Effects of Naltrexone During the Descending Limb of the Blood Alcohol Curve

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The neuropharmacological effects of alcohol are known to vary by limb of the blood alcohol curve, yet human laboratory studies of alcoholism pharmacotherapies have largely failed to consider limb of intoxication when examining medication effects on subjective responses to alcohol. This study examined the effects of naltrexone compared to placebo on subjective responses to alcohol at the descending limb of the blood alcohol curve following a controlled intravenous (IV) alcohol administration. Non-treatment-seeking hazardous drinkers (n = 38) completed two double-blind counterbalanced IV alcohol challenge sessions, one after taking naltrexone (50 mg) for three days and one after taking a placebo for three days. During each session, participants reported on subjective responses to alcohol during the descending limb of the blood alcohol curve. Analyses revealed significant main effects of naltrexone, reflecting significantly decreased alcohol-induced stimulation, craving, vigor, positive mood, and alcohol "high" and increased tension as compared to placebo. These findings suggest that naltrexone may exert some of its therapeutic effects via alterations to experiential aspects of intoxication during the descending limb of alcohol intoxication. Additionally, these results highlight the potential utility of considering limb of blood alcohol curve when examining the mechanisms of action of pharmacotherapies thought to alter subjective responses to alcohol. (Am J Addict 2008;17:257–264)

It has been postulated that medications that affect the subjective effects of alcohol may hold particular promise for treatment. Alcohol intoxication, in turn, is a complex pharmacological process involving multiple neurotransmitter systems and producing a host of physiological and behavioral effects.[1,2] Research on the subjective effects of alcohol ingestion indicates that alcohol's effects may be biphasic in nature.[3–7] While blood alcohol levels are rising (ie, the ascending limb of intoxication), alcohol produces robust stimulatory and other pleasurable subjective effects.[3–7] Conversely, while blood alcohol levels are declining (ie, descending limb), alcohol produces sedative and other unpleasant effects.[3–7] These subjective effects appear to predict subsequent alcohol use, such that greater alcohol-induced stimulation and reinforcement increases consumption[8,9] while greater sedative and unpleasant effects decrease drinking.[10,11]

One of the existing FDA-approved medications for treating alcohol dependence is naltrexone, an opioid receptor antagonist. Results from clinical trials have generally supported naltrexone's clinical efficacy, albeit with moderate effects. Clinical trials have found that naltrexone reduces the occurrence of heavy drinking days,[12–14] increases time to first relapse,[15–17] yields lower relapse rates,[18–20] and reduces both the number of drinking days[20,21] and the number of drinks per drinking episode.[16,21–23] A large multi-site trial has found that naltrexone was effective when delivered in combination with a medically-oriented behavioral intervention.[24] A few studies, however, have not found support for the efficacy of naltrexone.[25–27] Despite the generally promising clinical findings, the mechanisms of action of naltrexone through which drinking is reduced have not been definitively characterized.

To better understand how naltrexone works, a number of human pharmacology studies have examined the effects of naltrexone on subjective responses to alcohol.[28–37] Results have been somewhat mixed. Several studies indicated that naltrexone dampened feelings of alcohol-induced stimulation;[29,32,33] reduced craving;[35,36] decreased ratings of liking of the alcohol;[31,32] increased fatigue, tension, and confusion;[30] and reduced alcohol self-administration.[28,36] In contrast, others found no effect of naltrexone on subjective responses to alcohol among social drinkers.[38–41]

Despite the body of research suggesting that the pharmacological effects of alcohol vary by limb of blood alcohol curve (BAC), human laboratory studies have largely failed to

consider limb of intoxication when examining naltrexone's effects on the subjective responses to alcohol. Although based on the known pharmacokinetics of alcohol and methods of calculating circulating alcohol,[42] the limb of intoxication can be broadly inferred in most of the previous laboratory studies of naltrexone. While most studies appear to have typically examined the ascending limb,[35,36] there is nonetheless substantial ambiguity, considering that the limb of intoxication may be critically important in evaluating medications, such as naltrexone, that are thought to alter the subjective effects of alcohol. This is especially important given that the effects of alcohol clearly vary by limb of the BAC, with well-documented limb-dependent alcohol effects on expectancies,[43] memory,[44] cognitive performance,[45] and the unpleasant subjective effects of alcohol.[46] Light drinkers are more likely than heavy drinkers to activate negative and sedating alcohol expectancies associated with the descending limb[43] and report greater dislike of the alcohol during the descending limb of the alcohol challenge.[46] Additionally, impairments in executive cognitive functioning were found to be greater during the descending limb,[45] and word recognition was found to be impaired only on the ascending limb of intoxication.[44] Taken together, these findings argue for research that considers limb of the BAC when examining the effects of alcohol as well as medications thought to alter alcohol's subjective effects.

The present study sought to extend the literature in three ways. First, this study presented a theoretical rationale for examining the descending limb of the BAC in human pharmacology studies of the effects of alcohol. Second, this study explicitly and systematically examined the effects of naltrexone (50 mg) vs. placebo on subjective responses to alcohol during the descending limb of the BAC by conducting analyses on a double-blind placebo-controlled laboratory trial of oral naltrexone.[32] Our previous work in this trial found that on the ascending limb, naltrexone blunted alcohol-induced craving, stimulation, "high," vigor, liking and satisfaction with the alcohol.[32] Based on the naltrexone literature and the biphasic nature of alcohol's effects, it was hypothesized that naltrexone would increase the sedative and unpleasant effects of alcohol during the descending limb in the present study. Third, this study examined two putative moderators of the effects of naltrexone on subjective responses to alcohol during the descending limb, namely, family history of alcoholism and gender. Previous studies have found differential effects of naltrexone based on family history of alcoholism.[47–49] Thus, it was hypothesized that naltrexone's effects would be more pronounced among individuals with a family history positive for alcoholism. The moderating role of gender was examined on an exploratory basis without making directional hypotheses. Ultimately, understanding the ways in which medications may alter subjective experiences of alcohol intoxication during the descending limb of the BAC may have significant implications for research on naltrexone, and more broadly, for the development of efficacious pharmacotherapies for alcoholism.

METHOD

Participants

Participants were 38 (12 females) non-treatment-seeking hazardous drinkers, all of whom met the following inclusion criteria:

1. age between 21 and 35;
2. a score of 8 or higher on the Alcohol Use Disorders Identification Test (AUDIT)[50], indicating a hazardous drinking pattern;
3. self-reported drinking frequency of three or more drinks (two for women) at least twice per week;
4. no history of adverse reactions to needle puncture;
5. no history of prior treatment for an alcohol use disorder (AUD) and no current interest in treatment for an AUD;
6. no history of medical conditions that would counterindicate study participation; and
7. successfully completing a physical exam to ensure medical eligibility for the trial.

All female participants tested negative for pregnancy prior to the alcohol administration, and all subjects were required to have a breath alcohol concentration (BrAC) of zero before each session. The average age of the sample was 22.18 (SD = 2.23; range = 21–32) and 32 (84%) of the participants were Caucasian, 4 (11%) were Asian, and 2 (5%) were Latino. In this sample, the average number of drinks per drinking episode was 4.87 (SD = 2.31; range = 2–12), the average drinking frequency was twice per week, and the average AUDIT score was 12.32 (SD = 4.27; range = 8–21), indicating a hazardous drinking pattern. The study was approved by the appropriate institutional human subjects committee, and all participants provided written informed consent.

A total of 124 participants (39 women) were screened in the laboratory. Fifty-three completed the physical exam: 7 were ineligible for the study due to a medical reason and 6 decided not to participate in the trial, leaving us with 40 participants (12 women) who completed the trial. Two participants did not complete the descending limb assessment in one of the medication conditions, leaving a sample of 38 participants (12 women) who provided complete data for the descending limb analyses reported in this study. The main study used prospective genotyping to over sample for individuals with a copy of the G allele of the A118G SNP of the OPRM1 gene.[32]

Procedures

Upon arrival at the lab, eligible participants read and signed an informed consent form, and completed a series of individual difference measures. Next, participants completed a physical exam at the General Clinical Research Center (GCRC). Each participant completed two alcohol infusion sessions, one after taking naltrexone (50 mg) for three days and one after taking a matched placebo for three days. Medication was delivered in a counterbalanced and double-blind fashion. The wash-out period between infusions was at least seven days. During the

experimental sessions, participants were seated in a recliner chair and the IV was placed in their non-dominant arm. Participants were required to have a BrAC of zero at the beginning of each alcohol administration session and were told that they would receive IV doses of alcohol, but remained blind to their BrAC throughout the trial.

Participants completed a baseline assessment packet before receiving the intravenous (IV) doses of alcohol (ie, when BrAC = 0.00) and provided identical assessment measures at three points in the ascending curve of the BrAC (BrAC: 0.02, 0.04, and 0.06).[32] After the third assessment point at the ascending limb, the infusion procedure was stopped, and participants were given a meal. Immediately after the meal, approximately 20 minutes after the alcohol infusion had ceased and while blood alcohol levels were descending, participants were breathalyzed and asked to complete an identical assessment packet. The 20 minute post-infusion mark was designed to achieve a target descending BrAC of 0.03. Observed descending limb BrACs were: placebo $M = 0.033$; SD = 0.005; naltrexone $M = 0.032$; SD = 0.007. All participants stayed in the lab until their BrAC was below 0.02. The present study focuses exclusive on data collected during the descending limb of the blood alcohol curve.

A number of studies have highlighted the importance of effectively controlling blood alcohol levels in order to reduce experimental variability in alcohol administration studies.[51−53] Therefore, the alcohol administration paradigm used in this study consisted of delivering doses of ethanol intravenously, rather than orally. Consistent with the procedures developed in our laboratory,[54] each ethanol infusion session took place at the GCRC and were performed by registered nurses under the supervision of a physician. The infusion was performed using a 5% ethanol IV solution. The following infusion nomogram was developed taking into account participant's gender and weight: .166 ml/minute × weight, in kilograms, for males, and .126 ml/minute × weight, for females. Participants started the IV administration at their target infusion rate, and BrAC was monitored every 3 to 5 minutes. Details on the IV procedures are provided elsewhere.[54−56]

Medication Procedures

Participants were required to take the first medication (naltrexone 50 mg or placebo) once a day for two days prior to the first experimental session and on the morning of their appointment. After the first session, participants were given the second medication, which they took in the same fashion. Active medication and placebo were counterbalanced and double-blinded. Compliance was examined by packing the medication and placebo into capsules with 50 mg of riboflavin. Urine samples were collected prior to each infusion session and were analyzed for riboflavin content under an ultraviolet light, which makes the riboflavin detectable.[57] All samples tested positive for riboflavin content, which verified that the last dose was taken.

Measures

Participants completed a battery of individual difference measures that included demographics, drinking behavior, and family history of alcohol problems using the Family History Assessment Module (FHAM) for alcohol use disorders that was limited to affected first-degree relatives. During each alcohol infusion session, measures of subjective responses to alcohol and alcohol craving were administered at baseline and at the ascending and descending limbs of intoxication. The following measures were used:

Alcohol Urge Questionnaire (AUQ)

The AUQ is comprised of eight items related to urge to drink alcohol; each item is rated on a seven-point Likert scale and anchored by "strongly disagree" and "strongly agree." The AUQ has demonstrated high internal consistency in previous laboratory studies.[58,59]

Subjective High Assessment Scale (SHAS)

The SHAS was used to assess subjective feelings of alcohol intoxication. This measure has been adapted by Schuckit[60] and has since been widely used in alcohol challenge studies. The SHAS consists of 13 items, such as drunk, high, nauseated, dizzy, and drug effect.

Biphasic Alcohol Effects Scale (BAES)

The BAES assesses feelings of alcohol-induced stimulation and sedation, each subscale consisting of seven items. The BAES has been shown to be reliable and valid in studies of sensitivity to the effects of alcohol.[7]

Profile of Mood States (POMS)

The short version of the POMS,[61] consisting of 40 items, was used in this study to assess mood changes following alcohol consumption. The following subscales of the POMS, each composed of 10 items, were used in this study: vigor, tension, positive mood, and negative mood.

Alcohol Rating Scale (ARS)

The ARS measures participants' responses to the hedonic properties of alcohol, including alcohol-induced feelings of "high."

Systematic Assessment for Treatment Emergent Events (SAFTEE)

The SAFTEE was administered before each infusion session. The short form of the SAFTEE consists of 24 common medication side effects and has been recommended for use in clinical trials.[62,63]

Statistical Analysis

One-way repeated measures analyses of variance (ANOVAs) were conducted to examine the effects of medication vs. placebo on the subjective responses to alcohol. Mixed-design 2 × 2 ANOVAs were conducted to test moderators

of naltrexone's effects. Specifically, medication was a two-level within-subjects factor (ie, naltrexone vs. placebo), and moderator (ie, family history and gender, each tested separately) was a two-level between-subjects factor. The dependent variables were measures of subjective responses to alcohol (SHAS, BAES, POMS, and ARS) and craving (AUQ).

RESULTS

Baseline Comparisons

Analyses of the baseline data suggested no effect of medication, family history, or gender on the baseline measures of alcohol sensitivity and craving, with the exception of a main effect of gender indicating greater baseline stimulation (BAES) among male participants [$F(1,37) = 4.85$, $p < .05$], and a main effect of family history suggesting higher baseline negative mood (POMS) among individuals with a family history positive for alcoholism [$F(1,37) = 5.44$, $p < .05$]. Observed BrACs at the descending limb were placebo ($M = 0.033$; $SD = 0.005$) and naltrexone ($M = 0.032$; $SD = 0.007$). There were no significant differences in BrACs at the descending limb in the naltrexone vs. placebo conditions, $F(1,37) < 1.0$, $p = .34$. Given that this trial oversampled for the A118G single nucleotide polymorphism (SNP) of the OPRM1 gene,[32] we tested for its effects as a potential confound in this study and found that OPRM1 genotype was unrelated to the effects of naltrexone on subjective responses to alcohol during the descending limb ($p > .05$). A series of Fisher's exact tests, a non-parametric test appropriate for small cell sizes, were conducted comparing the medication vs. placebo on each of the 24 items from the side effects checklist (SAFTEE). There were no significant medication differences on any of the side effects measured by the SAFTEE ($p > .05$).

Effects of Naltrexone at the Descending Limb

Given that there were no medication effects at baseline, one-way ANOVAs were performed comparing the naltrexone vs. placebo conditions on subjective responses to alcohol during the descending limb of the BAC. As seen in Table 1, naltrexone
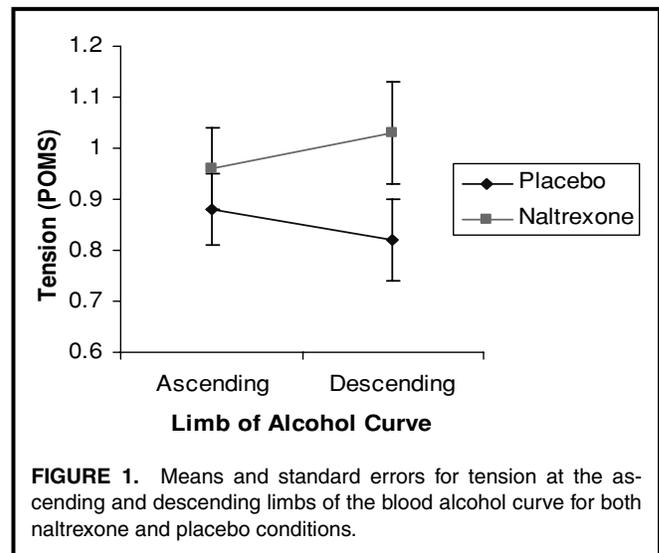
was found to significantly reduce alcohol-induced stimulation, craving, vigor, positive mood, and alcohol "high," as compared to placebo. Participants on naltrexone also reported higher levels of tension compared to placebo. Naltrexone did not have an effect on tension during the ascending limb of BrAC.[32] In order to further probe for the uniqueness of naltrexone's effect on tension at the descending limb, we performed a two-way ANOVA that explicitly tested a medication × BrAC limb interaction (i.e., ascending, BrAC = .040 vs. descending, BrAC = 0.33). As shown in Figure 1, naltrexone dampened the tension-reduction effects of alcohol during the descending limb only, $F(1,37) = 4.39$, $p < .05$.
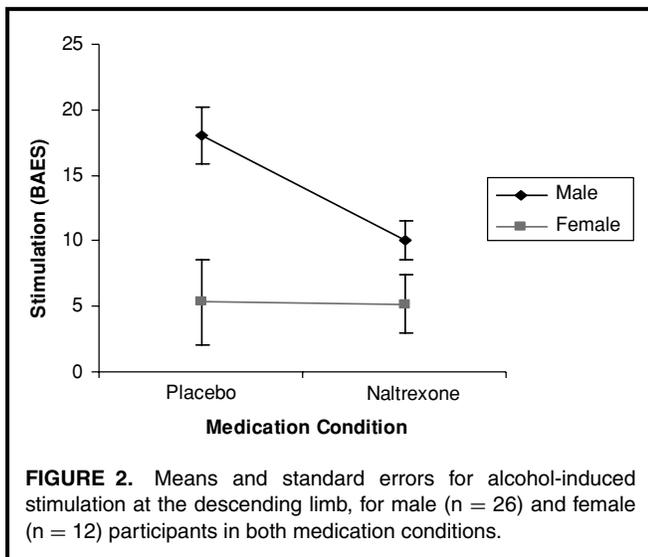
Moderators of the Effects of Naltrexone at the Descending Limb

A series of chi-square analyses revealed no significant participant overlap among the dichotomous moderating variables (ie, family history and gender) examined ($p > .10$). Regarding family history of alcoholism, analyses indicated a main effect of family history on multiple aspects of subjective

TABLE 1. Means and standard errors for the subjective effect of alcohol at the descending limb of intoxication in the placebo and naltrexone conditions, and within-subjects univariate ANOVAs along with effect sizes

Measure	Placebo	Naltrexone	ANOVA result	Effect size (R^2)
Subjective intoxication (SHAS)	15.41 (3.09)	14.92 (2.75)	$F(1,37) < 1.0$; $p = .74$	0.003
Stimulation (BAES)	14.26 (2.00)	8.50 (1.3)	$F(1,36) = 12.71$; $p < .01$[†]	0.256
Sedation (BAES)	9.92 (1.98)	10.45 (1.77)	$F(1,37) < 1.0$; $p = .76$	0.003
Craving (AUQ)	5.77 (1.05)	3.21 (0.94)	$F(1,37) = 8.81$; $p < .01$[†]	0.192
Tension (POMS)	0.82 (0.08)	1.03 (0.10)	$F(1,37) = 6.46$; $p < .05$[*]	0.149
Vigor (POMS)	1.18 (0.11)	0.88 (0.11)	$F(1,37) = 11.18$; $p < .01$[†]	0.232
Negative mood (POMS)	0.56 (0.08)	0.62 (0.07)	$F(1,37) < 1.0$; $p = .43$	0.017
Positive mood (POMS)	1.80 (0.13)	1.53 (0.15)	$F(1,37) = 6.69$; $p < .05$[*]	0.153
Alcohol "high" (ARS)	2.51 (0.36)	1.82 (0.31)	$F(1,37) = 5.05$; $p < .05$[*]	0.120

[*]$p < .05$; [†]$p < .01$

FIGURE 2. Means and standard errors for alcohol-induced stimulation at the descending limb, for male (n = 26) and female (n = 12) participants in both medication conditions.

responses to alcohol during the descending limb. Specifically, individuals with a family history positive for alcoholism (FH+, n = 12; FH-, n = 26) reported greater subjective feelings of intoxication [F (1,36) = 8.78, p < .01], alcohol-induced stimulation [F (1,36) = 4.73, p < .05], sedation [F(1,36) = 8.06, p < .01], and alcohol "high" [F (1,36) = 5.15, p < .05], as compared to family history-negative individuals and across medication conditions. Family history of alcoholism, however, did not moderate the effects of naltrexone on any of the dependent measures.

Analyses of the role of gender revealed a significant main effect of gender on alcohol-induced stimulation, such that male participants (n = 26) reported higher levels of stimulation than female participants (n = 12) across medication conditions, F (1,37) = 8.66, p < .01. Moreover, there was a significant gender × medication interaction, such that male participants reported greater naltrexone-induced decreases in alcohol-induced stimulation than female participants, F (1,37) = 6.31, p < .05 (see Figure 2). This interaction remained statistically significant even after controlling for baseline stimulation, which was higher among male participants, as mentioned above. There was a main effect of gender with regard to alcohol craving and vigor, such that male participants reported greater alcohol craving [F (1,36) = 6.43, p < .05] and alcohol-induced vigor [F (1,36) = 6.93, p < .05] across medication conditions. Regarding drinking patterns, females reported drinking less frequently than males [t(36) = 3.41, p < .01], but did not differ in terms of AUDIT scores or drinks per episode (p > .05). The gender × medication interaction on stimulation remained significant even after controlling for differences in drinking frequency among males and females.

DISCUSSION

The present study put forth a theoretical rationale for examining the descending limb of the BAC in human pharmacology studies of the effects of alcohol. Additionally, analyses of a double-blind placebo controlled laboratory trial revealed that naltrexone dampened alcohol craving and alcohol-induced feelings of stimulation, vigor, positive mood, and "high" during the descending limb of the BAC and compared to placebo. Although some of these effects are similar to naltrexone's effects during the ascending limb,[32,33,36] naltrexone significantly increased feelings of tension, or in other words dampened alcohol's tension-reduction effects, as compared to placebo, during the descending limb. The increase in tension is unique to this limb of intoxication and is consistent with prior research suggesting that naltrexone may intensify subjective ratings of the sedative and unpleasant effects of alcohol.[33,37] Importantly, these results are also consistent with the literature on the biphasic effect of alcohol, suggesting that the unpleasant and sedative effects of alcohol are most prominent during the descending limb, which in turn may have important implications to the overall effectiveness of naltrexone on drinking outcomes and its overall biobehavioral mechanisms of action.

In the study by McCaul and colleagues,[37] which found increases in the sedative and unpleasant effects of alcohol following naltrexone pre-treatment, participants were assessed for eight hours following alcohol administration. Given the known pharmacokinetics of alcohol,[42] most of the assessments collected in that study occurred during the descending limb of the BAC, at which time the sedative effects of alcohol are most salient. Thus, these data can be interpreted as converging with McCaul et al.,[37] which suggests that one of naltrexone's mechanisms of action may be its effects on experiential intoxication during the descending limb of alcohol intoxication.

Regarding moderators of the effects of naltrexone, analyses indicated a significant main effect of family history of alcoholism on the subjective effects of alcohol at the descending limb, such that family history-positive individuals reported greater subjective feelings of intoxication, alcohol-induced stimulation, sedation, and alcohol "high" as compared to family history-negative individuals. These findings are consistent with previous studies suggesting that family history-positive individuals show greater sensitivity to the effects of alcohol intoxication,[64,65] including investigations of the role of limb of intoxication on the effects of alcohol among family history-positive individuals.[6] Nevertheless, the present study found no evidence of a moderating role of family history of alcoholism on the effects of naltrexone on subjective responses to alcohol during the descending limb of the blood alcohol curve. Conversely, there was a significant naltrexone-by-gender interaction on feelings of stimulation during the descending limb. These findings suggest that naltrexone-induced blunting of the stimulant effects of alcohol during the descending limb may be an important mechanism for males only, whereas females show lower overall stimulation levels in the descending limb and no evidence of naltrexone-induced changes in stimulation at this limb of intoxication. Although the specific mechanisms underlying the observed

gender differences are unclear, recent clinical trials have suggested differential effectiveness of naltrexone among men,[66–68] which may be associated with the mechanistic effects reported herein. However, this is a novel finding and, given the exploratory nature of the analyses of gender as a moderator, it requires further study. Additionally, the medication effects are in the small-to-medium range, and their clinical significance has yet to be ascertained by studies that can more directly link naltrexone's effects on alcohol's subjective intoxication and alcohol use per se.

In this study, there was no main effect of OPRM1 genotype or gene-by-naltrexone interaction with regards to the subjective effects of alcohol at the descending limb. These null findings, however, are important and should be used to inform future research. Specifically, the opiodergic system is thought to mediate the rewarding pharmacological effects of alcohol, such as feelings of euphoria and analgesia;[69–71] these effects, in turn, are thought to be most prominent during the ascending limb of the BAC. Thus, one would expect a genetic polymorphism of functional significance to the reward mechanisms of alcohol to have an effect when that pathway is activated, which occurs primarily during the ascending limb, when blood alcohol levels are rising, as was found in previous reports.[32,54] In contrast, although the neurotransmitter systems subserving the experiential effects of alcohol during descending limb have not been clearly characterized, there is some evidence that they are mediated by glutamatergic antagonism.[72] Likewise, the sedative and anxiolytic effects of alcohol, thought to be more salient during the descending limb, have been proposed to be mediated by GABAergic neurotransmission.[73,74] If this is the case, the negligible influence of OPRM1 genotype is not surprising. These results further underscore the importance of considering the subjective effects of alcohol as a moving target, subserved by multiple neurotransmitter systems. These factors should be carefully considered when examining biological and pharmacological factors underlying responsivity to alcohol.

These results should be interpreted in light of a number of considerations. These include the study's limitations, such as the lack of a placebo alcohol condition (eg, using a saline solution), a sample that was relatively small and composed of non-treatment-seeking hazardous drinkers that may not generalize to clinical samples, a single assessment of subjective intoxication during the descending limb, and the use of an alcohol infusion administration that differs from oral alcohol consumption. The target BrACs in this study were relatively low, and sedative effects of alcohol tend to predominate at higher BrACs.[7] Also, the three-day dosing of naltrexone (50 mg) may not have produced steady levels of the medication, and those were not verified by blood assays. However, the study also had a number of strengths, including a double-blind within-subjects counterbalanced design and an IV alcohol administration that produces high levels of control over BrACs and allows us to focus more directly on the pharmacology of alcohol. Additionally, a previous study has suggested that the effects of naltrexone on subjective responses to alcohol may be most pronounced at moderate doses of alcohol.[29] Future studies examining the effects of naltrexone during the descending limb at higher doses of alcohol are clearly warranted. On balance, based on these considerations and because this study was one of the first to systematically examine naltrexone's effects during the descending limb, the present findings await replication.

Nonetheless, these results may have important implications for human laboratory studies seeking to characterize a given pharmacotherapy's mechanism of action. The rationale and results from the present study underscore the need to further integrate the empirical knowledge about the biphasic nature of the acute pharmacological effects of alcohol to the study of pharmacotherapies thought to alter alcohol responsivity. These efforts are important in order to fully and systematically understand the various mechanisms by which medication-induced alterations in subjective intoxication may take place and, importantly, how these changes may ultimately contribute to a medication's efficacy for the treatment of alcohol use disorders. Additional studies following the approach proposed herein are warranted before more definitive recommendations can be made.

In summary, this study examined the effects of naltrexone on subjective intoxication and craving during the descending limb of the BAC and found similarities and differences to the mechanisms of action of naltrexone during the descending limb relative to previous studies of the ascending limb. Specifically, naltrexone's dampening of craving and the rewarding and stimulant effects of alcohol, often observed during the ascending limb,[32] also took place during the descending limb, and, importantly, some medication effects, such as increased tension, appear unique to the descending limb. Understanding the ways in which medications may alter subjective experiences of alcohol intoxication may have significant implications for research on naltrexone and, more broadly, for the development of efficacious pharmacotherapies for alcoholism.

REFERENCES

1. Grobin AC, Matthews DB, Devaud LL, Morrow AL. The role of GABA(A) receptors in the acute and chronic effects of ethanol. *Psychopharmacology (Berl)*. 1998;139:2–19.

2. Herz A. Endogenous opioid systems and alcohol addiction. *Psychopharmacology (Berl)*. 1997;129:99–111.

3. Earleywine M. Confirming the factor structure of the anticipated biphasic alcohol effects scale. *Alcohol Clin Exp Res*. 1994;18:861–866.

4. Earleywine M. Anticipated biphasic effects of alcohol vary with risk for alcoholism: A preliminary report. *Alcohol Clin Exp Res*. 1994;18:711–714.

5. Earleywine M, Martin C. Anticipated stimulant and sedative effects of alcohol vary with dosage and limb of the blood alcohol curve. *Alcohol Clin Exp Res*. 1993;17:135–139.

6. Erblich J, Earleywine M, Erblich B, Bovbjerg DH. Biphasic stimulant and sedative effects of ethanol: Are children of alcoholics really different? *Addict Behav*. 2003;28:1129–1139.

7. Martin CS, Earleywine M, Musty RE, Perrine MW, Swift RM. Development and validation of the Biphasic Alcohol Effects Scale. *Alcohol Clin Exp Res*. 1993;17:140–146.

8. Lewis MJ, June HL. Neurobehavioral studies of ethanol reward and activation. *Alcohol*. 1990;7:213–219.

9. Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. *Psychol Rev*. 1987;94:469–492.

10. Leigh BC. Beliefs about the effects of alcohol on self and others. *J Stud Alcohol*. 1987;48:467–475.

11. O'Malley S, Maisto S. Factors affecting the perception of intoxication: Dose, tolerance, and setting. *Addict Behav*. 1984;9:111–120.

12. Balldin J, Berglund M, Borg S, et al. A six-month controlled naltrexone study: Combined effect with cognitive behavioral therapy in outpatient treatment of alcohol dependence. *Alcohol Clin Exp Res*. 2003;27:1142–1149.

13. Monti PM, Rohsenow DJ, Swift RM, et al. Naltrexone and cue exposure with coping and communication skills training for alcoholics: Treatment process and one-year outcomes. *Alcohol Clin Exp Res*. 2001;25:1634–1647.

14. Rubio G, Manzanares J, Lopez-Munoz F, et al. Naltrexone improves outcome of a controlled drinking program. *J Subst Abuse Treat*. 2002;23:361–366.

15. Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK. Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: Results of a placebo-controlled trial. *Am J Psychiatry*. 1999;156:1758–1764.

16. Guardia J, Caso C, Arias F, et al. A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder: Results from a multicenter clinical trial. *Alcohol Clin Exp Res*. 2002;26:1381–1387.

17. Kiefer F, Jahn H, Tarnaske T, et al. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: A double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2003;60:92–99.

18. Heinala P, Alho H, Kiianmaa K, Lonnqvist J, Kouppasalmi K, Sinclair JD. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: A factorial double-blind, placebo-controlled trial. *J Clin Psychopharmacol*. 2001;21:287–292.

19. Latt NC, Jurd S, Houseman J, Wultzke SE. Naltrexone in alcohol dependence: A randomized controlled trial of effectiveness in a standard clinical setting. *Med J Aust*. 2002;176:530–534.

20. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry*. 1992;49:876–880.

21. O'Malley SS, Jaffe AJ, Change 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.

22. Chick J, Anton R, Checinski K, et al. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. *Alcohol Alcohol*. 2000;35:587–593.

23. Morris PL, Hopwood M, Whelan G, Gardiner J, Drummond E. Naltrexone for alcohol dependence: A randomized controlled trial. *Addiction*. 2001;96:1565–1573.

24. 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.

25. Kranzler HR, Modesto-Lowe V, Van Kirk J. Naltrexone vs. nefazedone for treatment of alcohol dependence: A placebo-controlled trial. *Neuropsychopharmacology*. 2000;22:493–503.

26. Killeen TK, Brady KT, Gold PB, et al. Effectiveness of naltrexone in a community treatment program. *Alcohol Clin Exp Res*. 2004;28:1710–1717.

27. Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA. Naltrexone in the treatment of alcohol dependence. *N Engl J Med*. 2001;345:1734–1739.

28. 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.

29. Drobes DJ, Anton RF, Thomas SE, Vornin K. Effects of naltrexone and namefene on subjective response to alcohol among non-treatment seeking alcoholics and social drinkers. *Alcohol Clin Exp Res*. 2004;28:1362–1370.

30. King AC, Volpicelli JR, Frazer A, O'Brien CP. Effects of naltrexone on subjective alcohol response in subjects at high and low risk for future alcohol dependence. *Psychopharmacology (Berl)*. 1997;129:15–22.

31. McCaul ME, Wand GS, Stauffer R, Lee SM, Rohde CA. Naltrexone dampens ethanol-induced cardiovascular and hypothalamic-pituitary-adrenal axis activation. *Neuropsychopharmacology*. 2001;25:537–547.

32. Ray LA, Hutchison KE. A double-blind placebo-controlled study of the effects of naltrexone on alcohol sensitivity and genetic moderators of medication response. *Arch Gen Psychiatry*. 2007;64:1069–1077.

33. Swift RM, Whelihan W, Kusnetsov O, Buongiorno G, Hsuing H. Naltrexone-induced alterations in human ethanol intoxication. *Am J Psychiatry*. 1994;151:1463–1467.

34. Volpicelli JR, Watson NT, King AC, Sherman CE, O'Brien CP. Effects of naltrexone on alcohol "high" in alcoholics. *Am J Psychiatry*. 1995;152:613–615.

35. Davidson D, Palfai T, Bird C, Swift R. Effects of naltrexone on alcohol self-administration in heavy drinkers. *Alcohol Clin Exp Res*. 1999;23:195–203.

36. 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.

37. McCaul ME, Wand GS, Eissenberg T, Thode CA, Cheskin LJ. Naltrexone alters subjective and psychomotor responses to alcohol in heavy drinking subjects. *Neuropsychopharmacology*. 2000;22:480–492.

38. de Wit H, Svenson J, York A. Non-specific effect of naltrexone on ethanol consumption in social drinkers. *Psychopharmacology (Berl)*. 1999;146:33–41.

39. Doty P, de Wit H. Effects of naltrexone pretreatment on the subjective and performance effects of ethanol in social drinkers. *Behav Pharmacol*. 1995;6:386–394.

40. Doty P, Kirk JM, Cramblett MJ, de Wit H. Behavioral responses to ethanol in light and moderate social drinkers following naltrexone pre-treatment. *Drug Alcohol Depend*. 1997;47:109–116.

41. Peterson JB, Conrod P, Vassileva J, Gianoulakis C, Pihl RO. Differential effects of naltrexone on cardiac, subjective and behavioural reactions to acute ethanol intoxication. *Review of Psychiatric Neuroscience*. 2006;31:386–393.

42. Brick J. Standardization of alcohol calculations in research. *Alcohol Clin Exp Res*. 2006;30:1276–1287.

43. Dunn ME, Earleywine M. Activation of alcohol expectations in memory in relation to limb of the blood alcohol curve. *Psychol Addict Behav*. 2002;15:18–24.

44. Soderlund H, Parker ES, Schwartz BL, Tulving E. Memory encoding and retrieval on the ascending and descending limbs of the blood alcohol concentration curve. *Psychopharmacology (Berl)*. 2005;182:305–317.

45. Pihl RO, Paylan SS, Gentes-Hawn A, Hoaken PNS. Alcohol affects executive cognitive functioning differentially on the ascending versus descending limb of the blood alcohol concentration curve. *Alcohol Clin Exp Res*. 2003;27:773–779.

46. Evans SM, Levin FR. Differential response to alcohol in light and moderate female social drinkers. *Behav Pharmacol*. 2004;15:167–181.

47. Monterosso JR, Flannery BA, Pettinati HM, et al. Predicting treatment response to naltrexone: The influence of craving and family history. *Am J Addict*. 2001;10:258–268.

48. Rubio G, Ponce G, Rodriguez-Jimenez R, Jimenez-Arriero MA, Hoenicka J, Palomo T. Clinical predictors of response to naltrexone in alcoholic patients: Who benefits most from treatment with naltrexone? *Alcohol Alcohol*. 2005;40:227–233.

49. Rohsenow DJ, Miranda, R, Mcgeary J, Monti PM. Family history and antisocial traits moderate naltrexone's effects on heavy drinking in alcoholics. *Exp Clin Psychopharmacol*. 2007;15:272–281.

50. Allen JP, Litten RZ, Fertig JB, Babor T. A review of research on the Alcohol Use Disorders Identification Test (AUDIT). *Alcohol Clin Exp Res*. 1997;21:613–619.

51. Li T, Yin S, Crabb DW, O'Connor S, Ramchandani VA. Genetic and environmental influences on alcohol metabolism in humans. *Alcohol Clin Exp Res*. 2001;25:136–144.

52. O'Connor S, Morzorati S, Christian J, Li T. Clamping breath alcohol concentration reduces experimental variance: Application to the study of acute tolerance to alcohol and alcohol elimination rate. *Alcohol Clin Exp Res*. 1998;22:202–210.

53. Ramchandani VA, Bolane J, Li TK, O'Connor S. A physiologically-based pharmacokinetic (PBPK) model for alcohol facilitates rapid BrAC clamping. *Alcohol Clin Exp Res*. 1999;23:617–623.

54. Ray LA, Hutchison KE. A polymorphism of the mu-opioid receptor gene and sensitivity to the effects of alcohol in humans. *Alcohol Clin Exp Res*. 2004;28:1789–1795.

55. Ray LA, Meskew-Stacer S, Hutchison KE. The relationship between prospective self-rating of alcohol sensitivity and craving and experimental results from two alcohol challenge studies. *J Stud Alcohol Drugs*. 2007;68:379–384.

56. Ray LA, McGeary J, Marshall E, Hutchison KE. Risk factors for alcohol misuse: Integrating heart rate response to alcohol, alcohol sensitivity, and personality factors. *Addict Behav*. 2006;31:1959–1973.

57. Del Boca FK, Kranzler HR, Brown J, Korner PF. Assessment of medication compliance in alcoholics through UV light detection of a riboflavin tracer. *Alcohol Clin Exp Res*. 1996;20:1412–1417.

58. Bohn MJ, Krahn DD, Staehler BA. Development and initial validation of a measure of drinking urges in abstinent alcoholics. *Alcohol Clin Exp Res*. 1995;19:600–606.

59. MacKillop J. Factor structure of the alcohol urge questionnaire under neutral conditions and during a cue-elicited urge state. *Alcohol Clin Exp Res*. 2006;30:1315–1321.

60. Schuckit MA. Subjective responses to alcohol in sons of alcoholics and control subjects. *Arch Gen Psychiatry*. 1984;41:879–884.

61. McNair DM, Lorr M, Droppleman LF. *Manual for the Profile of Mood States*. San Diego: Educational & Industrial Testing Service; 1971.

62. Jacobson AF, Goldstein BJ, Dominguez RA, Steinbook RM. Interrater agreement and interclass reliability measure of SAFTEE in psychopharmacologic clinical trials. *Psychopharmacol Bull*. 1986;22:382–388.

63. Levine J, Schooler N. SAFTEE: A technique for systematic assessment of side effects in clinical trials. *Psychopharmacol Bull*. 1986;22:343–381.

64. Kaplan R, Hesslebrock V, O'Conner S, DePalma N. Behavioral and EEG responses to alcohol in nonalcoholic men with a family history of alcoholism. *Prog Neuropsychopharmacol Biol Psychiatry*. 1988;12:873–885.

65. Conrod P, Peterson J, Pihl R, Mankowski S. Biphasic effects of alcohol on heart rate are influenced by alcoholic family history and rate of alcohol ingestion. *Alcohol Clin Exp Res*. 1997;21:140–149.

66. Garbutt JC, Kranzler HR, O'Malley SS, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. *JAMA*. 2005;293:1617–1625.

67. Hernandez-Avila CA, Song C, Kuo L, Tennen H, Armeli S, Kranzler HR. Targeted versus daily naltrexone: Secondary analysis of effects on average daily drinking. *Alcohol Clin Exp Res*. 2006;30:860–865.

68. Pettinati HM, Kampman KM, Lynch KG, et al. Gender differences with high-dose naltrexone in the patients with co-occurring cocaine and alcohol dependence. *J Subst Abuse Treat*. 2008; 34:378–390.

69. Bond C, LaForge KS, Tian M, et al. Single-nucleotide polymorphism in the human μ-opioid receptor gene alters β-endorphin binding and activity: Possible implications for opiate addiction. *Neurobiology*. 1998;95:9608–9613.

70. Herz A. Endogenous opioid systems and alcohol addiction. *Psychopharmacology*. 1997;129:99–111.

71. Kreek MJ. Opioid receptors: Some perspectives from early studies of their role in normal physiology, stress responsivity, and in specific addictive diseases. *Neurochem Res*. 1996;21:1469–1488.

72. Krystal JH, Petrakis IL, Webb E, et al. Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. *Arch Gen Psychiatry*. 1998;55:354–360.

73. Grobin AC, Matthews DB, Devaud LL, Morrow AL. The role of GABA(A) receptors in the acute and chronic effects of ethanol. *Psychopharmacology*. 1998;139:2–19.

74. Buck KJ. Molecular genetic analysis of the role of GABAergic systems in the behavioral and cellular actions of alcohol. *Behav Genet*. 1996;26:313–323.