Original Investigation

Combination Varenicline and Bupropion SR for Tobacco-Dependence Treatment in Cigarette Smokers
A Randomized Trial

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IMPORTANCE Combining pharmacotherapies for tobacco-dependence treatment may increase smoking abstinence.

OBJECTIVE To determine efficacy and safety of varenicline and bupropion sustained-release (SR; combination therapy) compared with varenicline (monotherapy) in cigarette smokers.

DESIGN, SETTING, AND PARTICIPANTS Randomized, blinded, placebo-controlled multicenter clinical trial with a 12-week treatment period and follow-up through week 52 conducted between October 2009 and April 2013 at 3 midwestern clinical research sites. Five hundred six adult (≥18 years) cigarette smokers were randomly assigned and 315 (62%) completed the study.

INTERVENTIONS Twelve weeks of varenicline and bupropion SR or varenicline and placebo.

MAIN OUTCOMES AND MEASURES Primary outcome was abstinence rates at week 12, defined as prolonged (no smoking from 2 weeks after the target quit date) abstinence and 7-day point-prevalence (no smoking past 7 days) abstinence. Secondary outcomes were prolonged and point-prevalence smoking abstinence rates at weeks 26 and 52. Outcomes were biochemically confirmed.

RESULTS At 12 weeks, 53.0% of the combination therapy group achieved prolonged smoking abstinence and 56.2% achieved 7-day point-prevalence smoking abstinence compared with 43.2% and 48.6% in varenicline monotherapy (odds ratio [OR], 1.49; 95% CI, 1.05-2.12; $P = .03$ and OR, 1.36; 95% CI, 0.95-1.93; $P = .09$, respectively). At 26 weeks, 36.6% of the combination therapy group achieved prolonged and 38.2% achieved 7-day point-prevalence smoking abstinence compared with 27.6% and 31.9% in varenicline monotherapy (OR, 1.52; 95% CI, 1.04-2.22; $P = .03$ and OR, 1.32; 95% CI, 0.91-1.91; $P = .14$, respectively). At 52 weeks, 30.9% of the combination therapy group achieved prolonged and 36.6% achieved 7-day point-prevalence smoking abstinence compared with 24.5% and 29.2% in varenicline monotherapy (OR, 1.39; 95% CI, 0.93-2.07; $P = .11$ and OR, 1.40; 95% CI, 0.96-2.05; $P = .08$, respectively). Participants receiving combination therapy reported more anxiety (7.2% vs 3.1%; $P = .04$) and depressive symptoms (3.6% vs 0.8%; $P = .03$).

CONCLUSIONS AND RELEVANCE Among cigarette smokers, combined use of varenicline and bupropion, compared with varenicline alone, increased prolonged abstinence but not 7-day point prevalence at 12 and 26 weeks. Neither outcome was significantly different at 52 weeks. Further research is required to determine the role of combination therapy in smoking cessation.

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Smoking accounts for 62% of deaths among female smokers and 60% of deaths among male smokers.[1] Innovative pharmacotherapeutic approaches to tobacco-dependence treatment need investigation to reduce smoking-related death and disability.

Bupropion SR (sustained-release) and varenicline are nonnicotine pharmacotherapies indicated for tobacco-dependence treatment. Bupropion SR may mediate effects through noradrenergic and dopaminergic systems[2] with a competitive inhibitory effect on nicotinic acetylcholine receptors.[3] Varenicline is a partial agonist that binds with high affinity and selectivity at $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors.[4,5] Opportunities exist for additive or synergistic therapeutic effects from combination therapy with these 2 medications.

Combination pharmacotherapy for treating tobacco dependence may increase smoking abstinence compared with monotherapy. A combination of bupropion SR and the nicotine patch is more effective than nicotine patch therapy alone,[6] suggesting that an additive benefit is achieved by combining therapies. In an open-label pilot study evaluating combination therapy with varenicline and bupropion SR, the combination was well tolerated with smoking abstinence rates exceeding those observed in prior trials with either drug as monotherapy.[7] If proven to be more effective than single-drug therapy, this therapeutic approach may have important clinical implications for tobacco-dependence treatment. Exploration of combination therapy with existing drugs may provide the best opportunity to advance treatment in the absence of any new pharmacotherapies for tobacco dependence.

To investigate the efficacy of combination pharmacotherapy with varenicline and bupropion SR for smoking cessation, compared with varenicline monotherapy, we conducted a multicenter, randomized, phase 3 clinical trial.

Methods

Study Design

A randomized, blinded, placebo-controlled clinical trial was conducted at Mayo Clinic in Rochester, Minnesota, a Mayo Clinic Health System site in La Crosse, Wisconsin, and the University of Minnesota in Minneapolis between October 2009 and April 2013. The study consisted of a 12-week treatment period with follow-up through week 52. The institutional review boards of Mayo Clinic and the University of Minnesota approved all study procedures. The trial ended when recruitment was achieved and follow-up was completed.

Screening and Eligibility Criteria

Individuals were eligible to participate if they were at least 18 years of age, smoked at least 10 cigarettes per day for at least 6 months, were motivated to become smoking abstinent, completed written informed consent, and were in good health.

Potentially eligible participants were excluded if they were pregnant, lactating, or likely to become pregnant and not willing to use contraception or had (1) an unstable medical condition; (2) another household member in the study; (3) bupropion or varenicline allergies; (4) current use (previous 30 days) of tobacco-dependence treatment and unable to discontinue use; (5) unstable angina, myocardial infarction, or coronary angioplasty (previous 3 months) or an untreated cardiac dysrhythmia; (6) a history of renal failure or renal dialysis; (7) a history of seizures; (8) current nonspecific suicidal thoughts or lifetime history of a suicidal attempt (ie, "potentially self-injurious act committed with at least some wish to die, as a result of act" [as defined by the Columbia-Suicide Severity Rating Scale[8]]); (9) a history of closed head trauma with a greater than 30-minute loss of consciousness, amnesia, skull fracture, subdural hematoma, or brain contusion; (10) a history of psychosis, bipolar disorder, bulimia, or anorexia nervosa; (11) current depression (moderate or severe [as determined by a score of ≥20 on the Beck Depression Inventory, Second Edition[9]]); (12) active substance abuse other than nicotine; (13) current use (previous 14 days) of antipsychotics, monoamine oxidase inhibitors, or drugs with bupropion SR interactions; (14) recent antidepressant dose change (previous 3 months); (15) systolic blood pressure higher than 180 mm Hg or diastolic higher than 100 mm Hg; (16) current treatment (previous 30 days) with another tobacco dependence investigational drug; or (17) current (previous 30 days) bupropion or varenicline use.

Study Procedures

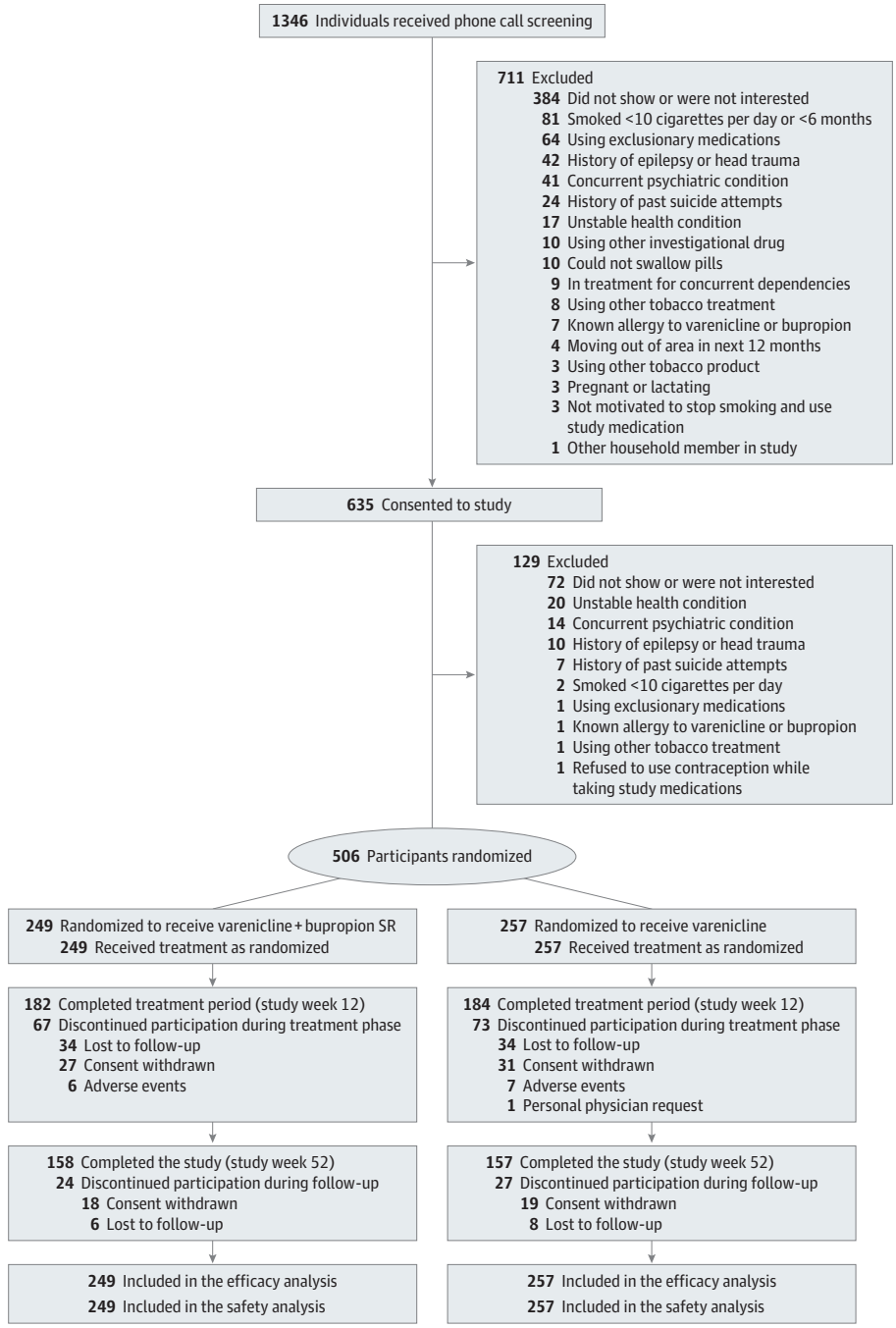
The study consisted of a telephone screening call, 11 clinic visits, and 3 follow-up telephone calls (**Figure**). One follow-up telephone call occurred during the medication phase at the time of the target quit date and 2 calls occurred after the medication phase. Two clinic visits occurred before the medication phase, 6 during the medication phase, and 3 after the medication phase.

For each participant, demographic data, tobacco use history, and self-reported information on race and ethnicity according to National Institutes of Health guidelines and recommendations for federally funded research were collected.[10] Smoking dependence was assessed using the Fagerström Test for Nicotine Dependence (score range, 0-10).[11]

Depressive symptomatology was assessed using the Beck Depression Inventory, second edition.[9] The Columbia-Suicide Severity Rating Scale assessed for suicidal ideation or behaviors.[8] Both assessments were completed at baseline and weeks 2, 4, 8, 14, 26, and 52.

A central pharmacy randomly assigned study medication in a 1:1 ratio using a computer-generated randomization sequence with variable-sized blocks ranging from 2 to 8 stratified by study site. Study medication was labeled and dispensed according to participant identification, ensuring that treatment assignment remained concealed from the participant, investigators, and all study personnel having participant contact. Following provision of informed consent, participants received randomly assigned medication at the baseline visit.

Figure. Flow of Participants in Tobacco-Dependence Treatment Study



During clinic visits, participants received brief (≤10 minutes) behavioral counseling,[12] and tobacco use status, vitals signs, exhaled-air carbon monoxide (CO) measurements (measured in parts per million [ppm]), and weight were obtained. Participants completed tobacco craving and nicotine withdrawal assessments using a daily diary containing the Minnesota Nicotine Withdrawal Scale, Revised (MNWS-R).[13] The MNWS-R consists of items assessing irritability, anxiety, tobacco craving, depressed mood, difficulty concentrating, hunger, impatience, insomnia, and restlessness. Items were rated on a 5-point scale ranging from 0 (not present) to 4 (severe) and reported symptoms for the previous day. Pill counts were conducted at clinic visits and through self reports of missed doses.

Study Medication

Participants were randomly assigned to receive varenicline + bupropion SR (combination therapy); or varenicline

+ matching bupropion SR placebo (varenicline monotherapy). Medication was started the day after the baseline visit and the target quit date was the eighth day of therapy.

Varenicline, taken orally, was administered in an open-label fashion and dispensed in blister packs. Participants started with a recommended oral dosage of 0.5 mg once daily for 3 days, titrated to 0.5 mg twice daily for days 4 to 7, and then to the maintenance dose of 1 mg twice daily (total, 2 mg/d) for 11 weeks.

Bupropion SR or identical-appearing placebo tablets were dispensed in pill bottles. Bupropion SR was titrated 1 tablet (150 mg) by mouth once per day for days 1 to 3, then 1 tablet by mouth twice per day (total of 300 mg/d) for a total of 12 weeks. Participants receiving placebo escalated dosing in the same fashion.

Study End Points

The primary end point was the biochemically confirmed prolonged and 7-day point-prevalence smoking abstinence rates at week 12. End points were selected using recommended outcomes for tobacco intervention studies.[14] A CO level of 8 ppm or less verified self-reported smoking abstinence.[15] Point prevalence was defined as CO-confirmed self-reported tobacco cessation in the previous 7 days. Participants who met criteria for CO-confirmed 7-day point-prevalence abstinence at week 12, 26, and 52 visits were defined as meeting criteria for prolonged abstinence if they submitted negative responses to both of the following questions: "Since 14 days after your target quit date, have you used any tobacco on each of 7 consecutive days?" and "Since 14 days after your target quit date, have you used any tobacco on at least 1 day in each of 2 consecutive weeks?" Secondary outcomes were prolonged and 7-day point-prevalence smoking abstinence rates at weeks 26 and 52, tobacco craving and nicotine withdrawal symptoms, and weight changes.

Statistics

All analyses were performed using the intention-to-treat approach. Smoking abstinence end points at 12 weeks (end of treatment), 26 weeks, and 52 weeks were analyzed separately using logistic regression. For these analyses, smoking abstinence was the dependent variable, treatment group was the independent variable, and study site was a covariate. Participants with missing smoking status information were adjudicated as smoking. A sample size of 250 participants per group was determined to provide statistical power (2-tailed, $\alpha = .05$) of greater than 80% to detect a difference between treatment groups for the primary end point of prolonged tobacco abstinence at end-of-treatment week 12. Sample size was based on reported smoking abstinence rates in previous trials of varenicline[16,17] and a minimum detectible odds ratio (OR) of 1.7 for the comparison of varenicline and bupropion SR vs varenicline and placebo. In addition, we conducted planned exploratory analyses to assess whether treatment effect was moderated by age, sex, baseline smoking rate (<20 cigarettes per day [lighter smokers] vs ≥20 cigarettes per day [heavier smokers]), or level of nicotine dependence (a Fagerström Test for Nicotine Dependence [FTND] score ≤5 indicating a low/moderate level of dependence vs an FTND score of ≥6 indicating a high level of dependence). For each characteristic, logistic regression analyses were performed with treatment, study site, and characteristic included as explanatory variables along with the treatment × characteristic interaction effect. If a significant interaction effect was detected, supplemental analyses were performed to compare treatment outcomes within subgroups defined by the characteristic.

The MNWS-R was completed daily. Tobacco craving was analyzed separately. A baseline score was calculated using MNWS-R data completed prior to starting medication. Scores obtained for the first 16 days after the target quit date were analyzed as change from baseline. Mixed linear models were used with the daily change score as the dependent variable and a lag-1 autoregressive covariance structure used to take into account the clustering of repeated measurements within participants. Models included effects for treatment group, study day, and the treatment × study-day interaction. Analyses were performed using all days for each participant and also using only data collected prior to the first reported tobacco use following the target quit date.

Among participants meeting criteria for prolonged abstinence, weight change from baseline was compared between groups using the 2-sample *t* test. Frequency of adverse events was compared between groups using the Fisher exact test. In all cases, 2-tailed *P* values were reported with values less than or equal to .05 considered statistically significant. Adverse events were adjudicated by the investigators. Analyses were conducted using SAS statistical software (version 9.3, SAS Institute Inc).

Results

Enrollment and Follow-up

Of 635 potentially eligible participants who consented, 506 (80%) were randomly assigned to varenicline and bupropion SR (n = 249) or varenicline and placebo (n = 257) (Figure). Overall study completion rates were 62% (315 participants), 63% (158 participants) in the varenicline and bupropion SR group (combination therapy) and 61% (157 participants) in the varenicline and placebo group (varenicline monotherapy). Patients assigned to study groups were similar at baseline (**Table 1**).

Smoking Abstinence

Combination therapy was associated with significantly higher prolonged smoking abstinence rates at 12 and 26 weeks compared with varenicline monotherapy (**Table 2**). No significant differences were observed in prolonged smoking abstinence rates between the 2 groups at 52 weeks. No significant differences were observed between the 2 groups in the 7-day point-prevalence smoking abstinence rates at any time point.

Nicotine Withdrawal and Tobacco Craving

After more than 16 days following the target quit date, no significant differences in nicotine withdrawal or craving

were observed between the 2 groups (mean treatment difference for nicotine withdrawal, 0.04 [95% CI, −0.02 to 0.10; P = .25] and mean treatment difference for craving, 0.05 [95% CI, −0.20 to 0.30; P = .70]). Similar results were obtained when the analysis included only data for days that participants reported abstinence (mean treatment difference for nicotine withdrawal, 0.03 [95% CI, −0.15 to 0.21; P = .74] and mean treatment difference for craving, 0.06 [95% CI, −0.47 to 0.59; P = .81]).

Weight Gain

Among participants meeting criteria for prolonged smoking abstinence at the end of treatment (week 12), the mean weight change from baseline to week 12 was significantly less in the combination therapy group compared with the varenicline monotherapy group (1.1 kg [95% CI, 0.5-1.7] vs 2.5 kg [95% CI, 2.0-3.0]; P < .001). At 26 weeks, differences in weight gain were not observed and participants in the combination therapy group gained 3.4 kg (95% CI, 2.5-4.3), and participants in the varenicline monotherapy group gained 3.8 kg (95% CI, 2.9-4.8) (P = .48). At week 52, weight gain from baseline for the combination therapy group was 4.9 kg (95% CI, 3.6-6.2), and for the monotherapy group it was 6.1 kg (95% CI, 4.6-7.6) (P = .23).

Adverse Events

Adverse events occurring in at least 2% of one of the study groups are listed in **Table 3**. Anxiety was reported more commonly with combination therapy than with varenicline monotherapy (7.2% vs 3.1%; P = .04). Depressive symptoms were also reported more commonly with combination therapy than with varenicline monotherapy (3.6% vs 0.8%; P = .03).

During the medication phase or within 7 days of stopping medication, 4 serious adverse events (SAEs) occurred. In the combination therapy group, 1 participant sustained trauma during a motor vehicle collision after receiving medication for 2 months. In varenicline monotherapy, the 3 events included food poisoning, diverticulitis, and breast cancer. No events were adjudicated to be related to study medication.

During follow-up and after medication discontinuation for at least 7 days, 8 SAEs were reported. Five occurred in the combination therapy group and included acute coronary syndrome, deep vein thrombosis complicated by acute coronary syndrome, prostate cancer, a new coronary artery disease diagnosis, and pneumothorax. In the varenicline monotherapy group, 3 SAEs occurred: 1 death due to complications from human immunodeficiency virus 6 months after study drug was discontinued, 1 attempted suicide 9 months after the study medication was completed, and 1 lung cancer. No events were adjudicated to be related to study medication.

Additional Analyses

Preplanned exploratory analyses were performed to assess potential moderators of the effect of treatment on abstinence. No evidence was observed showing that treatment effects differed according to age or sex (P > .25 for all age-by-treatment and sex-by-treatment interaction effects). However, evidence was observed showing that an effect of treatment on prolonged abstinence at 6 and 12 months was dependent on baseline smoking rate (interaction effect, P = .04 at 6 months and P = .01 at 12 months) and level of nicotine dependence (interaction effect, P = .03 at 6 months

Table 1. Participant Characteristics[a]

Characteristic	No. (%)	
	Varenicline + Bupropion SR (n = 249)	Varenicline + Placebo (n = 257)
Age, mean (SD), y	42.2 (12.2)	41.9 (12.7)
Sex		
Women	113 (45)	126 (49)
Men	136 (55)	131 (51)
Race		
White, non-Hispanic	234 (94)	240 (93)
Other	15 (6)	17 (7)
Marital status[b]		
Never married	73 (29)	69 (27)
Separated or divorced	53 (21)	70 (27)
Married or living as married	112 (45)	111 (43)
Widowed or other[c]	10 (4)	7 (3)
Highest level of education[b]		
≤High school graduate	54 (22)	67 (26)
Some college	156 (63)	137 (53)
≥College graduate	38 (15)	53 (21)
Current smoking rate, cigarettes per day, mean (SD)	19.5 (7.3)	19.7 (7.9)
<20 cigarettes per day	102 (41)	105 (41)
≥20 cigarettes per day	147 (59)	152 (59)
FTND, mean (SD)[d]	5.2 (2.0)	5.3 (2.0)
≤5	127 (51)	133 (52)
≥6	120 (49)	123 (48)
Duration of regular smoking, mean (SD), y[b]	23.5 (12.1)	23.3 (12.0)
Age when started smoking, mean (SD), y[b]	17.6 (3.9)	17.5 (4.1)
Ever made serious attempt to quit[b]		
No	28 (11)	19 (7)
Yes	220 (89)	238 (93)
Other tobacco users in household[b]		
No	155 (63)	162 (63)
Yes	93 (37)	95 (37)

Abbreviations: FTND, Fagerström Test for Nicotine Dependence; SR, sustained release.

[a] Data are reported as No. (%) unless otherwise indicated.

[b] Missing data for 1 participant in the varenicline + bupropion SR group.

[c] Other marital status indicates engaged or separating.

[d] Higher scores indicate greater levels of nicotine dependence (score range, 0-10; score ≤5 indicates a low/moderate level of dependence and ≥6 indicates a high level of dependence). Missing data for 1 participant in the varenicline + placebo group and 2 participants in the varenicline + bupropion group.

Table 2. Smoking Abstinence Outcomes

Overall	No. of Participants[c]	7-Day Point-Prevalence Smoking Abstinence[a] No. (%)	OR (95% CI)	P Value	Prolonged Smoking Abstinence[a,b] No. (%)	OR (95% CI)	P Value
Week 12							
Varenicline + bupropion SR	249	140 (56.2)	1.36 (0.95-1.93)	.09	132 (53.0)	1.49 (1.05-2.12)	.03
Varenicline + placebo	257	125 (48.6)			111 (43.2)		
Week 26							
Varenicline + bupropion SR	249	95 (38.2)	1.32 (0.91-1.91)	.14	91 (36.6)	1.52 (1.04-2.22)	.03
Varenicline + placebo	257	82 (31.9)			71 (27.6)		
Week 52							
Varenicline + bupropion SR	249	91 (36.6)	1.40 (0.96-2.05)	.08	77 (30.9)	1.39 (0.93-2.07)	.11
Varenicline + placebo	257	75 (29.2)			63 (24.5)		

Abbreviations: OR, odds ratio; SR, sustained release.

[a] Analyses were performed using logistic regression. In addition to treatment, the logistic regression analysis included a covariate for study site. ORs greater than 1.0 indicate an increased likelihood of abstinence for varenicline + bupropion SR compared with varenicline + placebo.

[b] Prolonged smoking abstinence indicates no smoking from 2 weeks after the target quit date.

[c] There were 179 participants (80 varenicline + bupropion SR; 99 varenicline + placebo) who did not attend the week 12 visit. Of these, 101 (47 varenicline + bupropion SR; 54 varenicline + placebo) reported smoking at the last visit or had already reported failing prolonged abstinence criteria at a prior visit. There were 203 participants (93 varenicline + bupropion SR; 110 varenicline + placebo) who had missing abstinence data at the week 26 visit of whom 118 (56 varenicline + bupropion SR; 62 varenicline + placebo) reported smoking at the last visit or had already failed prolonged abstinence criteria. There were 198 participants (93 varenicline + bupropion SR; 105 varenicline + placebo) who had missing abstinence data at the week 52 visit of whom 121 (59 varenicline + bupropion SR; 62 varenicline + placebo) reported smoking at the last visit or had already failed prolonged abstinence criteria. The number of participants with missing abstinence data is greater than the number who discontinued participation in the study.

Table 3. Adverse Events[a]

Adverse Events	No. (%) Varenicline + Bupropion SR (n = 249)	No. (%) Varenicline + Placebo (n = 257)	P Value[b]
Sleep disturbance	100 (40.2)	91 (35.4)	.27
Nausea	55 (22.1)	54 (21.0)	.83
Constipation	26 (10.4)	19 (7.4)	.28
Headache	21 (8.4)	22 (8.6)	>.99
Irritability	21 (8.4)	12 (4.7)	.11
Anxiety	18 (7.2)	8 (3.1)	.04
Difficulty concentrating	14 (5.6)	10 (3.9)	.41
Mood disturbance	13 (5.2)	7 (2.7)	.18
Dizziness	10 (4.0)	10 (3.9)	>.99
Abnormal dreams	9 (3.6)	19 (7.4)	.08
Restlessness	9 (3.6)	5 (1.9)	.29
Depressive symptoms	9 (3.6)	2 (0.8)	.03
Fatigue	7 (2.8)	17 (6.6)	.06
Dry mouth	7 (2.8)	9 (3.5)	.80
Dyspepsia	5 (2.0)	1 (0.4)	.12
Flatulence	1 (0.4)	9 (3.5)	.02

Abbreviation: SR, sustained release.

[a] Adverse events considered to be possibly, probably, or definitely related to study medication and reported by at least 2% of either study group are summarized.

[b] Fisher exact test.

and $P = .01$ at 12 months). From supplemental subgroup analyses, no differences were observed between the 2 groups at any time point for either prolonged or point-prevalence smoking abstinence among lighter smokers (<20 cigarettes per day). However, heavier smokers (≥20 cigarettes per day) receiving combination therapy were more likely to achieve prolonged smoking abstinence at weeks 12, 26, and 52 (**Table 4**) and 7-day point-prevalence smoking abstinence at weeks 26 and 52. For smokers with low/moderate levels of nicotine dependence (FTND ≤5), no difference in abstinence outcomes were detected at any time point. However, among participants with high levels of nicotine dependence (FTND ≥6), combination therapy was associated with an increased likelihood of prolonged abstinence at weeks 12, 26, and 52, and 7-day point-prevalence abstinence at week 52 (Table 4).

Table 4. Smoking Abstinence Outcomes According to Baseline Smoking Rate and Level of Nicotine Dependence

	No. of Participants	7-Day Point-Prevalence Smoking Abstinence[a]			Prolonged Smoking Abstinence[a,b]		
		No. (%)	OR (95% CI)	*P* Value	No. (%)	OR (95% CI)	*P* Value
Baseline Smoking Rate							
Lighter smokers[c]							
Week 12							
Varenicline + bupropion SR	102	61 (59.8)	1.20 (0.68-2.11)	.53	58 (56.9)	1.14 (0.65-2.01)	.65
Varenicline + placebo	105	59 (56.2)			57 (54.3)		
Week 26							
Varenicline + bupropion SR	102	41 (40.2)	0.94 (0.53-1.66)	.82	40 (39.2)	1.01 (0.57-1.80)	.97
Varenicline + placebo	105	45 (42.9)			42 (40.0)		
Week 52							
Varenicline + bupropion SR	102	40 (39.2)	1.10 (0.62-1.96)	.74	30 (29.4)	0.80 (0.43-1.46)	.47
Varenicline + placebo	105	40 (38.1)			37 (35.2)		
Heavier smokers[c]							
Week 12							
Varenicline + bupropion SR	147	79 (53.7)	1.52 (0.96-2.40)	.07	74 (50.3)	1.84 (1.16-2.93)	.01
Varenicline + placebo	152	66 (43.4)			54 (35.5)		
Week 26							
Varenicline + bupropion SR	147	54 (36.7)	1.79 (1.09-2.96)	.02	51 (34.7)	2.24 (1.32-3.81)	.003
Varenicline + placebo	152	37 (24.3)			29 (19.1)		
Week 52							
Varenicline + bupropion SR	147	51 (34.7)	1.76 (1.06-2.93)	.03	47 (32.0)	2.26 (1.31-3.92)	.004
Varenicline + placebo	152	35 (23.0)			26 (17.1)		
Level of Nicotine Dependence							
Low/Moderate[c]							
Week 12							
Varenicline + bupropion SR	127	77 (60.6)	1.20 (0.72-2.00)	.48	74 (58.3)	1.31 (0.79-2.18)	.30
Varenicline + placebo	133	74 (55.6)			68 (51.1)		
Week 26							
Varenicline + bupropion SR	127	55 (43.3)	1.16 (0.69-1.92)	.58	52 (40.9)	1.10 (0.66-1.84)	.71
Varenicline + placebo	133	54 (40.6)			52 (39.1)		
Week 52							
Varenicline + bupropion SR	127	49 (38.2)	1.11 (0.66-1.86)	.70	40 (31.5)	0.92 (0.53-1.57)	.76
Varenicline + placebo	133	49 (36.8)			45 (33.8)		
High[c]							
Week 12							
Varenicline + bupropion SR	120	62 (51.7)	1.55 (0.93-2.58)	.09	57 (47.5)	1.74 (1.04-2.93)	.04
Varenicline + placebo	123	50 (40.6)			42 (34.2)		
Week 26							
Varenicline + bupropion SR	120	39 (32.5)	1.74 (0.98-3.09)	.06	38 (31.7)	2.76 (1.47-5.21)	.002
Varenicline + placebo	123	27 (22.0)			18 (14.6)		
Week 52							
Varenicline + bupropion SR	120	41 (34.2)	2.04 (1.14-3.66)	.02	36 (30.0)	2.77 (1.44-5.30)	.002
Varenicline + placebo	123	25 (20.3)			17 (13.8)		

Abbreviations: FTND, Fagerström Test for Nicotine Dependence; OR, odds ratio; SR, sustained release.

[a] Analyses were performed using logistic regression. In addition to treatment, the logistic regression analysis included a covariate for study site. ORs greater than 1.0 indicate an increased likelihood of abstinence for varenicline + bupropion SR compared with varenicline + placebo.

[b] Prolonged smoking abstinence indicates no smoking from 2 weeks after the target quit date.

[c] The lighter smokers categories indicate less than 20 cigarettes per day; heavier smokers, at least 20 cigarettes per day; low/moderate level of nicotine dependence indicates FTND of 5 or less; high nicotine dependence, FTND of 6 or greater.

Discussion

Among cigarette smokers, the combined use of varenicline and bupropion SR, compared with varenicline alone, resulted in an increase in prolonged smoking abstinence but not 7-day point-prevalence smoking abstinence at 12 and 26 weeks. Neither outcome was significant at 52 weeks. Our observed rates of prolonged smoking abstinence with varenicline monotherapy were consistent with those of previous varenicline studies at all time points.[16,17]

We observed a greater attenuation of weight gain at 3 months in participants continuously abstinent from smoking with combination therapy compared with varenicline monotherapy. Meta-analyses have suggested that bupropion SR attenuates postcessation weight gain more than varenicline at the end of treatment.[18] In previous trials, mean weight gain with varenicline among smoking-abstinent participants from baseline to 12 weeks was 2.37 kg[16] and 2.89 kg,[17] and 2.12 kg[16] and 1.88 kg[17] for bupropion SR. Most weight gain after smoking cessation occurs in the first 3 months,[19] and weight gain has been shown in some studies to lead to smoking relapse.[20-23] Combination therapy could provide a clinical option for patients concerned about weight gain and for whom weight gain may undermine smoking cessation in the short term.

Anxiety and depressive symptoms were reported more commonly in combination therapy. In previous smoking cessation studies with varenicline and bupropion SR, no significant increases in anxiety were observed with either varenicline or bupropion SR compared with placebo.[16,17] Bupropion SR is known to be associated with anxiety when used in the treatment of tobacco dependence.[24] Tobacco withdrawal has also been associated with both anxiety and depressive symptoms.[25] All patients being treated with pharmacotherapy for tobacco dependence should be monitored for changes in anxiety and mood, an approach consistent with standard clinical practice.

This study has limited generalizability to the general population of smokers because patients with serious medical and psychiatric illnesses including those with active substance abuse were excluded. For this study, reported abstinence rates and treatment comparisons need to be interpreted with the knowledge that 38% of participants did not complete the study. This may lead to overestimation or underestimation of the true treatment effects. However, drop-out rate was comparable between the 2 groups and comparable with previous trials using varenicline for smoking cessation.[16,17] Additional analyses using multiple imputation to accommodate missing data were performed. An underlying assumption of multiple imputation analyses is that missing outcomes are absent at random. Empirical evidence suggests this is not true for smoking cessation studies in which participants who drop out are likely to have relapsed to smoking.[26] However, the assumption of this study that all who have dropped out have resumed smoking could underestimate actual abstinence rates. The analyses of the effect of treatment by smoking rate and nicotine dependence level were exploratory and hypothesis generating.

Conclusions

Among cigarette smokers, combined use of varenicline and bupropion, compared with varenicline alone, resulted in an increase in prolonged abstinence but not 7-day point-prevalence at 12 and 26 weeks; neither outcome was significantly different at 52 weeks. Further research is required to determine the role of combination treatment in smoking cessation.

ARTICLE INFORMATION

Author Contributions: Dr Ebbert had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Croghan, Schroeder, Hurt, Ebbert.
Acquisition of data: Hatsukami, Croghan, Allen, Hays, Hurt.
Analysis and interpretation of data: Hatsukami, Croghan, Schroeder, Hurt, Ebbert.
Drafting of the manuscript: Hatsukami, Croghan, Ebbert.
Critical revision of the manuscript for important intellectual content: Hatsukami, Croghan, Schroeder, Allen, Hays, Hurt.
Statistical analysis: Schroeder.
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Administrative, technical, or material support: Croghan, Hays, Hurt.
Study supervision: Hatsukami, Croghan, Allen, Ebbert.

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