

Family History of Alcoholism Influences Naltrexone-Induced Reduction in Alcohol Drinking

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Background: The purpose of this study was to examine the interactive effects of family history of alcoholism (FH+, FH-) and naltrexone dose (0, 50, 100 mg/day) on alcohol drinking.

Methods: Ninety-two, non-treatment-seeking alcohol-dependent participants received naltrexone daily for 6 days. On the 6th day, they participated in a laboratory paradigm involving exposure to a priming dose of alcohol followed by a 2-hour drinking period in which they made choices between consuming alcoholic drinks and receiving money.

Results: Total number of drinks consumed during the drinking period was significantly decreased by the 100-mg dose of naltrexone in FH+ drinkers. Secondary analyses in male drinkers ($n = 70$) indicated that 100 mg of naltrexone significantly decreased drinking in FH+ participants and increased drinking in FH- drinkers.

Conclusions: These results suggest that family history of alcoholism might be a significant clinical predictor of response to naltrexone and that FH+ men are more likely to benefit from naltrexone therapy for alcohol drinking.

Key Words: Alcohol, drinking, family history, naltrexone

The opioid antagonist naltrexone, a medication approved for the treatment of alcohol drinking, has been shown in clinical trials to attenuate continued alcohol drinking after a lapse in abstinence (Anton *et al.* 2006; O'Malley *et al.* 1992; Volpicelli *et al.* 1992). However, the efficacy of naltrexone in reducing alcohol drinking is modest (e.g., Srisurapanont and Jarusuraisin 2002), and identifying predictors of robust treatment response could improve clinical practice. Preliminary evidence suggests that naltrexone might be more efficacious in subgroups of alcohol-dependent patients (Gueorguieva *et al.* 2006; Kiefer *et al.* 2005), such as those with an early onset or a positive family history (FH) of alcoholism (Monterosso *et al.* 2001; Rubio *et al.* 2005) or particular polymorphisms of the opioid receptor gene *OPRM1* (Oslin *et al.* 2003). However, there have been few direct examinations of the influence of these predictors on naltrexone's efficacy in reducing drinking.

Naltrexone's effects have been evaluated with laboratory paradigms in social (King *et al.* 1997; Swift *et al.* 1994) and alcohol-dependent (Anton *et al.* 2004; O'Malley *et al.* 2002) drinkers. In non-treatment-seeking alcohol-dependent drinkers, naltrexone reduced the number of drinks consumed and urges to drink (Drobes *et al.* 2003; O'Malley *et al.* 2002), similar to the effects observed in clinical trials with treatment-seeking patients.

With a similar laboratory paradigm, the current study evaluated the interactive influence of FH of alcoholism and naltrexone treatment on drinking in alcohol-dependent heavy drinkers. On the basis of the clinical evidence suggesting that FH of alcoholism might predict treatment outcome with naltrexone (e.g., Monterosso *et al.* 2001), we hypothesized a reduction of drinking in FH+ but not in FH- drinkers. Moreover, given the conflicting

evidence on the efficacy of naltrexone in female drinkers (e.g., Garbut *et al.* 2005; Ponce *et al.* 2005), secondary analyses examined drinking within each gender.

Methods and Materials

We recruited non-treatment-seeking volunteers with (FH+) or without (FH-) a first-degree relative with alcoholism (FHAM; Rice *et al.* 1995) who met the Structured Clinical Interview for DSM-IV (SCID-IV) criteria for alcohol dependence (First *et al.* 1996), were not abstinent more than 3 days/week, and consumed 25–50 drinks/week for men and 20–45 drinks/week for women (90-day Alcohol Timeline Followback [TLFB]; Sobell and Sobell 1992). After written informed consent was obtained, psychiatric and physical evaluations and laboratory assessments including urine toxicology and liver function tests were completed. Exclusion criteria included current use of psychotropic medications, medical contraindications to naltrexone or alcohol, a history of significant alcohol withdrawal, abuse/dependence on substances other than alcohol or nicotine, or women who were pregnant or nursing. Procedures were approved by the Yale Institutional Review Board and followed the National Institute on Alcohol Abuse and Alcoholism guidelines for administering alcohol in human experimentation (National Advisory Council on Alcohol Abuse and Alcoholism 1989, 2005).

Eligible subjects within each FH group were randomly assigned to receive a 6-day take-home supply of study medication (MED; 0, 50, or 100 mg naltrexone); smoking status and gender were balancing variables. They were instructed to take their medications orally at 10:00AM daily and were contacted by phone daily to confirm medication compliance and determine adverse events.

On the 6th day, participants were admitted to the General Clinical Research Center (GCRC) at Yale-New Haven Hospital, and drinks/day during days 1–5 was determined. The study medication was administered at 10:00AM. At 4:00PM, participants initiated the laboratory session, on the basis of our earlier work (O'Malley *et al.* 2002), which involved consumption of a priming alcoholic drink (PD; .03 g/dl) followed by a 1-hour monitoring period and two 1-hour self-administration (SA) periods. During each SA period, participants were offered a choice of consuming four alcoholic drinks (.015 g/dl each) or receiving \$3/drink.

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Table 1. Demographics and Drinking Characteristics for the Family History Groups

	FH– (n = 54)	FH+ (n = 38)	FH	MED	FH × MED
Smokers	31.6%	58.3%	$\chi^2 = 5.81, p < .05$	ns	ns
Gender	16 M, 3 F	7 M, 5 F	ns	ns	ns
Age (SE)	31.1 (2.2)	34.5 (2.9)	$F(1,86) = 11.86, p < .01$		ns
Drinking Variables 90-Day TLFB (SE)					
Total # drinks	494 (22)	385 (24)	$F(1,86) = 8.35, p < .01$	ns	ns
Drinks/drinking day	6.5 (.4)	5.5 (.4)	$F(1,86) = 7.31, p < .01$	ns	ns
% Drinking days	86.8 (3)	80.6 (4)	ns	ns	ns

FH, family history of drinking; MED, study medication; TLFB, Alcohol Timeline Followback.

Blood alcohol levels (BALs) were measured at 10, 20, 30, 40, 80, 110, 150, and 180 min after the PD. After completion of the session, participants spent the night at the GCRC and were discharged the next morning after receiving an intervention that included feedback about their heavy-drinking behavior to motivate them to seek treatment (Sinha *et al.* 1999).

Data Analyses

Baseline characteristics were compared with analyses of variance (ANOVAs) with FH and MED groups as between-subjects factors or logistic regressions (for binary outcomes). Similar ANOVAs were used to compare total numbers of drinks consumed (TD) during the SA period, drinking within each gender, and total number of adverse events; analyses of BALs during the PD and SA periods and drinks/day during days 1–5 also incorporated time as a repeated-within-subjects factor.

Results

Baseline Characteristics

Participants (38 FH+, 54 FH–) were mostly male (70 men, 22 women) and Caucasian (70 Caucasians, 14 African-Americans, 4 Hispanics, 4 other). The FH groups differed in percentage of smokers, age of participants, and drinking during the 90 days before the laboratory session (see Table 1), but within each FH group all demographic variables were comparable for the MED conditions (Table 2). During the outpatient treatment period, no main or interactive effects of FH or MED were observed on drinks/day or on total number of adverse events. However, there was a trend toward a FH × MED interaction ($p = .13$) on drinks/day in male drinkers.

Drinking Outcomes

During the SA period, although there was no main effect of FH or MED status on TD, there was a significant FH × MED interaction [$F(2,86) = 3.2, p < .05$]. Post hoc analyses indicate

that TD was lower in FH+ participants receiving 100 mg of naltrexone compared with those receiving a placebo ($p < .05$; Figure 1A), whereas TD was not significantly altered by any naltrexone doses in FH– participants. Scatter plots examining individual drinking data indicated that these differences were not mediated by outliers. The interaction between FH and MED status persisted even after adjusting for baseline drinks/drinking day, age, and smoking status [$F(2,78) = 3.6, p < .05$]. Secondary analyses in male drinkers found a significant FH × MED interaction on TD [$F(2,64) = 4.6, p < .01$], with post hoc analyses indicating reduced TD in FH+ men after 100 mg of naltrexone ($p < .05$) but increased TD in FH– men after 50 mg ($p = .09$) and 100 mg ($p < .05$) naltrexone (Figure 1B). In female participants, there were no significant main or interactive effects of FH or MED status on TD (Figure 1C).

BALs

Analyses of BALs during the PD period revealed no significant main or interactive effects of FH or MED conditions. However, during the SA period, there was a significant FH × MED × time interaction [$F(6,74) = 3.58, p < .01$]. Post hoc analyses indicate that within each FH group there were significant MED × time interactions (p values $< .01$) such that BALs were dose-dependently reduced in FH+ drinkers ($p < .05$) and increased in FH– drinkers ($p < .01$; Figure 2).

Discussion

To our knowledge, this is the first study to directly test the dose-dependent influence of naltrexone on drinking behavior on the basis of FH status. The results suggest that FH+ drinkers reduced their drinking in response to naltrexone, with the 100-mg dose resulting in the greatest reduction. By contrast, naltrexone did not reduce drinking in FH– drinkers. Importantly, these results were not related to differences in absorption or metabolism of the PD of alcohol or to naltrexone-mediated

Table 2. Demographics and Drinking Characteristics for the Medication Groups Within Each Family History Condition

	FH–			FH+		
	Placebo (n = 19)	50 mg NTX (n = 21)	100 mg NTX (n = 14)	Placebo (n = 12)	50 mg NTX (n = 12)	100 mg NTX (n = 14)
Smokers	31.6%	28.6%	28.6%	58.3%	50%	57.1%
Gender	16 M, 3 F	18 M, 3 F	10 M, 4 F	7 M, 5 F	9 M, 3 F	10 M, 4 F
Age (SE)	31.1 (2.2)	27.7 (2)	28.1 (2.5)	34.5 (2.9)	37.8 (3.4)	36.9 (2.4)
Drinking Variables 90-Day TLFB (SE)						
Total # drinks	494 (22)	472 (17)	426 (29)	385 (24)	431 (40)	380 (37)
Drinks/drinking day	6.5 (.4)	7 (.4)	6.3 (.5)	5.5 (.4)	5.6 (.5)	5.6 (.6)
% Drinking days	86.8 (3)	77.7 (3)	78.5 (4)	80.6 (4)	85.9 (3)	78.4 (4)

No significant main or interactive effects of FH and MED conditions were noted. NTX, naltrexone; other abbreviations as in Table 1.

side effects, because BALs achieved in response to the PD dose or adverse events were not altered by FH or naltrexone condition.

The FH– participants had heavier baseline drinking patterns when compared with FH+ participants. Although this finding is counterintuitive and FH+ individuals are known to have more alcohol-related problems (e.g., Merikangas *et al.* 1998), FH-mediated differences in quantity/frequency of drinking among drinkers are rather ambiguous (Conway *et al.* 2003; Vanvoorst and Quirk 2003). It is possible that we excluded FH+ heavier drinkers because they exceeded our upper drinking limits or presented with other medical or psychiatric problems. Regardless, controlling for baseline drinking did not change the total number of drinks consumed during the session. Although we did not find a significant influence of FH or MED condition on drinking during the 5-day outpatient period, a trend toward a FH × MED interaction was observed in the men only, suggesting that perhaps a larger sample size might be needed to identify differences in drinking during outpatient treatment.

Secondary analyses found significant inverse effects of naltrexone on drinking in the male drinkers on the basis of FH status. Specifically, after a 100-mg dose of naltrexone, drinking was significantly reduced in male FH+ drinkers but increased in male FH– drinkers. Naltrexone’s robust effect in FH+ male drinkers might be related to more complete blockade of opioid receptors (Oswald and Wand 2004). In contrast, although speculative, naltrexone’s counter-therapeutic effect in FH– male drinkers could be related to potential FH differences in antagonism of κ opioid receptors, an effect that has been shown to increase alcohol drinking (Mitchell *et al.* 2005). In female drink-

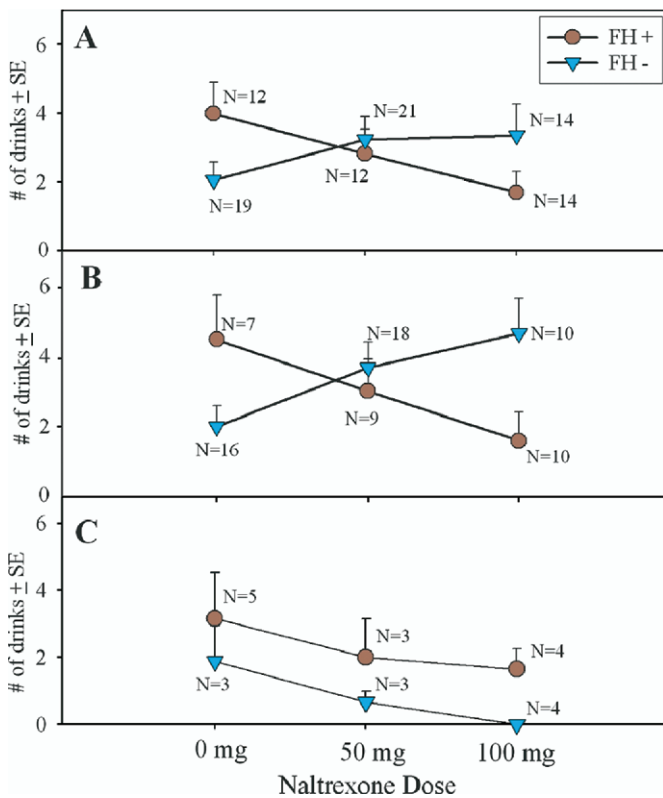


Figure 1. Total number of drinks consumed during the 2-hour choice period by family history (FH) status and naltrexone (NTX) dose; (A) Men and women; (B) Men only; (C) Women only (N = sample size within each group).

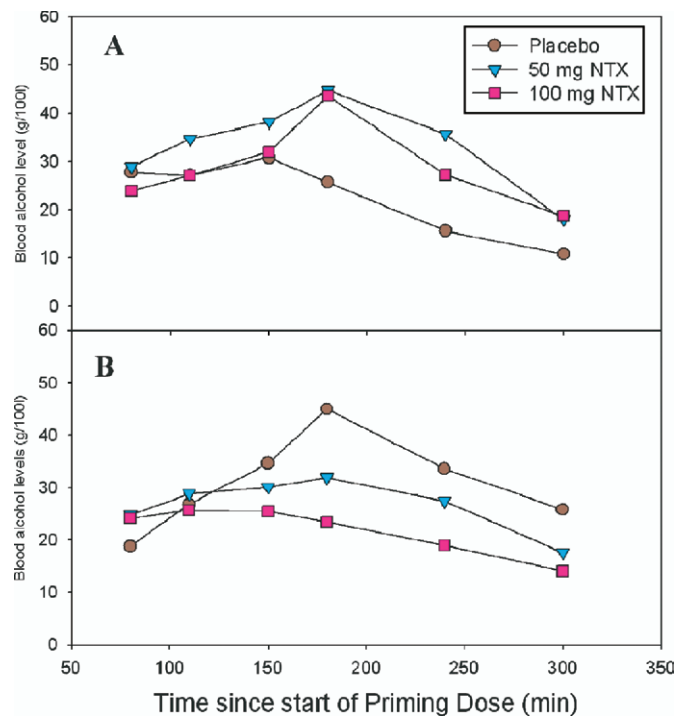


Figure 2. Blood alcohol levels during the self-administration period by family history (FH) status and naltrexone (NTX) dose; (A) FH– participants; (B) FH+ participants.

ers, drinking was not significantly altered by FH status or naltrexone and did not manifest this inverse phenomenon. Although a number of hypotheses could be proposed to explain these gender-related differences, including lower baseline levels of drinking in women or altered endogenous opioid status (Uhart *et al.* 2006), the small number of women in this sample suggests that these results should be interpreted with caution and precludes us from drawing specific mechanistic conclusions.

In summary, this study provides further evidence that FH of alcoholism might be an important predictor of clinical response to naltrexone. Regardless of the mechanisms mediating these differences, the results have significant practical implications for optimizing treatment of alcohol drinking with naltrexone. Given that family history of alcoholism is easily and routinely established by clinicians, this information could be used to guide clinical practice, leading to more efficient and effective use of treatment resources.

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- Anton RF, Drobos DJ, Voronin K, Durazo-Aziz R, Moak D (2004): Naltrexone effects on alcohol consumption in a clinical lab paradigm: Temporal effects of drinking. *Psychopharmacol* 173:32–40.
- Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, *et al.* (2006): Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. *JAMA* 295:2003–2017.
- Conway KP, Swendsen JD, Merinkangas KR (2003): Alcohol expectancies, alcohol consumption and problem drinking: The moderating role of family history. *Addict Behav* 28:823–836.
- Drobos DJ, Anton RF, Thomas SE, Voronin K (2003): A clinical laboratory paradigm for evaluating medication effects on alcohol consumption: Naltrexone and nalmefene. *Neuropsychopharmacol* 28:755–764.
- First MB, Spitzer RL, Gibbon M, Williams JBW (1996): *Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition*. New York: Biometrics Research, New York State Psychiatric Institute.
- Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, *et al.* (2005): Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. *JAMA* 293:1617–1625.
- Gueorguieva R, Wu R, Pittman B, O'Malley S, Krystal JH (2006): New insights into the efficacy of naltrexone for alcohol dependence from the trajectory-based analyses. *Biol Psychiatry* [Epub ahead of print].
- Kiefer F, Helwig H, Tarnaske T, Otte C, Jahn H, Wiedemann K (2005): Pharmacological relapse prevention of alcoholism: Clinical predictors of outcome. *Eur Addict Res* 11:83–91.
- King AC, Volpicelli JR, Frazer A, O'Brien CP (1997): Effect of naltrexone on subjective alcohol response in subjects at high and low risk for future alcohol dependence. *Psychopharmacol* 129:15–22.
- Merinkangas KR, Stolar M, Stevens DE, Goulet J, Preisig M, Fenton B, *et al.* (1998): Familial transmission of substance use disorders. *Arch Gen Psychiatry* 55:973–979.
- Mitchell JM, Liang MT, Fields HL (2005): A single injection of the kappa opioid antagonist norbinaltorphimine increases ethanol consumption in rats. *Psychopharmacol* 182:384–392.
- Monterosso JR, Flannery BA, Pettinati HM, Oslin DW, Rukstalis M, O'Brien CP, Volpicelli JR (2001): Predicting treatment response to naltrexone: the influence of craving and family history. *Am J Addictions* 10:258–268.
- National Advisory Council on Alcohol Abuse and Alcoholism (1989, 2005): *Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation, Revised May 2005*. Available at: <http://www.niaaa.nih.gov/Resources/ResearchResources/job22.htm>.
- O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B (1992): Naltrexone and coping skills therapy for alcohol dependence. *Arch Gen Psychiatry* 49:881–887.
- O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek J (2002): Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. *Psychopharmacol* 160:19–29.
- Oslin DW, Berrettini W, Kranzler HR, Pettinati H, Gelernter J, Volpicelli JR, *et al.* (2003): A functional polymorphism of the Mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacol* 28:1546–1552.
- Oswald LM, Wand GS (2004): Opioids and alcoholism. *Physiol Behav* 81:339–358.
- Ponce G, Sanchez-Garcia J, Rubio G, Rodriguez-Jimenez R, Jimenez-Arriero MA, Palomo T (2005): Efficacy of naltrexone in the treatment of alcohol dependence disorder in women. *Actas Esp Psiquiatr* 33:13–18.
- Rice JP, Reich T, Bucholz KK, Neuman RJ, Fishman R, Rochberg N, *et al.* (1995): Comparison of direct interview and family history of diagnoses of alcohol dependence. *Alcohol Clin Exp Res* 19:1018–1023.
- Rubio G, Ponce G, Rodriguez-Jimenez R, Jimenez-Arriero MA, Hoenicka J, Palomo T (2005): Clinical predictors of response to naltrexone in alcohol patients: Who benefits most from treatment with naltrexone? *Alcohol Alcohol* 40:227–233.
- Sinha R, Krishnan-Sarin S, Farren C, O'Malley SS (1999): Naturalistic follow-up of drinking behavior following participation in an alcohol administration study. *J Subst Abuse Treat* 17:159–162.
- Sobell LC, Sobell MB (1992): Timeline follow-back: A technique for assessing self-reported ethanol consumption. In: Allen J, Litten RZ, editors. *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods*. Totowa, New Jersey: Human Press, 41–72.
- Srisurapanont M, Jarusuraisin N (2002): Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev* CD001867.
- Swift RM, Whelihan W, Kuznetsov O, Burongiorno G, Hsuing H (1994): Naltrexone induced alterations in human ethanol intoxication. *Am J Psychiatry* 151:1462–1467.
- Uhart M, Oswald L, McCaul ME, Chong R, Wand GS (2006): Hormonal responses to psychological stress and family history of alcoholism. *Neuropsychopharmacol* 31:2255–2263.
- Vanvoorst WA, Quirk SW (2003): Are relations between paternal history of alcohol problems and changes in drinking moderated by positive expectancies? *Alcohol Clin Exp Res* 27:25–30.
- Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP (1992): Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 49:876–880.