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Mecamylamine treatment for alcohol dependence: a randomized controlled trial

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ABSTRACT

Background and aims The nicotinic acetylcholine receptor antagonist, mecamylamine, is a potential novel pharmacotherapy for alcohol use disorder. The aims were to compare alcohol consumption between mecamylamine and placebo and test if smoking status modified treatment effects. **Design** Out-patient, randomized, double-blind clinical trial for 12 weeks of treatment with mecamylamine (10 mg) (n = 65) versus placebo (n = 63). **Setting** Connecticut, USA. **Participants** Individuals had current alcohol dependence (n = 128), had an average age of 48.5 [standard deviation (SD) = 9.4], 110 (85.9%) were men, and included 74 smokers (57.8%) and 54 non-smokers (42.2%). Participants were randomized to mecamylamine 10 mg per day or placebo. All subjects also received medical management therapy administered by trained research personnel. **Measurements** Primary outcome was percentage of heavy drinking days during the last month of treatment; other outcomes included drinking days, drinks per drinking days, alcohol craving, smoking, symptoms of nicotine withdrawal and side effects. **Findings** There were no significant differences in the percentage of heavy drinking days at 3 months between the mecamylamine (mean = 18.4, SD = 29.0) and placebo treatment groups (mean = 20.4, SD = 29.2) [$F_{1,\ 100}$ = 1.3, P = 0.25; effect size d = 0.07; mean difference = 2.06, 95% confidence interval (CI) = −8.96 to 13.08]. There were no significant differences in percentage of drinking days or in drinks per drinking day at month 3 between the mecamylamine and placebo groups; there were no significant interactions. **Conclusions** Mecamylamine 10 mg per day did not reduce alcohol consumption significantly in treatment-seeking smokers and non-smokers with alcohol use disorder.

Keywords Alcohol, clinical trial, mecamylamine, nicotinic receptor, smoking.

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INTRODUCTION

The common medications used to treat alcohol use disorders (AUD) are limited by modest efficacy and low utilization; [1,2] therefore, the development of new medications to treat AUD is a high priority. Antagonists of nicotinic acetylcholine receptors (nAChR) may play a role in the treatment of AUD [3,4]. Pre-clinical studies implicate nAChRs in the behavioral effects of alcohol [4]. In humans, AUDs and smoking are highly comorbid [5] and craving for one substance primes craving for the other [6]. Further, perhaps through the nAChR, there is evidence to suggest there is a common genetic underpinning for both nicotine dependence and AUDs [7,8]. Recently, the partial nicotinic agonist, varenicline, which is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a treatment for smoking cessation, has been examined as a pharmacological support for AUD [9].

Mecamylamine hydrochloride (Inversine®) is a non-selective, non-competitive, antagonist for both peripheral and central nAChRs [10]. Systemically administered mecamylamine reduces alcohol consumption in rats and mice and injection of mecamylamine into the ventral tegmental area (VTA) reduces voluntary ethanol preference and consumption in ethanol-preferring rats (reviewed in [11]). Human laboratory studies have found that mecamylamine reduces the stimulant effects of ethanol [12]. It also attenuates ethanol craving in social drinkers [13] and in heavy drinkers [14]. In the latter study subjects

reported a significant decrease in craving, but it was not accompanied by a decrease in self-administration. One study in smokers [15] failed to find that mecamylamine reduced the rewarding effects of ethanol [blood alcohol concentration (BAC) 0.03 g/dl].

Mecamylamine also showed promise as a treatment for other conditions, including nicotine dependence [16,17], Tourette's syndrome [18] and depression (reviewed in [19]). For smoking cessation, mecamylamine was most effective when paired with nicotine replacement [17]. There is some evidence that the antidepressant effects of mecamylamine [20] were moderated by smoking status, i.e. non-smokers benefited the most from active treatment. In a small study of individuals with AUD and comorbid depression, mecamylamine augmentation of antidepressant was associated with reduced drinking among non-smokers [21].

We hypothesized that acute antagonism of nAChRs with mecamylamine would be a treatment for AUD and would be effective in reducing ethanol consumption in alcohol-dependent individuals and that this effect would be moderated by smoking status. The aims were to compare mecamylamine with placebo on the percentage of heavy drinking days in alcohol-dependent individuals; secondary aims included other measures of drinking, consequences of drinking and adverse events, including smoking and nicotine withdrawal among the smokers, as mecamylamine is a nicotinic antagonist. In this study, we hypothesized that outcomes would be moderated by smoking and that non-smokers would benefit the most from this medication.

METHODS

Design

The study was approved by the Human Subjects Subcommittees of the VA Connecticut Healthcare System (West Haven, CT) and the Yale Human Investigations Committee (New Haven, CT). This study was a 12-week, randomized, placebo-controlled out-patient trial in alcohol-dependent individuals. Both smokers and non-smokers were recruited in order to address the primary aims. Sample size was determined based on the outcome variables for drinking and smoking in our pilot data. The calculated effect sizes in our pilot data were medium to large by Cohen's definition [22] ($f = 0.37$ to $f = 0.4$). We based our power calculations conservatively on a smaller medium effect size ($f = 0.25$) for the primary outcome of percentage of heavy drinking days evaluated at 3 months. We estimated that we needed to have 64 mecamylamine (MEC) and 64 placebo (PLA) subjects to achieve 80% power to detect such an effect size for the primary and the secondary aims, assuming alpha = 0.05.

Participants

More than 400 individuals ($n = 407$) responded to advertisements. After signing informed consent ($n = 136$) potential participants, both male and female, were evaluated and included if they were between the ages of 18 and 70 years, and who met DSM-IV criteria for current alcohol dependence (AD), determined by structured clinical interview [23], and who reported on average at least 21 drinks per men or 14 drinks for women per week and at least 2 heavy drinking days (defined as ≥ 5 for men or ≥ 4 for women) during a consecutive 30-day period within the 90 days prior to baseline evaluation. Subjects were medically healthy by history, physical and laboratory examination, including electrocardiogram (ECG). Females were not pregnant and were using adequate birth control. Exclusion criteria included dependence on substances other than nicotine or marijuana, unstable psychotic symptoms or serious current psychiatric symptoms, such as suicidal or homicidal ideation, or medical problems that would contraindicate the use of mecamylamine. Subjects could not be taking medications thought to influence alcohol consumption (such as naltrexone, disulfiram, acamprosate or anticonvulsants such as topiramate or gabapentin) or other psychiatric medications.

Treatments

Participants were randomized to mecamylamine 10 mg per day or placebo in a double-blind fashion. All subjects also received medical management therapy [24] administered by trained research personnel. The focus was on alcohol use outcomes; while data were collected on smoking, subjects were not counseled to quit smoking.

Procedures

Following completion of baseline assessments, 136 subjects were randomized to one of two groups for 13 weeks, 12 weeks of treatment and 1 week of taper. Randomization was conducted by the pharmacist in blocks of size 4 with a 1 : 1 ratio between treatment conditions (mecamylamine or placebo). As both smoking status and gender were hypothesized to influence alcohol use outcomes, stratification by smoking status and gender was used to ensure equal representation of these factors in both medication groups. Only the pharmacist had access to the allocation sequence. Eight participants did not provide any post-baseline drinking data, so the analyzable sample was $n = 128$.

Mecamylamine study medication was titrated upwards during the first 2 weeks, starting at 2.5 mg per day, and then increased during the 2 weeks to 10 mg per day in divided doses (5 mg twice daily), and was dispensed in blister packs. During week 13, medication was tapered

downwards over 7 days. Medication compliance was monitored at every visit.

Regarding the measures used, all subjects completed an assessment of baseline demographic characteristics: the Structured Clinical Interview for DSM Diagnosis (SCID)-I; Alcohol Dependence Severity (ADS) [25]; the Drinker Inventory of Consequences (DrInC) scale to assess severity of dependence and consequences [26] and time-line follow-back (TLFB) [27] to assess alcohol use; and the Fagerström Test for Nicotine Dependence (FTND) to measure nicotine dependence [28].

The Substance Abuse Calendar, based on the TLFB interview [27], was administered by highly trained research personnel at each weekly visit throughout the 84-day treatment period as well as for the 90-day period prior to randomization. Biomarkers of alcohol consumption included serum gamma-glutamyl transferase (GGT) and carbohydrate-deficient transferrin (CDT), collected four times during the study (at baseline and weeks 4, 8 and 12). Craving was assessed weekly using the Obsessive Compulsive Drinking Scale (OCDS) [29]. Information on nicotine withdrawal symptoms was collected using the Minnesota Withdrawal Scale, and smoking urges were assessed using the Brief Questionnaire of Smoking Urges (QSU). Adverse events were evaluated by the research staff weekly using a modified version of the Systematic Assessment for Treatment Emergent Events (SAFTEE) [30]. Symptoms known to be associated with treatment with mecamylamine were screened for specifically on a weekly basis. Symptoms were then clustered into the following categories: gastrointestinal (GI), central nervous system (CNS), neurological (NE), musculoskeletal (MS), skin, ophthalmological (OPTH), cardiopulmonary (CAR) and genito-urinary (GU).

The primary outcome measure was the percentage of heavy drinking days at 3 months calculated based on all available data from the TLFB method. Secondary outcomes included percentage of drinking days and drinks per drinking day at 3 months, results from biological markers (GGT and CDT), craving for alcohol [Obsessive Compulsive Drinking Scale (OCDS)] and drinking consequences [26]. As mecamylamine is a nicotinic antagonist, smoking outcomes including the number of cigarettes per day (confirmed with cotinine levels), craving for cigarettes (based on the Tiffany scale [31]) and a measure of nicotine withdrawal [32] were assessed. Adverse medication effects were also collected.

Statistical analysis

Descriptive statistics were used to summarize the data on 128 individuals who were included in the analysis. All continuous variables were examined for adherence to the normal distribution using normal probability plots and Kolmogorov–Smirnov tests. Alcohol use outcome data were not skewed significantly and no data transformations were performed. Baseline demographic characteristics for the medication groups (MEC versus PLA) were compared using χ^2 tests for categorical variables, and using analysis of variance (ANOVA) for continuous variables. The analyses were performed on the modified intent-to-treat sample (i.e. individuals who had some post-baseline outcome data). For the primary analysis of percentage of heavy drinking days at 3 months, we used ANOVA that included medication (MEC versus PLA), smoking status (smokers versus non-smokers), gender and the corresponding baseline drinking measure (percentage of heavy drinking days at baseline) as factors in the model. An identical analysis was performed for percentage of drinking days (controlling for percentage of drinking days at baseline) and drinks per drinking day (controlling for drinks per drinking day at baseline). For the analysis of biomarkers, OCDS and smoking outcomes we used linear mixed models (LMMs). LMM were also fitted to the drinking outcomes over time in secondary analyses. We selected the appropriate correlation structure for each dependent variable based on the Schwartz Bayesian information criterion (BIC) (smaller is better). Medication group (MEC versus PLA) was entered as a between-subject factor and time was used as a within-subject factor; χ^2 tests were used for all categorical data. All analyses were performed using SPSS version 21.0. Statistical testing for the primary outcome was at a two-tailed alpha level of 0.05. Bonferroni adjustments were performed for the secondary analyses resulting in the following significance cut-offs: secondary drinking outcomes ($\alpha = 0.016$), craving ($\alpha = 0.016$), laboratory markers ($\alpha = 0.02$), drinking consequences ($\alpha = 0.01$) and smoking urges ($\alpha = 0.01$).

RESULTS

Characteristics of the sample

One hundred and twenty-eight (128) individuals were included in the analysis. They provided post-baseline drinking data with approximately an equal number of participants assigned to MEC ($n = 65$) and PLA ($n = 63$) groups (see Fig. 1). The first participant was recruited in September 2008 and the last follow-up was in August 2014. The follow-up rate for the primary outcome was 79.6% (102 participants), and there was no significant difference in follow-up rate between the medication groups (MEC = 83.1%; PLA = 76.2%). The treatment groups did not differ on the average number of days in the study [MEC mean = 77.38, standard deviation (SD) = 15.78; PLA mean = 74.13, SD = 21.67) ($F_{1,\ 126} = 0.95$, $P = 0.33$]. The average age of the sample was 48.5 (SD = 9.4), with no differences in age between those assigned to MEC or PLA (see Table 1). In this study, the

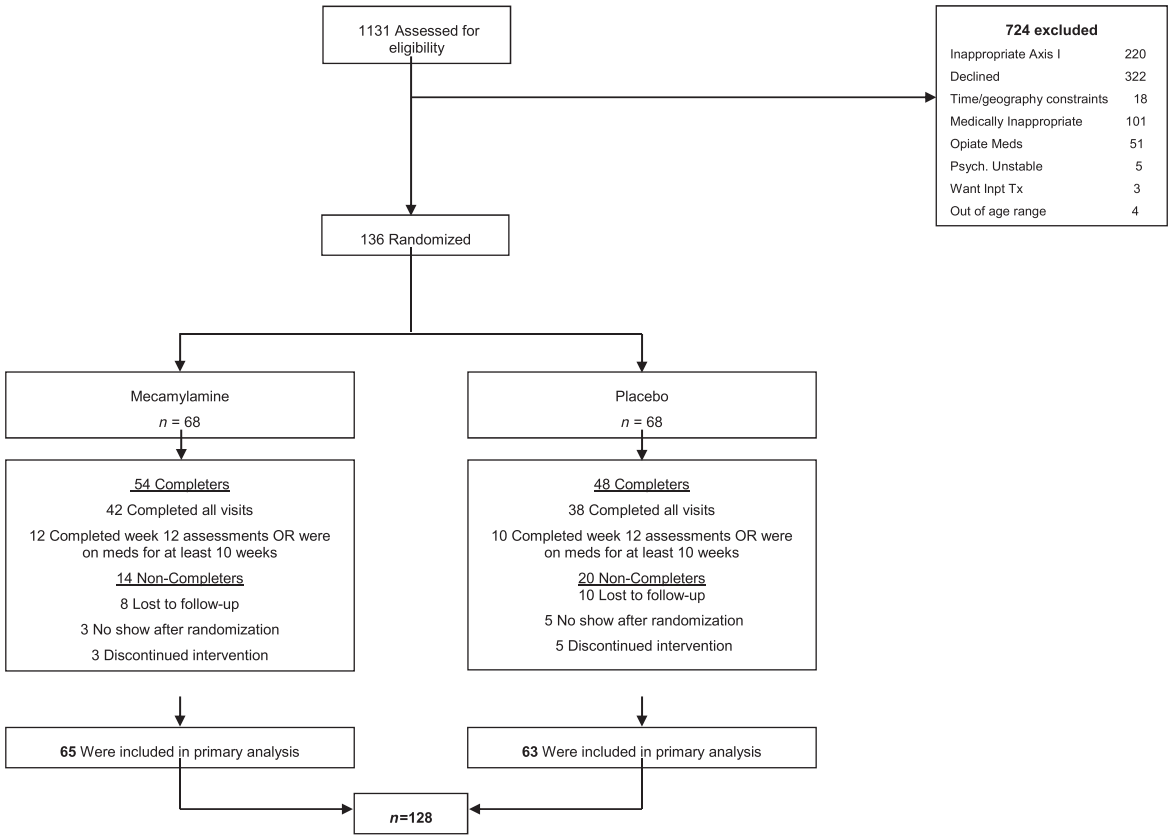

Figure 1 Consolidated Standards of Reporting Trials (CONSORT)

highest percentage were male (n = 110; 85.9%), single (43.6%) and African American (50%), with no differences between the groups based on treatment assignment. A majority of participants (n = 74, 57.8%) were smokers (non-smokers: n = 54; 42.2%) and they were randomized to the treatment groups as follows: MEC n = 39, PLA n = 35 and based on gender: female smokers n = 12, female non-smokers n = 8. On average, the smokers smoked 12.4 cigarettes per day (SD = 7.9) with no significant baseline differences between those assigned to MEC or PLA.

Adherence

The target dose of medication was 10 mg per day, with a starting dose of 2.5 mg and a titration leading to 10 mg per day by week 3. The average maximum MEC dose in this study was 9.6 mg (SD = 1.3). Compliance rates between MEC and PLA were not statistically different. Compliance with MEC was high: 63.1% of subjects were compliant with MEC for 12 weeks compared to 61.9% of subjects on PLA (χ^2_1 = 0.19, P = 0.89), and 72.3% were compliant with MEC for at least 10 weeks compared to 73.0% on PLA (χ^2_1 = 0.003, P = 0.92). The majority of subjects (92.3%) reached the maximum dose of 10 mg and more than half (53.8%) were on the highest dose for all 10 weeks (Fig. 2).

Drinking outcomes

Primary drinking outcome

Analysis of the percentage of heavy drinking days (%HDD) at month 3 showed no significant differences between the mecamylamine (mean = 18.4, SD = 29.0) and placebo treatment groups (mean = 20.4, SD = 29.2) ($F_{1,\ 100}$ = 1.3, P = 0.25; effect size d = 0.07; mean difference = 2.06, 95% confidence interval = −8.96 to 13.08). There were no differences in %HDD by smoking status (smokers versus non-smokers $F_{1,\ 100}$ = 0.60, P = 0.43) or gender ($F_{1,\ 100}$ = 0.69, P = 0.40). Baseline %HDD was also not significant after Bonferroni adjustment ($F_{1,\ 100}$ = 4.10, P = 0.04) (Table 2). To evaluate for potential moderating effects of smoking and gender, we considered interactions of these factors with treatment but those were dropped, as they were not significant.

Secondary drinking outcomes

Analysis of percentage of drinking days (%DD) at month 3 showed no significant differences between the mecamylamine (mean = 29.2, SD = 35.3) and placebo (mean = 31.2, SD = 35.0) ($F_{1,\ 100}$ = 0.00, P = 0.98); effect size d = 0.05; mean difference = 1.95, 95% confidence interval = −11.34 to 15.26). There were no differences

Table 1 Socio-demographics.

Variables	*Placebo* *n = 63*	*Mecamylamine* *n = 65*
Demographic characteristics		
	Mean (SD)	*Mean (SD)*
Age (years)	49.27 (9.59)	47.72 (9.35)
	n (%)	*n* (%)
Gender		
Male	55 (87.3)	55 (84.6)
Female	8 (12.7)	10 (15.4)
Ethnicity		
Caucasian	33 (52.4)	29 (44.6)
African American	29 (46.0)	35 (53.8)
Hispanic	1 (1.6)	0 (0.0)
Native American	0 (0.0)	1 (1.5)
Marital status		
Single	26 (41.3)	29 (44.6)
Married/cohabitating/partner	13 (20.6)	16 (24.6)
Separated/divorced/widowed	24 (38.1)	18 (27.7)
Drinking, smoking, and mood characteristics (past 90 days)		
	Mean (SD)	*Mean (SD)*
% Heavy drinking days	69.54 (27.79)	60.88 (28.44)
% Drinking days	76.61 (24.08)	69.11 (26.54)
Drinks per drinking day	13.58 (7.83)	13.65 (8.72)
Total ADS	12.44 (5.87)	13.75 (5.64)
HAM-D total	4.70 (3.67)	4.67 (3.46)
Smokers only (n = 74)		
Cigarettes per day	12.03 (8.37)	10.44 (9.01)
FTND	4.40 (2.14)	4.53 (2.17)

For all variables $n \neq 128$ there are some missing values. SD = standard deviation; ADS = alcohol dependence severity; HAM-D = Hamilton Depression Rating Scale; FTND = Fagerström Test for Nicotine Dependence.

in %DD by smoking status (smokers versus non-smokers $F_{1,\ 100} = 1.1$, $P = 0.29$) or gender ($F_{1,\ 100} = 0.08$, $P = 0.77$). Baseline %DD was also not significant after Bonferroni adjustment ($F_{1,\ 100} = 4.58$, $P = 0.03$). There were no significant interactions.

Analysis of drinks per drinking day (DDD) at month 3 showed no significant differences between the mecamylamine (mean = 4.7, SD = 5.0) and placebo groups (mean = 5.1, SD = 5.7) ($F_{1,\ 100} = 0.01$, $P = 0.91$); effect size $d = 0.07$; mean difference = 0.42, 95% confidence interval = 1.03 to −1.62). There were no differences in DDD by smoking status (smokers versus non-smokers $F_{1,\ 100} = 2.1$, $P = 0.14$), gender ($F_{1,\ 100} = 0.06$, $P = 0.80$) or baseline DDD ($F_{1,\ 100} = 0.00$, $P = 0.94$). There were no significant interactions.

Laboratory markers of alcohol use

Analysis of GGT data (log-transformed) indicated a significant effect of time ($F_{3,140.3} = 7.98$, $P = 0.0001$) and a non-significant (after Bonferroni adjustment) three-way interaction (time × medication × smoking status ($F_{3,\ 140.3} = 2.99$, $P = 0.03$). This finding is not consistent with the self-reported alcohol use or with the CDT analysis, and is of questionable clinical relevance. For a subset of participants ($n = 83$), samples were collected for CDT analysis. The model for the CDT analysis was identical to the model used for GGT. There were no significant main effects for time, medication or smoking status and no significant interaction effects.

Alcohol craving

Participants reported a decrease in their craving scores, based on total OCDS scores, as well as the obsession and compulsion subscales (for all scales $P < 0.001$). However, there were no significant medication effects, smoking effects, gender and interaction effects.

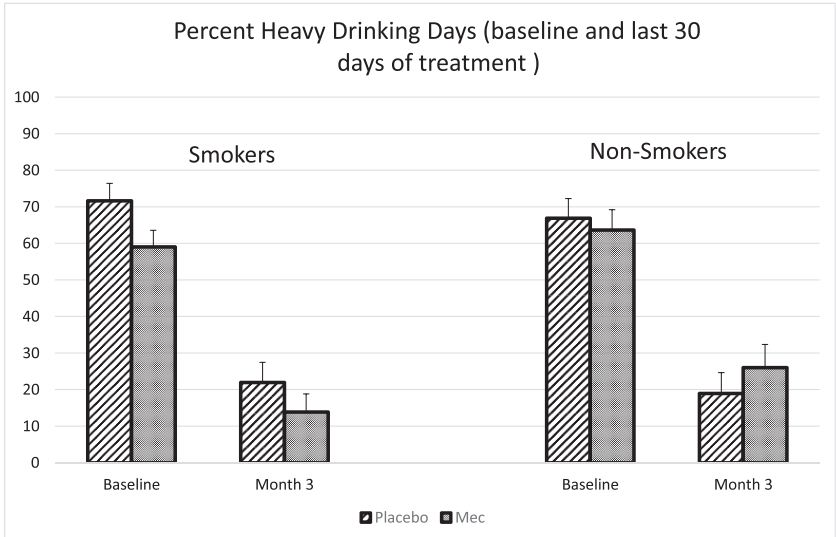

Figure 2 Percentage of heavy drinking days (baseline and last 30 days of treatment). *Baseline = 90 days before start of treatment

Table 2 Outcomes.

Variables	*Placebo n = 63*	*Mecamylamine n = 65*	*Statistics*		
Primary drinking outcomes					
% Heavy drinking days (%HDD)				*F*	*P*
	Mean (SD)	*Mean (SD)*	Medication	0.138	0.711
Before treatment (90 days)	69.54 (27.79)	60.88 (28.44)	Smoking	0.657	0.420
			Gender	0.750	0.388
Last 30 days	20.49 (29.28)	18.43 (29.04)	%HDD baseline	4.579	0.035
% Number of drinking days (%#DD)				*F*	*P*
	Mean (SD)	*Mean (SD)*	Medication	0.085	0.771
Before treatment (90 days)	76.61 (24.08)	69.11 (26.54)	Smoking	2.507	0.116
			Gender	0.165	0.686
Last 30 days	31.23 (35.03)	29.27 (35.32)	%# DD baseline	6.904	0.010
Drinks per drinking day (DDD)				*F*	*P*
	Mean (SD)	*Mean (SD)*	Medication	0.170	0.681
Before treatment (90 days)	13.58 (7.83)	13.65 (8.72)	Smoking	2.321	0.131
			Gender	0.005	0.943
Last 30 days	5.15 (5.71)	4.72 (5.08)	DDD baseline	0.179	0.673
Additional drinking outcomes					
OCDS total				*F*	*P*
	Mean (SD)	*Mean (SD)*	Medication	0.506	0.478
Baseline	17.00 (8.73)	18.90 (9.40)	Smoking	1.474	0.227
Week 12	8.03 (7.28)	8.69 (7.57)	Time	27.11	0.000
			Medication × smoking	0.492	0.484
			Medication × time	1.829	0.042
			Smoking × time	0.909	0.538
			Medication × smoking × time	0.230	0.997
Smokers only (n = 74)					
Number of cigarettes per day				*F*	*P*
	Mean (SD)	*Mean (SD)*	Medication	1.873	0.175
Baseline	12.03 (8.37)	10.44 (9.01)	Time	3.650	0.000
Week 12	10.68 (7.05)	8.19 (7.68)	Medication × time	0.536	0.876

SD = standard deviation; OCDS = Obsessive Compulsive Drinking Scale.

Drinking consequences

Drinking consequences were evaluated using the five categories in the DrInC scale [26]. Treatment decreased responses significantly in all five categories (for all subscales $P < 0.0001$). There were no other significant findings in any of the five categories.

Smoking outcomes

Because mecamylamine is a nicotine antagonist, we evaluated smoking and nicotine withdrawal. Smoking decreased significantly with treatment for smokers as a group ($F_{11,\ 155.1} = 3.65$, $P = 0.0001$), with no significant differences between treatment groups and no significant interactions. Analysis of smoking urges revealed no other significant decrease in urges to smoke in all four categories (*P*-values > 0.05). There was a significant decline in nicotine withdrawal symptoms over time ($F_{4,\ 105.4} = 26.1$, $P = 0.0001$) and no significant interactions.

Adverse effects

Six participants dropped out of the study due to medication side effects: urinary incontinence (1), lightheadedness (2), constipation and abdominal side effects (2) and sore throat (1); all were assigned to the active arm of the study. Adverse effects were analyzed, first by system and secondly examining the most frequently reported side effects with MEC. There were no differences between medication groups in the rate of reported adverse events by system ($P > 0.29$). GI symptoms (MEC = 85.3%, PLA = 83.8%) and CNS symptoms were reported most frequently (MEC = 89.7%), PLA = 86.7%). The analysis of individual symptoms revealed that significantly more participants receiving MEC reported constipation (MEC = 52.9%, PLA = 35.3%; $\chi^2_1 = 4.29$, $P = 0.03$).

Serious adverse events (SAE)

Five SAEs occurred among participants in this study. In the active MEC group, one participant presented to the emergency room (ER) with suicidal ideation (off study medication), one reported chest pain and one developed psychosis. In the PLA group, one participant was hospitalized for pneumonia and one presented to the ER for chest tightness. None were related to the study medication.

DISCUSSION

The principal finding of this study was that mecamylamine had no significant effect on alcohol consumption in patients with AUDs. Nonetheless, patients in both groups received medical management therapy and reduced the number of their heavy drinking days, drinking days, drinks per drinking days and alcohol craving relative to their baseline severity. Further, contrary to our hypothesis, there was no interaction between smoking status and medication on alcohol use outcomes. Also, the concern that mecamylamine, an nAChR antagonist, would precipitate nicotine withdrawal in smokers was not supported.

The current study did not find signals consistent with pre-clinical evidence or human laboratory studies suggesting that mecamylamine attenuates behavioral or subjective effects, conditioned place preference and consumption of ethanol [11] (e.g. [12]). The consistency in results for animals and humans suggests that species differences do not account for the current findings. Rather, it may be that the type of drinking studied in the laboratory-based paradigms versus treatment differ. Alternatively, it is possible that mecamylamine was not dosed adequately to demonstrate effects on drinking outcomes. In human subjects, dose-limiting adverse events (e.g. constipation, etc.) prevent administration of higher doses. nAChR antagonism might still play a role in the treatment of AUDs, but a different medication strategy might be needed, such as subtype-selective nAChR antagonism or partial agonism. The partial agonist varenicline has shown some promise in treating alcohol use disorders [33–37]. Varenicline binds to the α4β2 subunit of the nAChR as a partial agonist and is a full agonist at the α7 receptor. Its dual effects of increasing dopamine levels and inhibiting dopamine activation and reinforcement from smoking are thought to be important to its effect on reducing smoking [38,39]. Of interest, the efficacy of mecamylamine for smoking cessation is increased by concurrent use of a nicotine agonist [17], suggesting that partial agonists of nicotinic acetylcholine receptors rather than antagonists should be targeted for further development for smoking cessation and for reducing alcohol drinking.

Smoking effects on nAChR are complicated. Chronic nicotine exposure can lead to reduced sensitivity of nAChR which may, in turn, lead to up-regulation [40]. We hypothesized that mecamylamine's effects on drinking would be attenuated in smokers because of up-regulation of the nAChRs or because active smoking would over-ride mecamylamine's effect, as has been hypothesized for the lack of antidepressant efficacy of mecamylamine in smokers [20]. Contrary to our hypothesis, smoking did not play a role in the results related to alcohol consumption. Further, in this study there was no significant effect of mecamylamine on smoking. Smoking and alcohol relapse have been linked in numerous clinical trials (reviewed in [41]). Smoking may reduce alcohol dependence-related changes in γ-aminobutyric acid ($GABA_A$) receptors, reducing a hypothesized contributor to relapse [42,43]. Provocative recent data suggest that a constituent of tobacco smoke other than nicotine accounts for the protective effect on GABA systems [44]. Further analysis may be warranted to determine a relationship between smoking and alcohol consumption.

Limitations in this study include the relatively small number of non-smokers. Among the smokers, participants were not encouraged to quit smoking, so potential effects of mecamylamine on smoking may have been obscured. The small number of women in this study also limits its generalizability. The biological markers used in this study do not detect alcohol consumption, unlike other markers such as urine or hair samples of ethylglucuronide [45]. Further, there were high rates of relapse to drinking, which may also suggest that this group was not highly motivated to stop drinking.

In summary, this report presents the results of the first evaluation of the nicotinic antagonist mecamylamine as a treatment for alcohol dependence in a heterogeneous group of smokers and non-smokers. Mecamylamine was not effective in attenuating alcohol consumption in this group. This result suggests that broad-spectrum antagonism of high-affinity nAChRs is not an effective strategy for treatment of AUDs. Subsequent studies might explore subtype selective nAChR modulators, including partial agonists.

ClinicalTrials.gov Identifier

NCT00342563.

Declaration of interests

I.L.P. has served as a consultant to Alkemes; S.S.O'M. is a Member of the American Society of Clinical Psychopharmacology workgroup, the Alcohol Clinical Trials Initiative, supported with funding from Eli Lilly, Ethypharma, Lundbeck, Pfizer, Otsuka, Arbor Pharmaceuticals, Indivior; donated study medications, Pfizer Pharmaceuticals, Astra

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References

1. Jonas D. E., Amick H. R., Feltner C., Bobashev G., Thomas K., Wines R. *et al*. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA* 2014; **311**: 1889–900.
2. Donoghue K., Elzerbi C., Saunders R., Whittington C., Pilling S., Drummond C. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, Europe versus the rest of the world: a meta-analysis. *Addiction* 2015; **110**: 920–30.
3. Harris A. H., Kivlahan D. R., Bowe T., Humphreys K. N. Pharmacotherapy of alcohol use disorders in the veterans health administration. *Psychiatr Serv* 2010; **61**: 392–8.
4. Chatterjee S., Bartlett S. E. Neuronal nicotinic acetylcholine receptors as pharmacotherapeutic targets for the treatment of alcohol use disorders. *CNS Neurol Disord Drug Targets* 2010; **9**: 60–76.
5. Grant B. F., Hasin D. S., Chou S. P., Stinson F. S., Dawson D. A. Nicotine dependence and psychiatric disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2004; **61**: 1107–15.
6. Oliver J. A., Blank M. D., Van Rensburg K. J., MacQueen D. A., Brandon T. H., Drobes D. J. Nicotine interactions with low-dose alcohol: pharmacological influences on smoking and drinking motivation. *J Abnorm Psychol* 2013; **122**: 1154–65.
7. Grucza R. A., Bierut L. J. Co-occurring risk factors for alcohol dependence and habitual smoking: update on findings from the collaborative study on the genetics of alcoholism. *Alcohol Res Health* 2006; **29**: 172–8.
8. Schlaepfer I. R., Hoft N. R., Ehringer M. A. The genetic components of alcohol and nicotine co-addiction: from genes to behavior. *Curr Drug Abuse Rev* 2008; **1**: 124–34.
9. Erwin B. L., Slaton R. M. Varenicline in the treatment of alcohol use disorders. *Ann Pharmacother* 2014; **48**: 1445–55.
10. Papke R. L., Sanberg P. R., Shytle R. D. Analysis of mecamylamine stereoisomers on human nicotinic receptor subtypes. *J Pharmacol Exp Ther* 2001; **297**: 646–56.
11. Wu J., Gao M., Taylor D. H. Neuronal nicotinic acetylcholine receptors are important targets for alcohol reward and dependence. *Acta Pharmacol Sin* 2014; **35**: 311–5.
12. Blomqvist O., Hernandez-Avila C. A., Van Kirk J., Rose J. E., Kranzler H. R. Mecamylamine modifies the pharmacokinetics and reinforcing effects of alcohol. *Alcohol Clin Exp Res* 2002; **26**: 326–31.
13. Chi H., de Wit H. Mecamylamine attenuates the subjective stimulant-like effects of alcohol in social drinkers. *Alcohol Clin Exp Res* 2003; **27**: 780–6.
14. Houtsmuller E., Brasser S., Foster K. Effects of mecamylamine on alcohol effects, craving and self-admistration. Santa Barbara, CA: 28th Annual Meeting of the Research Society on Alcoholism; 2005.
15. Rose J. E., Brauer L. H., Behm F. M., Cramblett M., Calkins K., Lawhon D. Psychopharmacological interactions between nicotine and ethanol. *Nicotine Tob Res* 2004; **6**: 133–44.
16. Rose J. E., Behm F. M., Westman E. C. Nicotine–mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. *Exp Clin Psychopharmacol* 1998; **6**: 331–43.
17. Rose J. E., Behm F. M., Westman E. C., Levin E. D., Stein R. M., Ripka G. V. Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clin Pharmacol Ther* 1994; **56**: 86–99.
18. Silver A. A., Shytle R. D., Sheehan K. H., Sheehan D. V., Ramos A., Sanberg P. R. Multicenter, double-blind, placebo-controlled study of mecamylamine monotherapy for Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2001; **40**: 1103–10.
19. Philip N. S., Carpenter L. L., Tyrka A. R., Price L. H. The nicotinic acetylcholine receptor as a target for antidepressant drug development. *Scientific World J* 2012; **2012**: 104105.
20. George T. P., Sacco K. A., Vessicchio J. C., Weinberger A. H., Shytle R. D. Nicotinic antagonist augmentation of selective serotonin reuptake inhibitor-refractory major depressive disorder: a preliminary study. *J Clin Psychopharmacol* 2008; **28**: 340–4.
21. Ralevski E., Jane J. S., O'Brien A., Weiner J., Edens E., Arnaout B. *et al*. Mecamylamine for the treatment of patients with depression and alcohol dependence. *Alcoholism* 2012; **36**: 296a.
22. Cohen J. *Statistical power analysis for the behavioral sciences*, 2nd edn. Hillsdale, NJ: Lawrence Earlbaum Association; 1988.
23. First M. B., Spitzer R. L., Gibbon M., Williams J. B. W. *Structured Clinical Interview for DSM-IV Axis I Disorders (Patient Edition) (SCID-P)*. New York, NY: Biometric Research, New York State Psychiatric Institute; 1996.
24. Carroll K. M., Nich C., Ball S. A., McCance E., Rounsaville B. J. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction* 1998; **93**: 713–27.
25. Skinner H. A., Horn J. L. *Alcohol Dependence Scale (ADS): User's Guide*. Toronto: Addiction Research Foundation; 1984.
26. Miller W., Tonighan S., Longabaugh R. *The Drinker Inventory of Consequences (DrInC): An Instrument For Assessing Adverse Consequences of Alcohol Abuse*. Rockville, MD: US Department of Health and Human Services; 1995.
27. Sobell L. C., Sobell M. B. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten R. Z., Allen J., editors. *Measuring Alcohol Consumption: Psychosocial and Biological Methods*. Totowa, NJ: Humana Press; 1992, pp. 41–72.

28. Fagerstrom K. O., Schneider N. G. Measuring nicotine dependence: a review of the Fagerstrom tolerance questionnaire. *J Behav Med* 1989; **12**: 159–82.
29. Anton R. F., Moak D. H., Latham P. K. The obsessive compulsive drinking scale: a new method of assessing outcome in alcoholism treatment studies [published erratum appears in *Arch Gen Psychiatry* 1996;53:576]. *Arch Gen Psychiatry* 1996; **53**: 225–31.
30. Levine J., Schooler N. R. Strategies for analyzing side effect data from SAFTEE: a workshop held fall 1985 in Rockville, Maryland. *Psychopharmacol Bull* 1986; **22**: 343–56.
31. Tiffany A., Drobes D. Development and validation of a questionnaire on smoking urges. *Br J Addict* 1991; **86**: 1467–76.
32. Cappelleri J. C., Bushmakin A. G., Baker C. L., Merikle E., Olufade A. O., Gilbert D. G. Revealing the multidimensional framework of the Minnesota nicotine withdrawal scale. *Curr Med Res Opin* 2005; **21**: 749–60.
33. McKee S. A., Harrison E. L., O'Malley S. S., Krishnan-Sarin S., Shi J., Tetrault J. M. *et al*. Varenicline reduces alcohol self-administration in heavy-drinking smokers. *Biol Psychiatry* 2009; **66**: 185–90.
34. Litten R. Z., Castle I. J., Falk D., Ryan M., Fertig J., Chen C. M. *et al*. The placebo effect in clinical trials for alcohol dependence: an exploratory analysis of 51 naltrexone and acamprosate studies. *Alcohol Clin Exp Res* 2013; **37**: 2128–37.
35. Fucito L. M., Toll B. A., Wu R., Romano D. M., Tek E., O'Malley S. S. A preliminary investigation of varenicline for heavy drinking smokers. *Psychopharmacology (Berl)* 2011; **215**: 655–63.
36. Mitchell J. M., Teague C. H., Kayser A. S., Bartlett S. E., Fields H. L. Varenicline decreases alcohol consumption in heavy-drinking smokers. *Psychopharmacology (Berl)* 2012; **223**: 299–306.
37. de Bejczy A., Lof E., Walther L., Guterstam J., Hammarberg A., Asanovska G. *et al*. Varenicline for treatment of alcohol dependence: a randomized, placebo-controlled trial. *Alcohol Clin Exp Res* 2015; **39**: 2189–99.
38. Aubin H. J., Luquiens A., Berlin I. Pharmacotherapy for smoking cessation: pharmacological principles and clinical practice. *Br J Clin Pharmacol* 2014; **77**: 324–36.
39. Rollema H., Chambers L. K., Coe J. W., Glowa J., Hurst R. S., Lebel L. A. *et al*. Pharmacological profile of the alpha4beta2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. *Neuropharmacology* 2007; **52**: 985–94.
40. Sanberg P. R., Vindrola-Padros C., Shytle R. D. Translating laboratory discovery to the clinic: from nicotine and mecamylamine to Tourette's, depression, and beyond. *Physiol Behav* 2012; **107**: 801–8.
41. Cook J. W., Fucito L. M., Piasecki T. M., Piper M. E., Schlam T. R., Berg K. M. *et al*. Relations of alcohol consumption with smoking cessation milestones and tobacco dependence. *J Consult Clin Psychol* 2012; **80**: 1075–85.
42. Krystal J. H., Staley J., Mason G., Petrakis I. L., Kaufman J., Harris R. A. *et al*. Gamma-aminobutyric acid type a receptors and alcoholism—intoxication, dependence, vulnerability, and treatment. *Arch Gen Psychiatry* 2006; **63**: 957–68.
43. Staley J. K., Gottschalk C., Petrakis I. L., Gueorguieva R., O'Malley S., Baldwin R. *et al*. Cortical gamma-aminobutyric acid type A-benzodiazepine receptors in recovery from alcohol dependence: relationship to features of alcohol dependence and cigarette smoking. *Arch Gen Psychiatry* 2005; **62**: 877–88.
44. Cosgrove K. P., McKay R., Esterlis I., Kloczynski T., Perkins E., Bois F. *et al*. Tobacco smoking interferes with GABAA receptor neuroadaptations during prolonged alcohol withdrawal. *Proc Natl Acad Sci USA* 2014; **111**: 18031–6.
45. Salomone A., Baumgartner M. R., Lombardo T., Alladio E., Di Corcia D., Vincenti M. Effects of various sample pretreatment procedures on ethyl glucuronide quantification in hair samples: comparison of positivity rates and appraisal of cut-off values. *Forensic Sci Int* 2016; **267**: 60–5.