reinforcement (ie, craving and self-administration), no study has examined the putative mechanism of action of blunting hedonic responses to alcohol and/or potentiating aversive responses.[35,36] The importance of a quantitative review, as compared with a qualitative review, is underscored by the common practice in human laboratory research of collecting many outcomes within a given study.[24] As there are no established guidelines on the assessment of subjective alcohol responses, there is strong potential for systematic bias in reporting of statistical results and potentially inflating the apparent reliability and effect sizes of naltrexone.[37] Furthermore, most behavioral pharmacology studies involve small samples (approximately 20-40 subjects), which may increase these risks.[38] Therefore, the aims of this meta-analytic review are to examine the effects of naltrexone on subjective response to alcohol across the four domains of (*a*) craving, (*b*) stimulation, (*c*) sedation, and (*d*) negative affect. These four domains of subjective response to alcohol have been identified in previous factor-analytic work as capturing the full spectrum of SR in the human laboratory.[39,40] Specifically, by synthesizing data across a wide range of human laboratory studies of naltrexone, this meta-analysis examines whether naltrexone reduces alcohol-induced craving and stimulation while increasing alcohol-induced sedation and negative affect. These behavioral pharmacology endpoints, in turn, represent some of the strongest putative mechanisms of action of naltrexone, based on single studies and qualitative reviews of the literature.[22]

2 | METHODS

2.1 | Literature review and study coding

Inclusion criteria were (1) randomized placebo-controlled administration of naltrexone in individuals who consume alcohol for the purposes of testing AUD outcomes (eg, studies aiming to test smoking outcomes were not included), (2) alcohol administration in the laboratory to a target BrAC via alcohol challenge or priming for self-administration paradigms,* (3) subjective response outcomes measured via self-report questionnaires, (4) reported in the English language, or translated to English, and (5) publication in a peer reviewed and PubMed indexed journal.

Literature searching consisted of multiple stages. First, published reviews of AUD psychopharmacology were reviewed to identify studies of naltrexone on subjective responses to alcohol.[24,27,41,42] Second, PubMed searches were conducted with the following phrases: "naltrexone," "alcohol challenge," "alcohol response," "response* to alcohol," "alcohol response," "alcohol priming," "alcohol intoxication," "ethanol intoxication," "response* to ethanol," and "ethanol response." These PubMed searches yielded a total of 88 citations that were assessed for relevance in the present paper via abstract review.

Based on abstract reviews, from these 88 initial studies, 28 were deemed relevant for full text review. The 60 citations that were excluded from abstract review were excluded because they were (1) review papers, (2) animal studies, (3) clinical trials, or (4) observational studies, From the 28 studies reviewed in full, eight studies were excluded based on full text review (four for lack of controlled alcohol administration, two for lack of SR outcomes, and two for reporting previously published results, which were already included in this analysis; see Figure 1). This resulted in a final sample of 20 studies that were included in this analysis comprising 21 independent samples with

*Studies that only reported subjective response data in the context of a self-administration paradigm were excluded due to the potential for large confounding effects of BrAC differences between medication groups.

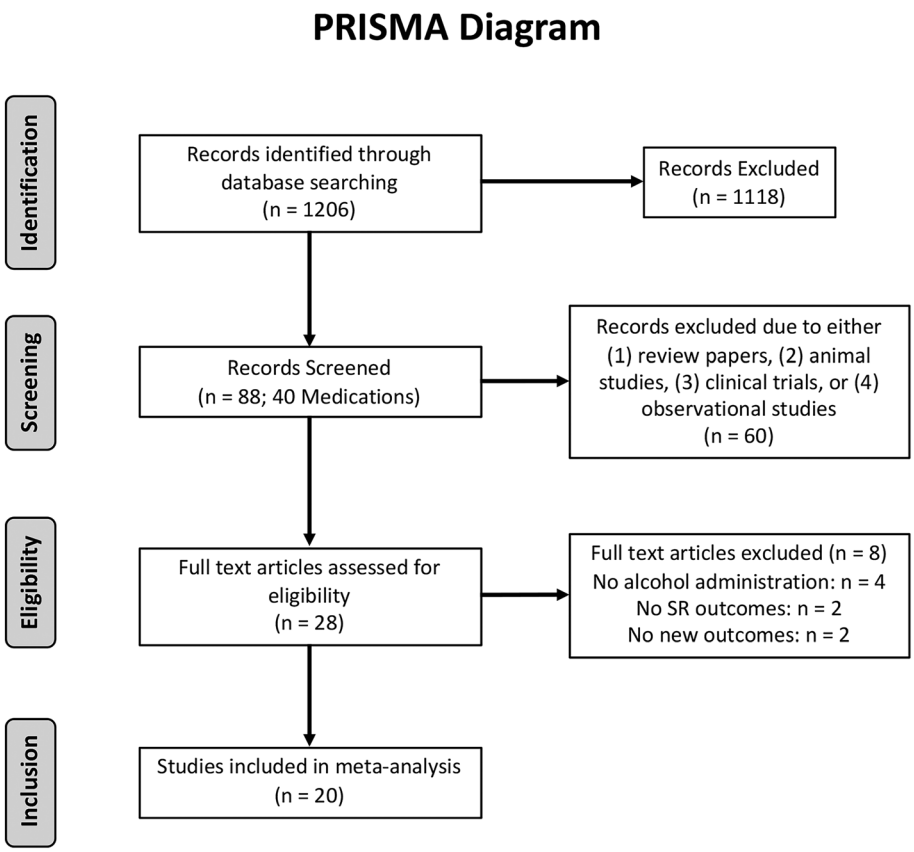

FIGURE 1 PRISMA diagram outlining the record identification, screening, eligibility, and inclusion

822 total subjects. All studies were coded by at least two raters (S.B., D.J.O.R., or R.G.). Where coding discrepancies arose, all raters met in person to reach a consensus. Furthermore, when sufficient data to generate effect size estimates were not reported in the published paper, corresponding authors were contacted via email in an attempt to obtain the necessary information. The DigitizeIt software[43] was also utilized to extract data from published figures[44] where necessary. Assigning of outcome variables to SR domains was also determined through consensus discussion among all study coders referencing the prior factor analytic work,[39,40] other published articles, and/or through referencing the specific items. The full list of variables included in each domain can be found in Figure 2. Studies were also coded on the following design and sample characteristics in order to control for them when estimating naltrexone effects on the laboratory outcomes of interest: (*a*) final/target BrAC, (*b*) mean drinks per month for the study sample, and (*c*) target naltrexone dose.

2.2 | Effect size computation

Hedges *g* effect sizes, which are unbiased estimators of standardized mean differences,[45] were computed for naltrexone main effects based on the reported results, extraction of data from published figures, or through contact with the study authors. Effect sizes from within-subjects studies were converted to a "raw score" metric that represents expected effect size and error variance as if the estimate was coming from a between-subject study design, thus permitting the comparison with other between-subject studies.[46] Where results were described as "nonsignificant" or omitted from the study results and data were not made available from the authors, two approaches were used. First, a moderate approach was employed wherein missing results were imputed with an effect size associated with a *P* value of 0.50. Second, a conservative approach was employed wherein a Hedges *g* estimate of 0 was imputed. These measures were taken to address effect size inflation resulting from publication bias. Importantly, this was a common occurrence (47 of the 171 total study-level outcomes), suggesting that there is a high risk of publication bias and associated effect size inflation. Our approach to measure selection was to include all available measures. Notably, however, while these methods will address the issue of publication bias from individual studies selectively reporting significant outcomes, it does not affect the related problem of whole studies going unreported.

2.3 | Meta-analytic approach

Because these laboratory studies typically reported several outcomes within each SR domain, robust variance estimation (RVE) meta-analysis methods were implemented via the *robumeta* package in R.[47] RVE techniques were utilized as opposed to more traditional analytic methods for the following reasons: (1) RVE methods allow for the estimation of an overall effect size accounting for the dependence of

Craving	Stimulation/Hedonia
AUQ	BAES Stimulation
Alcohol Craving Scale	POMS Arousal
"liking"	POMS Elation
"desire to drink"	POMS Vigor
All Beh. Econ Variables	POMS Friendliness
"Craving Score"	POMS Positive Mood
"Wanting"	ARCI BG (stimulant)
"Urge to drink"	Euphoria
Alcohol Choice Paradigm	Tired/Alert
"like a drink"	Elevated Mood
DEQ: "Willing to take again"	PANAS Positive
	Depressed/Happy
	"cheerful"
	"optimistic"
	"energetic"
	"confident"
	BVAS Stimulated
	BVAS friendly
	BVAS talkative
	"feel good"
	"content"
	BVAS social
	ARS "Satisfaction with alcohol"
	VAS mind racing
	VAS rush
	"great"
	"jittery"
	ARCI Amphetamine
	rush
	VAS elated
	VAS "good-natured"
	VAS "full of pep"
	ARCI MBG (Euphoria)
	ARCI BG

FIGURE 2 Domain assignment table describing the items used to capture each of the four domains of subjective response captured in this meta-analysis

multiple related outcomes reported in a given study,[47-49] and (2) RVE methods are able to correct for small sample sizes that are common in behavioral pharmacology studies.[49] Given the significant methodological variation between studies, we expected a substantial degree of heterogeneity. I^2 was used to test for interstudy heterogeneity[50-52] and τ^2 was used to provide an estimate of between study variance regardless of sample size.[53] Funnel plots were examined to detect signs of publication and other reporting biases.[54,55]

Because study population (ie, AUD, heavy drinking, or light drinking sample) is a potentially integral component to the transition of laboratory studies to clinical trials, further analysis was also conducted examining naltrexone's effect on subjective responses to alcohol in these different population groups separately. Due to the strong, nearly tautological relationship between study population and mean drinks per month, intercept-only models are reported for these analyses.

Random RVE intercept models were first conducted to estimate the average effect size of naltrexone on a given SR domain. Following the fitting of intercept-only models, meta-regression techniques were employed to determine whether between study factors impact naltrexone effect sizes and test whether naltrexone effects were robust to controlling for study differences. Specifically, the following continuous and objective metrics were entered into RVE meta-regression models: final target BrAC (centered at 0.06 g/dL) and mean drinks per month for the study sample (log centered at 100 drinks per month). Study population was not entered as a covariate because of (1) the limited number of categories as compared with the continuous

Sedation	Negative Mood
BAES Sedation	BVAS "Mellow"
"Dissociation"	Tense/Relax
Alcohol Sensation Scale "Anasthesia"	PANAS negative
SHAS	"relaxed"
"Drunk or Intoxicated"	POMS Anxiety
ARCI PCAG (sedation)	POMS Depression
dizzy	anxious VAS
drunk or intoxicated	calm
sleepy	fearful
Tired	BVAS Miserable
nauseated	POMS Tension
ALSS "nausea"	
"dislike effects"	
"fatique"	
CADSS Dissociation	
POMS Fatigue	
clumsy	
drowsy	
VAS nausea	
VAS dizziness	
tired	
ALSS "impaired function"	
POMS Confusion	
headache	
heaviness in limbs	
ALSS "impairment"	
"clear-headed" (reverse)	
BVAS Difficulty concentrating	
"Confusion"	
slurred speech	
VAS "lightheaded"	
ARCI LSD (Dysphoria)	
ALSS "Central Stimulant"	

FIGURE 2 Continued.

variable of mean drinks per month and (2) potential inconsistency in terminology, which was not an issue with the objective measures included.

3 | RESULTS

3.1 | Study characteristics

In total, 20 studies met the inclusion criteria for this analysis with 822 total subjects. On average, studies included 35.74 ± 21.39 subjects (range, 10-85). A majority of these studies (k = 14 of 20) utilized a within-subjects design for the primary medication condition (eg, naltrexone versus matched placebo). Studies typically employed controlled alcohol challenge paradigms (80%), with a smaller subset utilizing a priming dose of alcohol (20%). Overall, the average target BrAC of these alcohol administration studies was 0.054 ± 0.022 g/dL. However, as expected, there were sizeable differences in the target BrAC between alcohol challenge and priming paradigms (priming mean = 0.024 ± 0.009; challenge mean = 0.062 ± 0.017; $t_{8.84}$ = 5.94, P < 0.001). Only a minority of studies recruited AUD samples (25%), with most recruiting either light or heavy drinkers (40% and 35%, respectively). In terms of the average alcohol consumed by the study samples, there was a wide range of drinking behavior (mean drinks

TABLE 1 List of studies included in the meta-analysis and study characteristics[56,28,57,31,58,59,32,60-63,33,64-69,29]

Study	Max Naltrexone Dose	Within-Subjects Design	N	Alcohol Administration Paradigm	Study Population	Average Drinks per Month	Target Alcohol Administration Dose, g/dL	Outcomes Measured
[56]	50	Between-Subjects	40	Priming	Alcohol use disorder	160	0.03	Craving: AUQ Stimulation: BAES Stimulation Sedation: BAES Sedation, SHAS
[28]	50	Between-Subjects	83	Priming	Alcohol use disorder	174.9	0.025	Craving: AUQ Stimulation: BAES Stimulation Sedation: BAES Sedation, SHAS
[57]	50	Within-Subjects	35	Challenge	Heavy Drinkers	48.1	0.06	Craving: Intensity of Demand, Omax, Pmax, Breakpoint
[30]	50	Between-Subjects	85	Challenge	Alcohol Use Disorder & Light Drinkers	AUD Sample: 186.75 Light Drinking Sample: 17.82	0.055	Craving: ACQ Craving Stimulation: BAES Stimulation Sedation: BAES Sedation
[31]	50	Within-Subjects	27	Challenge	Light Drinkers	41.7	0.06	Stimulation: BAES Stimulation, POMS Vigor Sedation: BAES Sedation, POMS Fatigue, POMS Confusion Negative Mood: POMS Anxiety, POMS Depression, POMS Tension
[58]	100	Within-Subjects	23	Challenge	Heavy Drinkers	55.2	0.088	Craving: Desire to Drink, Liking Sedation: Worst, I've Felt, Clumsy, Confused, Slurred Speech, Sleepy, Nauseated, Trouble Concentrating, Dizzy, ARCI PCAG, Drunk
[59]	50	Within-Subjects	15	Challenge	Light Drinkers	19	0.074	Craving: Urge Stimulation: ASS Elated, ASS Happy, ASS Talkative Sedation: ASS Dizziness, ASS Headache, ASS Nausea, ASS Feel Sleepy Negative Mood: ASS Anxious, ASS Depressed ASS Relaxed (reverse scored)
[32]	50	Between-Subjects	16	Priming	Alcohol Use Disorder	142.7	0.03	Craving: AUQ Sedation: Nausea

(Continues)

TABLE 1 (Continued)

Study	Max Naltrexone Dose	Within-Subjects Design	N	Alcohol Administration Paradigm	Study Population	Average Drinks per Month	Target Alcohol Administration Dose, g/dL	Outcomes Measured
[60]	50	Within-Subjects	20	Challenge	Light Drinkers	Not Reported	0.07	Stimulation: POMS Confident Unsure (reverse scored), POMS Energetic-Tired (reverse scored) Sedation: SHAS, POMS Clearheaded-Confused Negative Mood: POMS Composed-Anxious, POMS Elated-Depressed
[61]	50	Within-Subjects	43	Challenge	Light Drinkers	14.14	0.0565	Stimulation: BAES Stimulation, POMS Vigor Sedation: BAES Sedation, SHAS, POMS Fatigue
Ray et al 2012	50	Within-Subjects	32	Challenge	Heavy Drinkers	48.4	0.06	Craving: AUQ Stimulation: BAES Stimulation, POMS Pos. Mood, POMS Vigor Sedation: BAES Sedation, SHAS Negative Mood: POMS Negative Mood, POMS Tension
[63]	25	Between-Subjects	60	Challenge	Heavy Drinkers	135.4	0.067	Craving: AUQ Stimulation: BAES Stimulation, POMS Pos. Mood, POMS Vigor Sedation: BAES Sedation Negative Mood: POMS Negative Mood, POMS Tension
[65]	50	Within-Subjects	40	Challenge	Heavy Drinkers	44	0.06	Craving: AUQ, ARS Liking Stimulation: BAES Stimulation, POMS Pos. Mood, POMS Vigor Sedation: BAES Sedation, SHAS Negative Mood: POMS Negative Mood, POMS Tension
[64]	50	Within-Subjects	38	Challenge	Heavy Drinkers	41.7	0.033	Craving: AUQ Stimulation: BAES Stimulation, POMS Pos. Mood, POMS Vigor Sedation: BAES Sedation, SHAS Negative Mood: POMS Negative Mood, POMS Tension

(Continues)

TABLE 1 (Continued)

Study	Max Naltrexone Dose	Within-Subjects Design	N	Alcohol Administration Paradigm	Study Population	Average Drinks per Month	Target Alcohol Administration Dose, g/dL	Outcomes Measured
[65]	50	Within-Subjects	10	Challenge	Heavy Drinkers	43.7	0.06	Craving: Urge
[66]	50	Within-Subjects	40	Priming	Light Drinkers	66.4	0.01	Craving: VAS Desire a Drink, VAS Want a Drink, VAS Like the Drink Stimulation: VAS Euphoria, VAS Mind Racing, VAS Alert, VAS Energetic, VAS Excited, VAS Rush Sedation: SHAS Nauseated, SHAS Trouble Concentrating, SHAS Clumsy, SHAS Sleepy, SHAS Drunk, SHAS Muddled/Confused, SHAS Dizzy, SHAS Slurred Speech, VAS Sedated, VAS Intoxicated
[67]	50	Between-Subjects	63	Challenge	Alcohol Use Disorder	336.6	0.08	Craving: DEQ Want More, DEQ Like Drug Sedation: DEQ Intoxicated
[68]	50	Within-Subjects	19	Challenge	Light Drinkers	17.9	0.05	Stimulation: BAES Stimulation Sedation: BAES Sedation, ASS Anesthesia, ASS Impaired Functioning, ASS Nausea, ASS Central Stimulant
[69]	50	Within-Subjects	25	Challenge	Light Drinkers	39	0.025	Craving: VAS Want More, VAS Like Stimulation: VAS Elated, VAS Good Natured, VAS Full of Pep, ARCI BG, ARCI MBG Sedation: VAS Confused, VAS Intoxicated, VAS Drowsy, VAS Lightheaded, ARCI LSD, ARCI PCAG, ARCI Central Stimulation Negative Mood: VAS Relaxed (reverse scored)
[29]	50	Within-Subjects	24	Challenge	Light Drinkers	34.3	0.09	Craving: DEQ More, DEQ Like

(Continues)

TABLE 1 (Continued)

Study	Max Naltrexone Dose	Within-Subjects Design	N	Alcohol Administration Paradigm	Study Population	Average Drinks per Month	Target Alcohol Administration Dose, g/dL	Outcomes Measured
								Stimulation: BAES Stimulation, POMS Elation, POMS Friendliness, POMS Vigor, ARCI MBG, ARCI Amphetamine, ARCI BG, VAS Stimulated Sedation: BAES Sedation, POMS Confusion, POMS Fatigue, ARCI PCAG, ARCI LSD, VAS Sedated, VAS Nauseous Negative Mood: VAS Down, VAS Anxious, POMS Depression, POMS Anxiety

per month = 84.37 ± 81.15); however, as expected, drinking magnitude was differentiated by the target population being enrolled in the study (light drinking mean = 33.7 ± 17; heavy drinking mean = 59.5 ± 33.8; AUD mean = 200 ± 78; $F_{2,7}$ = 23.53, P < 0.001). Nearly every study tested a 50-mg/d dose of NTX with one study testing a 25-mg/d dose and one study testing a 100-mg/d dose. Several studies included multiple (repeated) within-subjects observations of a given outcome. In those cases where multiple time points were available, a single effect size was derived by computing the effect size from the repeated measures analyses that encompass all time points, as opposed to deriving an effect size for each time point in analysis. Table 1 provides a description of each study that was included in this meta-analysis. Forest plots describing the effect size for study included in this meta-analysis are provided as Figures S1 to S4 for each of the four domains of subjective response examined.

In terms of individual outcomes, obtained from each study, a total of 171 outcomes (ie, study-level effects) were coded across these 20 studies. Sedation/motor intoxication outcomes were the most common with 77 outcomes, followed by stimulation/hedonic reward (44 outcomes), then craving (29 outcomes), and lastly negative affect (21 outcomes). As previously stated, 27.5% of all the outcomes reported in the methods section of these manuscripts did not have detailed statistical results suggesting a clear risk of publication bias and effect size inflation.

3.2 | Naltrexone effects on alcohol craving

A total of 16 studies reported one or more craving outcomes with a total sample size of 686 subjects and 29 total outcomes (ie, study-level effects), seven (24.14%) of which had no statistics reported. Using a moderate imputation of missing outcomes, naltrexone was found to have a significant, albeit small effect in reducing craving in the context of alcohol administration (Hedges g = −0.252; 95% CI, −0.375 to −0.130; SE = 0.054; $t_{8.99}$ = −4.65; P < 0.01). This effect was slightly diminished when controlling for mean drinks per month and target alcohol dose (Hedges g = −0.202; 95% CI, −0.326 to −0.077), although none of these covariates significantly predicted craving effect sizes ($P \geq 0.133$). Effect size heterogeneity was substantial (I^2 = 26.81%, τ^2 = 0.014; Figure 3A) and thus accurately modeled through a random effects approach.

Naltrexone's effect size in reducing craving did not differ substantially between study populations. Among the five studies recruiting AUD samples, the estimated effect size was −0.247 (95% CI, −0.366 to −0.127). For heavy drinking samples (seven studies), the effect size was −0.273 (95% CI, −0.452 to −0.094). For studies that recruited light drinking samples, the point estimate of the effect size nearly identical at −0.270, however, the variability was greater, and thus, this effect was not statistically significant (95% CI, −0.707 to 0.168). Thus, while the mean estimate across these three populations was consistent, these findings suggest that light drinking samples are more variable and thus less reliable in determining efficacy.

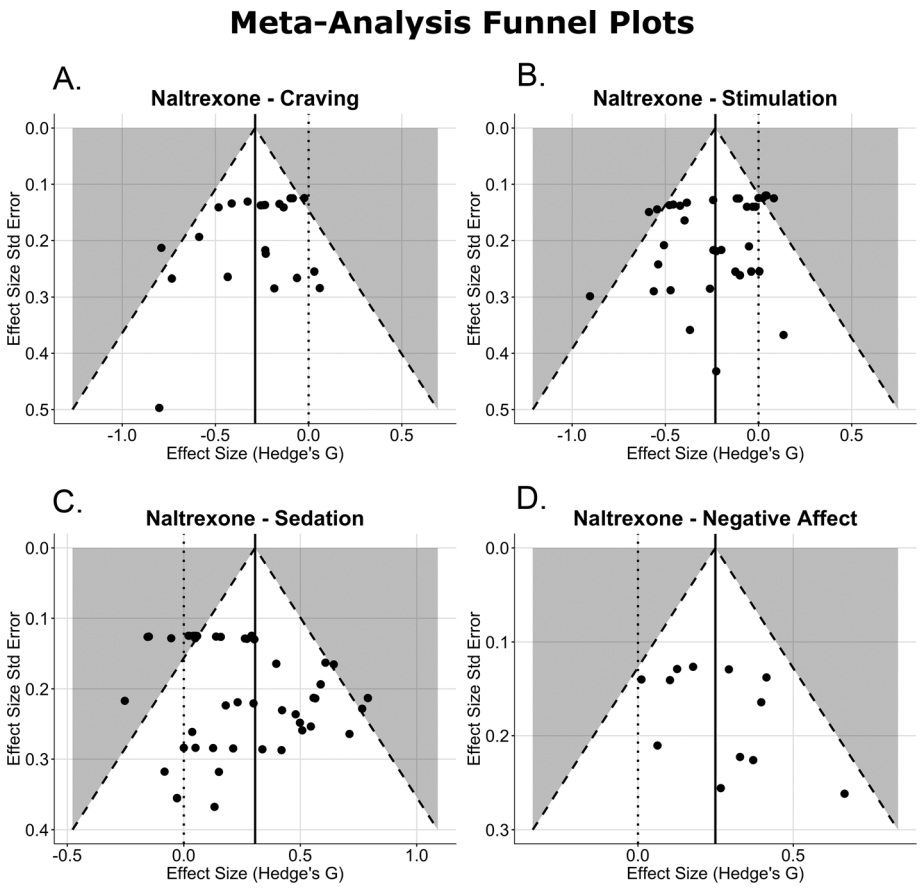

FIGURE 3 Funnel plots for NTX effect sizes on the SR domains of (A) craving, (B) stimulation, (C) sedation, and (D) negative affect. Each point represents an individual outcome, and thus, several points might be from the same study; however, the RVE meta-analysis approach that was used is able to account for this nested structure when computing an overall effect. The solid black vertical line represents the point estimate, or average effect size from all the studies reported in the literature (without any imputation for missing data) analyzed using a random effects RVE meta-analysis model without inclusion of study covariates. The sloping lines comprising the triangle represent the 95% CI range of variability based on study standard error (which is strongly related to study sample size), and thus, observations that fall in the grey region are those that are outside the 95% CI of the mean. Asymmetry in these plots can be interpreted as representing reporting bias. These funnel plots are relatively symmetric and thus are not indicative of bias, which would produce effect size inflation. The sign of the effect size is representative of the effect naltrexone had on that outcome (ie, a positive sign means that naltrexone increased this subjective response, and a negative sign means naltrexone blunted the response)

As expected, when employing a conservative approach to missing data, the effect of NTX was reduced, but remained statistically significant (Hedges g = −0.221; 95% CI, −0.333 to −0.108; SE = 0.052; $t_{11.9}$ = −4.28; P < 0.01). Again, no covariates predicted alcohol craving effect sizes ($P \geq 0.112$), but their inclusion in the meta-regression model reduced the effect size estimate further (Hedges g = −0.167; 95% CI, −0.272 to −0.063). Estimates of heterogeneity were relatively unchanged (I^2 = 29.04%, τ^2 = 0.015). The estimated effect of naltrexone on craving obtained without imputation was higher (Hedges g = −0.287; 95% CI, −0.429 to −0.145).

3.3 | Naltrexone effects on alcohol stimulation

Stimulation outcomes were measured in 15 studies, including 675 total subjects and 44 outcomes (ie, study-level effects), nine (20.45%) of which did not have reported statistics. With a moderate imputation approach, naltrexone significantly reduced alcohol stimulation, though again the effect size was small (Hedges g = −0.223; 95% CI, −0.372 to −0.074; SE = 0.067; $t_{10.3}$ = −3.31; P < 0.01). This effect size was virtually identical when accounting for study covariates (Hedges g = −0.228; 95% CI, −0.440 to −0.016), although, as with craving, none of the covariates significantly predicted the stimulation outcome ($P \geq 0.891$). Effect size heterogeneity was also observed (I^2 = 31.25%, τ^2 = 0.017; Figure 3B).

Only three studies recruited an AUD sample and measured stimulation outcomes; However, based on these three studies, the estimated effect size was −0.215 (95% CI, −0.287 to −0.143). Among the four studies that recruited heavy drinkers, the point estimate of naltrexone on stimulation was slightly larger, but with significantly more variability (Hedges g = −0.287; 95% CI, −0.711 to 0.138). Lastly, naltrexone's effect in blunting stimulation was considerably smaller for light drinking samples (nine studies; Hedges g = −0.151; 95% CI, −0.367 to 0.065). Thus, similar to craving, studies that recruited light drinkers demonstrated smaller and less reliable effect sizes.

Using a conservative imputation approach, naltrexone reduced alcohol stimulation, and this effect remained statistically significant, although the effect size was diminished (Hedges g = −0.186; 95% CI, −0.316 to −0.056; SE = 0.060; $t_{12.1}$ = −3.11; P < 0.01). No covariates were predictive of stimulation effect sizes ($P \geq 0.881$), and the inclusion of covariates had minimal effect on the effect size of NTX (Hedges g = −0.191; 95% CI, −0.371 to −0.011). Estimates of heterogeneity were greater using a conservative approach (I^2 = 41.61%, τ^2 = 0.023). The estimated effect of naltrexone on stimulation obtained without imputation was higher (Hedges g = −0.232; 95% CI, −0.384 to −0.079).

3.4 | Naltrexone effects on alcohol sedation

Alcohol sedation was the most common outcome reported, which was measured in 18 studies including 777 subjects and 77 total outcomes (ie, study-level effects), 22 (28.57%) of which were missing statistical outcomes. Naltrexone was found to modestly increase alcohol sedation (Hedges g = 0.251; 95% CI, 0.112-0.389; SE = 0.064; $t_{13.2}$ = 3.91; P < 0.01). Controlling for study covariates increased the estimate of naltrexone effects, though still within the small range (Hedges g = 0.321; 95% CI, 0.146-0.495). Alcohol dose was found to increase the effect sizes of naltrexone on alcohol sedation (B = 5.24, $t_{4.78}$ = 3.25, P < 0.05). Average drinks per month were not a significant covariate (P = 0.323). Substantial heterogeneity was observed (I^2 = 24.57%, τ^2 = 0.016; Figure 3C).

Among AUD samples, naltrexone did not significantly increase subjective sedation (five studies; Hedges g = 0.170; 95% CI, −0.308 to 0.648). The effect size was marginally larger among heavy drinking samples, though still not statistically significant (five studies; Hedges g = 0.297; 95% CI, −0.121 to 0.715). Studies that recruited light drinkers were the only subgroup where naltrexone produced a significant increase in sedation (nine studies; Hedges g = 0.211; 95% CI, 0.023-0.400). In sum, sedation was increased to a significant degree only among light drinkers, which was a different pattern of results than other domains.

The effect size of naltrexone on alcohol-induced sedation was still evident using a conservative approach (Hedges g = 0.214; 95% CI, 0.095-0.333; SE = 0.056; t_{15} = 3.83; P < 0.01). This effect was slightly increased with the inclusion of study covariates (Hedges g = 0.291; 95% CI, 0.145-0.437), and alcohol dose significantly predicted sedation effect sizes (B = 5.60, $t_{5.88}$ = 3.80, P < 0.01). Heterogeneity was substantially increased with a conservative imputation approach (I^2 = 51.32%, τ^2 = 0.038). The estimated effect of naltrexone on sedation obtained without imputation was higher (Hedges g = 0.306; 95% CI, 0.149-0.464).

3.5 | NTX effects on negative affect

Negative affect was substantially less likely to be included as a measured outcome in these studies. Specifically, it was measured in only nine studies, including 281 subjects, and only 21 total outcomes (ie, study-level effects), nine (42.86%) of which were unreported in the results. Naltrexone modestly increased negative affect in the context of alcohol administration (Hedges g = 0.227; 95% CI, 0.100-0.354; SE = 0.047; $t_{4.23}$ = 4.85; P < 0.01). Though the point estimate did not change much, when covarying for study characteristics, naltrexone no longer significantly impacted negative affect (Hedges g = 0.282; 95% CI, −0.797 to 1.360), though none of the covariates significantly predicted naltrexone's effect sizes ($P \geq 0.741$). Due to the small number of studies, heterogeneity was not able to be estimated in this model (Figure 3D).

In the four studies that recruited heavy drinkers, naltrexone was found to significantly increase negative mood (Hedges g = 0.220; 95% CI, 0.001-0.440). In the five studies on light drinkers, naltrexone was also associated with a significant increase in negative mood (Hedges g = 0.272; 95% CI, 0.232-0.312). No studies that recruited AUD patients included measures of negative affect; therefore, no estimate of effect size is possible. In sum, NTX was associated with an increase in negative mood for both heavy and light drinkers, but no information was available for AUD samples.

Using the conservative imputation of missing statistics, the effect size of naltrexone was smaller (Hedges g = 0.141; 95% CI, 0.037-0.245; SE = 0.044; $t_{7.15}$ = 3.20; P < 0.05). This effect was not robust to controlling for study covariates (Hedges g = 0.261; 95% CI, −0.830 to 1.350), though no covariates were significant predictors ($P \geq 0.597$). Heterogeneity was estimated to be a bit smaller than other outcome domains (I^2 = 15.42%, τ^2 = 0.005). The estimated effect of naltrexone on sedation obtained without imputation was higher (Hedges g = 0.249; 95% CI, 0.101-0.398).

4 | DISCUSSION

Naltrexone is by far the most widely studied pharmacotherapy for AUD. Studies of naltrexone encompass clinical trials as well as behavioral pharmacology trials combining alcohol administration with acute naltrexone dosing (typically ranging from 3 to 7 d of medication/placebo). The overall consensus regarding the clinical efficacy of naltrexone is that its effects are small in magnitude and stronger for outcomes involving reduced drinking, compared with abstinence outcomes.[70] Interestingly, recent analyses have suggested that the clinical effects of naltrexone may be "declining over time of publication," such that year of publication predicts trial outcomes with more recent trials having smaller effect sizes.[71] This may be due to increased quality of clinical trials over time or with the broader issue of replicability. On the other hand, recent studies have reported larger effect sizes for naltrexone when accounting for key variables such as smoking status[72,73] and reward drinking,[74] thus suggesting that it possible to identify naltrexone responders. Insofar as the effects of naltrexone are more robust for outcomes involving alcohol intake, the effects of naltrexone in altering the pharmacodynamic effects of alcohol and the associated subjective experience of alcohol have long been postulated.[75]

Given the mature status of the literature on naltrexone, including its effects during controlled alcohol administration, this quantitative review of the literature sought to quantify the effects of naltrexone across four domains of subjective response to alcohol, namely, craving, stimulation, sedation, and negative mood. Results revealed a significant effect of naltrexone, versus placebo, in attenuating craving and alcohol-induced stimulation, while exacerbating sedation and negative affect in the human laboratory (Hedges *g* of −0.252, −0.223, 0.251, and 0.227). Notably, the observed estimates were all in the small effect size range. The results presented using a moderate (ie, "middle of the road") imputation approach were generally consistent with those obtained with a more conservative imputation approach as well as with analyses that did not include an imputation of missing data. A clear pattern is observed by which the effect size estimate using the conservative imputation approach is smaller, followed by the effect size resulting from the moderate imputation approach next, and with the no-imputation method resulting in larger effect sizes. Nonetheless, as a whole, the complete set of results provided herein coalesces within the small effect size range and should be interpreted as such.

The effect sizes for naltrexone-induced increases in the sedative and aversive effects of alcohol were by and large similar to effect sizes for decreases in the stimulant and rewarding effects of alcohol. In the behavioral pharmacology literature, more studies tend to focus on naltrexone's attenuation of rewarding effects,[31,75] as compared with increases in the sedative and aversive effects of alcohol.[58,64] Nevertheless, the similar increase in aversive effects highlights how these biobehavioral mechanisms of action for naltrexone may be working in comparable magnitude, and possibly synergistically, towards the clinical efficacy of naltrexone for AUD. Importantly, analyses of naltrexone effects at each study population found that naltrexone potentiated the sedative effects of alcohol among light drinkers, but this effect was not significant in heavy drinking or AUD samples. It is plausible to hypothesize that perhaps light drinkers experience more of the sedative effects of alcohol and that naltrexone, in turn, may potentiate these effects more strongly in this subset of drinkers.

The similarity in effect size across study populations, particularly for craving, stimulation, and negative affect, suggests that naltrexone exerts a comparable effect on subjective responses to alcohol spanning a range of drinking levels. However, it should be noted that high levels of alcoholism severity are generally not well represented in human laboratory studies. This is critical given that the higher severity and associated "dark side" of addiction is thought to represent a discrete phenotype characterized by a chronic and relapsing pattern of alcohol misuse with significant dysregulation of mood and stress systems[76,77], although it should be noted that efforts to characterize the allostatic model in humans, including our own,[78,79] have not fully supported the model, particularly with regard to the "dark side" of addiction.[80]

Regarding naltrexone's effects on craving in the human laboratory, the results obtained in this study are largely consistent with those recently reported by Hendershot et al.,[34] which also found significant medication effects that were small in magnitude. When contrasted to the clinical trials literature, however, the effects of naltrexone have been somewhat smaller, with Hedges *g* of 0.116 and 0.189 for abstinence and heavy drinking, respectively.[70] Maisel et al.[70] also reported a somewhat smaller effect size for subjective craving with a Hedges *g* of 0.144. A possible explanation for the slight discrepancy in naltrexone effect size between laboratory studies and clinical trials is differences in sample characteristics. Recent studies from our group[81] and others[82] suggested that nontreatment seekers, which comprise the vast majority of participants in human laboratory studies of naltrexone, vary widely from treatment-seeking individuals with AUD. Further, a recent meta-analysis by Klemperer et al.[83] found that study characteristics accounted for 48% of the variance among naltrexone clinical trials for AUDs after controlling for medication characteristics.[83] In the context of laboratory studies, the covariates examined in the present analyses (mean drinks per month, target alcohol dose, and target NTX dose) did not alter the significance of our effects, except for negative affect. Whether study characteristics are more influential in the context of clinical trials than laboratory studies remains to be determined.

A number of limitations of the present study should be considered. These limitations include the fact that while recent studies have suggested a host of potential moderators of the clinical effects of naltrexone,[72-74,84-86] these were not assessed and/or reported frequently enough in human laboratory trials to allow for a systematic examination of predictors of medication response. Notably, genetic factors, including variants at OPRM1 loci, were not accounted for in this meta-analysis and may clearly play a role in subjective responses to NTX in the laboratory.[33,87] Additionally, the present study relied heavily on US-based studies, and recent work has suggested discrepancies in AUD pharmacotherapy trials between the United States and European countries,[6] although the results for naltrexone were consistent across countries. This study does not directly address the degree to which naltrexone effects in the laboratory in fact predict clinical trial outcomes. Such comparisons are ultimately needed, yet they would require within-subject collection of both human laboratory outcomes and clinical outcomes. Lastly, as described in detail above, our approach to measure selection was to include all available measures. While these methods address the issue of publication bias from individual studies selectively reporting significant outcomes, it does not affect the related problem of whole studies going unreported. However, given the relative difficulty and costs associated with pharmacotherapy studies, we believe unreported outcomes will be a significantly larger problem than unreported studies. Nevertheless, the issue of selective reporting remains a problem, and recent calls for transparency in science, across a range of disciplines,[88] underscore this important issue. This meta-analysis suggested that selective reporting was in fact an issue in the literature on the effects of naltrexone on subjective responses to alcohol. Requirements to preregister trials and a priori outcomes as well as to share data represent a few of the steps towards addressing this broader issue of scientific integrity and accountability.[89]

In conclusion, the current meta-analysis aggregates across multiple human laboratory studies of naltrexone effects on subjective

responses to alcohol, providing a comprehensive summary of key putative mechanisms of naltrexone efficacy, namely, alteration of the subjective experience of alcohol intake. While the effect sizes in the laboratory are marginally larger than those obtained in clinical trials, both are uniformly small in magnitude. Insofar as these putative mechanisms of action, in this case subjective response to alcohol, are closer to the underlying biological effects of naltrexone, larger effect sizes might be expected. This expectation is also consistent with an endophenotype approach to psychiatric phenotypes, AUD included.[90-92] Thus, a broader conclusion from the meta-analytic findings on naltrexone, both in the clinic and in the human laboratory, is that the small effect size estimates are prevalent across levels of analysis and that until reliable predictors of treatment efficacy are detected, the clinical utility of naltrexone for the treatment of AUDs remains limited. Whether the prediction of naltrexone response will be driven by human laboratory constructs, by self-report measures (eg,[74]), or by emerging research on brain imaging (eg,[73]), the overarching goal is to optimize the use of this pharmacotherapy for AUD.

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DISCLOSURE/CONFLICT OF INTEREST

L.A.R. has received study medication from Pfizer Medicinova and consulted for GSK and Mitsubishi Tanabe. None of the authors have conflicts of interest to disclose.

AUTHORS CONTRIBUTION

LR and SB conceptualized the study and its design. SB acquire the data through literature reviews. SB, DJOR, and RG coded all studies. SB conducted the data analysis. SB and LR interpreted the results and drafted the manuscript. All authors provided a critical revision of the manuscript.

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REFERENCES

1. Grant BF, Goldstein RB, Saha TD, et al. Epidemiology of DSM-5 alcohol use disorder: results from the national epidemiologic survey on alcohol and related conditions III. *JAMA Psychiat*. 2015;72:757-766.
2. Litten RZ, Wilford BB, Falk DE, Ryan ML, Fertig JB. Potential medications for the treatment of alcohol use disorder: an evaluation of clinical efficacy and safety. *Subst Abus*. 2016b;37:286-298.
3. Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. *Int J Psychiatry Med*. 2011;42:227-266.
4. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet*. 2009;373:2223-2233.
5. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA*. 2006;295:2003-2017.
6. Donoghue K, Elzerbi C, Saunders R, Whittington C, Pilling S, Drummond C. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, Europe versus the rest of the world: a meta-analysis. *Addiction*. 2015;110:920-930.
7. O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Arch Gen Psychiatry*. 1992;49:881-887.
8. Rosner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M (2010) Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev:CD001867.
9. Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review. *Addiction*. 2006;101:491-503.
10. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA*. 2014;311:1889-1900.
11. Ray LA, Krull JL, Leggio L. The effects of naltrexone among alcohol non-abstainers: results from the COMBINE study. *Front Psych*. 2010c;1:26.
12. Vengeliene V, Bilbao A, Molander A, Spanagel R. Neuropharmacology of alcohol addiction. *Br J Pharmacol*. 2008;154:299-315.
13. Gianoulakis C. Endogenous opioids and addiction to alcohol and other drugs of abuse. *Curr Top Med Chem*. 2004;4:39-50.
14. Gianoulakis C. Endogenous opioids and addiction to alcohol and other drugs of abuse. *Curr Top Med Chem*. 2009;9:999-1015.
15. Gonzales RA, Weiss F. Suppression of ethanol-reinforced behavior by naltrexone is associated with attenuation of the ethanol-induced increase in dialysate dopamine levels in the nucleus accumbens. *J Neurosci*. 1998;18:10663-10671.
16. Ray LA, Bujarski S, MacKillop J, Courtney KE, Monti PM, Miotto K. Subjective response to alcohol among alcohol-dependent individuals: effects of the mu-opioid receptor (OPRM1) gene and alcoholism severity. *Alcohol Clin Exp Res*. 2013;37(Suppl 1):E116-E124.
17. Ray LA, Hutchison KE. A polymorphism of the mu-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans. *Alcohol Clin Exp Res*. 2004;28:1789-1795.
18. Ray LA, Miranda R Jr, Tidey JW, et al. Polymorphisms of the mu-opioid receptor and dopamine D4 receptor genes and subjective responses to alcohol in the natural environment. *J Abnorm Psychol*. 2010d;119:115-125.
19. Hendershot CS, Claus ED, Ramchandani VA. Associations of OPRM1 A118G and alcohol sensitivity with intravenous alcohol self-administration in young adults. *Addict Biol*. 2016;21:125-135.
20. Ramchandani VA, Umhau J, Pavon FJ, et al. A genetic determinant of the striatal dopamine response to alcohol in men. *Mol Psychiatry*. 2011;16:809-817.
21. Heilig M, Thorsell A, Sommer WH, et al. Translating the neuroscience of alcoholism into clinical treatments: from blocking the buzz to curing the blues. *Neurosci Biobehav Rev*. 2010;35:334-344.
22. Ray LA, Chin PF, Miotto K. Naltrexone for the treatment of alcoholism: clinical findings, mechanisms of action, and pharmacogenetics. *CNS Neurol Disord Drug Targets*. 2010a;9:13-22.
23. Weerts EM, Kim YK, Wand GS, et al. Differences in delta- and mu-opioid receptor blockade measured by positron emission tomography in naltrexone-treated recently abstinent alcohol-dependent subjects. *Neuropsychopharmacology*. 2008;33:653-665.

24. Bujarski S, Ray LA. Experimental psychopathology paradigms for alcohol use disorders: applications for translational research. *Behav Res Ther*. 2016;86:11-22.
25. Ray LA, Hutchison KE, Tartter M. Application of human laboratory models to pharmacotherapy development for alcohol dependence. *Curr Pharm Des*. 2010b;16:2149-2158.
26. Zimmermann US, O'Connor S, Ramchandani VA. Modeling alcohol self-administration in the human laboratory. *Curr Top Behav Neurosci*. 2013;13:315-353.
27. Yardley MM, Ray LA. Medications development for the treatment of alcohol use disorder: insights into the predictive value of animal and human laboratory models. *Addict Biol*. 2017;22:581-615.
28. Anton RF, Voronin KK, Randall PK, Myrick H, Tiffany A. Naltrexone modification of drinking effects in a subacute treatment and bar-lab paradigm: influence of OPRM1 and dopamine transporter (SLC6A3) genes. *Alcohol Clin Exp Res*. 2012;36:2000-2007.
29. de Wit H, Svenson J, York A. Non-specific effect of naltrexone on ethanol consumption in social drinkers. *Psychopharmacology (Berl)*. 1999;146:33-41.
30. Drobes DJ, Anton RF, Thomas SE, Voronin K. Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers. *Alcohol Clin Exp Res*. 2004;28:1362-1370.
31. King AC, Volpicelli JR, Frazer A, O'Brien CP. Effect of naltrexone on subjective alcohol response in subjects at high and low risk for future alcohol dependence. *Psychopharmacology (Berl)*. 1997;129:15-22.
32. O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. *Psychopharmacology (Berl)*. 2002;160:19-29.
33. Ray LA, Hutchison KE. Effects of naltrexone on alcohol sensitivity and genetic moderators of medication response: a double-blind placebo-controlled study. *Arch Gen Psychiatry*. 2007;64:1069-1077.
34. Hendershot CS, Wardell JD, Samokhvalov AV, Rehm J. Effects of naltrexone on alcohol self-administration and craving: meta-analysis of human laboratory studies. *Addict Biol*. 2017;22:1515-1527.
35. King AC, McNamara PJ, Hasin DS, Cao D. Alcohol challenge responses predict future alcohol use disorder symptoms: a 6-year prospective study. *Biol Psychiatry*. 2014;75:798-806.
36. Rueger SY, McNamara PJ, King AC. Expanding the utility of the Biphasic Alcohol Effects Scale (BAES) and initial psychometric support for the Brief-BAES (B-BAES). *Alcohol Clin Exp Res*. 2009;33:916-924.
37. Simmons JP, Nelson LD, Simonsohn U. False-positive psychology: undisclosed flexibility in data collection and analysis allows presenting anything as significant. *Psychol Sci*. 2011;22:1359-1366.
38. Gelman A, Carlin J. Beyond power calculations: assessing type S (sign) and type M (magnitude) errors. *Perspect Psychol Sci*. 2014;9:641-651.
39. Bujarski S, Hutchison KE, Roche DJ, Ray LA. Factor structure of subjective responses to alcohol in light and heavy drinkers. *Alcohol Clin Exp Res*. 2015;39:1193-1202.
40. Ray LA, MacKillop J, Leventhal A, Hutchison KE. Catching the alcohol buzz: an examination of the latent factor structure of subjective intoxication. *Alcohol Clin Exp Res*. 2009;33:2154-2161.
41. Litten RZ, Egli M, Heilig M, et al. Medications development to treat alcohol dependence: a vision for the next decade. *Addict Biol*. 2012;17:513-527.
42. Litten RZ, Falk DE, Ryan ML, Fertig JB. Discovery, development, and adoption of medications to treat alcohol use disorder: goals for the phases of medications development. *Alcohol Clin Exp Res*. 2016a;40:1368-1379.
43. Bormann I (2012) DigitizeIt.
44. Rakap S, Rakap S, Evran D, Cig O. Comparative evaluation of the reliability and validity of three data extraction programs: UnGraph, GraphClick, and DigitizeIt. *Comput Hum Behav*. 2016;55:159-166.
45. Hedges LV. Distribution theory for Glass's estimator of effect size and related estimators. *J Educ Stat*. 1981;6:107-128.
46. Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychol Methods*. 2002;7:105-125.
47. Fisher Z, Tipton E (2015) Robumeta: an R-package for robust variance estimation in meta-analysis. arXiv preprint arXiv:150302220.
48. Hedges LV, Tipton E, Johnson MC. Robust variance estimation in meta-regression with dependent effect size estimates. *Res Synth Methods*. 2010;1:39-65.
49. Tipton E. Small sample adjustments for robust variance estimation with meta-regression. *Psychol Methods*. 2015;20:375.
50. Deeks JJ, Higgins JP, Altman DG. Analysing data and undertaking meta-analyses. In: *Cochrane handbook for systematic reviews of interventions: Cochrane book series*; 2008:243-296. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=deeks+higgins+analysing+data+and+undertaking&btnG=
51. Higgins JP. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol*. 2008;37:1158-1160.
52. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
53. Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol*. 2008;8:79.
54. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
55. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.
56. Anton RF, Drobes DJ, Voronin K, Durazo-Avizu R, Moak D. Naltrexone effects on alcohol consumption in a clinical laboratory paradigm: temporal effects of drinking. *Psychopharmacology (Berl)*. 2004;173:32-40.
57. Bujarski S, MacKillop J, Ray LA. Understanding naltrexone mechanism of action and pharmacogenetics in Asian Americans via behavioral economics: a preliminary study. *Exp Clin Psychopharmacol*. 2012;20(3):181-190.
58. McCaul ME, Wand GS, Eissenberg T, Rohde CA, Cheskin LJ. Naltrexone alters subjective and psychomotor responses to alcohol in heavy drinking subjects. *Neuropsychopharmacology*. 2000;22:480-492.
59. Na C, Lee YS. Alcohol urge and plasma beta-endorphin change after alcohol challenge with naltrexone pretreatment in social drinkers. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26:663-670.
60. Peterson JB, Conrod P, Vassileva J, Gianoulakis C, Pihl RO. Differential effects of naltrexone on cardiac, subjective and behavioural reactions to acute ethanol intoxication. *J Psychiatry Neurosci*. 2006;31:386-393.
61. Plebani JG, Oslin DW, Lynch KG. Examining naltrexone and alcohol effects in a minority population: results from an initial human laboratory study. *Am J Addict*. 2011;20:330-336.
62. Ray LA, Bujarski S, Chin PF, Miotto K. Pharmacogenetics of naltrexone in Asian Americans: a randomized placebo-controlled laboratory study. *Neuropsychopharmacology*. 2012b;37:445-455.
63. Ray LA, Courtney KE, Ghahremani DG, Miotto K, Brody A, London ED. Varenicline, low dose naltrexone, and their combination for heavy-

drinking smokers: human laboratory findings. *Psychopharmacology (Berl)*. 2014;231:3843-3853.

64. Ray LA, Hutchison KE, MacKillop J, et al. Effects of naltrexone during the descending limb of the blood alcohol curve. *Am J Addict*. 2008;17:257-264.
65. Ray LA, Miranda R Jr, Kahler CW, et al. Pharmacological effects of naltrexone and intravenous alcohol on craving for cigarettes among light smokers: a pilot study. *Psychopharmacology (Berl)*. 2007;193:449-456.
66. Setiawan E, Pihl RO, Cox SM, et al. The effect of naltrexone on alcohol's stimulant properties and self-administration behavior in social drinkers: influence of gender and genotype. *Alcohol Clin Exp Res*. 2011;35:1134-1141.
67. Spagnolo PA, Ramchandani VA, Schwandt ML, et al. Effects of naltrexone on neural and subjective response to alcohol in treatment-seeking alcohol-dependent patients. *Alcohol Clin Exp Res*. 2014;38:3024-3032.
68. Swift RM, Whelihan W, Kuznetsov O, Buongiorno G, Hsuing H. Naltrexone-induced alterations in human ethanol intoxication. *Am J Psychiatry*. 1994;151:1463-1467.
69. Doty P, Kirk JM, Cramblett MJ, de Wit H. Behavioral responses to ethanol in light and moderate social drinkers following naltrexone pretreatment. *Drug Alcohol Depend*. 1997;47:109-116.
70. Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction*. 2013;108:275-293.
71. Del Re AC, Maisel N, Blodgett J, Finney J. The declining efficacy of naltrexone pharmacotherapy for alcohol use disorders over time: a multivariate meta-analysis. *Alcohol Clin Exp Res*. 2013;37:1064-1068.
72. Anton RF, Latham PK, Voronin KE, et al. Nicotine-use/smoking is associated with the efficacy of naltrexone in the treatment of alcohol dependence. *Alcohol Clin Exp Res*. 2018;42:751-760.
73. Schacht JP, Randall PK, Latham PK, et al. Predictors of naltrexone response in a randomized trial: reward-related brain activation, OPRM1 genotype, and smoking status. *Neuropsychopharmacology*. 2017;42:2640-2653.
74. Mann K, Roos CR, Hoffmann S, et al. Precision medicine in alcohol dependence: a controlled trial testing pharmacotherapy response among reward and relief drinking phenotypes. *Neuropsychopharmacology*. 2018;43:891-899.
75. Volpicelli JR, Watson NT, King AC, Sherman CE, O'Brien CP. Effect of naltrexone on alcohol "high" in alcoholics. *Am J Psychiatry*. 1995;152:613-615.
76. Koob GF. Neurobiological substrates for the dark side of compulsivity in addiction. *Neuropharmacology*. 2009;56(Suppl 1):18-31.
77. Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. *Nat Neurosci*. 2005;8:1442-1444.
78. Bujarski S, Jentsch JD, Roche DJO, Ramchandani VA, Miotto K, Ray LA. Differences in the subjective and motivational properties of alcohol across alcohol use severity: application of a novel translational human laboratory paradigm. *Neuropsychopharmacology*. 2018;43(9):1891-1899.
79. Bujarski S, Ray LA. Subjective response to alcohol and associated craving in heavy drinkers vs. alcohol dependents: an examination of Koob's allostatic model in humans. *Drug Alcohol Depend*. 2014;140:161-167.
80. King AC, Hasin D, O'Connor SJ, McNamara PJ, Cao D. A prospective 5-year re-examination of alcohol response in heavy drinkers progressing in alcohol use disorder. *Biol Psychiatry*. 2016;79:489-498.
81. Ray LA, Bujarski S, Yardley MM, Roche DJO, Hartwell EE. Differences between treatment-seeking and non-treatment-seeking participants in medication studies for alcoholism: do they matter? *Am J Drug Alcohol Abuse*. 2017;43:703-710.
82. Rohn MC, Lee MR, Kleuter SB, Schwandt ML, Falk DE, Leggio L. Differences between treatment-seeking and nontreatment-seeking alcohol-dependent research participants: an exploratory analysis. *Alcohol Clin Exp Res*. 2017;41:414-420.
83. Klemperer EM, Hughes JR, Naud S. Study characteristics influence the efficacy of substance abuse treatments: a meta-analysis of medications for alcohol use disorder. *Drug Alcohol Depend*. 2018;190:229-234.
84. Garbutt JC, Greenblatt AM, West SL, et al. Clinical and biological moderators of response to naltrexone in alcohol dependence: a systematic review of the evidence. *Addiction*. 2014;109(8):1274-1284.
85. Garbutt JC, Kampov-Polevoy AB, Kalka-Juhl LS, Gallop RJ. Association of the sweet-liking phenotype and craving for alcohol with the response to naltrexone treatment in alcohol dependence: a randomized clinical trial. *JAMA Psychiat*. (2016);73:1056-1063.
86. Savulich G, Riccelli R, Passamonti L, et al. Effects of naltrexone are influenced by childhood adversity during negative emotional processing in addiction recovery. *Transl Psychiatry*. 2017;7:e1054.
87. Ray LA, Barr CS, Blendy JA, Oslin D, Goldman D, Anton RF. The role of the Asn40Asp polymorphism of the mu opioid receptor gene (OPRM1) on alcoholism etiology and treatment: a critical review. *Alcohol Clin Exp Res*. 2012a;36:385-394.
88. Miguel E, Camerer C, Casey K, et al. Promoting transparency in social science research. *Science*. 2014;343:30-31.
89. Alberts B, Cicerone RJ, Fienberg SE, et al. Self-correction in science at work. *Science*. 2015;348:1420-1422.
90. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160:636-645.
91. Gottesman I, Shields J. *Schizophrenia and Genetics: A Twin Study Vantage Point*. London: Academic; 1972.
92. Hines LM, Ray L, Hutchison K, Tabakoff B. Alcoholism: the dissection for endophenotypes. *Dialogues Clin Neurosci*. 2005;7:153-163.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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