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# Tobacco use during a clinical trial of mecamylamine for alcohol dependence: Medication effects on smoking and associations with reductions in drinking

Walter Roberts[a,*], Elizabeth Ralevski[a,b,c], Terril L. Verplaetse[a], Sherry A. McKee[a], Ismene L. Petrakis[a,b,c]

[a] Yale University School of Medicine, Department of Psychiatry, 300 George Street, New Haven, CT 06511, United States of America
[b] VA Connecticut Healthcare System, 950 Campbell Ave, West Haven, CT 06516, United States of America
[c] VISN I Mental Illness Research Education Clinical Center (MIRECC), 950 Campbell Ave, West Haven, CT 06516, United States of America

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ABSTRACT

Mecamylamine is a nicotinic acetylcholine receptor (nAChR) antagonist that was recently used in a clinical trial to treat alcohol use disorder (AUD) in both smokers and non-smokers. The current manuscript reports a re-analysis of data from this clinical trial in which we examine changes in smoking that occurred over the course of the trial. We focused on examining the effects of mecamylamine on smoking and the association between reductions in alcohol use and smoking. Participants were the subgroup of smokers who participated in the clinical trial of mecamylamine (10 mg/day) to treat their AUD ($n$ = 76). Smoking was assessed prior to randomization and tracked throughout the course of the 12-week medication treatment phase. Participants were categorized as treatment responders or non-responders based on their changes in drinking over the course of the clinical trial. Participants showed a reduction in smoking over the course of the clinical trial, but there were no significant differences in smoking outcomes between the mecamylamine and placebo groups. Among moderate/high dependence smokers, those who successfully reduced drinking showed a significant reduction in cigarettes smoked per day over the clinical trial. Mecamylamine had no detectable effect on smoking outcomes. Reductions in alcohol use predicted more favorable smoking outcomes among moderate/high tobacco dependence smokers irrespective of medication condition. The reduction in smoking among patients who decreased their alcohol use responders highlights an opportunity for patients being treated for AUD to reduce their smoking.

## 1. Introduction

People receiving treatment for AUD smoke at rates higher than the general population (Baca & Yahne, 2009). There is a well-documented relationship between alcohol and tobacco: overlap in the neurobiological mechanisms of action of alcohol and nicotine (Dani & Harris, 2005; Tizabi, Copeland, Louis, & Taylor, 2002) may promote co-use of these drugs. Specifically, nicotinic acetylcholine receptors (nAChR) are involved in pleasurable reinforcing effects of both tobacco and alcohol (Soderpalm, Ericson, Olausson, Blomqvist, & Engel, 2000). This association between smoking and problem alcohol use is further supported by epidemiological evidence showing that smokers are at higher risk for heavy drinking compared to nonsmokers (McKee, Falba, O'Malley, Sindelar, & O'Connor, 2007). The high degree of overlap between these two commonly abused drugs has led to interest in the interaction of smoking and alcohol drinking during treatment for either condition. There are several recent examples of medications indicated for smoking cessation showing efficacy for drinking reduction and vice versa (Litten et al., 2013; O'Malley et al., 2006, 2018). Given the close relationship between drinking and smoking, it is important to understand how treatment-related changes in the primary substance-of-abuse can alter patterns of use of the co-abused drug. For example, researchers have examined how reductions in smoking related to treatment outcomes in a clinical trial of varenicline for AUD, showing that reductions in smoking predict more favorable drinking outcomes among those receiving varenicline (Falk, Castle, Ryan, Fertig, & Litten, 2015; O'Malley et al., 2018).

Mecamylamine is a nAChR antagonist that has been investigated as a smoking cessation medication. By blocking the pharmacologic effects of nicotine, mecamylamine is hypothesized to reduce rates of cigarette use via an extinction learning mechanism (Rose, Westman, & Behm, 1996). In a pair of randomized clinical trials, Rose et al. (1994, 1996) found that mecamylamine combined with nicotine replacement therapy (NRT) improved abstinence rates among smokers attempting to quit.

* Corresponding author at: 2 Church St. South, Suite 109, Yale University School of Medicine, New Haven, CT 06519, United States of America.
*E-mail address:* walter.roberts@yale.edu (W. Roberts).

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These results were later replicated in a Phase 3 clinical trial (Rose, 2006). However, a subsequent large, multi-center, randomized controlled trial found no effect of mecamylamine on smoking cessation rates in a sample of 540 smokers (Glover et al., 2007). No prior research has reported on the effects of mecamylamine on smoking behavior in heavy drinking smokers. Considering the role of nAChRs in both tobacco and alcohol use (Tizabi et al., 2002), mecamylamine may be more effective at reducing tobacco use among smokers who also engage in heavy alcohol use. Further, given the close association between tobacco and alcohol use, reductions in alcohol use may lead to changes in tobacco use. Because many heavy drinkers also smoke tobacco (Grant et al., 2015), there is interest in understanding whether treatment-related reductions in drinking are associated with changes in smoking. Reductions in drinking during treatment for AUD may be associated with reductions or increases in smoking. Laboratory research indicates that alcohol cue exposure (Gulliver et al., 1995) and alcohol administration can prime smoking behavior (Kahler et al., 2014), suggesting that reduced tobacco use will naturally follow reductions in drinking. On the other hand, participants may increase their smoking to help cope with the demands of reduced drinking.

Our group recently conducted a randomized, placebo-controlled clinical trial testing mecamylamine as a treatment for alcohol use among smokers and non-smokers with alcohol dependence (Petrakis et al., 2017). Participants were randomized to receive placebo or 10 mg/day mecamylamine for a 12-week treatment period. The goal of this reanalysis was to examine changes in smoking that occurred over the course of this clinical trial. The primary outcome variable for this reanalysis was cigarettes per day, and secondary smoking outcomes included tobacco craving and withdrawal symptoms. Consistent with the primary endpoint from the clinical trial (i.e., alcohol use during the final month of treatment), we examined smoking outcomes during the final month of treatment. We also examined changes in smoking that occurred early in the medication treatment period since prior research has found that mecamylamine causes an increase in smoking immediately following medication initiation (Rose et al., 1996). As such, we examined changes in smoking that occurred during the first week of the medication phase. We hypothesized that participants receiving active medication would show an increase in smoking from baseline.

Participants were further classified based on selected pre- and post-medication-treatment characteristics. First, participants were classified according to their level of tobacco dependence. The parent project included participants with variable smoking habits, ranging from infrequent nondaily smokers to daily smokers. Tobacco dependence severity is a robust predictor of smoking cessation treatment outcome (Bolt et al., 2009; Fagerström, Russ, Yu, Yunis, & Foulds, 2012; Baker et al., 2007) and it moderated treatment outcomes in previous smoking cessation trials (Fucito et al., 2011; Fucito, Latimer, Salovey, & Toll, 2010; McGeary et al., 2012). As such, it is important to account for pretreatment smoking habits when examining changes that occur over the course of treatment. Second, to examine whether reductions in drinking were associated with changes in smoking, we classified participants as treatment responders or non-responders according to their alcohol use treatment outcomes. A recent clinical trial of varenicline for AUD in smokers identified a group of patients receiving active medication who showed a reduction in cigarette use as they stopped drinking (O'Malley et al., 2018). This finding suggests a link between reductions in alcohol and tobacco use that may occur in the context of medication treatment targeting the cholinergic system.

## 2. Method

### 2.1. Participants

Participants in this study were recruited from the community through advertisements. After signing informed consent, volunteers were evaluated and included in the clinical trial if they were between the ages of 18–70 years, met *DSM-IV* criteria for current alcohol dependence, determined by the structured clinical interview for *DSM-IV* (First, Spitzer, Gibbon, & Williams, 1995) and reported on average at least 21/14 drinks per week for men/women and at least two heavy drinking days per week (defined as ≥5/4 for men/women) during a consecutive 30-day period within the 90 days prior to baseline evaluation. Participants were screened for medical problems by interview and physical examination, including EKG. Females were not pregnant and were using adequate birth control. Exclusion criteria included dependence on illicit drugs (aside from marijuana), unstable psychotic symptoms or current serious psychiatric symptoms, such as suicidal or homicidal ideation, or medical problems that would contraindicate use of mecamylamine. Volunteers who were currently taking psychiatric medication, including those thought to influence alcohol consumption (e.g., naltrexone), did not participate. Randomization to medication condition was stratified by smoking status: participants who endorsed any cigarette use over 90 days preceding intake were classified as smokers. The current reanalysis of these data focused on cigarette use, so only data from participants who endorsed smoking were included ($n$ = 76). This sample included three participants who were randomized as nonsmokers in the parent clinical trial but later endorsed some cigarette use.

### 2.2. Medication conditions

Participants completed a baseline assessment during intake. Eligible volunteers were randomized to one of two groups for a 13-week medication treatment period, including 12 weeks of treatment and 1 week of taper. Participants were randomly assigned to receive mecamylamine (10 mg/day; $n$ = 41) or placebo ($n$ = 35), and both participants and clinical staff were blind to participants' medication condition. During the first two weeks, mecamylamine was titrated upward, starting at 2.5 mg/day and then increased over two weeks to 10 mg per day in a divided dose (5 mg twice daily). Recognizing the high rate of adverse side effects (e.g., constipation) associated with the 10 mg mecamylamine dose, participants were allowed dose reductions as needed. All medications were dispensed in blister packs. During week 13, medication was tapered down over 7 days. All participants ($n$ = 76) also received medical management therapy (Carroll, Nich, Ball, McCance, & Rounsavile, 1998; O'Malley et al., 2018) conducted by trained research personnel. Medical management therapy benefits patients by providing them with non-specific common factors of a psychotherapeutic relationship (e.g., support, positive regard, empathy) and ongoing assessment and management of their substance use. Participants were motivated to reduce or stop drinking alcohol, but smoking cessation was not a goal of the study. Medication compliance was assessed at each visit.

### 2.3. Measures

#### 2.3.1. Tobacco use outcomes

Daily cigarette use was assessed using the Substance Abuse Calendar, which is based on the timeline follow-back interview. The Substance Abuse Calendar was administered by highly trained research personnel at each weekly visit throughout the 12-week treatment period. Self-reported smoking was biologically verified by measuring breath carbon monoxide and urine cotinine levels. Baseline (past 90-day) substance use was assessed at intake. Those who smoked every day over the past 90 days were classified as daily smokers ($n$ = 40), and those who reported any days without cigarette use were categorized as nondaily smokers ($n$ = 32). Tobacco use was biologically confirmed by urine cotinine levels during each clinic visit. Craving was assessed using the Questionnaire of Smoking Urges QSU; Visual Analog Scale (VAS) 1–100 (Tiffany & Drobes, 1991). Tobacco craving was assessed during the baseline assessment and again at 1, 3, 6, and 12 weeks following randomization and medication initiation. Dependence severity was