An RCT with the Combination of Varenicline and Bupropion for Smoking Cessation: Clinical Implications for Front Line Use

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Abstract

Background and Aims—Despite the availability of several efficacious smoking cessation treatments, less than 25% of smokers who quit remain abstinent 1 year post treatment. This study aimed to determine if varenicline and bupropion combination treatment would result in higher abstinence rates than varenicline alone.

Design—A double-blind, randomized, parallel groups smoking cessation clinical trial in which participants were exposed to 12 weeks of treatment and followed for 12 months.

Setting—Hospital-based outpatient clinic in Texas, USA specializing in cancer prevention.

Participants—385 community smokers (56% male) who smoked 1 pack cigarettes/day (Mean = 19.66 cigs/day, S.D. = 9.45); had an average CO of 26.43 ppm (S.D. = 13.74); and were moderately dependent (FTCD = 4.79; S.D. = 2.07).

Interventions and comparator—Smokers were randomized in a 3:1 (Active: Placebo) ratio to 12 weeks of treatment as follows: Placebo (n=56), Varenicline (Var; n=166), and Varenicline + Bupropion (Combo; n=163).

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Conflict of Interest Declaration: Dr. Cinciripini served on the scientific advisory board of Pfizer Pharmaceuticals, conducted educational talks sponsored by Pfizer on smoking cessation (2006–2008), and has received grant support and medication support from Pfizer. Dr. Karam-Hage participated in two multi-site Pfizer-funded trials and received varenicline from Pfizer to conduct 4 NIH-funded trials. Pfizer (New York, NY) provided the active and matching placebo varenicline capsules. All other authors declare that they have no conflicts of interest.

Measurements—A priori primary outcome: Prolonged abstinence at 12 months. Secondary outcomes: Seven-day point prevalence abstinence and continuous abstinence; all abstinence measures at end of treatment and 6 month follow-ups.

Findings—Intent to treat analysis: the Combo group (n=163) failed to demonstrate superiority to the Var group (n=166) for prolonged abstinence at 12 months [odds ratio (OR) = 0.91, 95% confidence interval (CI) = 0.50–1.64], supported by Bayes Factor = 0.06. Both the Var [OR = 6.66, 95% CI = 1.61–59.27] and Combo groups [OR = 6.06, 95% CI = 1.45–54.09] demonstrated superiority to Placebo group (n=56; Score = 8.38, $p < 0.016$).

Conclusions—The addition of bupropion to varenicline treatment does not appear to increase smoking abstinence rates above that of varenicline alone. The findings support previous research showing a consistently favorable effect of both varenicline and the combination of varenicline and bupropion on smoking cessation compared with placebo.

Introduction

While global reductions in the prevalence of daily cigarette smoking have been observed, the worldwide number of smokers continues to increase as the population grows, resulting in substantial adverse effects on health. (1) Cigarette smoking remains the leading cause of premature death and disease in the United States, yet frontline treatments have yielded one year post-treatment quit rates of less than 25%. (2) While several approved smoking cessation medications exist with demonstrated efficacy against placebo, (3–6) there is considerable heterogeneity in response across treatments that may in part be due to the complex effects of nicotine on a smokers' cognition and mood. (7–9) Combining therapies with different mechanisms of action might improve treatment efficacy by addressing some of these individual differences.

Varenicline is a highly selective partial agonist of the $\alpha^4\beta^2$ nicotine cholinergic receptor (nAChR) that ultimately stimulates dopamine release while preventing full stimulation of the nicotine receptor that ensues with co-administered nicotine. (10) Recent meta-analyses (11, 12) and results from the largest RCT for smoking cessation conducted to date (13) have shown that varenicline is more effective than all other monotherapies for smoking cessation, including all single NRTs and bupropion, with few exceptions. (14)

Bupropion (amfebutamone) is an atypical antidepressant whose mechanism of action is thought to be mediated through both dopaminergic (DA) and noradrenergic (NE) systems. Pre-clinical research suggests that bupropion may also act as a noncompetitive nicotine antagonist, possibly reducing the reinforcing properties of nicotine. (15) Recent meta-analyses (11, 16) and results from the same large RCT noted above (13) show bupropion is more effective than placebo, with effectiveness similar to NRT. (11, 13)

Plausible differences in the mechanisms of action of varenicline and bupropion as well as differences in their intensity of action within the same pathways suggests that their combination could offer broader coverage of the neuronal mechanisms implicated in smoking cessation. Both drugs demonstrated reductions in negative affect, craving, and some indices of smoking reinforcement (satisfaction), (17, 18) with varenicline showing

potentially stronger effects for many of these outcomes, including craving. (2) Simultaneously, bupropion may offset the deficits in cognitive and attentional functioning related to smoking cessation. (19) This raises the possibility that additive effects may occur during co-administration of these drugs for smoking cessation. While both varenicline and bupropion monotherapies have established efficacy versus placebo as noted above, the combination of these medications may result in unexpected or previously undocumented adverse events when compared to placebo. Therefore, we included a placebo group in this trial to account for that possibility.

A recent RCT by Ebbert and colleagues (20) found that a combination of varenicline and bupropion may be more effective than varenicline alone up to 6 months post-treatment. Unexpectedly, a small but significant increase in anxiety and depressive symptoms was also noted in the combination group. Two similar RCTs that randomized pre-treatment nicotine patch non-responders (and a small group of responders in the latest trial) to receive the combination of varenicline and bupropion or varenicline alone reported increased abstinence rates in the combination group up to 6 months, among male and highly dependent smokers. (21, 22)

Replication and extension of these findings will clarify the degree to which combined pharmacotherapy results in differential benefit based on individual differences in affect and nicotine withdrawal. We hypothesized that combination treatment would (a) result in higher prolonged abstinence rates at the 12 month follow-up (primary outcome), and, secondarily, at the end of treatment (EOT) and the 6 month follow-up; and (b) would result in lower levels of withdrawal, including negative affect and craving.

Method

Study Design

In this study, community smokers were recruited at a hospital-based outpatient clinic in Texas to participate in a double-blind, randomized, parallel groups smoking cessation clinical trial in which 385 participants were randomized to receive Varenicline, Varenicline + Bupropion, or Placebo, exposed to 12 weeks of treatment, and followed for 12 months.

Procedures

Figures 1 and 2 show the study CONSORT diagram and timeline respectively. Participant screening for eligibility used a three step process: 1) initial phone screen, 2) in-person group orientation visit, and 3) subsequent in-person screening/baseline visit to assess medical and other eligibility criteria and conduct baseline assessments (also see Figure 2).

Randomization of N = 385 participants in a 3:1 (Active: Placebo) ratio resulted in: Placebo (n=56; Placebo), Varenicline (n=166; Var), and Varenicline + Bupropion (n=163; Combo). This ratio was used to minimize the number of participants who were not offered active pharmacological treatment while preserving the ability to characterize the adverse events in the combination group compared to placebo. Adaptive randomization (minimization) (23) balanced groups on gender, race, history of depression, baseline nicotine dependence, and previous treatment with either Varenicline or Bupropion. Participants were enrolled onto the

trial by study staff and group assignment was generated with an algorithm developed and managed by study data managers, whose role was limited to data quality and integrity management. Participants, medical and research staff who interacted with participants, and the study investigators were blinded to group assignment.

Participants

Paid and unpaid media advertising from May, 2010 through July, 2013 recruited volunteer smokers from the Houston, Texas metropolitan area. Inclusion criteria included: 25–65 years of age; smoke 5 or more cigarettes per day; baseline expired carbon monoxide (CO) level greater than 6 ppm; fluent in English; stable residence and a working telephone; and be the only participant in his/her household. Exclusion criteria included: currently taking psychotropic medication; having a current psychiatric disorder, psychiatric hospitalization within the last year; lifetime history of a psychotic disorder; scoring moderate or higher on the suicidality scale of the Mini International Neuropsychiatric Interview (MINI) (24); being involved in any cessation activities; being pregnant or of childbearing potential without the use of birth control; have an uncontrolled chronic medical illness; or having contraindications for bupropion (e.g., history of seizures) or varenicline (e.g., severe renal impairment). The University of Texas MD Anderson Cancer Center Internal Review Board approved this research and the trial ended when the sample size was reached.

Interventions

Pharmacotherapy—All participants took both types of study medication twice daily: placebo varenicline capsules plus placebo bupropion tablets (Placebo); active varenicline capsules plus placebo bupropion tablets (Var), or both active varenicline capsules and active bupropion tablets (Combo). Pfizer (New York, NY) provided the active and matching placebo varenicline capsules and the Biomedical Research Institute of New Mexico (Albuquerque, NM) provided the active and matching placebo bupropion tablets.

Pharmacotherapy was initiated the day after the first treatment visit (see Figure 2), 7–8 days prior to the quit date and followed the recommended dosing for a total of 12 weeks for varenicline (i.e., 0.5 mg/day for days 1–3; 0.5 mg bid for days 4–7; and 1 mg bid thereafter) and bupropion (150 mg/day for days 1–3; 150 mg bid thereafter). Dose adjustments by the blinded study physician were permitted in an effort to control adverse events throughout the trial. Medication compliance was computed using physical pill count in returned bottles, at each visit.

Behavioral Counseling—As shown in Figure 2, following randomization, all smokers received individual behavioral smoking cessation counseling conducted over 13 in-person visits (15 minutes each) and 2 brief supportive phone calls (5 to 10 minutes each) during the 12 week active treatment phase (see on-line supplement for counseling details).

Follow-up

As shown in Figure 2, follow-up sessions were conducted at the end of the 12 week treatment and at 6 and 12 months post-quit, and involved abstinence and other assessments as noted below.

Assessments

During the baseline screening phase participants were assessed for basic demographics, health and smoking history, psychiatric disorders (using version 5.0 of the M.I.N.I. International Neuropsychiatric Interview) (24), and nicotine dependence (using the Fagerstrom Test for Cigarette Dependence; FTCD). (25–27)

At baseline and at each in-person counseling and follow-up visit, participants completed the Positive and Negative Affect Scale (PANAS) (28), the Wisconsin Smoking Withdrawal Scale (WSWS), (29) which included subscales of Anger, Anxiety, Concentration, Craving, Hunger, Sadness and Sleep, and the Center for Epidemiologic Studies Depression Scale (CES-D), which has been used to measure depressive symptoms in community samples. (30, 31) Additionally, participants reporting smoking between visits completed the Modified Cigarette Evaluation Questionnaire (mCEQ). (32) Administration of the Sleep Problems Scale occurred at baseline, and 4, 8, and 12 weeks after treatment onset.

Abstinence data were collected at all contacts using a timeline follow-back (TLFB) procedure (33, 34) and abstinence outcomes conformed to the Society of Research on Nicotine and Tobacco (SRNT) (35) guidelines. Measures included prolonged abstinence, defined as no smoking from the quit date to a future time point (e.g., EOT, 6, and 12 months post-quit date) with relapse defined as smoking on 7 or more consecutive days or smoking at least 1 cigarette over two consecutive weeks within that same time interval. Seven-day point prevalence abstinence was defined as a self-report of no smoking, not even a puff, in the 7 days prior to the selected time point of interest. Continuous Abstinence (2-week grace) was defined as no smoking, not even a puff from 2 weeks past the quit-date (grace period) to a future time point. Continuous Abstinence (FDA) was similarly defined as no smoking but beginning with the last 4 weeks of treatment, or week 8 of medication in this trial. In-person reports of abstinence were verified by expired CO < 4 ppm. Participants unavailable for assessment were considered non-abstinent.

Adverse Event Monitoring

Adverse events were monitored at each contact and were classified and graded using the Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria provided by the National Cancer Institute. (36)

Compensation

Participants received compensation for completing assessments for a maximum possible total of \$415 across all visits.

Outcome Measures

The primary outcome for this study is prolonged abstinence at the 12 month follow-up as a function of treatment, specifically between the two active treatment groups: Var and Combo. Secondary outcomes included prolonged abstinence at EOT and the 6-month follow-up, all other abstinence definitions at all three time points, as well as nicotine withdrawal, affect, smoking reinforcement/satisfaction, and sleep problems.

Statistical Analysis

All analyses were conducted using SAS v. 9.3 and utilized intention to treat (ITT) principles, analyzing outcomes for all participants exposed to any level of treatment, with missing abstinence observations imputed as smoking. Logistic regression was used to evaluate the prolonged abstinence at 12 months (primary outcome) as well as secondary abstinence outcomes including EOT and 6 months abstinence and all other abstinence definitions at each time point. The primary contrast of interest compared the Combo and Var groups. Missing abstinence observations were imputed as smoking. Longitudinal analyses of nicotine withdrawal (WSWS), negative and positive affect (PANAS), smoking reinforcement/satisfaction (MCEQ), and sleep problems utilized multilevel linear models. Post-hoc follow-up of main effects and interactions used Tukey's HSD to correct for Type 1 error.

Sample Size

At the time of the proposal, there were no extant estimates of the effect of combination treatment relative to varenicline alone. Based on our own preliminary clinical data, we estimated the abstinence differences between Var and Combo would range from 10% to 18% across the follow-ups. We calculated that a sample size of 385 (165 in active medication groups; 55 placebo) would provide 80% power to detect a difference of ~14% between Var and Combo at 12 months (primary outcome), assuming a 22%–23% 12 month abstinence rate for VAR, based on pivotal trials. (10, 37)

Results

Demographics and Baseline Characteristics

Demographics are presented in Table 1. The sample was 62% non-Hispanic White, 27% non-Hispanic African-American, 8% Hispanic, 4% other, and 58% male, with an average age of 48.97 (S.D. = 10.17) years. Participants smoked approximately one pack of cigarettes per day at baseline (Mean number of cigs/day = 19.66, SD = 9.45), with an average baseline CO of 26.43 ppm (SD = 13.74) and were moderately dependent (FTCD = 4.79; SD = 2.07).

Retention and Compliance

Pharmacotherapy—Table 2 summarizes treatment compliance for pharmacotherapy. Retention of participants through all 12 weeks of treatment ranged from 80.98% to 67.86%, and did not differ by group. Mean percentage of visits completed was comparable across treatments, averaging 78.52%. Compliance with prescribed medication dosages averaged > 90% across groups, with the caveat that a physical pill count as used in this study may overestimate adherence. (38) Importantly, we observed no systematic differences in compliance between groups.

Behavioral Counseling—Overall, participants attended an average of 10.8 (SD=3.6) in-clinic counseling sessions, and completed an average of 1.5 (0.8) telephone visits. No differences were noted between medication groups.

Treatment Effects on Smoking Abstinence

At month twelve, Var and Combo failed to demonstrate a difference for prolonged abstinence (primary outcome; see Table 3). Secondary outcomes of prolonged abstinence at EOT and 6 months; as well as continuous abstinence (2-week grace) FDA continuous abstinence, and seven-day point prevalence for all time points are also presented in Table 3 and in each case, no differences between Var and Combo were noted. The calculation of Bayes Factors (BF) using the approach described by Wagenmakers (39) permitted evaluation of the evidence favoring the alternative hypothesis for each treatment comparison, at each time point, for each of the four abstinence measures. As stipulated by this journal's editorial guidelines, a $BF < 0.3$ in favor of the alternative hypothesis provides adequate evidence of no effect. In the case of all abstinence measures at all time-points, the BF was less than 0.3 for contrasts between the combination and varenicline conditions.

To reconcile our findings with the previous bupropion/varenicline medication trials, (20–22) we conducted additional analyses testing for moderation of the treatment effect on abstinence by gender, baseline nicotine dependence, and baseline smoking rate. Neither gender, baseline nicotine dependence, nor baseline smoking rate moderated the effects of treatment on abstinence. We also tested these same potential moderators in a comparison that included only the two active treatment groups since none of the previous studies using the combination therapy used a placebo only group. In this sub-analysis, we found that the effect of treatment (Var vs. Combo) on continuous abstinence from a two-week post-quit grace period to EOT was moderated by level of dependence (FTCD ≥ 6 vs. FTCD < 6 ; $p = 0.038$). The results showed that Combo treatment was superior to Var only among smokers with FTCD ≥ 6 : Combo 35% versus Var 16%; OR=2.81, 95% CI= 1.07, 7.92. This pattern was consistent at the later time points but not statistically reliable and no treatment differences were observed in less-dependent and lighter smokers. Evaluation of the differential continuous abstinence outcomes for the Combo versus Var groups as a function of baseline dependence (FTCD ≥ 6 and Cigarettes/day ≥ 20) among male did not replicate Rose and Behm (22) (Zelen's Exact Test $p < 0.99$).

Other Secondary Outcomes

All secondary outcome measures are discussed in detail in the on-line supplement (see text and Tables S1–S4) and summarized below:

PANAS—Treatment group differences existed for negative affect ($F(2,4078) = 5.24$, $p = 0.005$), which in post hoc analyses (Tukey) showed that participants in the two active conditions reported lower levels of negative affect relative to Placebo but did not differ from each other (see supplementary Table S3).

WSWS—WSWS-Craving Scale demonstrated a time by treatment interaction ($F(2,4077) = 3.93$, $p = 0.02$) characterized by a faster rate of decline for varenicline relative to the other groups (see supplementary Table S4).

The WSWS subscales for Anger ($F(2,3617) = 6.60$, $p = 0.001$), Anxiety ($F(2,3841) = 5.88$, $p = 0.003$), and Sadness ($F(2,3974) = 7.84$, $p = 0.0001$) demonstrated main effects for

treatment (See supplementary Table S1). Post-hoc analyses showed that smokers in the Combo group reported less anger and sadness than those in the Var condition; while both groups reported lower anxiety relative to placebo but did not differ from each other (See supplementary Table S3).

No significant group differences were noted for the CES-D scales, Sleep Problems Scale, or the MCEQ (see Tables S1–S3).

Adverse Events

There were a total of 36 serious adverse events (SAEs): 24 in the Combo arm, involving 8 people; 2 in the Placebo arm, involving 1 person; and 10 in the Var arm, involving 4 people. All SAEs were rated as unlikely or unrelated to medication, except one in the Var arm which involved a suicide attempt. This SAE was rated as possibly related although there were extenuating circumstances surrounding the event (see on-line supplement for further information).

Tables S5 and S6 in the online supplement report rates for Adverse Events within each System Organ Class for which an overall treatment group difference was noted (see Table S5; $\alpha=.05$ uncorrected for multiple comparison) as well as all individual Adverse Events. Relative to placebo, Combo smokers showed decreased appetite and increased dry mouth, insomnia, dysgeusia, creatinine, and edema, while those in the Var group showed higher levels of abnormal dreams, diarrhea, and nausea. Pre-existing medical conditions may have contributed to elevations of creatinine, edema and dysgeusia in the combination group (see on-line supplement for further discussion).

Negative binomial regression was used to evaluate rates of AEs as a function of treatment, complier status (i.e. 80% compliance with all medication-taking), and their interaction. The natural logarithm of number of visits attended functioned as an offset to control for participants' treatment exposure time. In participants receiving Combo, compliers reported a lower rate of AE's than non-compliers (R.R. = 0.53, 95% C.I. = 0.34–0.82, while no such differences were noted for those for Var or Placebo. Using a similar approach we found that among the Combo group, compliers reported a lower rate of psychiatric AE's than non-compliers (R.R. = 0.39, 95% C.I. = 0.22–0.70), while similar differences were not found for Var or Placebo. Analyses of psychiatric AEs, excluding abnormal dreaming and insomnia, failed to find this moderating effect.

Discussion

Contrary to previous studies, we did not find evidence that the combination treatment resulted in higher abstinence rates than varenicline alone. Both active treatments demonstrated superiority to placebo on all measures of continuous and prolonged abstinence at all time points but did not differ from each other. The results confirm previous varenicline trials in demonstrating its efficacy for smoking cessation compared with placebo.(20) Results for seven day point prevalence were similar although less consistent. This is likely due to the volatility of the measure resulting from individuals being abstinent at one time point and not in another.(35)

We did not find evidence of any treatment interactions with gender or baseline nicotine dependence, as previously reported, (20–22) in an analysis that included both active treatments and placebo. However, in a sub-analysis using only the two active treatments, we found that among more dependent smokers (FTCD ≥ 6), continuous abstinence at the end of treatment was significantly higher for those on combination treatment vs. varenicline alone. Both medication groups reduced general negative affect, anxiety, and craving. Although there was some evidence that the combination treatment resulted in lower levels of anger and sadness than varenicline and placebo, which did not differ from each other, the differences were relatively small. No differences were noted for depressive symptomatology (CES-D), sleep, or reward (MCEQ).

Combination treatment participants reported more occurrences of decreased appetite, dry mouth, edema, abnormal taste, increased creatinine, and insomnia. Additionally, participants in the varenicline group reported more diarrhea, nausea, and abnormal dreams. No group differences in psychiatric adverse events were noted with the exception of abnormal dreams (higher in Varenicline) and insomnia (higher in Combo), neither of which are unexpected with these medications. Ebbert et al. (20) noted increases in anxiety and depression in the combination group compared to the varenicline group, which we did not find. Finally, treatment non-compliers in the combination group, but not in the varenicline group, reported more general and psychiatric adverse events than compliers.

The discrepancy between our results and Ebbert and colleagues (20), which was most similar to our design, is worthy of comment. A potential limitation is our sample size, which contained 86 and 91 fewer smokers in the combination and varenicline groups, respectively. However, the odds ratios between the studies were quite dissimilar. For Ebbert et al (20) significant differences between the two active treatments were noted for EOT and 6 month continuous abstinence only with ORs of 1.49 (95% CI 1.05–2.12) and 1.52 (95% CI 1.04–2.22), respectively. The corresponding figures for this study were 1.18 (95% CI .75–1.86) and .96 (95% CI .56–1.64), respectively. An increased sample size would be unlikely to rectify these differences. When our study was proposed there was no published evidence for combination therapy. Our sample size calculations were based on preliminary data from our clinic, from which we estimated a treatment difference of 10%–18%, favoring combination. Our actual difference was only 4% at EOT and –1.7% at 6 months for continuous abstinence. Corresponding differences in the Ebbert trial were 9.8% and 9% respectively. Thus while our projections were somewhat higher than Ebbert and colleagues observed, our actual outcomes were substantially different. Some differences of note between the studies is that our sample was more diverse (38% non-white vs. 6.5%), less educated, and overall less dependent, although mean CPD was nearly identical.

Taken together, there appears to be little evidence from this trial to recommend combination varenicline and bupropion over varenicline alone, as a first-line treatment to all smokers. While we did note in one subgroup analysis superiority of combination therapy for highly dependent smokers (FTCD ≥ 6) at EOT similar to those of Ebbert et al. (20), the findings were not reliable over time, nor were we able to replicate the advantage noted for those smoking >20 CPD in that same study, or for males with FTCD scores ≥ 6 and baseline CPD >20 , noted in other previous studies. (21, 22) Admittedly these later two studies involved

patch non-responders while ours did not, but in our view the evidence favoring combination therapy even for this small subgroup appears murky at best. Further study on this subgroup may be warranted, particularly since combination NRT vs patch monotherapy, as used in those studies, is more effective (40, 41) and likely to become more of a front line treatment. The lack of overall abstinence differences, the absence of consistent subgroup effects, the potential for higher adverse events, which also reduces compliance, and the lack of substantial differences in withdrawal symptoms argue against use of this combination as a front line treatment at this time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Consolidated Standards of Reporting Trials diagram for patient allocation. By design, the randomization ratio was 3:1 (Active: Placebo).

Figure 2.
Study visit timeline. EOT indicates end of mediation treatment and final counseling session; IPC, in-person counseling; PC, phone counseling; IPF, in-person 3, 6, and 12-month post-quit follow-up

Table 1

Demographic and Baseline Characteristics

Variable	Varenicline + Bupropion (Combo; N=163)	Varenicline (Var; N=166)	Placebo (N=56)	Total (N=385)
Race/Ethnicity	% (N)	% (N)	% (N)	% (N)
African-American, Non-Hispanic	26.99 (44)	25.90 (43)	28.57 (16)	26.75 (103)
White, Non-Hispanic	62.58 (102)	62.05 (103)	57.14 (32)	61.56 (237)
Hispanic	6.13 (10)	8.43 (14)	10.71 (6)	7.79 (30)
Other	4.29 (7)	3.61 (6)	3.57 (2)	3.90 (15)
Gender				
Male	58.28 (95)	59.04 (98)	57.14 (32)	58.44 (225)
Female	41.72 (68)	40.96 (68)	42.86 (24)	41.56 (160)
Marital Status				
Married or Living With Partner	42.94 (70)	53.01 (88)	62.50 (35)	50.13 (193)
Other	57.06 (93)	46.99 (78)	37.50 (21)	49.87 (192)
Employment Status				
Employed/Student	82.72 (134)	80.72 (134)	78.57 (44)	81.25 (312)
Unemployed	17.28 (28)	19.28 (32)	21.43 (12)	18.75 (72)
Depression History				
Positive	9 (5.52)	10 (6.02)	4 (7.14)	23 (5.97)
Negative	154 (94.48)	156 (93.98)	52 (92.86)	362 (94.03)
Smoking & Other	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age	49.36 (9.38)	48.75 (10.89)	48.48 (10.33)	48.97(10.17)
Years of Education	13.89 (2.11)	13.60 (1.92)	13.80 (1.89)	13.75(2.00)
Current Smoking Rate (cigs/day)	19.64 (9.49)	19.02 (9.49)	19.71 (11.20)	19.66(9.45)
Baseline Carbon Monoxide (ppm)	25.93(12.58)	27.89(15.11)	23.59(12.29)	26.43(13.74)
FTCD Total Score	4.74 (2.01)	4.65 (2.04)	5.34 (2.24)	4.79(2.07)

Table 2

Retention and Compliance.

Variable	Varenicline + Bupropion (Combo; N=163)	Varenicline (Var; N=166)	Placebo (N=56)	Total (N=385)
	% (N)	% (N)	% (N)	% (N)
Retained for 12 Week Treatment	80.98 (132)	73.49 (122)	67.86 (38)	75.84 (292)
Took 80% of Medication Dose				
Varenicline	93.17 (150)	90.38 (141)	92.16 (47)	91.85 (338)
Bupropion	93.17 (150)	90.38 (141)	90.20 (46)	91.58 (337)
Mean Percent Visit Compliance	79.72	77.79	76.98	78.52
	% (N)	% (N)	% (N)	% (N)
Stopped Medication-Total Subjects	16.56 (27)	22.90 (38)	23.21 (13)	20.26 (78)
Stopped Medication & Continued in Counseling	6.13 (10)	5.42 (9)	3.57 (2)	5.45 (21)
Stopped Medication & Dropped	10.43 (17)	17.47 (29)	19.64 (11)	14.80 (57)
Mean Percent of Total Pills Taken	%	%	%	%
All Participants				
Varenicline	92.61	91.09	93.34	92.07
Bupropion	92.64	90.59	92.76	91.79
Treatment Completers Only				
Varenicline	93.20	93.24	93.16	93.21
Bupropion	93.06	92.62	92.60	92.82
Treatment Non-completers Only				
Varenicline	89.94	83.65	93.82	87.81
Bupropion *	90.75	83.54	93.20	87.96

* Difference with uncorrected p-value: $\chi^2(2) = 6.12$, $p = 0.047$.

Table 3

Abstinence Outcome Measures over Time

	Prolonged Abstinence %Abstinent (N)	Continuous Abstinence (2-week grace) %Abstinent (N)	Continuous Abstinence (FDA) %Abstinent (N)	7-Day Point Prevalence %Abstinent (N)
Twelve Month Follow-up				
Combination Group	18.40 (30)	17.18 (28)	20.25 (33)	29.45 (48)
Varenicline Group	19.88 (33)	18.07 (30)	22.29 (37)	32.53 (54)
Placebo Group	3.57 (2)	5.36 (3)	5.36 (3)	19.64 (11)
OR (95% CI): C vs. P	6.06 (1.45, 54.09)	3.65 (1.06, 19.53)	4.46 (1.31, 23.71)	1.76 (0.84, 3.68)
Bayes Factor C vs. P	6.92	1.15	3.87	0.20
OR (95% CI): V vs. P	6.66 (1.61, 59.27)	3.88 (1.13, 20.70)	5.04 (1.49, 26.65)	1.97 (0.95, 4.11)
Bayes Factor V vs. P	13.76	1.63	9.39	0.40
OR (95% CI): C vs. V ***	0.91 (0.50, 1.64)	0.94 (0.53, 1.66)	0.89 (0.50, 1.55)	0.89 (0.56, 1.42)
Bayes Factor C vs. V	0.06	0.06	0.06	0.07
Test for Group	Score = 8.38, p 0.016 **	Score = 5.44, p 0.066 **	Score = 8.10, p 0.017 **	$\chi^2_{(2)} = 3.29$, p 0.193 *
Six Month Follow-up				
Combination Group	26.38 (43)	23.31 (38)	28.22 (46)	32.52 (53)
Varenicline Group	24.70 (41)	24.10 (40)	28.92 (48)	38.55 (64)
Placebo Group	3.57 (2)	5.36 (3)	7.14 (4)	19.64 (11)
OR (95% CI): C vs. P	9.61 (2.35, 84.82)	5.34 (1.58, 28.22)	5.08 (1.72, 20.45)	1.97 (0.94, 4.12)
Bayes Factor C vs. P	350.02	14.68	35.11	0.39
OR (95% CI): V vs. P	8.80 (2.15, 77.75)	5.78 (1.67, 29.40)	5.26 (1.79, 21.12)	2.57 (1.24, 5.32)
Bayes Factor V vs. P	147.97	21.27	49.48	2.39
OR (95% CI): C vs. V	1.09 (0.65, 1.85)	0.96 (0.56, 1.64)	0.97 (0.58, 1.60)	0.77 (0.49, 1.21)
Bayes Factor C vs. V	0.06	0.06	0.06	0.11
Test for Group	Score = 13.40, p 0.0001 **	Score = 9.71, p 0.008 **	Score = 11.57, p 0.003 **	$\chi^2_{(2)} = 6.58$, p 0.037 *
End of Treatment				
Combination Group	38.04 (62)	36.20 (59)	47.24 (77)	55.21 (90)
Varenicline Group	31.93 (53)	32.53 (54)	48.80 (81)	57.23 (95)
Placebo Group	10.71 (6)	10.71 (6)	16.07 (9)	25.00 (14)
OR (95% CI): C vs. P	5.12 (2.07, 12.63)	4.73 (1.91, 11.69)	4.68 (2.15, 10.16)	3.46 (1.77, 6.73)
Bayes Factor C vs. P	280.48	113.13	735.10	189.24
OR (95% CI): V vs. P	3.91 (1.58, 9.69)	4.02 (1.62, 9.95)	4.98 (2.29, 10.80)	3.66 (1.88, 7.12)
Bayes Factor V vs. P	16.43	21.35	1769.58	560.60
OR (95% CI): C vs. V	1.31 (0.83, 2.06)	1.18 (0.75, 1.86)	0.94 (0.61, 1.45)	0.94 (0.61, 1.46)
Bayes Factor C vs. V	0.11	0.07	0.06	0.06
Test for Group	$\chi^2_{(2)} = 12.62$, p 0.002 *	$\chi^2_{(2)} = 11.34$, p 0.004 *	$\chi^2_{(2)} = 17.21$, p 0.0002 *	$\chi^2_{(2)} = 15.62$, p 0.0004 *

* Wald Chi-Square.

** Exact Conditional Score Statistic.

*** Primary Outcome

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