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Characterizing reward and relief/habit drinking profiles in a study of naltrexone, varenicline, and placebo

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Abstract

Introduction: This study aims to clarify differences in mood, craving, and treatment response between reward and relief/habit individuals in a study of naltrexone, varenicline, and placebo. We hypothesized that relief/habit individuals would have a poorer mood during early abstinence and higher levels of alcohol craving than reward individuals. We hypothesized that reward individuals would demonstrate better drinking outcomes on naltrexone versus placebo.

Methods: Data were culled from a randomized, double-blind, placebo-controlled human trial of 53 individuals (18F/16M) with alcohol use disorder randomized to varenicline ($n = 19$), naltrexone ($n = 15$), or matched placebo ($n = 19$). In this 6-day practice quit trial, participants attempted to abstain from drinking and completed daily diaries. Participants were classified into reward or relief/habit subgroups based on self-reported motivation for drinking. Multilinear models tested differences in mood and alcohol craving between reward and relief/habit individuals. General linear models tested differences between reward and relief/habit individuals' drinking outcomes on each medication versus placebo.

Results: Relief/habit individuals showed decreases in positive mood and increases in negative mood over the quit attempt across medications, compared to reward individuals (P's $< .05$). Reward individuals' tension decreased on naltrexone, while relief/habit individuals' tension remained stable ($F = 3.64$, $P = .03$). Reward individuals in the placebo group had higher percent days abstinent than relief individuals in the placebo group ($P < .001$).

Discussion: This study suggests relief/habit individuals' mood worsens during early abstinence. Our finding that reward individuals' tension decreased on naltrexone and increased on placebo may suggest a clinical response to the medication.

Keywords: alcohol use disorder; reward; relief; NCT04249882; naltrexone; varenicline

Introduction

Alcohol use disorder (AUD) is a chronic, relapsing condition characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences (Fischman 2018). AUD is highly prevalent in the United States, with 10.5% of people ages 12 and older receiving a past-year AUD diagnosis (SAMHSA 2022). Despite the high prevalence of AUD, treatment for AUD remains only modestly effective (Litten et al. 2016). Therefore, it is imperative to improve treatment options for individuals with AUD. As a highly heterogeneous disorder (Linden-Carmichael et al. 2019), research shows variation in which subsets of individuals with AUD respond to treatment (Litten et al. 2016). One promising way to improve care is by developing personalized treatments for subpopulations with AUD to improve the overall efficacy of pharmacotherapies (Grodin et al. 2019).

There is a rich history of parsing heterogeneity in AUD by identifying subtypes of the disorder (Jellinek 1960; Cloninger et al. 1981; Yoshino et al. 1994; Babor 1996; Del Boca and Hesselbrock 1996; Cox and Klinger 1988; Sannibale and Hall 1998; for a review of the history of classifying subtypes of AUD, see Leggio et al. 2009). From this history, drinking motives emerged as a clinically useful factor associated with co-occurring symptomatology (Windle and Windle 2018), particularly the concept that individuals drink for positive or negative reinforcement (Cox and Klinger 1988). Using the Inventory of Drinking Situations, a 30-item self-report questionnaire, Mann et al. (2018) classified individuals with AUD into four empirically-derived drinking subtypes using factor mixture models: "high reward/high relief," "low reward/low relief," "high reward/low relief," and "low reward/high relief" (Mann et al. 2018). Individuals were evaluated in terms of their motivation to drink to promote a positive mood and enhance the well-documented rewarding effects of alcohol (i.e. enhancement motives; Mann et al. 2018). They were also evaluated based on their motivation to drink to alleviate stress and negative affect (i.e. coping motives; Mann et al. 2018). In an effort to improve the efficiency of characterizing individuals with AUD based on their drinking motives, Grodin et al. (2019) reported on a four-item questionnaire to assess reward versus relief drinking profiles and to examine a third possible drinking profile: drinking for habit motives. Those are individuals who report drinking primarily as a result of habitual drinking patterns. This classification revealed significant overlap in clinical characteristics between relief and habit individuals, and thus, relief/habit individuals were combined into a relief/habit group (Grodin et al. 2019). Relief/habit

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individuals report decreases in negative affect during alcohol administration and report significantly higher levels of alcohol craving, while reward individuals report lower levels of alcohol craving (Grodin et al. 2019).

While researchers have started to establish the clinical utility of reward and relief drinking profiles, gaps in the current literature remain. For instance, while relief/habit individuals demonstrate more mood/anxiety symptoms than reward individuals (Grodin et al. 2019), little is known about how these groups differ in mood and alcohol craving during a period of early abstinence (i.e. an early quit attempt). We predict that relief/habit individuals, who drink to manage negative emotions, may experience heightened low mood and tension/anxiety during the early abstinence period. Given that relief/habit individuals report higher levels of alcohol craving (Grodin et al. 2019), we hypothesize that relief/habit individuals will show higher levels of alcohol craving than reward individuals. The current study will advance this line of research by testing the effect of reward and relief/habit subgroups on mood, craving, and drinking outcomes during a practice quit attempt, using data from a medication trial study (Ray et al. 2023).

Given the moderate effects of medications for AUD (Jonas et al. 2014; Litten et al. 2016) and the heterogeneity of AUD, there is an opportunity to improve treatment response by tailoring treatments based on distinctive psychological and behavioral characteristics. Research applying the reward/relief characterization approach found that individuals who drink predominately for reward motives respond better to naltrexone than placebo, which may be explained by naltrexone's ability to block mu-opioid receptors and thereby diminish alcohol's positive reinforcement effects (Spanagel and Holter 1999; Verheul et al. 1999). By contrast, individuals who drink primarily for relief motives do not show the same response (Mann et al. 2018; Witkiewitz et al. 2019; Roos et al. 2021). Little is known about how the reward/relief characterization predicts response to varenicline, an FDA-approved smoking cessation treatment with clinical efficacy for treating AUD (Erwin and Slaton 2014; Litten et al. 2016). The literature suggests that varenicline may be effective for relief individuals who drink to cope with stress and negative affect. Studies have shown that varenicline may enhance mood (Patterson et al. 2009) or reduce withdrawal-related negative affect (Gonzales et al. 2006; Jorenby et al. 2006; West et al. 2008; Patterson et al. 2009). Researchers hypothesize that varenicline's agonist effects at $\alpha 7$ nAChRs contribute to the observed mood-enhancing effects, given the role of $\alpha 7$ nAChRs in nicotine-induced dopamine release (Patterson et al. 2009). However, it remains unclear whether varenicline could impact individuals' urge to drink in response to a negative mood. Thus, our exploratory hypothesis is that mood improvements on varenicline may be particularly beneficial to individuals categorized in the relief drinking profile.

This study will help enhance our understanding of reward and relief/habit profiles and their differences in mood and craving during a practice quit attempt. In addition, responses to medications within these groups will be explored. The parent study tested the practice quit model (Ray et al. 2023), which has previously been validated in trials of smoking cessation medications and asks participants with intrinsic motivation to abstain from alcohol for 1 week (Perkins 2012). This secondary analysis focuses on reward/relief profiles to test the following aims: First, we will compare differences in mood and craving between reward and relief/habit individuals during the practice quit period. Second, we will explore the effects of each active medication versus placebo on mood and alcohol craving and examine whether medication effects differ between reward and relief/habit individuals. We will also compare the response to each active medication versus placebo (as measured by drinking outcomes) during the practice of quitting between reward and relief/habit individuals. In line with the first aim, we hypothesize that relief/habit individuals will show higher levels of negative mood and tension and lower levels of positive mood than reward individuals. We predict that relief/habit individuals will show higher levels of craving compared to reward individuals. In line with aim two, we hypothesize that reward individuals randomized to naltrexone will show greater reductions in alcohol use compared to placebo. We expect that relief/habit individuals randomized to varenicline will show improvements in drinking outcomes and mood outcomes compared to placebo.

Methods

Participants

Fifty-three people with AUD and self-reported motivation to quit drinking were randomized to receive oral naltrexone ($n = 15$), varenicline ($n = 19$), or placebo ($n = 19$) for 2 weeks (see Ray et al. 2023). Eligible participants were 21–65 years old, met (past 12-month) DSM-5 criteria for current moderate or severe AUD, endorsed heavy drinking ($\geq$14 drinks per week for males and $\geq$7 drinks per week for females) in the 28 days before the initial screening visit, reported intrinsic motivation to reduce or quit drinking, and had reliable internet for accessing electronic daily diary assessments (DDAs). Exclusion criteria included current DSM-5 diagnosis for substance use disorder other than AUD and nicotine use disorder; lifetime DSM-5 diagnosis of bipolar disorder, schizophrenia, or another psychotic disorder; testing positive for drugs, excluding cannabis, on a urine drug screen; significantly elevated alcohol withdrawal symptoms as demonstrated by at least 10 on the Clinical Institute Withdrawal Assessment for Alcohol Revised (CIWA-R; Sullivan et al., 1989); and circumstances (e.g. pregnancy, medical conditions, etc.) that interfere with safe participation as determined by the study physicians. All participants provided written consent upon discussing the study medications with a physician. AQ10

Study design

Data for this secondary analysis were culled from a double-blind, randomized, placebo-controlled trial of 53 individuals with AUD randomized to varenicline (VAR; 1 mg twice a day), naltrexone (NTX; 50 mg once a day), or matched placebo (ClinicalTrials.gov identifier: NCT04249882; Ray et al. 2023). On Day 1 of the study, participants completed baseline questionnaires and started a week-long medication titration (Days 1–7). After the titration period, participants completed an in-person visit and began the 6-day quit attempt (Days 8–13). Throughout the quit attempt, participants reported on their previous day's alcohol use, mood, and alcohol craving by completing an electronic DDA. Alcohol use data was collected daily using the Timeline Followback (TLFB) interview administered over the telephone (Sobell et al. 1986). On the last day of the study (Day 14), participants returned to the laboratory to complete questionnaires. Participants were required

to have a 0.00 g/dl percent breath alcohol concentration at each visit.

The University of California, Los Angeles' Institutional Review Board approved all study procedures. After an initial telephone screening, eligible participants completed an in-person screening visit to evaluate their alcohol/drug use history, demographic information, and psychiatric diagnoses (assessed by the Structured Clinical Interview for The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (SCID-5; First, 2015). 53 out of the 121 people who completed the initial in-person screening visit were deemed eligible and participated in the randomization.

UCLA reward relief habit drinking scale

Reward and relief/habit drinking profiles were assessed via the UCLA Reward, Relief, and Habit Drinking Scale (UCLA RRHDS), a brief four-item self-report questionnaire asking participants to identify their primary reason for drinking alcohol and how often they drink alcohol for reward or relief purposes (Grodin et al. 2019). Reward and relief/habit individuals were not significantly different across medication assignments ($\chi^2(2) = .515$, $P = .773$). The UCLA RRHDS has good test–retest reliability for both reward and relief subtypes and good validity (Grodin et al. 2019).

Drinking outcomes

Percent days abstinent (PDA) and Drinks per drinking day (DPDD) were used as dependent variables in our models because they were the co-primary registered clinical outcomes in the parent trial (Ray et al. 2023). These variables were assessed using daily diary data, which asked participants to retrospectively report on their previous day's alcohol use. Reported alcoholic beverage consumption was converted to standard drinks for consistency. DPDD is a measure of the number of drinks consumed within one 24-h drinking day. PDA is the percentage of days during the six days of the practice quit when the participant reported abstinence from alcohol.

Individual differences

Smoking status and AUD severity were assessed to account for individual differences between participants. Smoking status was a binary variable (Yes/No) measured based on the first question of the Fagerstrom Test for Nicotine Dependence (FTND). AUD severity was assessed using the number of AUD symptoms endorsed on the SCID-5.

Electronic daily diary assessment data

Daily mood

Daily mood was assessed via daily diary surveys using eight select items from the POMS-SF, a short form of the Profile of Mood States (POMS) survey (Curran et al. 1995; McNair et al. 1971). The following scales and prompts were included in the DDA: negative mood was measured by the items "downhearted" and "discouraged"; positive mood was measured by the items "joyful" and 'cheerful'; tension was measured by uneasy and anxious. The two-item sub-scales were highly correlated: negative mood items ($r = 0.73$, $P < .001$); positive mood items ($r = 0.90$, $P < .001$); and tension items ($r = 0.73$, $P < .001$).

Daily craving

Alcohol craving was assessed via daily diary surveys using two Alcohol Urge Questionnaire (AUQ) items assessing the previous day's craving (Bohn et al. 1995). The real-time AUQ assessment was modified to assess past-day cravings. The items were: (i) I craved a drink yesterday and (ii) All I wanted to do yesterday was to have a drink. AUQ items one and two were summed to create a craving variable. Two AUQ items were selected a priori based on their overall loading on the AUQ total score and to improve the efficiency of daily assessments. The average sum of AUQ items one and two over the 6-day practice quit period was moderately correlated with the AUQ total score measured at baseline ($r = 0.64$, $P < .001$), suggesting the AUQ items 1 and 2 are a reasonable indicator for alcohol craving.

Statistical analyses

All statistical analyses were completed in SAS version 9.4 on the sample of participants randomized to the study medications or placebo ($n = 53$). Frequencies, means, standard deviations, and/or percentiles were computed for all demographic variables for the whole sample and separately by reward/relief profiles. T-tests and chi-square tests were run to assess differences between reward and relief/habit profiles.

In line with the first aim, which examined differences in mood and craving among reward and relief/habit profiles, we conducted multilevel mixed models. All models were fit in SAS using the PROC MIXED procedure with restricted maximum likelihood (REML) estimation. PROC MIXED with REML accounts for repeated measures data that is missing at random (Dickey, 2008). To assess whether medication condition and reward versus relief/habit profiles were associated with mood states during the quit attempt, individual multilevel mixed models were conducted to test the effects of time, reward versus relief/habit, previous-day alcohol consumption, and time by reward versus relief/habit on each POMS subscale (i.e. positive mood, negative mood, and tension) during the practice quit attempt.

In line with the second aim, which assessed whether medication condition and reward versus relief/habit profiles were associated with mood states during the quit attempt, individual multilevel mixed models were conducted to test the effects of time, reward versus relief/habit, medication (naltrexone vs. varenicline vs. placebo), previous-day alcohol consumption, and medication by reward versus relief/habit interaction on each POMS subscale during the practice quit attempt. First, the models were run without the time × reward/relief × medication condition interaction, and next, the models were estimated including the three-way interaction. The same analytic method was utilized to assess whether medication condition and reward versus relief/habit profiles were associated with alcohol craving. Given the exploratory nature of these analyses, corrections for multiple comparisons were not employed.

In line with the second aim, we also compared the effects of each active medication versus placebo on alcohol use during the practice quit between reward and relief/habit individuals by utilizing a series of regression models to test the interaction between medication and reward/relief profiles. Interaction effects were followed by tests of simple effects to inform the interpretation of each interaction. Analyses were run using PROC GLM, where the dependent measures were DPDD

Table 1. Demographic and clinical characteristics of reward and relief/habit individuals.

Demographic factor	Reward ($n = 34$)	Relief/habit (n = 19)	Statistic	*P*-value
Medications	Placebo Naltrexone Varenicline $n = 13$ $n = 10$ $n = 11$	Placebo Naltrexone Varenicline $n = 6$ $n = 5$ $n = 8$		
Age	41.74 ± **10.62**	41.74 ± **13.72**	$F = 0.00$	1.00
Sex (%)			$X^2 = 0.57$	.45
Male	16 (47.06%)	11 (57.89%)		
Female	18 (52.94%)	8 (42.10%)		
Race (%)			$X^2 = 5.04$	.54
White	17 (50%)	6 (31.58%)		
Black	8 (23.52%)	6 (31.58%)		
American Indian	0 (0%)	1 (5.26%)		
Asian	1 (2.94%)	2 (10.52%)		
Pacific Islander	1 (2.94%)	0 (6.67%)		
Mixed	6 (21.05%)	3 (15.79%)		
Other/Unknown	1 (2.94%)	1 (5.26%)		
Hispanic/Latino	10 (29.41%)	4 (21.05%)	$X^2 = 0.43$	.51
Last 28 days total drinks	108.66 ± **42.44**	249.00 ± **181.02**	$F = 1.949$	.26
Drinks per drinking day (past 28 day)	5.73 ± **3.21**	5.72 ± **3.21**	$F = 0.00$	.99
Past month percent day abstinent	19.9 ± **23.31**	20.0 ± **26.08**	$F = 0.009$	.93
Past week alcohol craving (PACS)	12.00 ± **6.28**	12.11 ± **6.08**	$F = 0.004$	.95
Alcohol use disorder symptom count	6.34 ± **1.99**	7.39 ± **2.14**	$F = 3.09$	.08

Data are presented as mean ± standard deviation or as number of participants (percent of sample).

and PDA (each tested separately), and the covariates were baseline DPDD (or baseline PDA), smoking status (smoker or nonsmoker), sex at birth, and AUD symptoms count.

Results

Participant characteristics

The sample consisted of 53 participants with current AUD (50.9% male; average age 41.75 (SD = 11.7 years; see Table 1). The reward versus relief/habit groups did not significantly differ on demographic factors or alcohol use variables (see Table 1). In the 30 days prior to their baseline visit, participants had an average of 21 drinking days and 6.70 (SD = 4.22) DPDD.

Differences in daily mood and craving among reward and relief/habit individuals

Drinking profiles and negative mood

An MLM model predicting negative mood based on reward/relief, time, previous-day alcohol consumption, and reward/relief × time was estimated (see Table 2). The interaction between time and reward versus relief/habit was statistically significant ($F = 6.09$, $P = .01$), such that relief/habit individuals' negative mood increased over time across all medication conditions, whereas reward individuals' negative mood decreased (see Fig. 1). The main effect of drinking was significant, endorsing previous-day alcohol consumption was associated with a greater negative mood ($F = 7.45$, $P < .01$). No other main or interaction effects were significant (P's > .33).

Drinking profiles and positive mood

An MLM model predicting positive mood based on reward/relief, time, previous-day alcohol consumption, and reward/relief ×time was estimated (See Table 2). The interaction between time and reward versus relief/habit was statistically significant ($F = 7.22$, $P < .01$), such that relief/habit individuals showed significant decreases in positive mood over time across all medication conditions, whereas reward individuals remained relatively stable. The main effect of time was also significant ($F = 7.77$, $P < .01$), but was not interpreted given the significant interaction effect. No other main or interaction effects were significant (P's > .21).

Drinking profiles and tension

An MLM model predicting tension on reward/relief, time, previous-day alcohol consumption, and reward/relief ×time was estimated (see Table 2). The main effect of drinking was significant, endorsing previous-day alcohol consumption was associated with greater tension ($F = 8.29$; $P < .01$). All other interactions and main effects were non-significant (P's > .20).

Effects of reward/relief on daily craving

An MLM model predicting craving based on reward/relief, time, previous-day alcohol consumption, and reward/relief × time was estimated. There were no significant interactions or main effects on craving (P's > .16).

Differences in medication response among reward and relief/habit individuals

Effects of reward and relief/habit profiles and medication condition on mood and craving

Drinking profiles and negative mood.

The MLM model predicting negative mood was rerun to include medication condition, reward/relief × time, reward/relief × medication condition, and medication condition × time (see Supplement Table 1a). The interaction between time and reward versus relief/habit remained statistically

Table 2. Multilevel Models Predicting POMS Mood Scales: negative mood, positive mood, and tension.

Effect	Estimate	SE	DF	*F* value	*P*-value
Negative Mood					
Reward and relief/habit	−0.33	0.42	1	0.58	.45
Time	−0.04	0.03	1	0.93	.33
Time by reward and relief/habit	0.14	0.05	1	6.09	.01
Previous-day alcohol consumption	1.67	0.61	1	7.45	<.01
Positive Mood					
Reward and relief/habit	0.77	0.61	1	1.58	.21
Time	−0.003	0.05	1	7.77	<.01
Time by reward and relief/habit	−0.26	0.10	1	7.22	<.01
Previous-day alcohol consumption	0.35	1.06	1	0.11	.74
Tension					
Reward and relief/habit	−0.32	0.43	1	0.58	.45
Time	−0.04	0.03	1	0.93	.34
Time by reward and relief/habit	0.14	0.05	1	6.09	.07
Previous-day alcohol consumption	1.67	0.61	1	7.45	<.01

The reference group for Reward and Relief/habit was the Reward drinking profile. The reference group for medication was placebo. Placebo was coded as zero, naltrexone was coded as one, and varenicline was coded as two.

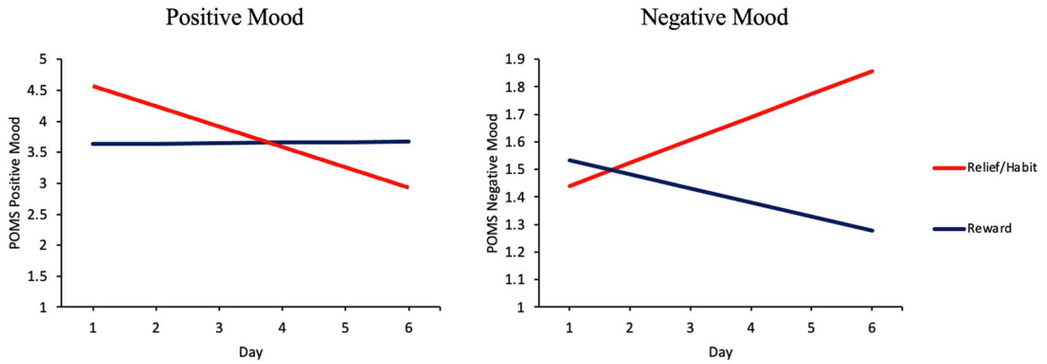

Figure 1 Predicted Values for Daily Level of Positive Mood and Daily Level of Negative Mood across the 6 days of Assessment among Reward versus Relief/habit Individuals across All Medications. There was a significant decrease in daily positive mood among Relief/Habit individuals during the 6-day practice quit trial. Positive mood remained stable among Reward individuals during the trial $P < .001$.

significant ($F = 6.49$, $P = .01$). The main effect of drinking remained significant ($F = 7.52$, $P < .01$). No other main or interaction effects were significant (P's > .34).

This MLM model predicting negative mood was estimated with the addition of the three-way interaction (including medication × reward/relief × time; see Supplement Table 1b). The three-way interaction between time, reward versus relief/habit, and medication was not statistically significant ($F = 1.02$, $P = .36$). All other interactions and main effects remained the same.

Drinking profiles and positive mood.

The MLM model predicting positive mood was rerun to include medication condition, reward/relief × medication condition, and medication condition × time (see Supplement Table 1a). The interaction between time and reward versus relief/habit remained statistically significant ($F = 8.30$, $P < .01$). No other main or interaction effects were significant (P's > .34).

The same MLM model predicting positive mood based on time, medication condition, reward versus relief/habit, previous-day alcohol consumption, and their interactions (including medication × reward/relief × time) was estimated (See Supplement Table 1b). The three-way interaction between time, reward versus relief/habit, and medication was not statistically significant ($F = 1.10$, $P = .33$). All other interactions and main effects remained the same.

Drinking profiles and tension.

The MLM model predicting tension was rerun to include medication condition, reward/relief × medication condition, and medication condition × time (see Supplement Table 1a). The main effect of drinking remained significant ($F = 8.29$; $P < .01$). All other interactions and main effects were non-significant (P's > .20).

The same MLM model predicting tension based on time, medication condition, reward versus relief/habit, previous-day alcohol consumption, and their interactions (including medication × reward/relief × time) was estimated (see Supplement Table 1b). The three-way interaction between time, reward versus relief/habit, and medication was significant ($F = 3.64$; $P = .03$; see Fig. 2). In the placebo group, reward individuals showed an increase in tension over the course of the study, while relief/habit individuals showed a decrease in tension. In the naltrexone group, reward individuals showed a decrease in tension over the practice quit period, while relief/habit individuals showed an increase in tension. In the varenicline group, there were no differences in changes in tension over time between reward and relief/habit individuals. The main effect of drinking was significant, endorsing previous-day alcohol

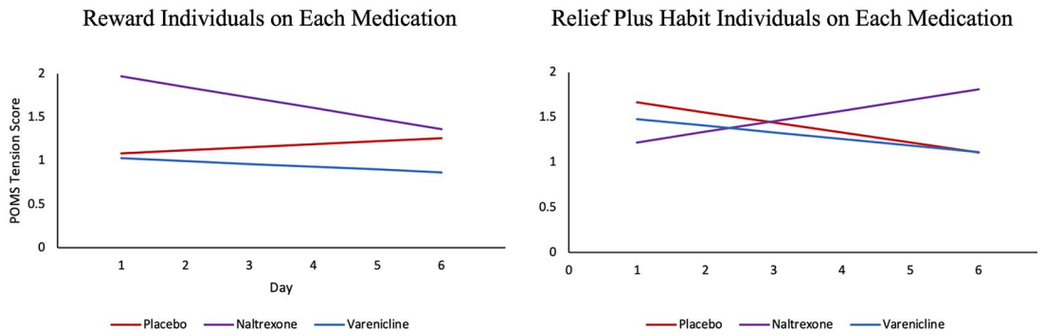

Figure 2 Predicted Values for Daily Level of Tension (POMS Scale) across the 6 days of Assessment for Reward Individuals (A) and for Relief/habit Individuals (B) for Each Medication Condition. There was a significant decrease in daily tension among Reward individuals on naltrexone during the 6-day practice quit trial. There was a significant increase in daily tension among Relief/Habit individuals on naltrexone during the 6-day practice quit trial. Tension remained stable among Reward and Relief/Habit individuals on placebo and varenicline.

consumption was associated with greater tension ($F = 2.79$; $P < .01$). All other interactions and main effects were non-significant (P's > .20).

Medication effects of reward/relief on daily craving.

The MLM model predicting craving was rerun to include medication condition, reward/relief × medication condition, and medication condition × time. There were no significant interactions or main effects on craving (P's > .15). A model with the three-way (medication × reward/relief × time) was also estimated, and there were no significant interactions or main effects on craving (P's > .18).

Effects of reward and relief/habit profiles and medication condition on drinking outcomes

Percent days abstinent (PDA)

Naltrexone versus placebo.

A linear regression model predicting PDA from medication condition (naltrexone versus placebo), reward versus relief/habit profiles, and medication × reward versus relief/habit profiles, was performed ($R^2 = 0.44$, $F(7, 25) = 2.81$, $P = .03$). After accounting for the covariates, reward/relief moderated the effects of medication conditions on PDA ($F = 3.18$, $P = .01$). Reward individuals in the placebo group had higher PDA compared to relief/habit individuals in the placebo group ($P < .01$; see Fig. 3a and b).

Varenicline versus placebo.

A linear regression model predicting PDA from medication condition (varenicline versus placebo), reward versus relief/habit profiles, and medication × reward versus relief/habit profiles was performed ($R^2 = 0.37$, $F(7, 27) = 1.01$, $P = .45$). There were no significant main or interaction effects.

Drinks per drinking day (DPDD)

Naltrexone versus placebo.

A linear regression model predicting DPDD from medication condition (naltrexone versus placebo), reward versus relief/habit profiles, and medication × reward versus relief/habit profiles was performed ($R^2 = 0.31$, $F(7, 25) = 1.58$, $P = .19$). After accounting for the covariates, the relationship between medication condition and DPDD was significantly moderated by reward versus relief/habit profiles ($F = 4.64$, $P = .04$), such that reward individuals in the placebo group had significantly fewer DPDD than reward individuals in the naltrexone group ($P = .03$; see Fig. 3a and b).

Varenicline versus placebo.

A linear regression model predicting DPDD from medication condition (varenicline versus placebo), reward versus relief/habit profiles, and medication × reward versus relief/habit profiles was performed ($R^2 = 0.37$, $F(7, 27) = 2.26$, $P = .06$). Baseline DPDD was significantly associated with DPDD ($F = 11.65$, $P < .01$). There were no other main effects or interaction effects.

Discussion

The present study examined differences in mood, craving, and drinking outcomes among reward and relief/habit individuals during a medication trial. This study contributes to the emerging literature on characterizing differences between reward and relief/habit individuals.

We examined daily mood and alcohol craving ratings across medication groups for both reward and relief/habit profiles. We hypothesized that relief/habit individuals would endorse poorer mood ratings during the abstinence period compared to reward individuals. Indeed, we found that while reward individuals' negative mood decreased throughout the practice of quitting, relief/habit individuals' negative mood increased. We also found that reward individuals showed stable positive mood over time, whereas relief/habit individuals showed decreases in their daily positive mood over time across all medication conditions. Given that relief/habit individuals have shown a decrease in negative mood during alcohol administration (Grodin et al. 2019), abstaining from alcohol during the practice of quitting may have led to increases in negative mood and decreases in positive mood in the relief/habit group.

While we predicted that relief/habit individuals would demonstrate higher craving during the practice quit trial compared to reward individuals, there was no main effect of reward/relief on craving during the practice quit period. Unlike Grodin et al. (2019) comparison of reward and relief/habit individuals' Obsessive Compulsive Drinking Scale (OCDS) scores, the use of AUQ items may further explain the null findings. Unlike the AUQ, the OCDS includes items related to distress and disturbance from craving as well as anxiety due to not being able to drink (Anton 1996), which may be particularly salient for relief/habit individuals

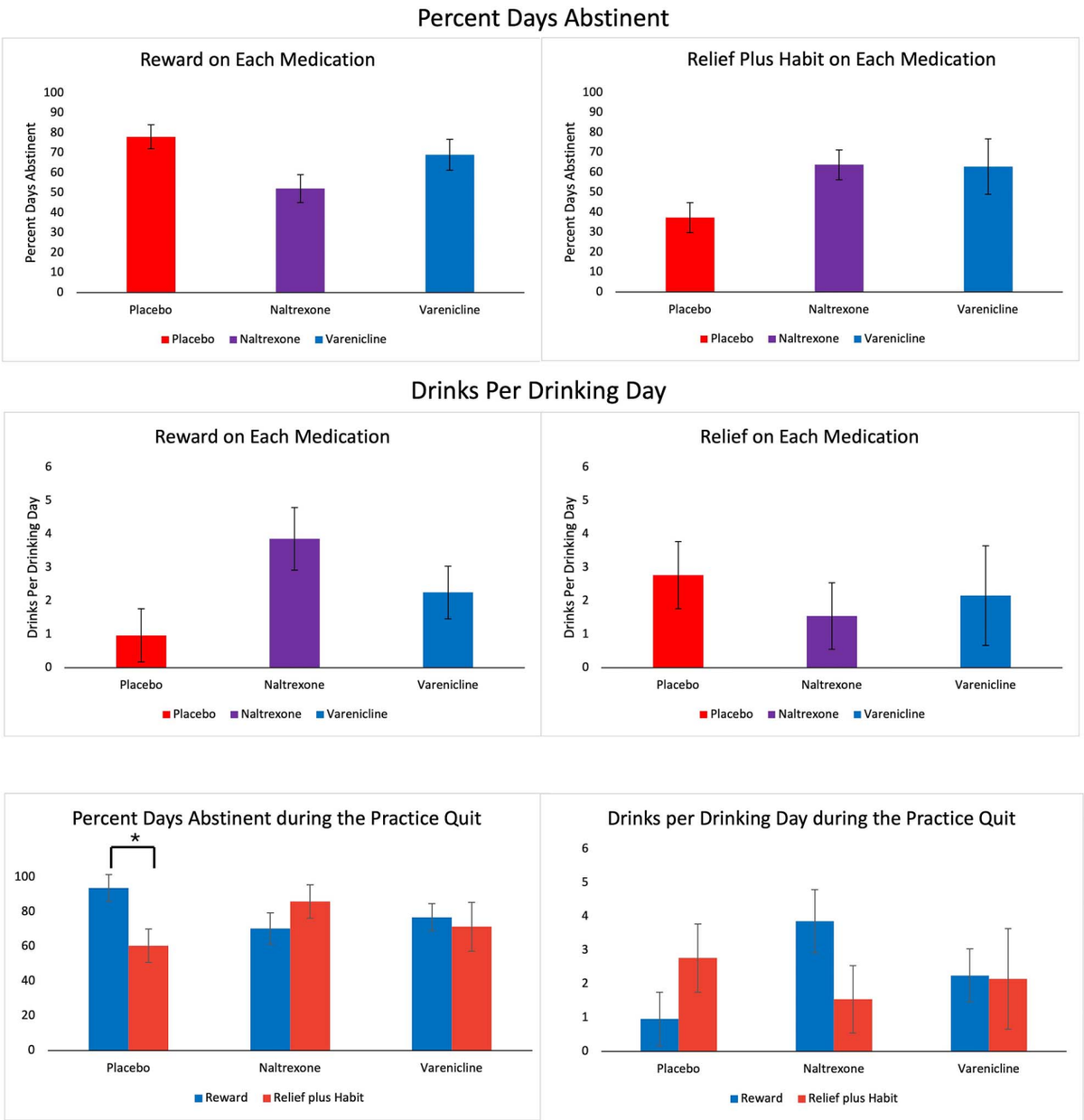

Figure 3 (a) Percent Days Abstinent (PDA) during the Practice Quit Attempt (6-day) for Reward Individuals (A) and for Relief/habit Individuals (B) for Each Medication Condition, There was a significant difference between PDA for Reward versus Relief/Habit Individuals ($P < .01$). There were no other statistically significant group differences for PDA. There was a significant difference between DPDD for Reward versus Relief/Habit Individuals ($P = .03$). There were no other statistically significant group differences. (b) PDA and DPDD during the Practice Quit Attempt (6-day) for Reward and Relief/Habit Individuals There was a significant difference between PDA for Reward versus Relief/Habit Drinkers ($P < .01$). There were no other statistically significant group differences. $* < .05$

who drink to relieve withdrawal-related negative affect. This finding may highlight the importance of considering measurement tools that include details about affective reactions to craving when examining differences between reward and relief/habit individuals.

Reward individuals treated with naltrexone reported decreases in tension over the course of the practice quit period, while relief/habit individuals' tension increased. The naltrexone-induced decrease in tension among reward individuals may help explain why previous research has shown that reward individuals show a more favorable clinical response to naltrexone in randomized clinical trials (Mann et al. 2018; Witkiewitz et al. 2019). Given that endorsing feeling uneasy and anxious (POMS items for the tension scale) may be an indicator of protracted withdrawal (Gallus et al. 2023), the finding that tension decreased for reward individuals is clinically meaningful.

While we hypothesized that reward individuals would respond better (in terms of DPDD and PDA) to naltrexone than placebo, our results did not replicate past findings (Mann et al. 2018; Witkiewitz et al. 2019). Instead, we found that reward individuals in the placebo group had significantly

fewer DPDD than reward individuals in the naltrexone group. We speculate that the absence of a naltrexone effect on reward individuals may be the result of the shorter duration of the practice quit model, compared to a traditional randomized controlled trial where the benefit of naltrexone for reward individuals has previously been examined. Our outcome variables, DPDD and PDA, differed from past studies that focused on heavy drinking outcomes rather than measures of drinking intensity, which may further clarify the null findings (Pettinati et al. 2006). Similarly, the present reward/relief measure was different from previous studies, which derived four, rather than two, reward and relief subgroups, and this distinction in measurement may have resulted in different outcomes. Specifically, previous studies identified high and low levels of reward and relief, producing four groups (high reward/high relief, high reward/low relief, high relief/low reward, and low reward/low relief). In contrast, in the present study, individuals in the reward group may have had significant relief drinking motives and thus would not be expected to respond well to naltrexone, given that high reward/high relief individuals do not consistently demonstrate decreases in drinking on naltrexone (Witkiewitz et al. 2019).

An exploratory hypothesis was that relief/habit individuals would respond better (in terms of PDA and DPDD) to varenicline than placebo. While the relief/habit individuals endorsed higher PDA on varenicline versus placebo (60.4% days abstinent in the placebo condition and 71.4% days abstinent in the varenicline condition), this difference did not reach statistical significance. Interestingly, as discussed below, positive mood decreased and negative mood remained stable among the varenicline group. Therefore, mood effects may not be a primary mechanism of action for varenicline in AUD.

Unexpectedly, there were significant differences in drinking outcomes in the placebo group between reward and relief/habit individuals. The effects were such that reward individuals reported significantly higher PDA than relief/habit individuals. This finding may suggest that reward individuals may be more likely to experience a placebo response and may reduce their drinking more effectively during the practice quit period, compared to individuals with relief/habit drinking profiles. We speculate that reward individuals may be more likely to reduce their drinking without formal intervention, beyond the instruction to abstain from alcohol for one week. Previous randomized-controlled trials of naltrexone versus placebo did not show evidence of a strong placebo response (Roos et al. 2017; Mann et al. 2018; Witkiewitz et al. 2019; Roos et al. 2021). Thus, the placebo response may be unique to the practice quit model, which has a shorter duration than RCTs and formally asks participants to abstain for only a short period of time. The unexpected placebo effect among reward individuals has implications for medication development for AUD and may clarify a potential challenge for detecting medication effects in clinical trials in this patient profile. However, results would require replication to draw any firm conclusions about this difference in placebo response.

The present findings should be considered in light of the study's limitations. The brief duration of the practice quit trial may have reduced our ability to observe medication responses to naltrexone and varenicline among reward and relief/habit individuals, which is consistent with the primary trial findings (Ray et al. 2023). Longer trials may be warranted to effectively investigate the early alcohol abstinence period. Additionally, future trials may benefit from recruiting participants who are at the high severity end of the AUD spectrum and drink daily to observe the most noticeable differences in early abstinence outcomes during a practice quit. The sample size was consistent with those of human laboratory trials, yet further dividing individuals in each study medication by reward/relief groups resulted in modest sample sizes and therefore limited the study's power. Additionally, by contrast to practice quit trials for smoking cessation, alcohol use in this study was self-reported and bioverification could not be implemented (i.e. largely due to the trial being conducted during the COVID-19 pandemic). Given that participants were asked to abstain from alcohol, respondents may have under-reported drinking during the practice quit due to desirability effects. Finally, the use of the AUQ real-time scale and reliance on two AUQ items to measure past-day cravings may have limited our ability to effectively capture cravings in the daily diary data.

Despite the limitations, this study has notable strengths. The study's use of daily diary data allowed for a granular examination of the effect of varenicline and naltrexone on mood and craving. This micro-longitudinal design offered insights into daily mood changes among reward and relief/habit individuals during a brief practice quit. Broadly, this study clarified differences in mood and craving between reward and relief/habit individuals during a medication trial and can inform future investigations into clinically relevant differences between reward and relief/habit individuals, including their responses to pharmacotherapies.

Conclusion

The present study provides an investigation into differences in clinical characteristics and treatment response among reward and relief/habit individuals on naltrexone, varenicline, and placebo. By examining differences in craving and mood (i.e. AUD maintenance factors) between reward and relief/habit profiles, this study elucidates clinically relevant differences between reward and relief/habit individuals. Namely, reward individuals responded better to naltrexone in terms of tension reduction during the practice quit, while relief individuals reported an increase in negative mood and a decrease in positive mood during the abstinence period. These findings suggest that mood variability may characterize relief individuals, and mood may worsen during early abstinence. Lastly, naltrexone's clinical efficacy for reward individuals may be explained by the medication's ability to alleviate tension, a plausible indicator of protracted withdrawal.

Author contributions

Annabel Kady (Conceptualization, Data curation [equal], Formal analysis [lead], Methodology [equal], Visualization [lead], Writing—original draft [lead], Writing—review & editing [equal]), Lara A. Ray (Conceptualization, Data curation, Formal analysis [equal], Funding acquisition [lead], Methodology [equal], Resources, Supervision [lead], Visualization [supporting], Writing—original draft [supporting], Writing—review & editing [equal]), and Erica N. Grodin (Formal analysis, Project administration, Supervision, Visualization [supporting], Writing—review & editing [supporting])

Conflict of interest

None declared.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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