Dose-dependent reduction of hazardous alcohol use in a placebo-controlled trial of naltrexone for smoking cessation

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Abstract

The opiate antagonist naltrexone (Ntx) has demonstrated efficacy in the treatment of alcohol dependence and as a component of treatment to reduce heavy drinking. At present, there are no published dose-ranging clinical trials of the oral preparation for treatment of problem drinking. The present study evaluated the effects of Ntx on alcohol use among the subset of hazardous drinkers (n = 102) who participated in a placebo-controlled, dose-ranging trial of oral Ntx (25-mg, 50-mg and 100-mg doses) combined with open-label transdermal nicotine patch for enhancing smoking cessation. On the primary outcome—no hazardous drinking (drinking that exceeded weekly or daily limits)—during treatment ~ 25 mg and 50 mg Ntx were superior to placebo (each p < 0.05). These findings remained after controlling for baseline predictors or smoking abstinence during treatment. Time to remission of hazardous drinking was examined as a secondary outcome with definitions of hazardous drinking based on weekly limits, daily limits and the combination of weekly and daily limits and the results were consistent with the primary findings. In conclusion, the findings suggest that Ntx can reduce the risk of hazardous drinking in smokers who are not seeking or receiving alcohol treatment, providing strong evidence for the pharmacological effects of Ntx on drinking. This effect appears to favour lower doses that may be better tolerated and less expensive than the higher 100-mg dose. Given its efficacy and favourable side-effect profile, the 25-mg dose should be considered for future studies of combination therapy.

Introduction

Naltrexone (Ntx) is an opioid antagonist that was FDA-approved for the treatment of alcohol dependence in 1994 based in part on two efficacy studies of 50 mg/d (O’Malley et al., 1992; Volpicelli et al., 1992). The majority of subsequent clinical trial findings support Ntx’s efficacy. A recent meta-analysis including 27 randomized controlled trials, mostly involving the approved oral dose of 50 mg, showed that Ntx treatment in conjunction with psychosocial therapy decreased the likelihood of relapse to heavy drinking in the short-term (Srisurapanont and Jarusuraisin, 2005). Since this meta-analysis was completed, reports from two large, multi-site trials have been published: one examined two doses of long-acting extended-release Ntx (XR-Ntx) in combination with brief counselling (Garbutt et al., 2005; O’Malley et al., 2007); the other tested 100 mg oral Ntx along with brief medically oriented counselling or coupled with a more intensive form of psychosocial therapy (the COMBINE Study; Anton et al., 2006). Both provided evidence of Ntx’s efficacy in reducing heavy drinking in conjunction with some form of psychosocial therapy. In the study of XR-Ntx, the 380-mg dose of XR-Ntx, in contrast to the 190-mg dose, was the most efficacious compared to placebo.

The majority of clinical trials of Ntx have enrolled alcohol-dependent patients presenting for alcohol...
treatment who had some level of motivation to quit drinking. However, it is known that some drinkers, primarily those without severe alcohol dependence, are capable of reaching goals of moderate drinking (Miller and Wilbourne, 2003). Recent work has explored the use of Ntx for this indication. Kranzler et al. (2003) conducted a placebo-controlled study of 50 mg Ntx taken either daily or on a targeted basis (i.e. as needed in anticipation of drinking situations) in a sample of 150 early problem drinkers, of whom the majority (83%) had a goal of reduced drinking. In this 8-wk trial, Ntx, especially daily dosing, reduced the frequency of heavy drinking compared with placebo. While the findings of Kranzler’s trial argue that Ntx can be efficacious for heavy drinkers not interested in stopping drinking, it is important to note that participants in this study were nonetheless motivated to change their drinking behaviour and psychosocial therapy aimed at drinking reduction was provided along with Ntx.

Another test of the pharmacological effects of Ntx on reducing drinking would be to evaluate it among individuals who are not counselled to modify their drinking. A recent investigation by Tidey and colleagues (2008) found that 50 mg Ntx reduced the frequency of drinking in a 2-wk double-blind, placebo-controlled treatment period in heavy drinkers who were not advised to change their drinking; 63% of these subjects met criteria for current alcohol dependence. Similarly, using a cross-over design in which 25 heavy-drinking participants received either 50 mg/d Ntx or placebo for 1 wk and were not instructed to change their drinking, Mitchell et al. (2007) found a significant decrease in the number of drinks consumed while on Ntx. In addition, laboratory studies have shown that Ntx can decrease the amount of alcohol consumed during a drinking episode by non-treatment-seeking heavy drinkers or alcohol-dependent subjects (Anton et al., 2004; Krishnan-Sarin et al., 2007; O’Malley et al., 2002).

Surprisingly, there are no published placebo-controlled clinical trials of multiple doses of oral Ntx and only a handful of alcohol administration laboratory studies that have systematically examined different Ntx doses (Doty and deWit, 1995; Doty et al., 1997; Krishnan-Sarin et al., 2007; McCaul et al., 2000a,b, 2001). Of these laboratory studies, only the report by Krishnan-Sarin and colleagues (2007) examined Ntx effects on drinking behaviour.

The present study provides information about the effects of different doses of oral Ntx on alcohol drinking by conducting analyses of drinking data obtained in a Ntx clinical trial designed to test the primary hypothesis involving smoking cessation (O’Malley et al., 2006). In this study, 400 smokers received 6-wk treatment with a transdermal nicotine replacement (21 mg/d) along with either placebo or one of three doses of oral Ntx: 25, 50 or 100 mg/d. Prior to randomization, a substantial proportion of the participants met the National Institute on Alcohol Abuse and Alcoholism’s (NIAAA, 2005) criteria for hazardous drinking, which is determined by exceeding daily or weekly drinking limits. This category of drinkers has public health relevance because hazardous drinking is four times more prevalent than alcohol dependence (Reid et al., 1999; Wilk et al., 1997), and these drinkers consume sufficient quantities of alcohol to be at risk for alcohol-related consequences (e.g. impaired driving, liver disease, hypertension). It is known that hazardous drinkers represent 80% of all individuals who experience alcohol problems (Institute of Medicine, 1990). As a result, data from this subsample provided a unique opportunity to examine the dose-dependent effects of Ntx on drinking behaviour among individuals not motivated to reduce their drinking and in the absence of alcohol counselling. In making these comparisons, we explored the utility of several distinct definitions of reduced drinking to determine their ability to distinguish among different drug doses in terms of efficacy. We examined whether weekly limits, daily limits or the combination of daily and weekly limits was most sensitive to the effects of Ntx. The final goal of this effort was to identify a group of independent and important baseline predictors of outcome. Such information could prove useful in the design and analysis of future studies.

Methods

Participants

Participants included in this analysis were a subgroup of those enrolled in O’Malley et al.’s (2006) trial who met criteria for hazardous drinking at baseline and who provided any drinking data during treatment. The methods of the original trial, including a CONSORT flow diagram, were described in detail in O’Malley et al. (2006). Briefly, participants were recruited primarily through advertisements. Inclusion criteria were: smokers had to be ≥18 yr, be able to speak English, weigh at least 45 kg (≥100 lb), smoke ≥20 cigarettes/d for at least the past year, give an expired carbon monoxide (CO) level >10 ppm and report at least one prior quit attempt. Only one individual per household was allowed to enrol. Women were not allowed to enrol if pregnant, nursing or not using a reliable form of contraception. Other exclusion
criteria included unstable cardiac disease, use of psychotropic medications, opioid use, elevated liver function tests [i.e. aspartate amino transferase (AST) or alanine amino transferase (ALT) > 3 times normal or elevated bilirubin] and current alcohol dependence.

Those exceeding the gender-specific recommendations for maximum weekly or daily drinking delineated by the National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2005) during the 6 wk prior to randomization were considered to be heavy drinkers and were included in the present study; specifically, male heavy drinkers consuming >14 drinks/wk or >4 drinks on at least one occasion and female drinkers consuming >7 drinks/wk or >3 drinks on at least one occasion. A drink was defined as a beverage containing 0.5 oz (14.12 g) of ethanol.

**Procedures**

Participants were enrolled at two sites: the Connecticut Mental Health Center, New Haven and the Veterans Affairs (VA) Connecticut Healthcare System, Newington. The trial was approved by the following institutional review boards: the VA Connecticut Healthcare System, Yale University School of Medicine, New Haven and the University of Connecticut Health Center, Farmington. Eligible participants were randomized using a block randomization procedure, stratified by sex for the final 250 individuals. All participants received open-label 21-mg transdermal nicotine patches (Nicoderm CQ, GlaxoSmithKline, Research Triangle Park, NC, USA), brief weekly smoking cessation counselling with handouts and one of four doses of medication: placebo, 25 mg, 50 mg or 100 mg oral Ntx (Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA) to be taken daily for a period of 6 wk. Ntx was titrated up to the target dose over the first week (i.e. 12.5 mg for 1 d, 25 mg for 1 d, 50 mg for 2 d, 100 mg thereafter). Medication compliance was monitored with the use of eDEM caps, which record the time of bottle openings [Aprex (Aardex), Union City, CA, USA] and plasma levels of Ntx and 6β-naltrexol. Participants and study staff members interacting with participants were blind to Ntx dose assignment.

No formal alcohol-related counselling was provided. The only information about alcohol use was limited to written advice to avoid alcohol, as well as other beverages associated with smoking. Smoking cessation counselling was provided and assessments were conducted on a weekly basis during the 6-wk treatment. At each appointment, self-reported tobacco and alcohol use were assessed using a Timeline Followback Interview (TLFB). Other baseline assessments reported in this paper include the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1992), the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) and the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). Tobacco use was biochemically verified using CO levels at weekly appointments. Individuals were considered continuously abstinent from smoking if they abstained from smoking ‘not even a puff’ for the 6 wk and had a CO level ≤10 ppm.

**Statistical analyses**

Our primary outcome used the definition of hazardous drinking above to classify patients in a binary fashion as either a ‘success’ or ‘failure’ at the completion of their treatment based on whether they continued to meet heavy-drinking criteria during any week of the 6-wk treatment period. This categorical outcome was analysed with logistic regression in which each active dose was contrasted to placebo.

Several additional distinct definitions of reduction-in-drinking ‘success’ were also examined using survival or time-to-event analyses. NIAAA Guidelines define hazardous drinking as exceeding either weekly limits or daily limits. We examined three definitions of success based on either the composite of weekly and daily limits, weekly limits alone, or daily limits alone and modelled success defined by time to the first week when hazardous drinking stopped and non-hazardous drinking was maintained for the remainder of the treatment period. The first definition (Definition 1 – Composite Outcome) defined hazardous drinking as exceeding either the NIAAA weekly or daily limits and involved the time to the first week without hazardous drinking and with continued adherence to drinking under the composite drinking limit for the remainder of the treatment period, where continued adherence required that drinking was less than both daily and weekly limits defined above. The second definition (Definition 2 – Weekly Limits) of reduction-in-drinking ‘success’ involved examination of only one category of hazardous drinking, i.e. >14 drinks/wk among males and >7 drinks/wk among females. For this single-category definition, we measured the time to the first week without hazardous weekly drinking and with continued adherence to this criterion for the remainder of the study period. A third definition (Definition 3 – Daily Limits) involved measuring the time to the first week without hazardous drinking defined by daily limits (>4 drinks/d for males and >3 drinks/d for females) and with...
continued adherence to this criterion for the remainder of the study period. Finally, we repeated the analysis of the primary outcome of success or failure based on whether or not the person met criteria for the composite definition of hazardous drinking at any point during the 6-wk treatment period, this time controlling for baseline patient characteristics using logistic regression in which each active dose was contrasted to placebo. The baseline characteristics reported in Table 1 were included in these analyses. The backward selection method was used in this process to eliminate any non-significant factors ($\alpha = 0.05$). Medication groups were forced into every model. Logistic regression analyses were also used to compare the medication groups to placebo on continuous abstinence from smoking following randomization to first examine whether Ntx promoted smoking abstinence in this subsample and then to examine the effects of Ntx on the primary outcome of hazardous drinking controlling for smoking abstinence, which could potentially influence drinking behaviour. Time-to-event analyses were performed using the Kaplan–Meier method to display the curves, and using the log-rank test to compare the curves. SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. All $p$ values in this report are of the two-sided type.

**Results**

**Demographic and baseline characteristics**

One hundred and two participants met hazardous-drinking criteria at baseline. Of these, 16 exceeded weekly limits only, 37 exceeded daily limits only, and 49 exceeded both daily and weekly limits. The demographic and clinical characteristics of the 102 hazardous drinkers are presented in Table 1 for the Ntx and placebo groups. The medication groups are similar with respect to race, body mass index, number of cigarettes smoked per day, and CES-D score. However, several factors differed to varying degrees among the treatment groups. These differences were noted in the 100-mg group only which had an older average age, a higher percentage of males, fewer college graduates, a higher average FTND score (Heatherton et al., 1991) and higher AUDIT scores and amount of alcohol consumed per occasion at baseline.

| Table 1. Baseline characteristics for the entire sample and by dose group |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                            | Overall ($n = 102$)         | Placebo ($n = 26$)          | 25 mg ($n = 23$)            | 50 mg ($n = 25$)            | 100 mg ($n = 28$)           | $p$ value overall |
| Age (yr)                   | 42.37 ± 11.91               | 41.19 ± 11.57               | 40.87 ± 13.92               | 40.68 ± 13.67               | 46.21 ± 7.84               | 0.259 |
| Female sex (%)             | 45.1                        | 42.31                       | 52.17                       | 52                          | 35.71                       | 0.568 |
| White race (%)             | 87.25                       | 88.46                       | 82.61                       | 92                          | 85.71                       | 0.79  |
| Body mass index            | 28.00 ± 4.70                | 28.75 ± 5.48                | 27.41 ± 4.20                | 27.08 ± 4.28                | 28.62 ± 4.70                | 0.487 |
| Education (%)              |                             |                             |                             |                             |                             | 0.149 |
| High-school graduate or less | 30.53                      | 33.33                       | 18.18                       | 26.09                       | 42.31                       |       |
| Some education after high school | 43.16                      | 54.17                       | 50                          | 30.43                       | 38.46                       |       |
| College graduate or more   | 26.32                       | 12.5                        | 31.82                       | 43.48                       | 19.23                       |       |
| Married or cohabitating (%) | 49.5                        | 61.54                       | 30.43                       | 50                          | 53.57                       | 0.169 |
| Full-time employment (%)   | 75.76                       | 84                          | 65.22                       | 73.91                       | 78.57                       | 0.479 |
| No. of cigarettes smoked per day | 25.87 ± 7.73               | 26.59 ± 7.83                | 23.58 ± 5.00                | 25.37 ± 5.93                | 27.55 ± 10.35               | 0.303 |
| Years of smoking cigarettes | 25.59 ± 11.47              | 24.88 ± 11.81               | 24.82 ± 11.99               | 24.08 ± 13.13               | 28.30 ± 9.05                | 0.546 |
| FTND score                 | 5.12 ± 1.65                 | 4.81 ± 1.67                 | 5.13 ± 1.55                 | 5.04 ± 1.54                 | 5.50 ± 1.82                 | 0.504 |
| Other smokers in household (%) | 37                         | 42.31                       | 27.27                       | 44                          | 33.33                       | 0.596 |
| Family history of alcoholism (%) | 45.92                     | 52                          | 36.36                       | 40                          | 53.85                       | 0.534 |
| CES-D score                | 13.03 ± 4.87                | 12.85 ± 5.61                | 13.57 ± 4.51                | 12.96 ± 5.15                | 12.81 ± 4.32                | 0.947 |
| AUDIT score                | 4.37 ± 3.17                 | 4.96 ± 2.88                 | 3.18 ± 2.04                 | 3.96 ± 3.66                 | 5.15 ± 3.50                 | 0.108 |
| Baseline drinks per occasion | 4.15 ± 3.02                | 3.68 ± 2.03                 | 3.56 ± 1.60                 | 4.14 ± 2.64                 | 5.08 ± 4.54                 | 0.247 |
| Baseline percent days abstinent | 58.52 ± 35.23              | 53.15 ± 34.18               | 66.33 ± 32.28               | 57.81 ± 39.17               | 57.74 ± 35.60               | 0.631 |

AUDIT, Alcohol Use Disorders Identification Test; CES-D, Center for Epidemiologic Studies Depression Scale; FTND, Fagerström Test for Nicotine Dependence.
Although none of these differences was statistically significant, analyses were performed to examine their influence on the end of treatment primary outcome variable of continued hazardous drinking.

Treatment compliance and adverse events

There were no differences between the groups on the number of weeks in treatment (mean = 5.25, S.D. = 1.58, p = 0.96), the percentage of Ntx doses taken (mean = 76.83, S.D. = 27.53, p = 0.99), or the number of weeks that nicotine patch was used (mean = 5.18, S.D. = 1.66, p = 0.98). The groups did not differ in the percentage of participants for whom Ntx was either discontinued or the dose was reduced (p = 0.17). However, dose changes occurred in 8% of the 50-mg group and 10.7% of the 100-mg group with no changes made in the placebo and 25-mg groups. The percentage reporting any moderate-severe adverse event did not differ significantly by dose (p = 0.36). As expected, serum Ntx and 6β-naltrexol concentrations were approximately dose proportional (data not shown).

Primary outcome results

On the primary outcome measure (incidence of any hazardous drinking during treatment), there was a statistically significant overall difference among the four groups (p = 0.024), with the placebo group being most likely to continue meeting hazardous-drinking criteria [85% (22/26) vs. 43% (10/23), 56% (14/25), and 64% (18/28)] for the 25-mg, 50-mg, and 100-mg groups, respectively. Pairwise treatment comparisons indicate that placebo was worse than the 25-mg group [relative risk (RR) 0.14, two-sided 95% confidence interval (CI) 0.04–0.54, p = 0.004] and worse than the 50-mg group (RR 0.23, two-sided 95% CI 0.06–0.87, p = 0.031). There was a trend for the placebo group to be worse than the 100-mg group (RR 0.33, two-sided 95% CI 0.09–1.22, p = 0.096).

Secondary definitions of success

Figure 1 shows the time to remission of hazardous drinking defined by weekly and daily limits (i.e. Definition 1). There was a statistically significant difference overall (log rank test, p = 0.028), with all three treatment groups having a shorter time compared to placebo. The 25-mg group had a statistically significantly shorter time to termination of hazardous drinking compared to placebo (log rank test, p = 0.002), with a RR of 2.48 indicating that one was 2.48 times more likely to stop hazardous drinking earlier if randomized to receive 25 mg Ntx. The estimated median time to continued remission of hazardous drinking was 1 wk for the 25-mg Ntx group vs. 6 wk for the placebo group. There were non-significant trends for improvement seen in the other two Ntx groups as well, with a RR of 1.64 for the 50-mg group (log rank test, p = 0.14) and a RR of 1.68 for the 100-mg group (log rank test, p = 0.09). Compared to the estimated median time to remission of hazardous drinking of 6 wk for the placebo group, the 50-mg and 100-mg Ntx groups had median times to remission of 2 wk and 3 wk, respectively.

Figure 2 shows the time to the first week of remission of hazardous drinking with hazardous drinking defined as exceeding weekly limits (i.e. Definition 2: consuming >14 drinks/wk for males and >7 drinks/wk for females). Unlike the previous analysis in which Ntx was significantly superior to placebo when remission meant that both weekly and daily non-hazardous drinking criteria were met and maintained, the analysis of a remission outcome based on only weekly drinking limits only showed a trend overall favouring the Ntx groups when all four groups are included in the analysis (overall log rank test, p = 0.14). There was a statistically significantly shorter time to remission in the 25 mg vs. placebo (log rank test, p = 0.028), which was not seen in the 50 mg vs.
placebo comparison (log rank test, $p = 0.67$) or the 100 mg vs. placebo comparison (log rank test, $p = 0.16$).

The estimated median time to remission from hazardous drinking based on weekly drinking limits was 3.5, 1.0, 1.0, and 1.0 wk for the placebo, 25-mg, 50-mg, and 100-mg groups, respectively. Thus, compared to the dual-criteria hazardous-drinking outcome in Figure 1, the definitional change of remission in Figure 2 to a single weekly drinking limit reduced the median time to remission for the placebo group from 6 wk to 3.5 wk, while the active treatment median estimates changed less. Between-treatment sensitivity seems to be substantially enhanced when hazardous drinking is defined using both daily and weekly limits. When the analysis of remission based on weekly limits was restricted to the smaller subsample of 65 participants who exceeded weekly limits at baseline, the results were not statistically significant.

When we compared the time to remission of hazardous drinking with hazardous drinking defined as exceeding daily limits (i.e. Definition 3), we found there was a highly statistically significant difference among the four groups ($p < 0.001$ overall), with significantly more rapid remission seen in the 25-mg and 50-mg dose Ntx groups compared to placebo ($p = 0.006$ and 0.007, respectively). This is presented graphically in Figure 3. Only a trend in time to remission was seen in the high-dose Ntx comparison vs. placebo ($p = 0.08$).

The estimated median time to remission from hazardous drinking defined by daily limits was 6, 1.0, 1.0, and 3 wk for the placebo, 25-mg, 50-mg, and 100-mg groups, respectively. The statistically significant difference between the four groups remained when the analysis was restricted to the 86 participants who exceeded daily limits at baseline, the results were not statistically significant.

Analyses controlling for baseline predictors and smoking cessation success

After controlling for baseline predictors of the primary composite outcome of any hazardous drinking during treatment, our findings were similar to that in which the simple model without covariates was used. Subjects in the 25-mg (OR 0.132, 95% CI 0.027–0.657) and 50-mg (OR 0.178, 95% CI 0.038–0.833) dose groups were less likely than the placebo group to report any hazardous-drinking activity during treatment in the final model controlling for significant baseline predictors. The significant baseline predictors of drinking outcome were age, FTND scores, years of daily smoking and percent days abstinent from alcohol. Specifically, continued hazardous drinking was associated with younger age (OR 0.816, 95% CI 0.682–0.976), lower FTND scores (OR 0.665, 95% CI 0.461–0.961), longer duration of daily smoking (OR 1.198, 95% CI 1.005–1.428) and fewer days of abstinence in the 6 wk prior to treatment (OR 0.960, 95% CI 0.938–0.984).

In this subsample of hazardous drinkers, Ntx did not increase smoking abstinence rates significantly at any dose compared to placebo. The number and percentage who achieved continuous smoking abstinence from the quit date was 12 (47.2%), 11 (47.8%), 8 (32%) and 14 (50%) for the placebo, 25-mg, 50-mg and 100-mg conditions respectively. The dose-dependent effects of Ntx on the primary composite outcome of no hazardous drinking were unchanged when continuous abstinence from smoking was entered as a covariate into a logistic regression analysis. Continuous abstinence from smoking was not significantly associated with reduced risk of hazardous drinking during treatment ($\chi^2 = 2.22$, 1 d.f., $p = 0.14$; OR 1.938, 95% CI 0.811–4.631).

Discussion

This placebo controlled 6-wk study presents new findings about the effect of different doses of oral Ntx on alcohol drinking in a hazardous-drinking sample that was not seeking treatment to reduce hazardous drinking and in the absence of specific counselling to reduce or abstain from alcohol. Most prior investigations have recruited alcohol-dependent patients and have made use of the FDA-approved oral dose of 50 mg, although the COMBINE Study, the largest study to date, used 100 mg/d (Anton et al., 2006). Our data suggest that among individuals who are smokers and are not currently alcohol dependent, 25 and 50 mg/d are optimally effective for reducing

![Figure 3](image-url)
hazardous drinking, with somewhat less efficacy found for 100 mg/d. These findings persisted even in analyses that controlled for potential baseline predictors of outcome. The results of the baseline predictors, however, suggest that those who are younger, have smoked longer, have lower FTND scores and have fewer days of abstinence are less likely to reduce their hazardous drinking during a smoking cessation effort that does not include counselling to help them reduce their drinking. In contrast to some but not all prior studies (e.g. Garbutt et al., 2005; Krishnan-Sarin et al., 2007), gender and family history of alcoholism did not alter these findings; these differential effects could be related to the non-dependent nature of the population examined in our study.

A further strength of this investigation is that it provided an unbiased endpoint determination of drinking, since the primary purpose of this trial involved the comparative evaluation of smoking cessation outcomes. Even in trials involving high proportions of patients interested in moderate drinking rather than abstinence (e.g. Kranzler et al., 2003), these individuals were still seeking treatment for their alcohol use, and alcohol consumption was the primary focus prior studies in non-treatment-seeking subjects (e.g. Mitchell et al., 2007; Tiede et al., 2008). The finding that Ntx reduced risky drinking adds to the growing literature on the benefits of Ntx on heavy alcohol consumption (Anton et al., 2006; Garbutt et al., 2005; Kranzler et al., 2003, for a review see Pettinati et al., 2006), and extends this to a sample of individuals who were not seeking or receiving counselling for their drinking. This provides strong evidence for a pharmacological effect of Ntx, and is consistent with the results of laboratory studies demonstrating reductions in drinking among non-treatment-seeking hazardous and alcohol-dependent drinkers (Anton et al., 2004; Krishnan-Sarin et al., 2007; O’Malley et al., 2002) and two short-term outpatient studies in non-treatment-seeking heavy alcohol drinkers (Mitchell et al., 2007; Tiede et al., 2008). One clinical implication of the current study is that Ntx may be helpful in reducing hazardous drinking among individuals who are lacking in motivation for alcohol treatment.

The efficacy of the 25-mg dose is particularly promising and warrants replication given that 25 mg was associated with somewhat better compliance and fewer side-effects than the 100-mg dose in the larger parent study (O’Malley et al., 2006) and did not require dose reductions in the subsample of hazardous drinkers. The observed dose-dependent effects of Ntx could reflect differences in opioid receptor specificity with different doses of Ntx and changes in receptor levels produced by chronic Ntx. Ntx is more specific for µ-opioid receptors at lower doses with greater activity at δ- and κ-opioid receptors at higher doses. Recent evidence suggests that a dose of 50 mg Ntx results in complete occupancy of the µ-opioid receptors (Bencherif et al., 2004), indicating that the reduction in drinking observed with a 25-mg dose in our study is probably related to μ-receptor occupancy. Additionally, chronic treatment with higher doses of Ntx may result in greater up-regulation of μ-opioid receptors (Brady, 1992).

In the present study we chose to examine three different definitions for remission from hazardous drinking during the course of a 6-wk smoking intervention trial. The first remission definition being the joint requirement of termination of both weekly and daily excessive drinking, the remaining two definitions of remission being based on termination of drinking that exceeded either weekly or daily drinking limits. We also presented data in terms of ‘time to event’ analysis in order to develop a good ‘sensitivity’ assay in terms of time to remission and the ability to discriminate between active treatment groups, and between active treatment groups vs. placebo. With regard to these definitions, the findings suggest that in order to discern treatment effects, it is best if both daily and weekly criteria for drinking ‘success’ be met and maintained and that these outcomes can show between-treatment differences that are highly statistically significant (certainly \( p < 0.01 \)). However, when the components making up this composite were examined separately, the effects of Ntx were most apparent on drinking that exceeded daily limits rather than weekly limits. In designing future studies, the data suggest that there may be an advantage in using a composite measure of success, in which several components of drinking reduction (e.g. weekly success and daily success) are combined and that this composite endpoint be maintained over the entire treatment course as well. Of note, in the COMBINE Study, the strongest effect of Ntx was found for a composite index of good clinical outcome that incorporated information on drinks per week, days of heavy drinking and drinking-related problems over the final weeks of the 16-wk trial (Anton et al., 2006). Composite outcomes seem to be most relevant and attractive from a practical viewpoint, since it is the total drinking experience of an individual that is probably important.

Several limitations may impact the generality of the results. First, this was a secondary analysis using a subset of hazardous drinkers participating in a larger dose-ranging study of Ntx for smoking cessation and
randomization was not stratified on the basis of hazardous-drinking status. While there were non-significant differences between the groups at baseline, accounting for baseline characteristics did not change the findings. The sample was comprised exclusively of smokers who did not meet current criteria for alcohol dependence. Thus, the findings may not generalize to non-smokers, to those meeting current criteria for alcohol dependence, and to conditions in which participants are seeking to change their drinking with more intensive counselling. Related to this last point, the COMBINE Study found that Ntx was beneficial when provided in conjunction with medical management, but not in combination with a more intensive behavioural treatment and medical management (Anton et al., 2006). Additionally, all participants received open-label 21-mg transdermal nicotine patch combined with Ntx. Prior research has demonstrated that nicotine patch can attenuate drinking behaviour (Acheson et al., 2006; McKee et al., 2008), and it is possible that transdermal nicotine limited differences observed between placebo and active Ntx groups. Another important limitation is that drinking was only examined during 6 wk of treatment. We do not know how drinking would be affected by a longer duration of treatment. Despite these qualifiers, this study provides important information about oral Ntx dosing and on measures of treatment success that are most sensitive to Ntx.

In conclusion, the results of this study suggest that Ntx can reduce the risk of hazardous drinking in smokers who are not seeking or receiving counselling to reduce their drinking. This effect appears to favour lower doses of Ntx that may be better tolerated and less expensive than the higher 100-mg dose. Given the favourable side-effect profile and efficacy of the 25-mg dose, this dose should be considered for future studies of combination therapy. Based on the present results, Ntx in combination with nicotine replacement may provide an effective strategy for reducing hazardous alcohol consumption in the context of a smoking cessation intervention.

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Statement of Interest

Drs O’Malley, Krishnan-Sarin and Meandzija are inventors on unlicensed patents held by Yale University for the use of naltrexone for smoking cessation. Dr O’Malley has received research support (medication supplies or contracts) from Alkermes Inc., Dupont, GlaxoSmithKline Inc., Forest Laboratories, Lharma Pharmaceuticals, Ortho-McNeil Inc., Bristol–Myers Squibb, Pfizer Inc., Sanofi-Aventis, and Mallinckrodt Pharmaceuticals; served as a consultant for Alkermes Inc., Forest Laboratories, GlaxoSmithKline Inc., Ortho-McNeil/Johnson & Johnson, and Eli Lilly; received travel reimbursement from Alkermes; and gave a talk for the Medical Education Speakers Network. Dr McKee received nicotine patches from GlaxoSmithKline and worked on contracts to Yale University from Pfizer Pharmaceuticals. Dr Meandzija worked on clinical trial contracts to Yale University from Alkermes Inc., Bristol–Myers Squibb, and Ortho-McNeil Inc. Dr Krishnan-Sarin received research support from Pfizer Inc. Dr Cooney’s spouse is on the speakers’ bureau of Pfizer Pharmaceuticals.

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