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

Suchitra Krishnan-Sarin, John H. Krystal, Julia Shi, Brian Pittman, and Stephanie S. O’Malley

**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

**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.
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 \((p < .05, \text{ Figure 1A})\), 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 \((p < .05)\) such that BALs were dose-dependently reduced in FH+ drinkers \((p < .05)\) and increased in FH− drinkers \((p < .05; \text{ Figure 2})\).

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 1. Demographics and Drinking Characteristics for the Family History Groups

<table>
<thead>
<tr>
<th></th>
<th>FH− ((n = 54))</th>
<th>FH+ ((n = 38))</th>
<th>FH</th>
<th>MED</th>
<th>FH × MED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>31.6%</td>
<td>58.3%</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Gender</td>
<td>16 M, 3 F</td>
<td>7 M, 5 F</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Age (SE)</td>
<td>31.1 (2.2)</td>
<td>34.5 (2.9)</td>
<td>F((1,86) = 11.86, p &lt; .01)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Drinking Variables 90-Day TLFB (SE)</td>
<td></td>
<td></td>
<td>F((1,86) = 5.81, p &lt; .05)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Total # drinks</td>
<td>494 (22)</td>
<td>385 (24)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Drinks/drinking day</td>
<td>6.5 (4)</td>
<td>5.5 (4)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>% Drinking days</td>
<td>86.8 (3)</td>
<td>80.6 (4)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

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

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

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

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 drinkers, 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.

This research was supported by the National Institute on Alcohol Abuse and Alcoholism Center Grant P50AA12870, M01RR00125 and Pfizer. Dr. Krystal has served as a consultant to the following pharmaceutical companies: Atlas Venture, Aventis Pharmaceuticals, Biomedisin Corporation, Bristol-Meyers Squibb, Centre de Recherche Pierre Fabre, Cypress Bioscience, Eli Lilly and Company, Fidelity Biosciences, Forest Laboratories, Glaxo-SmithKline, Janssen Research Foundation, Merz Pharmaceuticals, Organon International (CNS Advisory Board), Pfizer Pharmaceuticals, Shire Pharmaceuticals, Sumitomo Pharmaceutical America, Takeda Industries, UCB Pharma, and US Micron. Dr. O’Malley has received research support through contracts (principally for company-sponsored trials) or donated clinical supplies from Alkermes, Lipha Pharmaceuticals, Glaxo-SmithKline, Forest Laboratories, Dupont, OrthoMcNeil, Bristol-


