Cigarette Smoking Predicts Differential Benefit from Naltrexone for Alcohol Dependence

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Background: Identifying factors that modify responsiveness to pharmacotherapies for alcohol dependence is important for treatment planning. Cigarette smoking predicts more severe alcohol dependence and poorer treatment response in general. Nevertheless, there is limited research on cigarette smoking as a potential predictor of differential response to pharmacological treatment of alcoholism.

Methods: We examined the association between cigarette smoking and drinking outcomes in the COMBINE (Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence) study, a randomized, double-blind placebo-controlled 16-week trial comparing combinations of medications (i.e., acamprosate and naltrexone) and behavioral interventions (i.e., medical management, combined behavioral therapy) in 1383 alcohol-dependent individuals.

Results: Smokers (i.e., more than one half the sample) significantly differed from nonsmokers on several demographic and drinking-related variables at baseline and generally had poorer treatment outcomes than nonsmokers. However, smokers who received naltrexone had better drinking outcomes than smokers who received placebo, whereas alcohol use among nonsmokers did not vary by naltrexone assignment. This pattern of findings occurred independent of whether patients received combined behavioral intervention or medical management and remained after controlling for alcoholism typology and baseline demographic differences. Approximately 9% of smokers quit smoking, and an additional 10% reduced their cigarette intake during treatment. Reductions in smoking did not vary by treatment assignment.

Conclusions: These results suggest that naltrexone might be particularly beneficial for improving alcohol use outcomes in alcohol-dependent smokers.

Key Words: Acamprosate, alcohol dependence, behavioral treatment, cigarette smoking, naltrexone, pharmacotherapy

Current pharmacotherapies for alcohol dependence have small to moderate effects on drinking (1,2). Consequently, there is growing interest in identifying factors that predict optimal responsiveness to these interventions (3). Some identified predictors such as alcoholism typology and *OPRM1* genotype are complex (4–7). Typology is derived from a multidimensional assessment of alcoholism vulnerability, severity, and consequences but might be an impractical treatment matching strategy in clinical settings (8). Likewise, the functional polymorphism of the *OPRM1* genotype might infrequently occur among subgroups of alcoholic subjects (9), and genetic testing might not be readily available to many clinicians. In contrast, cigarette smoking, a robust predictor of alcohol dependence and severity and an important potential moderator, is easy to assess and common among alcohol-dependent individuals (10–11). Moreover, cigarette smoking screening is already a recommended practice for healthcare providers (12) and could identify alcoholic subjects who might preferentially benefit from a particular treatment approach.

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An estimated 45% of alcohol-dependent individuals smoke cigarettes (10). Cigarette smoking and higher nicotine dependence levels at the start of inpatient behavioral treatment for alcoholism are associated with greater urge to drink, an increased risk of relapsing, and a greater number of drinks consumed upon relapse (13–14). However, research on the potential moderating role of cigarette smoking on response to alcohol pharmacotherapies, including naltrexone and acamprosate, is limited.

Naltrexone reduces heavy drinking among hazardous drinkers receiving naltrexone for smoking cessation treatment (15–16). Nevertheless, it remains to be determined whether the effect of naltrexone on alcohol use varies by smoking status among alcohol-dependent individuals seeking to reduce or stop drinking. Results from a secondary analysis of the United States Acamprosate trial found that alcohol-dependent smokers were less likely to achieve alcohol abstinence than alcohol-dependent nonsmokers, irrespective of whether they received acamprosate or placebo (17).

Furthermore, identifying pharmacotherapies that could concurrently reduce both cigarette smoking and heavy drinking in this population would be valuable. Prior research suggests that reductions in cigarette smoking during alcohol treatment might promote better drinking outcomes (18,19). There is little evidence that naltrexone reduces smoking among alcoholic subjects (20,21), and the potential effect of acamprosate on smoking has not been investigated.

The COMBINE (Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence) study—the largest multisite, randomized, placebo-controlled pharmacotherapy trial for alcoholism—tested the efficacy of naltrexone and acamprosate along with two levels of behavioral therapy (22). The main results demonstrated moderate efficacy on drinking outcomes for naltrexone in combination with medical management and no efficacy for acamprosate. The study provides a unique opportunity to examine smoking status as a potential moderator of alcohol treatment effi-

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cacy across several interventions and the potential efficacy of these interventions on smoking. We hypothesized that smokers would exhibit differential benefit from naltrexone relative to placebo for several reasons. Compared with nonsmokers, smokers are more likely to report strong cravings to drink and are at greater risk of relapsing during treatment with behavioral alcohol interventions (13,14). Naltrexone has been shown to attenuate crucial components of alcohol dependence such as cue-induced craving and the amount of alcohol consumed after a lapse (23). Thus, naltrexone might be particularly helpful for reducing drinking and drinking-related problems among alcohol-dependent smokers. We did not anticipate, on the basis of existing literature, that smoking status would moderate acamprosate efficacy (17). Lastly, we explored the potential effect of naltrexone on smoking among this sample of alcohol-dependent smokers who were not attempting to quit smoking.

Methods and Materials

Design and Procedures

In the COMBINE study, participants across 11 sites were randomly assigned to 1 of 9 groups. Eight groups received medical management (MM) with 16 weeks of naltrexone (100 mg/day) or acamprosate (3 g/day), both, and/or both placebos, with or without a combined behavioral intervention (CBI). A ninth group (cell 9) received CBI alone with no pills.

Participants completed research assessments at baseline and Weeks 1, 2, 4, 6, 8, 10, 12, 16 (end of treatment), 26, 52, and 68. Medications were provided under double-blind conditions: 1) naltrexone and matching placebo as 2 pills daily; and 2) acamprosate and matching placebo as 2 pills 3 times daily. Participants assigned to MM attended an initial session and then 8 subsequent sessions over 16 weeks. The MM visits with a study physician/nurse practitioner focused on medication side effects, adverse events, medication adherence, drinking, and self-help group attendance. The CBI incorporated cognitive-behavioral skills training, motivational enhancement techniques, community reinforcement, and encouragement of self-help attendance. Session number (up to 20 over 16 weeks) and content was flexible and determined by the study therapist in collaboration with the participant.

Participants

Thirteen hundred and eighty-three abstinent alcohol-dependent volunteers were enrolled. Key eligibility criteria included: 1) DSM-IV alcohol dependence diagnosis; 2) 4–21 days of alcohol abstinence before randomization; and 3) $\geq$2 heavy drinking days and an average of $\geq$21 (for men) or $\geq$14 (for women) drinks/week during a 30-day consecutive period within 90 days of intake. Individuals were excluded for psychiatric illness requiring pharmacotherapy, medical contraindications, or a substance use disorder other than nicotine or cannabis.

Treatment conditions were equivalent on 76 pretreatment characteristics (22). Participants who received either naltrexone or CBI without naltrexone demonstrated a shorter time to the first heavy drinking day and a greater percentage of days abstinent compared with participants who received MM + placebo.

More detail about the study, including the CONSORT diagram, is available in the original report (22).

Measures

Cigarette Smoking. Smoking status, number of days smoked, and number of cigarettes smoked/day were measured at baseline and Weeks 8 and 16 with the Form-90 Interview (24), a semistructured interview of alcohol and drug use and related behaviors within the past 90 days that integrates the Timeline Followback Interview (25) calendar method to reconstruct daily use, weekly patterns, and atypical episodes of drinking. The following categorical smoking variables were derived from this data: 1) smoking status at baseline and Week 16 (i.e., 0 = nonsmoker, 1 = nondaily smoker, 3 = daily smoker); 2) quit smoking by Week 16 (i.e., 1 = yes, 0 = no); 3) initiated smoking by Week 16 (i.e., 1 = yes, 0 = no); and 4) changes in smoking quantity from baseline to Week 16 (i.e., 0 = decreased, 1 = stayed constant, 2 = increased). Smokers whose intake changed by $\leq$5 cigarettes were considered to have stayed constant, consistent with prior research on smoking transitions in the Project MATCH (Matching Alcoholism Treatment to Client Heterogeneity) trial (26).

Frequency and Quantity of Drinking. Daily drinking data were measured at baseline and at Weeks 1, 2, 4, 6, 8, 10, 12, and 16 with the Timeline Followback Interview (25). In this analysis we examined percentage of heavy drinking days (PHDD), percentage of days abstinent from drinking (PDA), and number of drinks/drinking day (DPDD) from baseline through the first 8 weeks of treatment (i.e., Week 8) and from Week 8 through the end of treatment (i.e., Week 16) to reflect the assessment periods available for the smoking measures. We also evaluated time to first drinking relapse during the entire 16-week treatment period.

Drinking Consequences. The 50-item Drinker Inventory of Consequences questionnaire was used to assess adverse consequences of drinking at baseline and Weeks 8 and 16. For this investigation, we used the total drinking consequences score (27).

Clinical Outcome. A secondary dichotomous drinking outcome variable at Week 16 was derived in which a good clinical outcome was defined as abstinence or moderate drinking without drinking-related problems. Participants who did not meet this criterion were classified as having a bad clinical outcome (i.e., 1 = good clinical outcome, 0 = bad clinical outcome). Moderate drinking was defined as $\leq$11 (women) or $\leq$14 (men) drinks/week, with $\leq$2 days of consuming 3 drinks (women) or 4 drinks (men). Drinking problems were defined as endorsing $\geq$3 items on the Drinker Inventory of Consequences. This variable was used in the main COMBINE study (22).

Alcohol Dependence. The Structured Clinical Interview for DSM-IV Axis I Disorders (28) assessed history of alcohol abuse, dependence/abuse, and age of onset at baseline. Alcohol dependence severity was also measured with the Alcohol Dependence Scale (29), a self-report scale of alcohol withdrawal symptoms, tolerance, impaired control over drinking, compulsion to drink, and drink-seeking behavior yielding a total severity score.

Demographic Data. A baseline questionnaire, designed for this study, assessed marital status, employment status, education history, age, gender, race, and ethnicity.

Alcoholism Typology. Participants were categorized as either Type A or Type B alcoholic subjects on the basis of prior COMBINE study analyses (5). In that analysis, typology coding was based on composite variables derived from baseline assessments for: 1) standard drinks/drinking day; 2) drinking for withdrawal relief; 3) alcohol-related medical conditions; 4) physical, social, and interpersonal drinking consequences; and 5) onset of alcoholism, family history risk, and comorbid psychopathology. Compared with Type A alcoholic subjects in the COMBINE study, Type B subjects were younger, less educated, more likely to be single and male, and reported an earlier onset, more severe dependence, a greater family history risk, and more childhood risk factors. Type A subjects had better drinking outcomes with naltrexone than placebo (5). Type B