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Nicotine-Use/Smoking Is Associated with the Efficacy of Naltrexone in The Treatment of Alcohol Dependence

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Abstract

Background—The opioid antagonist naltrexone is not efficacious for every alcohol treatment seeker. However, various individual factors, such as genetic differences and nicotine use/smoking status, have been suggested as predictors of naltrexone response. In a randomized clinical trial, we previously reported that nicotine use/smoking status might be a stronger predictor of naltrexone efficacy than *OPRM1* A118G single nucleotide polymorphism (SNP) genotype. In this report, we further characterize the nicotine users in that trial, examine other drinking outcomes, examine the influence of smoking change on naltrexone effects on drinking, and validate the result in smokers with %dCDT change as an independent biomarker of response.

Methods—Individuals (n=146) meeting DSM-IV criteria for alcohol dependence who were genotyped for the *OPRM1* A118G SNP and who did, or did not, use nicotine/cigarettes were randomized, in a balanced fashion, to naltrexone (50 mg/day) or placebo and provided medical management over a 16-week clinical trial. Alcohol use and smoking during the trial were assessed and analyzed.

Results—Nicotine-use/smoking status significantly interacted with medication in reducing percent heavy drinking days (PHDD) during the trial ($p=0.003$), such that nicotine users/smokers showed significantly lower PHDD on naltrexone vs. placebo ($p=0.0001$, Cohen's $d=0.89$) while non-users showed no significant difference between naltrexone and placebo ($p=0.95$, Cohen's $d=0.02$). Similar effects were shown for drinks per day and percent days drinking. The superiority of naltrexone over placebo on PHDD reduction in nicotine-users/smokers was confirmed with

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%dCDT (Cohen's d range 0.3 – 0.9 over the study). Naltrexone did not significantly change cigarette use in smokers, and change in use did not influence naltrexone's effect on PHDD.

Conclusions—These data confirm past findings that naltrexone is more efficacious in those who use nicotine/cigarettes. Compared to previous work on the *OPRM1* A118G SNP, it appears that nicotine use might be a more salient predictor of naltrexone treatment response. While naltrexone did not change cigarette use during the study, and smoking change was not related to alcohol reduction, it should be noted that participants were not seeking smoking cessation and medical management did not address this issue.

Keywords

Alcohol; Nicotine-Use; Naltrexone; Treatment; Alcohol Use Disorder

Introduction

While pharmacological treatments for alcohol use disorder (AUD) are effective in some individuals, effects are variable and do not work for everyone (Litten et al., 2016). Several factors, such as smoking (Weinberger et. al. 2015, Hufnagel et. al. 2017), have the potential to influence overall treatment response rates, while others such as genetic background (Goldman et al., 2005) may modify the efficacy of specific medications. Better understanding of how these factors (and potentially others) might influence response to specific medications would enhance our ability to tailor pharmacotherapy to AUD individuals, thereby allowing a more predictable therapeutic response (i.e., precision medicine). While a specific single nucleotide polymorphism (SNP) in the mu opioid receptor gene, *OPRM1* A118G, which codes for an aspartate substitution for asparagine (Asp40Asn) in the coding region of the gene, might predict naltrexone response (Oslin et al., 2003, Anton et al., 2008, Ray et al., 2012) in AUD, recent studies have been inconsistent (Setiawan et al., 2012, Oslin et al., 2015). In a large randomized clinical trial in which subjects were prospectively randomized to naltrexone or placebo on the basis of their A118G genotype, we recently reported that there was evidence of a naltrexone by A118G interaction only when considering a post-medication follow-up period and among the most adherent subjects (Schacht et al., 2017). However, in an exploratory analysis of that study, we reported that smoking status might be a better predictor of naltrexone response than *OPRM1* genotype, a finding previously observed in a retrospective analysis of the COMBINE Study (Fucito et al., 2012). Since smoking is a salient factor in alcohol use and treatment, further evaluation of this effect is imperative.

Both nicotine and alcohol are widely used, and the prevalence of Nicotine Use Disorder in individuals with concurrent AUD is almost double the rate (45%) of the general population (Grant et al., 2004). A number of studies have found that the interaction of nicotine and alcohol influences ability to quit either, or both, substances (Kalman et al., 2010). While not yet definitive, a number of studies suggest that treatment efficacy for those trying to abstain or reduce their drinking is reduced in current smokers (Hufnagel et al., 2017) and smokers have higher relapse rates to heavy drinking than non-smokers (Mason and Lehart, 2009, Weinberger et al., 2015).

While there are effective pharmacological treatments for both disorders (Zindel and Kranzler, 2014, Yardley et al., 2015, Kalman et al., 2010) the influence of nicotine use on alcohol pharmacotherapy, while becoming of greater interest, has not been widely evaluated. For instance, varenicline, a nicotine receptor partial agonist approved for smoking cessation, has been shown to reduce drinking in a large multisite study (Litten et al., 2013), but its effect on drinking was modified by smoking (Falk et al., 2015), such that, among those who reduced the number of cigarettes smoked per day, varenicline reduced drinking, while among those who did not reduce smoking, varenicline was no more effective than placebo. Another medication studied for both AUD and smoking is naltrexone. An older Cochrane report found efficacy of naltrexone compared to placebo for smoking cessation to be equivocal (David et al., 2006), but a confluence of data in heavy drinkers seeking smoking-cessation treatment suggests that while naltrexone might reduce smoking, that reduction might be specifically linked to reduction in alcohol use (King et al., 2009)(Fridberg et al., 2014) (Yardley et al., 2015). On the other hand, a naltrexone-induced reduction in hazardous alcohol use was observed in treatment-seeking smokers that appeared independent of smoking cessation (O'Malley et al., 2009). Perhaps most germane to this report, a reanalysis of the large multisite COMBINE Study (Anton et al., 2006) found that almost all of the naltrexone effect on alcohol use was observed among smokers, while naltrexone did not differ from placebo among non-smokers (Fucito et al., 2012). To our knowledge, this is the only large clinical trial in which this effect was observed. Further investigation of that unique finding appeared necessary to further evaluate whether naltrexone might be especially beneficial in this subgroup of nicotine user/smokers (40–50% of AUD treatment seekers).

Our previous report gave a brief description of the effect of “smoking” on naltrexone response in a randomized controlled clinical trial that was primarily designed to evaluate the effect of the *OPRM1* A118G polymorphism on *AUD* treatment response (Schacht et al., 2017). Given the potential importance of the initial data in which smoking did not seem to influence the *OPRM1* interaction with naltrexone but did, in itself, influence naltrexone response, it seemed imperative to further investigate those findings. This report further defines that group of individuals considered “smokers” and subsequently clarified as “nicotine-users”, provides further analyses to better characterize the smoking effect on a range of drinking outcomes, provides supporting evidence using alcohol biomarkers of the validity of the observed drinking reduction, and further considers the effect of naltrexone on smoking as a moderator of its effect on drinking.

Patients and Methods

Trial Design and Participants

The study design, participants and methods were previously described (Schacht et al., 2017). In sum, the study was a 16-week randomized clinical trial (clinical trial.gov #NCT00920829) comparing naltrexone vs. placebo that was designed to evaluate differential effect of naltrexone in *OPRM1* A (Asn40)-allele homozygotes vs. G (Asp40)-allele carriers. Participants had to meet *DSM-IV* criteria for alcohol dependence by SCID interview (First MB et al., 1997), be aged 18–70 years, and not be of African American descent (secondary

to low frequency of the G allele in this population), report drinking, on average, 5 drinks per day in the 90 days prior to assessment, and have at least 4 days of abstinence prior to randomization. Participants could not meet *DSM-IV* criteria for dependence on any other drug but nicotine, and had to have a negative urine drug screen at study entry. No other psychoactive medication use except antidepressants (stable dose for at least one month) was allowed, and participants could not meet *DSM-IV* criteria for a current Axis I psychiatric disorder. Participants were medically stable and had liver enzymes (ALT and AST) no greater than 3 times normal. Females could not be pregnant and were required to be using a reliable form of contraception, or were post-menopausal.

Recruitment

Participants were not engaged in other alcohol treatment and generally were recruited using public advertising from the community. The study was approved by the IRB at the Medical University of South Carolina and participants signed informed consent before formal assessment and genotyping. Those with at least one G allele and approximately 1/3 of A-allele homozygotes (recruited temporally proximal to Asp40 individuals) were offered clinical trial participation (see Figure 1, Consort Diagram). Nicotine use was assessed prior to medication assignment using both verbal report of estimates of use during screening and during post-screening assessment using the smoking items of the Addiction Severity Index (ASI) (McLellan et al., 1992). Based on information reported on screening interview and ASI interview (done independently by two research staff), participants were classified as nicotine users/smokers or non-nicotine users. None of the participants expressed a desire to alter their nicotine or smoking use and the focus of treatment was only on alcohol use. Nicotine use was used as an *a priori* urn randomization variable to assure similar distribution across medication and gene groups (see Consort Diagram – Figure 1 and Table 1).

Interventions

Medication—Participants were randomized after at least four days of abstinence, to identical looking capsules of either naltrexone (25 mg for 2 days, then 50 mg thereafter) or placebo for 16 weeks.

Medical Management (MM): Medical management (MM) (Pettinati et al., 2004) (Pettinati et al., 2005), as used in the COMBINE Study (Anton et al., 2006), was provided along with study drug. MM was delivered over 15–20 minutes on weeks 1, 2, 3, 4, 6, 8, 10, 12, 16 of the study where compliance enhancement, alcohol drinking education, and goal review was utilized. Medication adverse effects using the SAFTEE (Johnson et al., 2005) were collected. Participants were encouraged, but not required, to attend Alcoholics Anonymous meetings. Important for this report, there was no attempt to counsel participants regarding their use of nicotine or smoking.

Assessment

A number of assessments were utilized prior to randomization to adequately describe the participant population and to assure consistency across treatment groups (see Table 1 for the assessments utilized). Also done prior to randomization was a health screen chemistry panel, liver function tests, pregnancy test (females) and alcohol use markers gamma-

glutamyltransferase (GGT) and carbohydrate-deficient transferrin (Litten et al., 2010, Helander et al., 2010) (Anton and Youngblood, 2006).

Daily drinking at baseline, and during treatment between MM visits, was assessed with the Timeline Follow-back (TLFB) (Sobell and Sobell, 2000) calendar method. At weeks 8 and 16, the ASI was repeated, and nicotine use/smoking status was assessed again. Study drop-outs were offered \$50 to provide drinking data at the end of the study (week 16).

Outcome Measures

The primary, *a priori* defined, outcome measure was percent heavy drinking days (PHDD; 5 or more standard drinks per day for men and 4 or more for women) per month, over the course of treatment. However, to assure complete evaluation of the drinking profile and medication effectiveness, drinks per day and percent days drinking (converse of percent-days abstinence) were also analyzed. To confirm veracity of reporting and to further confirm the effect of naltrexone versus placebo in the nicotine use/smoking group, change in %dCDT levels over the 16 weeks of treatment were also compared. %dCDT was measured with a reference high-performance liquid chromatography assay (Helander et al., 2010), and other blood chemistries, including GGT, were measured with an autoanalyzer.

Randomization

After initial assessment, subjects were genotyped for the *OPRM1* A118G SNP and randomized as previously described (Schacht et. al. 2017, and Consort Diagram Figure 1). Importantly, based on prior knowledge regarding differences in alcohol use and potential treatment response between nicotine user/smokers and non-nicotine users (e.g. Fucito et al., 2012), a pre-planned urn randomization procedure was utilized that randomly assigned subjects to treatment groups based on nicotine use/smoking status in conjunction with other *a priori* defined variables of interest including: sex, AUD family history, antidepressant and cocaine use. All participants, as well as assessment and treatment staff, were blind to genotype and medication assignment and, importantly, how the various urn variables, including nicotine use/smoking, were disturbed across treatment groups.

Statistical Analysis

Baseline descriptive data was analyzed by chi square or routine ANOVA. An evaluation of baseline covariates suggested that “time since the last drinking day prior to randomization” and “employment status” significantly predicted within-study PHDD, the primary outcome measure. They were therefore used in the intent-to-treat (ITT) analysis (all subjects with at least 1 week of drinking data) using a linear mixed model (SPSS ver.22, Linear Mixed) with an unstructured variance/covariance matrix, in which the main effects of time, medication, and nicotine use/smoking and all interactions of these factors on 4 bins of monthly drinking data were evaluated. This analysis was repeated for the secondary outcome variables, drinks per day and percent days drinking. To further evaluate the naltrexone vs. placebo effect in nicotine-users/smokers, effect sizes were calculated using PHDD (over each 1 month block) and mean %dCDT level (at weeks 3, 6, 10 and 16 - when available) as the dependent variables. The same baseline covariates were used in those univariate analyses as above, except in the %dCDT analysis, where only baseline %dCDT level was used as a covariate.

In addition, among only smokers ($n = 52$), we compared the number of cigarettes smoked per day in the 30-day period prior to randomization (baseline), at mid-trial (week 8), and end of trial (week 16), by medication group using a univariate model at each time point. Finally, we conducted several sensitivity analyses to evaluate the effect of medication and study compliance on final outcomes as well as how differences in baseline drinking between the nicotine and non-nicotine users might have affected the results.

Results

Randomization and Baseline Characteristics

Figure 1 provides the CONSORT recruitment and randomization diagram for the study. Since the initial goal of the study was to balance groups on *OPRM1* A118G genotype and nicotine use without oversampling for nicotine use, there were fewer individuals in the study who used nicotine (Table 1 and Table 2), but *OPRM1* genotype was well-balanced across nicotine-use and medication groups. Similarly, evaluable subjects, as well as drop-outs, were similar across nicotine use and medication groups.

Demographic, alcohol use and severity measures are given in Table 1. Generally, important demographic variables were equally balanced across all four nicotine-use by medication groups. However, age, employment and education (less vs. more than 12 years) did vary significantly between groups. Drinks per drinking day and drinks per day also varied significantly between groups, such that nicotine users also had more drinks per day and drinks per drinking day, but not more PHDD. Alcohol severity was also higher in the nicotine users than non-users. Initial analysis found that of these demographic variables, only “employment status” influenced PHDD during the study and therefore only it was used as a covariate in the drinking analysis. Although days from last drink did not differ in the four study groups prior to randomization, as in our prior work (Schacht et al., 2017), it did influence overall drinking during the study, and was therefore also used as a covariate in the drinking analyses. While %dCDT was generally higher in the nicotine-user group, it did not predict drinking during the study, but was used as a covariate in the %dCDT analysis.

An overall description of the distribution of nicotine-users/smokers within the medication groups, as well as the amount of use, is given in Table 2. Out of 58 nicotine users, 52 were cigarette smokers and 6 used other nicotine products (4 were daily tobacco chewers, 1 used nicotine gum daily, and 1 used a nicotine patch daily). The 52 cigarette smokers smoked, on average, 26 days per month and used, on average, 16.4 cigarettes per day, which did not differ between the medication groups. Six participants who smoked cigarettes occasionally (less than 10 times in a month, but no more than 1 cigarette on those days) were classified as “non-smokers” for this analysis and were well-distributed within the medication groups.

Drinking During Treatment

Figure 2 displays medication and nicotine use effects on PHDD. There was a significant interaction between medication and nicotine use ($F = 9.43$, $df = 1, 140$, $p = 0.003$), such that, in nicotine users, naltrexone, relative to placebo, reduced PHDD ($F = 16.18$, $df = 1, 142$, $p = 0.0001$), while in non-users, there was no significant difference between medication groups

($F=0.004$, $df=1, 136$, $p=0.95$). The effect size of naltrexone compared to placebo in reducing PHDD was $d=0.89$ among nicotine users and $d=0.02$ among non-users.

Other alcohol consumption variables were consistent with the PHDD findings. For drinks per day (DPD) (Figure 3), there was a significant interaction between medication group and nicotine use ($F=7.19$, $df=1, 144$, $p=0.008$), such that, in nicotine users, naltrexone, relative to placebo, reduced DPD ($F=11.59$, $df=1, 146$, $p=0.0001$), while in non-users, there was no significant difference between medication groups ($F=0.005$, $df=1, 139$, $p=0.94$). The effect size of naltrexone compared to placebo in reducing DPD was $d=0.72$ among nicotine users and $d=0.02$ among non-users.

For percent days drinking (PDD) (Figure 4), there was also a significant interaction between medication group and nicotine use ($F=6.13$, $df=1, 140$, $p=0.015$), such that, in nicotine users, naltrexone, relative to placebo, reduced PDD ($F=5.98$, $df=1, 142$, $p=0.016$), while in non-users, there was no significant difference between medication groups ($F=0.92$, $df=1, 137$, $p=0.34$). The effect size of naltrexone compared to placebo in reducing PDD was $d=0.62$ among nicotine users and $d=-0.19$ among non-users.

To further evaluate the effect of naltrexone on drinking in the nicotine-use group, and as a further check on veracity of reporting, we evaluated change in both PHDD and %dCDT change over the course of the study. The patterns, significance, and effect sizes (Cohen's d) of naltrexone compared to placebo on PHDD and %dCDT were very consistent (Figure 5). The effect size of naltrexone compared to placebo for PHDD ranged between $d=0.6$ to 1.1 over the course of the study, while for %dCDT, it ranged from $d=0.3$ to 0.9 . This remarkable consistency between verbally reported heavy drinking and a specific biomarker for heavy drinking, strongly supports the validity of the finding that naltrexone had marked efficacy in those heavy drinkers who also used nicotine compared to those that did not.

To evaluate the relationship between nicotine-use and drinking over the course of the study we focused only on the 52 individuals who smoked cigarettes, as we captured change in use only in those individuals. We evaluated PHDD and cigarette use per day in the month prior to the midpoint (week 8) and end of the study (week 16). There was a significant difference between naltrexone and placebo in PHDD at week 8 ($F=5.64$, $df=1, 46$, $p=0.02$) and at week 16 ($F=6.40$, $df=1, 41$, $p=0.02$), but there was no significant difference in cigarettes smoked per day between the naltrexone- and placebo-treated groups at those times (week 8 ($F=0.20$, $df=1, 39$, $p=0.66$); week 16 ($F=1.35$, $df=1, 38$, $p=0.25$)). Also, when cigarettes smoked per day was entered as a covariate in the ANOVA examining medication effects on PHDD at week 8, and at week 16, the significant efficacy of naltrexone over placebo did not materially change at either time point, implying that naltrexone's effect on drinking was largely independent of any effects on smoking.

Sensitivity Analyses

Effect of Baseline Drinking—One concern might be that baseline drinking differences between the nicotine and non-nicotine user groups might have biased or accounted for the naltrexone effect. In fact, drinks per day did statistically differ the most across all groups ($p=0.01$) (see table 1) with the nicotine users reporting more drinks per day than non-

nicotine users ($p=0.002$). Therefore, a secondary analyses was conducted to evaluate the effects of “drinks per day” on outcome. Using baseline drinks per day as a covariate in the mixed model did not materially alter the nicotine-use by medication interaction on percent heavy drinking days, which continued to show superiority of naltrexone over placebo only in the nicotine using group ($F= 9.3$, $df 1,86$, $p=0.003$). Further analysis used a median split on baseline drinks per day to define “low and high drinkers” in the nicotine-using group. In nicotine- users, naltrexone compared to placebo reduced drinks per day in both the low and high drinking groups ($p=.042$ and $p<.001$, respectively). These analyses suggest that the effect of naltrexone in reducing drinking in the nicotine-using group was largely independent of their level of alcohol consumption.

Effect of Compliance and Study Treatment Completion—There was no difference between the nicotine users and non-users in number of pills taken ($p=0.273$), urine riboflavin positive samples ($p=0.07$) or treatment completion rates ($p=0.16$). In addition, using these adherence variables as covariates in the percent heavy drinking days analysis did not change the overall significance of the interaction between nicotine- use and medication group (i.e. the superiority of naltrexone over placebo in the nicotine-user compared to non-user groups remained positive with $p < 0.01$ for each of the adherence covariates).

Discussion

Few studies have evaluated the role of nicotine-use/smoking in alcohol pharmacotherapy trials. While this clinical trial was not designed to specifically evaluate nicotine use as a moderator of naltrexone response, we did randomize nicotine-use status across both medication and *OPRM1* A118G cells based on *a priori* knowledge of the effects of smoking on alcohol use and in treatment outcomes generally. This turned out to be advantageous, since, in general, the treatment groups were well-balanced on nicotine use. Our randomization scheme had the added advantage of proportionally distributing nicotine users across the *OPRM1* allele groups, leading to similar proportion of G-allele carriers across the medication and nicotine-use cells. This allowed for a more direct evaluation of nicotine use directly on naltrexone response without the potential confound of salient genetic differences leading to interpretation bias. Importantly, since we used urn randomization techniques in the study design, other potentially salient clinical variables such as depression, cocaine use, and sex were also balanced across nicotine-use and medication groups.

Our finding of a significant and consistent interaction of nicotine-use status on naltrexone response, both in our *a priori* defined drinking outcome variable (PHDD) and secondary drinking variables (DPD and PDD), offers strong support for the interaction of naltrexone and nicotine-use status. The fact that %dCDT, a blood biomarker used to validate verbal reports of heavy drinking (Anton et al., 2002, Litten et al., 2010, Bergstrom and Helander, 2008), showed a similar effect size favoring naltrexone over placebo specifically in smokers provides further support for the existence of this effect. It should be noted, however, consistent with many previous reports (Weinberger et. al. 2015, Hufnagel et. al 2017, Fucito et. al. 2012), that nicotine users/smokers drank more during the trial than non-users, perhaps allowing the naltrexone effect to be more noticeable or profound. However, our secondary

analyses suggest that the naltrexone effect in nicotine users was largely independent of the amount of baseline drinking.

These findings are also largely consistent with data from the COMBINE Study (Anton et al., 2006), in which a post-hoc analysis revealed that smokers drank more than non-smokers during the trial but that naltrexone's effect in smokers was clearly better than in non-smokers (Fucito et al., 2012). Given the post-hoc nature of that analysis, there might have been concern regarding the validity of that original finding. Nevertheless, our data seem to confirm that observation.

One added issue of concern is whether the observed effect on alcohol reduction is primary to naltrexone treatment, or secondary to change in smoking status. For naltrexone, a number of previous studies have indicated a link between reductions in alcohol consumption and smoking (King et al., 2009, Fridberg et al., 2014, Yardley et al., 2015), while at least one reported that the naltrexone effect on drinking in smokers appeared to be independent of smoking effects (O'Malley et al., 2009). For varenicline, a medication developed specifically for smoking cessation, the initial enthusiasm for its efficacy for alcohol use reduction (Litten et al., 2012) was tempered by the finding that a reduction in cigarette-use moderated the reduction in alcohol consumption (Falk et al., 2015). Therefore, this issue required more evaluation in the current study. Unfortunately, daily nicotine-use/smoking over the full course of the study was not captured by using a daily calendar method such as the TLFB for drinking, but assessments of smoking rates halfway through the study and again at the end of the study showed no significant difference in cigarette use between the naltrexone and placebo groups. Also, when smoking was co-varied in the drinking analyses at these time points, the effect of naltrexone on drinking did not substantially change. Therefore, in our hands, change in smoking did not seem to significantly influence the observed naltrexone effects on drinking reduction.

Furthermore, the effect size between naltrexone and placebo on percent heavy drinking days in nicotine-using individuals in this study was large ($d=0.89$ overall, and 0.92 at the end of the study). This is much larger than the effect sizes often associated with naltrexone response in clinical trials, which tend to be in the small to moderate range (Srisurapanont and Jarusuraisin, 2005, Maisel et al., 2013). One possible explanation for the larger effect size is that nicotine-user/smokers drink more, thereby showing less of a placebo response as evident in this study. The reduced placebo affect might allow the naltrexone effects to be magnified. This, however, does not negate the fact that nicotine products might biologically mediate this greater drinking thereby providing the substrate for naltrexone to be more effective. Nevertheless, as shown in our sensitivity analyses, the amount of drinking in and off itself is not the prime reason for the greater utility of naltrexone in nicotine-user/smokers, since even lower-level drinkers in that group responded better to naltrexone.

The moderating effect of nicotine use on naltrexone response in individuals with AUD might be at first surprising, but there are biological reasons that support this finding. In animals, concurrent exposure to alcohol and nicotine increases ventral striatal (VS) dopamine levels than either alone (Tizabi et al., 2002), and human smokers reported heightened reward sensitivity to the effects of alcohol consumption (Piasecki et al., 2011). Elevated VS

dopamine is associated with drug reward and reinforcement (e.g. (Koob and Le Moal, 1997, Volkow et al., 2007)), and naltrexone blocks alcohol-induced elevation of VS dopamine release in animals (Benjamin et al., 1993, Gonzales and Weiss, 1998, Middaugh et al., 2003), as well as alcohol cue-elicited VS activation in humans (Myrick et al., 2008, Schacht et. al. 2017). Thus, it is possible that excess dopamine release in nicotine-using smokers might make them more treatment-resistant in general, but more sensitized to naltrexone's effect – leading to greater treatment response than non-smokers. This might imply that other drugs that reduce alcohol-induced VS dopamine release and/or alcohol cue-elicited VS activation might work best in AUD individuals who use nicotine. Perhaps more unique to naltrexone efficacy is that alcohol dependent smokers were shown to have blunted mu-opiate receptor binding in various areas of the brain, suggesting that smokers may have more beta-endorphin release/availability than non-smoking alcoholics (Weerts et al., 2014). This finding would also be predictive of a greater alcohol treatment response to naltrexone's opiate receptor blockade in nicotine using/smoking AUD individuals.

While we did not find a significant effect of naltrexone on reducing smoking in this study, individuals entering the study were not seeking treatment for smoking reduction/cessation, and medical management did not focus on smoking reduction. Nevertheless, it would appear there is no support for a direct pharmacological effect of naltrexone in altering cigarette-use in this population of only alcohol treatment-seeking individuals. Further prospective studies randomizing nicotine-using treatment-seeking individuals with AUD and those additionally seeking nicotine-use reduction appear warranted.

The main limitations of this study were: 1) not stratifying on nicotine-use initially (although urn randomization afforded similar utility); 2) not recruiting an equal number of nicotine users and non-users (e.g., not oversampling for nicotine users); 3) not further characterizing the level of nicotine dependence; and 4) not recording daily nicotine use across each day of the treatment period or confirming use with urine cotinine levels. Nevertheless, there was little bias in the distribution of salient demographic features in the nicotine and non-nicotine-use groups and, where there were differences, they did not affect the results. Also, since participants were not seeking nicotine treatment, there should have been no motivation to underreport nicotine use.

In conclusion, this study confirmed past findings of greater naltrexone efficacy for heavy drinking reduction in nicotine users/smokers, which could have significant clinical implications, such as choice of patients to whom naltrexone could/should be offered. While there is no evidence from this trial that naltrexone reduced nicotine use/smoking, or that change in use was a moderator of the naltrexone effect on drinking, the design of the study was not intended to specifically evaluate these issues in AUD individuals seeking smoking-reduction. Since recent emphasis has been placed on identifying specific individual predictors of pharmacotherapeutic response, our data and that of others strongly suggest that nicotine-use/smoking status should be considered as a powerful predictor of naltrexone response in those seeking treatment for AUD.

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Figure 1.
Consort diagram of study design and recruitment and randomization.

Figure 2.

Percent heavy drinking days (means $\pm$ SEM) during the study in non-nicotine and nicotine users treated with naltrexone or placebo. * significant interaction of nicotine-use by medication group ($p = 0.003$). ** significant difference in naltrexone vs. placebo in nicotine users ($p = 0.0001$).

Figure 3.

Drinks per day (means $\pm$ SEM) during the study in non-nicotine and nicotine users treated with naltrexone or placebo. * significant interaction of nicotine-use by medication group ($p = 0.008$). ** significant difference in naltrexone vs. placebo in nicotine users ($p = 0.0001$).

Figure 4. Percent drinking days (means $\pm$ SEM) during the study in non-nicotine and nicotine users treated with naltrexone or placebo. * significant interaction of nicotine-use by medication group ($p = 0.015$). ** significant difference in naltrexone vs. placebo in nicotine users ($p = 0.016$).

Change in Percent Heavy Drinking days and %dCDT

Figure 5.

A) Percent heavy drinking days (means $\pm$ SEM) over the course of the study in nicotine users treated with naltrexone or placebo. **B)** Parallel change in %dCDT, a blood marker of heavy drinking, in the same individuals over the course of the study. Effect sizes (Cohen's d) and significance is provided for the naltrexone vs. placebo contrast at various study weeks for both verbally reported heavy drinking days and %dCDT blood marker of heavy drinking days.

Heavy Drinking and Smoking Across The Study In Smokers (N=52) By Treatment Group

Figure 6.

Means (SEM) of percent heavy drinking days (left axis and stippled color) and cigarettes per smoking day (right axis and solid color) in 52 smokers over the course of the study in those treated with naltrexone or placebo. Naltrexone treatment led to significantly less PHDD than placebo at both week 8 ($p=0.02$) and week 16 ($p=0.02$) of treatment. There was no significant difference between naltrexone or placebo in cigarette use at either week 8 or week 16.

Table 1

Demographic, alcohol use and severity measures.

Characteristic	Total (n=146)				Non-Nicotine Users				Nicotine Users				Statistic ^f	
	No.	%	No.	%	Placebo (n=47)	Naltrexone (n=41)	Placebo (n=26)	Naltrexone (n=32)						
Demographics														
Sex, M	101	69.2	31	66.0	26	63.4	19	73.1	25	78.1	p=0.52			
Married	94	64.4	37	78.7	24	58.5	15	57.7	18	56.3	p=0.10			
Employed	114	78.1	40	85.1	27	65.9	18	69.2	29	90.6	p=0.03			
Education 12 years	24	16.4	7	14.9	2	4.9	5	19.2	10	31.3	p=0.03			
Cocaine Use	19	13.0	6	12.8	3	7.3	5	19.2	5	15.6	p=0.52			
Current antidepressant use	48	32.9	13	27.7	12	29.3	14	53.8	9	28.1	p=0.10			
Family history positive	92	63.0	29	61.7	24	58.5	16	61.5	23	71.9	p=0.69			
Alcohol biomarkers														
GGT>36 IU/L ^a	46	31.5	13	27.7	9	22.0	8	31	16	50.0	p=0.068			
dCDT 1.7%	73	51.0	17	36.2	18	46.2	19	76	19	59.4	p=0.01			
Genotype														
OPRM1 asp40 carrier	73	50.0	23	48.9	22	53.7	12	46	16	50.0	p=0.94			
Demographics														
Age ^b , y	49.3				10.1	49.2	11.3	53.4	10.0	45.6	9.6	47.2	7.0	p=0.01
Alcohol use and severity indicators														
Drinks per drinking day	11.2				4.8	10.1	4.2	10.9	5.4	11.3	4.3	13.2	4.8	p=0.04
Drinks per day	9.6				5.0	8.3	4.5	9.0	4.9	10.1	4.4	12.0	5.5	p=0.01
Drinking Days (%)	85.3				19.3	82.5	20.8	83.9	20.5	88.3	15.2	88.8	18.2	p=0.42
Heavy drinking days (%)	79.7				22.3	77.3	22.5	77.5	23.1	82.5	20.4	83.6	22.6	p=0.50
Days from last drink to randomization	6.9				4.3	7.4	4.3	6.6	4.3	7.1	5.2	6.5	3.8	p=0.80
ADS score ^c	15.4				6.4	14.5	6.4	13.8	6.7	16.4	6.0	17.8	5.7	p=0.04
OCDS score ^d	25.6				8.1	24.4	7.6	23.7	8.8	28.7	7.7	27.2	7.3	p=0.04

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	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Statistics ^g
Lifetime DrInC score ^e	28.8	8.0	26.7	8.9	28.3	7.9	29.6	6.6	p=0.05
^a GGT n=143 (3 people were not measured)									
^b The sample age range was [18,70]									
^c ADS has range of possible values [0,47]									
^d OCDS has range of possible values [0,56]									
^e DrInC has range of possible values [0, 45]									
^f From chi-squared test									
^g From one-way analysis of variance (ANOVA)									

Table 2

Nicotine/Smoking Descriptions

Characteristic	Total		Placebo		Naltrexone		Statistic ^b
	No.	%	No.	%	No.	%	
Current Nicotine User	58	39.7	26	35.6	32	43.8	p=0.31
Cigarette Smokers	52	89.7	21	80.8	31	96.9	p=0.05
Non-Cigarette	6	10.3	5	19.2	1	3.1	

	Mean	SD	Mean	SD	Mean	SD	Statistic ^c
Smokers							
Number of days (out of 30)	26.0	7.5	26.7	6.2	25.6	8.4	p=0.63
Cigarettes per day	16.4	12.1	14.6	10.8	17.6	13.0	p=0.38
Non-Cigarette Nicotine Users							
Number of days (out of 30)	27.3	6.5	26.8	7.2	30.0	-	p=0.70
Non-Smokers^a							
Number of days (out of 30)	0.3	1.4	0.2	1.1	0.4	1.7	p=0.57
Cigarettes per day	0.0	0.2	0.0	0.1	0.1	0.3	p=0.26

^a n=87 (1 person was not measured)^b From a chi-squared test^c From one-way analysis of variance (ANOVA)