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Moderators of Naltrexone's Effects on Drinking, Urge and Alcohol Effects in Non-Treatment-Seeking Heavy Drinkers in the Natural Environment

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Abstract

Background: Naltrexone (NTX) has proven to be effective with alcoholics in treatment, with most controlled clinical trials showing beneficial effects on heavy drinking rates. However, little is known about the behavioral mechanisms underlying the effects of NTX on drinking, or about patient characteristics that may moderate NTX's effects on drinking. In this study, ecological momentary assessment (EMA) techniques were used to investigate some of the putative mechanisms of naltrexone's effects on drinking in heavy drinkers who were not seeking treatment for alcohol problems. Polymorphisms in the D4 dopamine receptor (DRD4) gene and the μ -opiate receptor (OPRM1) gene, family history of alcohol problems, age of onset of alcoholism and gender were explored as potential moderators of NTX's effects.

Methods: After a one-week placebo lead-in period, heavy drinkers ($n = 180$), 63% of whom were alcohol-dependent, were randomized to 3 weeks of daily naltrexone (50 mg) or placebo. Throughout the study, participants used EMA on palm-pilot computers to enter, in real time, drink data, urge levels, and subjective effects of alcohol consumption.

Results: NTX reduced percentage drinking days in all participants and reduced percent heavy drinking days in DRD4-L individuals; NTX decreased urge levels in participants with younger age of alcoholism onset; NTX increased time between drinks in participants who had more relatives with alcohol problems; and NTX reduced the stimulating effects of alcohol in women. OPRM1 status did not moderate any of NTX's effects.

Conclusions: These results confirm earlier findings of NTX's effects on drinking and related subjective effects, and extend them by describing individual difference variables that moderate these effects in the natural environment, using data collected in real time.

Keywords

naltrexone; family history; genetics; treatment; pharmacology

Treatment with the opioid antagonist naltrexone (NTX) has been found to reduce drinking days and relapse rates after three months of treatment (O'Malley et al., 1992; Volpicelli et al., 1992). With some exceptions (Gastpar et al., 2002; Krystal et al., 2001), most studies have shown beneficial effects on heavy drinking rates, particularly among those who comply with the medication (reviewed in Rohsenow, 2004; Srisurapanont and Jarusuraisin, 2005). However, the behavioral mechanisms that mediate the effects of NTX on drinking are not well understood. Such knowledge could facilitate the development of other treatment strategies, such as combining medications with complementary mechanisms of action (Mason, 2005).

There are several pathways by which NTX may decrease drinking (Davidson et al., 1999). First, NTX may attenuate craving for alcohol, which is supported by findings from some treatment trials that measured craving using weekly self-reports (Balldin et al., 2003; O'Malley et al., 1992; Volpicelli et al., 1992). Most laboratory studies have found that NTX decreases urge intensity (Davidson et al., 1999; Drobos et al., 2004; McCaul et al., 2000; O'Malley et al., 2002; Palfai et al., 1999; Rohsenow et al., 2000), or probability (Monti et al., 1999). However, other studies have not found an effect of NTX on urge to drink (Davidson et al., 1996; de Wit et al., 1999; Kranzler et al., 1998).

Second, NTX may attenuate the positive effects or increase the negative subjective effects of alcohol. These mechanisms may underlie the clinical finding that NTX reduces the likelihood that a drinking lapse will lead to relapse (O'Malley et al., 1992; Volpicelli et al., 1992). Most laboratory studies have found that NTX reduces the stimulating and positive mood effects of alcohol (Davidson et al., 1999; Drobos et al., 2004; King et al., 1997; Swift et al., 1994) or increases sedation and negative mood effects of alcohol (Davidson et al., 1996; McCaul et al., 2000; Swift et al., 1994). NTX has also been found to increase the time to finish each drink and to reduce the number of drinks consumed in an experimental bar session, suggesting that NTX reduced interest in continuing to drink (Davidson et al., 1999).

While these studies are suggestive, the clinical studies collected craving ratings during periods that included both abstinence and drinking, which complicates the interpretation of these results. Laboratory studies, even those that take place in a bar-lab, use a somewhat artificial setting (e.g., drinking in an unfamiliar bar with unfamiliar people). Furthermore, craving and other subjective mood states fluctuate rapidly and retrospective ratings of these states are subject to recall and summary biases (Hammersley, 1994; Shiffman et al., 1997b). Ecological momentary assessment (EMA) techniques, involving the collection of real-time data in real-world settings (Stone and Shiffman, 1994), have several advantages over retrospective reports. Urge and other data can be collected without delay, several times per day and in participants' natural environments. These data are time- and date-stamped and stored to allow accurate correlation with other events.

Although Kranzler et al. (2004) conducted a pilot study that supported the feasibility of using EMA to collect assessments in a NTX pharmacotherapy study, to our knowledge there have been no published reports that have used EMA to examine the effects of NTX on alcohol consumption. Thus, the primary aim of this study was to use EMA techniques to investigate NTX's effects on alcohol consumption and related subjective effects.

A second aim was to use EMA to investigate moderators of NTX's effects. There appears to be considerable variability in responsiveness to NTX. For example, NTX reduced both euphoric and unpleasant sedating effects of alcohol in family-history-positive individuals but not in individuals with no family history of alcoholism (King et al., 1997; 2002). Three clinical trials found that alcoholics who had more family member with alcohol-related problems benefited more from NTX than those with fewer such family members (Monterosso et al., 2001; Rohsenow et al., 2007; Rubio et al., 2005). Early-onset alcoholism has also been found

to predict positive response to NTX treatment in a study of men (Rubio et al., 2005). However, early-onset alcoholism did not predict NTX effects on drinking in a recent, larger study (Rohsenow et al., 2007). Results from two recent studies also indicate that NTX may reduce drinking more in men than in women (Garbutt et al., 2005; Hernandez-Avila et al., 2006).

Genetic factors may also moderate NTX effects. The variable number of tandem repeats (VNTR) polymorphism of the dopamine D4 receptor (DRD4) gene moderated urge to drink in lab studies and in a clinical trial (Hutchison et al., 2002, 2003, 2006). In those studies, carriers of the 7-repeat allele of the VNTR polymorphism of the DRD4 gene (DRD4-L group) experienced higher alcohol craving levels after consuming alcohol, and were more responsive to the mixed histamine/dopamine/serotonin antagonist olanzapine, than carriers of the short-repeat allele (DRD4-S group). Although DRD4 status did not moderate the effects of NTX on alcohol cue-elicited urge in a sub-group of participants who participated in a laboratory cue-reactivity test during the present project (McGeary et al., 2006), it is of interest to determine whether this polymorphism is associated with differential urge levels and with drinking when such measurements are collected in the natural environment.

The Asp variant of the Asn40Asp single nucleotide polymorphism in the μ opiate receptor gene has been found to moderate the effects of NTX. In a treatment study, alcohol-dependent participants on NTX who carried at least one Asp40 variant of the OPRM1 gene (Asp group), had less relapse and longer latency to relapse to heavy drinking than those homozygous for the Asn allele (Oslin et al., 2003). These findings suggest that Asp carriers are more likely to experience therapeutic effects of NTX on drinking. However, in a laboratory study, NTX *increased* alcohol cue-elicited drinking urge levels in Asp carriers relative to placebo (McGeary et al., 2006). These disparate findings may suggest that NTX's effects on alcohol drinking are not mediated by its effects on cue-elicited craving or that the effects of NTX on drinking may depend on whether the drinker is seeking treatment. Examining the effects of NTX on drinking and urge levels concurrently in the same participants may help to disentangle these relationships.

To summarize, this study had two main objectives. The first was to use EMA techniques to investigate effects of NTX on alcohol consumption and putative behavioral and subjective mechanisms underlying NTX's effects (urge for alcohol, time between drinks and alcohol effects) in heavy drinkers in their natural environments. It was hypothesized that NTX would reduce drinking, urge and stimulation, while increasing time between drinks. The second objective was to examine whether family history, age of onset of alcoholism, gender, VNTR polymorphism of the DRD4 gene and Asn40Asp single nucleotide polymorphism of the OPRM1 gene moderate effects of NTX on drinking and on the targeted mechanisms in these participants. It was hypothesized that individuals with a family history of alcoholism, individuals with early-onset alcoholism, DRD4-L individuals, Asp40 individuals and men would have a greater response to NTX compared to their respective comparison groups.

MATERIALS AND METHODS

Participant Characteristics

Study participants were recruited using newspaper advertisements aimed at heavy drinkers who were not seeking treatment for alcohol problems. Participants were required to be at least 21 years of age, to drink at least 4 days per week, and to have drunk heavily on at least 2 days per week on average over the preceding month (> 6 standard drinks for men, > 4 standard drinks for women; Flannery et al., 2002). Exclusionary criteria included abuse of or dependence on drugs other than nicotine and alcohol, current interest in or past treatment for alcohol problems, positive urine opiate screen, positive pregnancy test, nursing, not using birth control (women), and contraindicated medications and medical conditions.

Procedures

A timeline of study procedures is shown in Figure 1. Participants were told that the purpose of the project was to study the effects of a medication on urges to drink, mood, and alcohol drinking in people's home environments. They were not given instructions to reduce or otherwise alter their drinking. Participants were informed that their compensation would be based partly on satisfactory medication and palm top assessment compliance, and that they were expected to take the study medication daily, enter the beginning and end of drinks when they occurred, respond to palm pilot prompts as they occurred, use the delay and suspend functions only when absolutely necessary, and attend all study sessions.

After providing informed consent, participants completed the individual difference measures described below. Participants were then trained to use EMA on palm top computers and initiated their daily EMA recording. After two practice days, participants returned to the laboratory so that the EMA data could be downloaded and reviewed. The data collected over the next five days constituted the pre-medication baseline. At the end of the baseline period, research staff downloaded participants' EMA data and reviewed their EMA compliance. One participant failed to meet the minimal EMA compliance criterion of responding to at least 50% of random prompts and was discontinued from the study at this point.

At the start of week 2, all participants received placebo medication in bottles capped with eDEM-view microelectronic monitors (AARDEX Ltd., Zurich, Switzerland), which recorded the date and time of each bottle opening. At the end of this week, research staff downloaded participants' eDEM caps and reviewed their medication compliance. All participants met the compliance criterion of taking 80% or more of their scheduled medication as verified by the eDEM monitors. Participants ($n = 180$) were then randomized to daily NTX (50 mg) or matching placebo and received a one-week supply of medication under double-blind conditions. At subsequent weekly visits, research staff downloaded the eDEM cap and EMA data, discussed medication and EMA compliance, interviewed participants regarding medication side effects, and refilled the medication bottles with one-week supplies of medication.

Between the end of week 3 and the end of week 4, participants underwent a laboratory assessment of their reactivity to drinking cues. These findings have been described previously (McGeary et al., 2006). At the end of weeks 3 and 4, participants provided blood samples to determine medication compliance. At the end of week 5, participants returned their palmtop computers and medication bottles and received study compensation of up to \$599. At this point, participants underwent separate consent for DNA collection and provided buccal swabs using established procedures (Freeman et al., 1997; Lench et al., 1988).

Individual Difference Measures

Individual difference assessments included a demographics questionnaire and the 90-day Timeline Followback interview to assess quantity and frequency of drinking (Sobell and Sobell 1992). Alcohol diagnoses were based on the criteria of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)—Patient Version (First et al., 1995). The Drinker Inventory of Consequences (DrInC-2R; Miller et al., 1995) version for recent drinking was administered to provide a baseline description of the number and frequency of various drinking related consequences. The Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) was used to assess depressive symptoms. The Family Tree Questionnaire for Assessing Family History of Alcohol Problems (Mann et al., 1985) was used to assess alcohol problems in first- and second-degree biological relatives of participants. From this measure, we calculated family history proportion, which refers to the number of the participants' first- and second-degree relatives with alcohol problems relative

to the total number of adult relatives with sufficient information to evaluate alcohol problems (Turner et al., 1993; Rohsenow et al., 2007).

EMA Measures

The electronic diary (ED) system was implemented on handheld computers (PalmPilot IIIxe; Palm, Inc.) running software designed for this study (invivodata, inc., Pittsburgh, PA). Participants completed assessments on the ED (1) upon awakening (Morning Report), (2) in response to audible prompts presented at random times during the waking day, approximately 5 times per day (Random Prompts), (3) at the start of each of the first two drinks each day (Begin Drink Report), and (4) when completing each of the first two drinks each day (End Drink Report).

Morning Reports—Upon awakening, the ED queried participants about the type and number of standard drinks (1 1/2 oz. liquor, 12 oz. beer, 4 oz. wine) consumed on the previous day. Current urge and drinking-related physical states (e.g., hangover) were also assessed.

Random Prompts—The Random Prompt assessment included measures of urge to drink alcohol, mood, activity, location and setting. Urge to drink was measured on a 0 (No urge) to 10 (Strongest ever) Likert scale (Shiffman et al., 1997a). Random prompt reports that were collected after the initiation of drinking were excluded from analyses as these assessments could be affected by drinking. The EMA software permitted the delay (maximum 20 min) or suspension (maximum 2 hours per day) of random prompts when necessary, and recorded instances when participants failed to respond to a prompt within 2 minutes.

Begin and End Drink Reports—Participants were asked to initiate assessments when beginning and immediately after finishing the first two drinks of each day. Data were collected after the first two drinks only, due to concern that intoxication could decrease measurement reliability. In the Begin Drink Report, participants were asked to rate their urge “just before drinking”. The End Drink Report included questions about the type and quantity of beverage consumed, alcohol effects (stimulation, sedation, satisfaction, pleasantness) and urge for another drink. Satisfaction and pleasantness of the drink were rated on 0 (Not at all) to 10 (Extremely) Likert scales. Responses to these items were found to be highly correlated so the average of these scores was used in analyses. The stimulation and sedation ratings were derived from the Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993), and items were rated on scales from 0 (Not at all) to 10 (Extremely).

Candidate Genotyping

Candidate genotyping methods for this study have been described previously (McGeary et al., 2006). Briefly, the Asn40 SNP in the OPRM1 gene was assayed using a modification of restriction fragment length polymorphism procedures reported by Bergen et al. (1997). Samples were genotyped again using the ABI Taqman assay for rs1799971 to ensure that the high frequencies of the Asp variant found were not due to genotyping error. The primer sequences were forward, 5'-CCTTGGCGTACTCAAGTTGCTC-3' (fluorescently labeled), and reverse, 5'-TTCGGACCGCATGGGACGGAC-3'. The 48-bp VNTR in exon 3 of the DRD4 gene was assayed using modifications of previously reported methods (Sander et al., 1997). The primer sequences were forward, 5'-AGGACCCTCATGGCCTTG-3' (fluorescently labeled), and reverse, 5'-GCGACTACGTGGTCTACTCG-3' (Lichter et al., 1993). Participants were grouped by OPRM1 status using the convention reported by Oslin et al. (2003), with the Asp40 variant group consisting of participants who were either heterozygous or homozygous for the Asp40 variant and the Asn40 group consisting of those homozygous for the Asn40 variant. Participants were grouped by DRD4 status using conventional methods (Hutchison et al., 2002, 2003), with the DRD4-long group (DRD4-L) composed of individuals with at least

1 copy of the 7 or greater repeats and the DRD4-short (DRD4-S) group composed of individuals who had neither copy greater than 6 repeats.

Data Reduction and Analysis

EMA compliance criteria—To ensure that data used in analysis reflected real time reports, periods of poor compliance were dropped from analysis. Poor compliance was operationally defined as: (a) completing fewer than 50% of random prompt assessments per week, (b) using the ED sleep function for 13 or more hours on 4 or more days in a week, and (c) suspending Random Prompts for more than 14 hours in a week. If any of these criteria were met, all Random Prompt data from that week were deleted. If criteria (b) or (c) were met, the Begin and End Drink Reports for that week were also discarded. Morning reports occurring at unusual times (e.g., before 5:30 a.m. or after 3:00 p.m.) were investigated and dropped, if warranted. Begin Drink and End Drink Reports were discarded if the participant indicated that the start or end of the drink had occurred more than 10 minutes before the initiation of the report.

Medication compliance criteria—Compliance with medication was determined by quantitative analysis of NTX and 6- β -naltrexol levels in participants' blood samples (National Medical Services, Willow Grove, PA). Among participants randomized to NTX, if either NTX or 6- β -naltrexol levels were 0 for a sample, all EMA data for the previous week were deleted. If blood test results indicated noncompliance with medication for both weeks 3 and 4, week 5 data were also deleted.

Data analysis—All analyses were performed using the SPSS mainframe statistical package SPSS, Inc., Chicago, IL). Variables were first checked for distributional assumptions. Group comparisons on demographic and other individual difference measures were conducted using independent-samples *t*-tests for continuous variables and chi-square tests for categorical variables. To check the validity of EMA assessments, Generalized Estimating Equations (GEE; Zeger et al., 1988) were performed to determine whether alcohol diagnosis was related to drinking urge levels and number of drinks consumed per day during the 5-day pre-medication baseline period in week 1. GEE allows for varying numbers of observations per subject, while controlling for autocorrelation (we used the AR1 structure). Interrelationships among the moderator variables were investigated using correlations and chi-square tests to determine the percentage of shared variance between pairs of variables.

One-way Analysis of Variance tests (ANOVAs) were used to examine the effects of medication (NTX versus placebo) on variables, such as percent drinking days, for which each participant contributes only one observation to the dataset. GEE analyses were used to analyze effects of medication on variables, such as urge levels, for which the number of observations in the dataset varied across participants. Average scores from the 5-day pre-medication baseline period were used as covariates in all analyses. Effects of moderators (DRD4 genotype, OPRM1 genotype, family history proportion, age of onset and gender) were examined by adding a subject-level interaction term to the analytic model. On variables for which moderator analyses were significant, main effects of moderators were also examined using GEE. Due to the large number of analyses and possibility of Type 1 error, only effects that were statistically significant throughout the 3-week medication period were considered important and interpreted.

RESULTS

Participant Characteristics

Of the 180 participants randomized to medication, 4 were found to be non-compliant with medication in weeks 3 and 4 based on quantitative NTX and 6- β -naltrexol levels. Data from these participants were removed from all analyses. Data from 3 participants were entirely

missing due to technical problems. Baseline characteristics of the remaining 173 participants are shown in Table 1. Based on quantitative NTX and 6- β -naltrexol levels, 2 participants were found to be non-compliant with medication in week 3 only, and two others were non-compliant with medication in week 4 only. EMA data from those participants for those weeks were removed from analyses. Thus, analysis sample sizes were $n = 171$ for weeks 3-4 and $n = 173$ for week 5. As genotyping in this study began about 12 months into recruitment, the sample sizes for the DRD4 and OPRM1 analyses are $n = 115$ and $n = 107$, respectively.

On average, participants were 29 years old, 59% male, and predominantly Caucasian (92% white, 4% black, 1% Pacific Islander, 3% mixed race). Sixty-three percent met criteria for alcohol dependence and 18% met criteria for alcohol abuse but not dependence. Thirty-nine percent had a first- or second-degree family history of alcoholism. 38% carried at least one 7-repeat allele of the DRD4 gene (DRD4-L group) and 31% carried at least one Asp40 variant of the OPRM1 gene (Asp group). At enrollment, participants reported consuming on average 4.7 ± 2.2 ($M \pm SD$) drinks per day in the past 3 months, with 65.3 ± 16.6 percent drinking days and 44.7 ± 18.6 percent heavy drinking days. There were no significant between-groups differences on these baseline characteristics.

EMA Compliance and Validation

Participants completed 79% of the Random Prompt assessments and made infrequent use of the suspend and delay options. Applying the EMA compliance criteria resulted in the deletion of 332 Morning Reports (6%; analysis $N = 4,882$), 2087 Random Prompts (11%; $N = 16,983$), 649 Begin First Drink Reports (19%; $N = 2,826$), 594 End First Drink Reports (17%; $N = 2,844$), 407 Begin Second Drink Reports (17%; $N = 2,002$), and 374 End Second Drink Reports (16%; $N = 2,020$). Compliance with drink reports was excellent. When non-drinking days were excluded, participants completed 1.80 ± 0.58 drink reports per day of 2 reports possible. Participants reported initiating drink reports within 3.10 ± 2.89 minutes of starting a drink. Only 3.9% of morning reports indicated that participants had forgotten to enter a drink report on the previous day.

To check the validity of EMA assessments, we examined whether alcohol diagnosis was related to baseline drinking urge levels and number of drinks consumed per day. As expected, alcohol-dependent participants reported significantly higher drinking urge levels (dependent: 3.98 ± 2.81 , no diagnosis: 2.87 ± 2.48 ; $r = 0.18$, $p < 0.0001$) and consumed more drinks per day (dependent: 5.77 ± 6.55 , no diagnosis: 3.76 ± 4.33 ; $r = 0.14$, $p < 0.001$) than participants without an alcohol diagnosis.

Main effects of NTX

NTX significantly decreased percent drinking days ($F(1, 152) = 5.64$, $p < 0.05$). Baseline-adjusted mean percent drinking days were 57.2% for the NTX group and 65.1% for the PLA group. NTX did not have significant main effects on other variables (Table 2).

Moderator analyses

Several moderator variables were significantly correlated with each other, but these relationships were small in magnitude (Table 3). Men in this sample were more likely to have the DRD4-S genotype than the DRD4-L genotype (74% DRD4-S, 26% DRD4-L), whereas women were equally distributed (53% DRD4-S, 47% DRD4-L). Women were more likely to have 20% or more relatives with alcohol problems than the men (65% of women, 35% of men). However, only 4% of variance was shared between gender and DRD4 genotype, and only 2% of variance was shared between gender and FHP. Therefore, these individual difference variables were largely independent in this sample.

Genetic moderators

DRD4 genotype significantly moderated the effects of NTX on percent heavy drinking days ($F(1, 94) = 8.08, p < .01$), without having a significant main effect on this variable ($p = 0.34$). One-way ANOVAs conducted within each DRD4 genotype group indicated that NTX significantly reduced percent heavy drinking days in DRD4-L carriers (NTX: $25.5 \pm 4.7\%$ ($M \pm SEM$); PLA: $46.5 \pm 4.7\%$; $F(1, 34) = 10.20, p < .01$) but did not affect percent heavy drinking days in DRD4-S carriers (NTX: $39.2 \pm 3.2\%$; PLA: $38.1 \pm 3.3\%$). There were no other significant NTX x DRD4 interactions. OPRM1 genotype did not significantly moderate the effects of NTX on any measure.

Family History Proportion

Seventy-eight percent of first drinks of the day were followed by a second drink (NTX: 76%; PLA: 79%; NS). Family history proportion significantly moderated the effects of NTX on time between the first and second drinks (GEE parameter estimate = 0.51, $SE = 0.175, p < .005$) without having a significant main effect on this variable ($p = 0.50$). To illustrate the interaction, the group was trichotomized into participants with no family history of alcoholism ($n = 102$), low FHP (1-19% problem drinkers, $n = 57$) and high FHP ($\geq 20\%$ problem drinkers, $n = 23$), consistent with Rohsenow et al. (2007). NTX did not increase the time between drinks for the participants with either 0% (NTX: 13.87 ± 2.47 min; PLA: 14.83 ± 2.94 min) or 1-19% (NTX: 15.87 ± 3.38 min; PLA: 13.75 ± 3.45 min) family history positive relatives, but tended to increase this latency for those participants with $\geq 20\%$ problem-drinking relatives (NTX: 22.19 ± 8.00 min; PLA: 13.21 ± 5.00 min). Family history proportion did not significantly moderate the effects of NTX on other measures.

Age of onset

Age of onset significantly moderated the effects of NTX on drinking urge level reported during random prompt assessments (GEE parameter estimate = 0.07, $SE = 0.03, p < 0.05$) without having a significant main effect on this variable ($p = 0.13$). To illustrate the interaction, this group was dichotomized into participants with early- (before age 25) versus late-onset alcoholism. In subjects with earlier age of onset, participants in the NTX group reported lower urge levels at random prompts compared to those in the placebo group (NTX: 3.13 ± 0.06 ; PLA: 3.96 ± 0.06 ; GEE parameter estimate = $-0.83, SE = 0.23, p < 0.0005$). In participants with later age of onset, NTX did not affect urge levels reported at random prompts (NTX: 4.02 ± 0.13 ; PLA: 3.49 ± 0.12 ; GEE parameter estimate = 0.53, $SE = 0.65, p = 0.41$).

Likewise, age of onset significantly moderated the effects of NTX on urge level reported after the second drink of the day (GEE parameter estimate = 0.06, $SE = 0.03, p < 0.05$), without having a significant main effect on this variable ($p = 0.30$). However, neither of the follow-up simple effects tests reached significance. In participants with earlier age of onset, NTX tended to reduce urge levels collected after the second drink (NTX: 6.79 ± 0.15 ; PLA: 7.25 ± 0.15 ; GEE parameter estimate = $-0.49, SE = 0.30, p = 0.10$) but NTX had no effect on urge levels after the second drink in participants with older age of onset (NTX: 6.32 ± 0.26 ; PLA: 6.38 ± 0.25 ; GEE parameter estimate = $-0.06, SE = 0.75, p = 0.93$). Age of onset did not significantly moderate the effects of NTX on other measures.

Gender

Gender significantly moderated the effects of NTX on stimulation scores after the first and second drinks of the day (first drink: GEE parameter estimate = $-0.78, SE = 0.37, p < 0.05$; second drink: GEE parameter estimate = $-0.83, SE = 0.42, p < 0.05$) without having a main effect on these variables (p 's > 0.89). Follow-up tests within each gender indicated that NTX significantly reduced BAES stimulation scores after the first drink in women (NTX: $5.12 \pm$

0.11; PLA: 5.74 ± 0.10 ; GEE parameter estimate = -0.64 , $SE = 0.29$, $p < 0.05$) but not in men (NTX: 5.27 ± 0.07 ; PLA: 5.15 ± 0.07 ; GEE parameter estimate = 0.15 , $SE = 0.23$, $p = 0.52$). NTX also significantly reduced BAES stimulation scores after the second drink in women (NTX: 5.43 ± 0.13 ; PLA: 6.22 ± 0.12 ; GEE parameter estimate = -0.77 , $SE = 0.29$, $p < 0.05$) but not in men (NTX: 5.39 ± 0.09 ; PLA: 5.34 ± 0.09 ; GEE parameter estimate = 0.06 , $SE = 0.23$, $p = 0.81$). Gender did not significantly moderate the effects of NTX on other measures.

DISCUSSION

This study adds to the literature on NTX by providing detailed data, collected using EMA methods, on how NTX treatment affects drinking, urge and alcohol effects in heavy drinkers in the natural environment. There are numerous advantages of using EMA to collect these data. The data were collected in real time, which reduces memory and summary biases intrinsic to retrospective reports (Hammersley, 1994; Shiffman et al., 1997b). Although laboratory studies also collect measures in real-time and under controlled conditions, EMA methods allow for the collection of data in the participants' natural environments in the presence of their customary drinking cues and drinking situations. Finally, using EMA enabled us to conduct multiple daily assessments over a continuous 35-day period, providing sufficient power to test potential moderators of NTX's effects.

The finding that NTX reduced percentage drinking days in this study is consistent with its effects in treatment studies (e.g., O'Malley et al., 1992; Volpicelli et al., 1992). Beneficial effects of NTX on drinking frequency have been noted by most meta-analyses of this medication's effects on alcohol consumption (Bouza et al., 2004; Kranzler and Van Kirk, 2001; Streeton and Whelan 2001; but see Srisurapanont and Jarusuraisin, 2005). Kranzler and Van Kirk (2001) noted that NTX's effect on percentage drinking days was the most robust effect of this medication, but that its effects were highly heterogeneous across studies. Likewise, Rohsenow (2004) concluded that, across studies, the strongest effects of NTX were found on time to relapse, number of drinking days and number of heavy drinking days.

In the current study, participants in the NTX group had 8% fewer drinking days than subjects treated with placebo, which is comparable to or slightly smaller than the mean effect size in the Kranzler and Van Kirk (2001) meta-analysis. It is possible that the effect of NTX on percent drinking days in this study was smaller than that found in some treatment studies because the participants in this study were not trying to change their drinking behavior. Presumably, participants who were motivated to quit would make changes in their behavior that could add to or interact with the pharmacological effects of the medication. Furthermore, several studies have found that the beneficial effects of NTX are contingent on background psychosocial treatment (e.g., O'Malley et al., 1992), which may further motivate or reinforce reduction in drinking and thus is synergistic with NTX's pharmacological effects. Alternatively, the smaller effects of NTX found in this study, which are based on daily reports, may be more valid than other data that have been collected retrospectively using weekly reports.

NTX reduced percent heavy drinking days in participants with the DRD4-L genotype. This polymorphism of the DRD4 receptor gene has also been found to moderate effects of the mixed dopamine/histamine/serotonin antagonist olanzapine on drinking urge, with DRD4-L individuals showing greater decrease in urge after a priming drink with olanzapine than DRD4-S individuals (Hutchison et al., 2003). However, DRD4 genotype did not moderate effects of NTX on drinking urge in the present project or in a laboratory cue reactivity component of this project (McGeary et al., 2006). OPRM1 status did not moderate the effects of NTX in this study, which was unexpected based on previous findings suggesting its relevance to NTX response (Oslin et al., 2003; McGeary et al., 2006). A recent genetic substudy of 215 alcohol-dependent individuals from the Veterans Affairs Cooperative study of naltrexone's effects on

drinking also found no evidence that this OPRM1 polymorphism moderated NTX treatment response (Gelernter et al., 2007). Thus, with regard to both DRD4 VNTR and OPRM1, the pharmacogenetics of NTX's effects on drinking appears to remain a developing area and further research is needed to fully characterize the functionality of these alleles and their interaction with NTX. As such, we regard these findings as preliminary.

Naltrexone decreased drinking urge levels reported over the course of the day, when not drinking (i.e., at random prompts), and after the second drink, in participants with a younger age of onset of alcoholism. This is consistent with one previous study that found that early-onset alcoholics had better response to NTX treatment (Rubio et al., 2005), but inconsistent with another study that found no moderating effect (Rohsenow et al., 2007). Another significant finding of this study was that NTX increased the time between the first and second drinks of the day in participants who had a higher proportion of relatives with alcohol problems. This finding is consistent with a number of studies showing that individuals with a family history of alcoholism have greater response to NTX (Monterosso et al., 2001; Rohsenow et al., 2007; Rubio et al., 2005; but see Davidson et al., 1999). The present study examined this moderator using degree of alcohol problems within the family, which is similar to the family density method of Turner et al. (1993), and inherently more sensitive than a dichotomous measure of family history status (Rohsenow et al., 2007). Although gender was significantly associated with FHP in this sample, the magnitude of this association was small, and gender did not significantly moderate NTX's effects on latency between first and second drinks of the day. Thus, we consider it unlikely that a gender effect underlies the moderating effect of FHP on this outcome variable.

Interestingly, NTX reduced alcohol's stimulating effects in women but not men. There are few reports of gender mediating the effects of NTX on alcohol drinking or alcohol's subjective effects, although two studies have found NTX to be more effective in men (Garbutt et al., 2005; Hernandez-Avila et al., 2006). The present study had a fairly large sample of women compared to laboratory studies of NTX's effects on alcohol drinking; combined with the powerful EMA and GEE methods, this may have enabled us to detect gender differences not seen in those studies.

This study has several limitations. First, the participants in this study were not trying to change their drinking behavior. As with other studies that seek to characterize NTX's effects on ongoing drinking behavior and subjective effects of alcohol consumption, we excluded treatment-seeking alcohol drinkers for ethical and scientific reasons. We chose instead to study heavy drinkers, most of whom were diagnosed as alcoholics. Nevertheless, it is possible that the results of this study may not generalize to those individuals seeking to change their drinking behavior. Another limitation is the fact that individuals with comorbid substance abuse disorders other than nicotine abuse were excluded from the study population, consistent with many of the clinical trials of NTX (Rohsenow, 2004). Since many treatment-seeking alcoholics (40% or more) are likely to have comorbid substance abuse/dependence disorders (Kessler et al., 1994; 2005), generalization of the present findings to those seeking treatment is again limited. However, if alcoholics with such comorbidities have better response to NTX than those without (Rubio et al. 2005), then our positive results in this trial are especially noteworthy. Limitations with the genetic association research include the possibility that moderation of NTX's effects by the OPRM1 or DRD4 genes may be due to population stratification, a functional variant in linkage disequilibrium with the polymorphisms that were examined in this study, or with an unidentified third variable.

Along with its limitations, this study had several strengths. Medication compliance was very high, with only 4% of randomized participants not meeting medication compliance based on quantitative NTX and 6- β -naltrexol levels. Likewise, EMA compliance was very good overall:

89% of random prompt reports and 80% or more of drink reports met satisfactory compliance criteria, resulting in the collection of over 36,000 drinking and control assessments during the 5-week study period. Thus, this study adds to the literature on NTX by providing detailed data, collected in real time using EMA methods, on how NTX treatment affects the dynamics of drinking in heavy drinkers who are not trying to change their drinking. The findings converge with a number of previous findings with regard to the effects of NTX on alcohol use and bridge the gap between laboratory and treatment studies. Moreover, these results point to the importance of considering individual differences in the use of NTX. Interestingly, there was no single moderator that accounted for most of NTX's effects on drinking, urge and subjective effects of alcohol. Rather, a number of individual difference variables conferred sensitivity to different effects of NTX, each of which may contribute to NTX's ability to reduce alcohol intake.

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	Week 1		Week 2	Week 3	Week 4	Week 5
Medication status	No medication		All placebo	NTX or placebo		
EMA status	EMA training	EMA baseline	EMA monitoring and weekly visits to lab			

Fig. 1.
Study Timeline

Table 1
Participant Characteristics at Baseline [$M \pm (SD)$ or Percentage]

	Naltrexone* (<i>n</i> = 88)	Placebo (<i>n</i> = 85)
Age	29.9 $\pm$ 12.0	28.1 $\pm$ 10.7
Gender (% male)	58	60
Alcohol dependent (%)	65	60
Caucasian (%)	90	95
Years of education	14.9 (1.7)	14.8 (1.6)
Family history positive for alcoholism (%)	39	39
Smoker (%)	33	37
DRD4: % with ≥ 7 repeats (<i>n</i> = 115)	37	39
OPRM1: % with aspartate (<i>n</i> = 107)	33	29
Drinks per day	4.9 (2.6)	4.5 (1.8)
Drinks per drinking day	7.6 (3.8)	6.9 (2.6)
Drinking days (%)	65.0 (17.0)	65.6 (16.0)
Heavy drinking days (%)	45.8 (18.3)	43.6 (18.8)
CES-D sum	10.6 (8.9)	10.4 (6.6)
FTND score in smokers (<i>n</i> = 61)	2.5 (2.3)	1.7 (2.6)
DRINC score	23.6 (17.8)	21.2 (14.9)

* There are no significant differences between the groups on these measures.

Table 2Effects on Drinking and Related Subjective Measures [Means or Percentage $\pm$ (SEM)]

	Naltrexone	Placebo
Drinks per day	3.69 (0.13)	4.13 (0.12)
Drinks per drinking day	3.84 (0.13)	3.94 (0.12)
Drinking days (%) *	57.17 (2.3)	65.08 (2.4)
Heavy drinking days (%)	34.32 (2.4)	39.45 (2.4)
Drinking urge		
At random prompts	3.45 (0.04)	3.83 (0.04)
Before first drink	7.13 (0.08)	7.33 (0.08)
After first drink	6.62 (0.08)	6.99 (0.08)
After second drink	6.97 (0.09)	7.22 (0.09)
Stimulation		
After first drink	5.23 (0.06)	5.39 (0.06)
After second drink	5.42 (0.08)	5.68 (0.07)
Sedation		
After first drink	2.56 (0.05)	2.46 (0.05)
After second drink	2.68 (0.06)	2.69 (0.06)
Drink satisfaction/pleasantness		
After first drink	7.82 (0.04)	7.95 (0.05)
After second drink	7.91 (0.07)	8.12 (0.07)
Time between first and second drinks (min.)	15.2 (1.95)	14.3 (2.07)

*
p < .05

Table 3

Relationships among Moderators

Pearson or Phi coefficients	Gender	FHP	Age of Onset	DRD4	OPRM1
FHP	0.15*	–			
Age of Onset	0.15	0.03	–		
DRD4	0.21*	0.14	0.21	–	
OPRM1	–0.17	–0.05	0.00	–0.05	–

FHP refers to family history proportion; DRD4 refers to the variable number of tandem repeats (VNTR) polymorphism of the dopamine D4 receptor gene; OPRM1 refers to the Asn40Asp single nucleotide polymorphism of the μ opiate receptor gene.

*
p < .05