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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—Outpatient, randomized, double-blind clinical trial for 12 weeks of treatment with mecamylamine (10mg) (n=65) vs. placebo (n=63).

Setting—Connecticut, USA.

Participants—Individuals had current alcohol dependence (n=128), had an average age of 48.5 (SD=9.4), 110 (85.9%) were men, and included 74 smokers (57.8%) and 54 non-smokers (42.2%)

Intervention and comparator—Participants were randomized to mecamylamine 10mg per day or placebo. All subjects also received Medical Management therapy administered by trained research personnel.

Measurements—Primary outcome was percent 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 percent 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 percent of

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drinking days or in drinks per drinking day at month 3 between the mecamlamine and placebo groups; and were no significant interactions.

Conclusions—Mecamlamine 10mg pd did not significantly reduce alcohol consumption in treatment seeking smokers and non-smokers with alcohol use disorder.

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). Preclinical 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 pharmacologic support for AUD (9).

Mecamlamine hydrochloride (Inversine ®) is a non-selective, non-competitive, antagonist both peripheral and central nAChRs, (10). Systemically administered mecamlamine reduces alcohol consumption in rats and mice injection of mecamlamine into the ventral tegmental area (VTA) reduces voluntary ethanol preference and consumption in ethanol-preferring rats (reviewed in (11)). Human laboratory studies found that mecamlamine 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 mecamlamine reduced the rewarding effects of ethanol, (Blood Alcohol Concentration (BAC) 0.03g/dl).

Mecamlamine 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, mecamlamine was most effective when paired with nicotine replacement (17). There is some evidence that the antidepressant effects of mecamlamine (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, mecamlamine augmentation of antidepressant was associated with reduced drinking among the nonsmokers (21).

We hypothesized that acute antagonism of nAChRs with mecamlamine 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 mecamlamine with placebo on the percent 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 since mecamlamine 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 outpatient 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 conservatively based our power calculations on a smaller medium effect size ($f=0.25$) for the primary outcome of percent heavy drinking days evaluated at 3 months. We estimated that we will need to have 64 MEC and 64 PLA subjects to achieve 80% power to detect such an effect size for the primary and the secondary aims assuming $\alpha=0.05$.

Participants

Over 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 18–70, 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 EKG. 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 10mg 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 was 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 1:1 ratio between treatment conditions (mecamylamine or placebo). Since 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 upward during the first 2 weeks, starting at 2.5 mg per day and then increased over the 2 weeks to 10 mg per day in divided doses (5mg twice daily) and was dispensed in blister packs. During week 13, medication was tapered down over 7 days. Medication compliance was monitored at every visit.

Measures

All subjects completed an assessment of baseline demographic characteristics; the Structured Clinical Interview for DSM Diagnosis (SCID)-I; Alcohol Dependence Severity (ADS) (25) and the Drinker Inventory of Consequences (DrInC) scale to assess severity of dependence and consequences (26) and Timeline Follow Back (TLFB) (27) to assess alcohol use; and the Fagerstrom Test for Nicotine Dependence (FTND) to measure nicotine dependence (28).

The Substance Abuse Calendar, based on the *Timeline Follow-Back 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 4 times during the study (baseline, week 4, week 8 and week 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 specifically screened for on a weekly basis. Symptoms were then clustered into the following categories: gastrointestinal (GI), central nervous system (CNS), neurological (NE), musculoskeletal (MS), skin, ophthalmological (OPHTH), cardio/pulmonary (CAR), and genito-urinary (GU).

The primary outcome measure was the percent of heavy drinking days at 3 months calculated based on all available data from the Timeline Follow back Method. Secondary outcomes included percent 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). Since 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 N=128 individuals that 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 significantly skewed and no data transformations were performed. Baseline demographic characteristics for the medication groups (MEC vs. PLA) were compared using chi-square 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 percent heavy drinking days at 3 months, we used ANOVA that included medication (MEC vs PLA), smoking status (smokers vs non-smokers), gender and the corresponding baseline drinking measure (percent heavy drinking days at baseline) as factors in the model. An identical analysis was performed for percentage of drinking days (controlling for percent drinking days at baseline) and drinks per drinking day (controlling for drinks per drinking day at baseline). For the analysis of bio markers, OCDS and smoking outcomes we used linear mixed models (LMMs). LMM were also fit to the drinking outcomes over time in secondary analyses. We selected the appropriate correlation structure for each dependent variable based on Schwartz Bayesian information criterion (BIC) (smaller is better). Medication group (MEC vs PLA) was entered as a between subject factor and time was used as a within subject factor. Chi squared (χ^2) tests were used for all categorical data. All analyses were performed using 21.0 Version of SPSS. 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 cutoffs: 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 about equal number of participants assigned to MEC (n=65) and PLA (n=63) groups (See Figure 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, 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, highest percentage were male (85.9%), single (43.6%), African American (50%) with no differences between the groups based on treatment assignment. A majority of participants (n=74, 57.8%) were smokers 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 10mg 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 ($\chi^2_{11}=0.19$, $p=0.89$) and 72.3% were compliant with MEC for at least 10 weeks compared to 73.0% on PLA ($\chi^2_{11}=0.003$, $p=0.92$). The majority of subjects (92.3%) reached the maximum dose of 10mg and more than half (53.8%) were on the highest dose for all 10 weeks.

Drinking Outcomes

Primary drinking outcome—Analysis of the percent heavy drinking days (%HDD) at month 3 showed no significant differences between the mecamlamine (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 vs. non-smokers $F_{1,100}=0.60$, $p=.43$), or gender ($F_{1,100}=0.69$, $p=.40$). Baseline %HDD was also not significant after Bonferroni adjustment ($F_{1,100}=4.10$, $p=0.04$). To evaluate for potential moderating effects of smoking and gender we considered interactions of these factors with treatment but those were dropped since they were not significant.

Secondary drinking outcomes—Analysis of percent of drinking days (%DD) at month 3 showed no significant differences between the mecamlamine (mean=29.2, SD=35.3) and placebo (mean=31.2, SD=35.0) ($F_{1,100}=0.00$, $p=.98$); effect size $d=0.05$; mean difference=1.95, 95% confidence interval=-11.34 to 15.26). There were no differences in %DD by smoking status (smokers vs. non-smokers $F_{1,100}=1.1$, $p=.29$), or gender ($F_{1,100}=0.08$, $p=.77$). 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 mecamlamine (mean=4.7, SD=5.0) and placebo groups (mean=5.1, SD=5.7) ($F_{1,100}=0.01$, $p=.91$); 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 vs. non-smokers $F_{1,100}=2.1$, $p=.14$), gender ($F_{1,100}=0.06$, $p=.80$) 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 $\times$ medication $\times$ 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 interactions effects.

Alcohol Craving—Participants reported a decrease in their craving scores, based on total ODCS 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.

Drinking consequences—Drinking consequences were evaluated using the five categories in the DrInC scale (26). Treatment significantly decreased responses 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 second 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 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, 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 mecamlamine, an nAChR antagonist, would precipitate nicotine withdrawal in smokers was not supported.

The current study did not find signals consistent with preclinical evidence or human laboratory studies suggesting that mecamlamine 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 mecamlamine was not adequately dosed 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 that 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 $\alpha 4\beta 2$ subunit of the nAChR as a partial agonist and is a full agonist at the $\alpha 7$ 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 mecamlamine 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 upregulation (see (40)). We hypothesized that mecamlamine's effects on drinking would be attenuated in smokers because of upregulation of the nAChR's or because active smoking would override mecamlamine's effect, as has been hypothesized for the lack of antidepressant efficacy of mecamlamine 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 mecamlamine on smoking. Smoking and alcohol relapse have been linked in numerous clinical trials (reviewed in (41)). Smoking may reduce alcohol dependence-related changes in 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 and so potential effects of mecamlamine 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.

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Figure 1.
Consort

Figure 2.
Percent Heavy Drinking Days (baseline and last 30 days of treatment)
* baseline = 90 days before start of treatment

Table 1

Socio-Demographics

Variables	Placebo n=63	Mecamylamine N=65
Demographic Characteristics		
	<i>Mean (SD)</i>	<i>Mean (SD)</i>
Age	49.27 (9.59)	47.72 (9.35)
	<i>n (%)</i>	<i>n (%)</i>
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)		
	<i>Mean (SD)</i>	<i>Mean (SD)</i>
% 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)

Note: For all variables N = 128 there are some missing values

Table 2

Outcomes

Variables	Placebo n=63	Mecamylamine n=65	Statistics	
Primary Drinking Outcomes				
% Heavy drinking days (%HDD)			F	p
	Mean (SD)	Mean (SD)		
Before treatment (90 days)	69.54 (27.79)	60.88 (28.44)	Medication Smoking	0.138 0.657
Last 30 days	20.49 (29.28)	18.43 (29.04)	Gender % HDD Baseline	0.750 4.579
% Number of drinking days (%#DD)			F	p
	Mean (SD)	Mean (SD)		
Before treatment (90 days)	76.61 (24.08)	69.11 (26.54)	Medication Smoking	0.085 2.507
Last 30 days	31.23 (35.03)	29.27 (35.32)	Gender %# DD Baseline	0.165 6.904 0.010
Drinks per drinking day (DDD)				
	Mean (SD)	Mean (SD)	F	p
Before treatment (90 days)	13.58 (7.83)	13.65 (8.72)	Medication Smoking	0.170 2.321
Last 30 days	5.15 (5.71)	4.72 (5.08)	Gender DDD Baseline	0.005 0.179
Additional Drinking Outcomes				
OCDS Total				
	Mean (SD)	Mean (SD)	F	p
Baseline	17.00 (8.73)	18.90 (9.40)	Medication Smoking Time	0.506 1.474 27.11
				0.478 0.227 0.000

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Variables	Placebo n=63	Mecamylamine n=65	Statistics			
Week 12	8.03 (7.28)	8.69 (7.57)	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						
Baseline	Mean (SD)	Mean (SD)				
	12.03 (8.37)	10.44 (9.01)	Medication	1.873	0.175	
Week 12	10.68 (7.05)	8.19 (7.68)	Time	3.650	0.000	
			Medication × Time	0.536	0.876	