

# Varenicline, an $\alpha 4\beta 2$ Nicotinic Acetylcholine Receptor Partial Agonist, vs Sustained-Release Bupropion and Placebo for Smoking Cessation

## A Randomized Controlled Trial

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**A**LTHOUGH NEARLY 41% OF smokers try to quit smoking each year, relapse is common, and only about 10% achieve and maintain abstinence.<sup>1</sup> The negative effects of nicotine withdrawal account, in part, for low success rates.<sup>2,3</sup> Approved pharmacotherapies to treat nicotine dependence (eg, nicotine replacement therapy and bupropion) have had important, albeit moderate, efficacy, with reported rates of quitting generally twice those of placebo.<sup>4</sup> Thus, additional and more efficacious therapies are needed.

Recent evidence supports a primary role of the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor (nAChR) subtype in the reinforcing effects of nicotine, as measured through dopamine turnover and release in the nucleus accumbens.<sup>5-8</sup> It

**Context** The  $\alpha 4\beta 2$  nicotinic acetylcholine receptors (nAChRs) are linked to the reinforcing effects of nicotine and maintaining smoking behavior. Varenicline, a novel  $\alpha 4\beta 2$  nAChR partial agonist, may be beneficial for smoking cessation.

**Objective** To assess efficacy and safety of varenicline for smoking cessation compared with sustained-release bupropion (bupropion SR) and placebo.

**Design, Setting, and Participants** Randomized, double-blind, parallel-group, placebo- and active-treatment-controlled, phase 3 clinical trial conducted at 19 US centers from June 19, 2003, to April 22, 2005. Participants were 1025 generally healthy smokers ( $\geq 10$  cigarettes/d) with fewer than 3 months of smoking abstinence in the past year, 18 to 75 years old, recruited via advertising.

**Intervention** Participants were randomly assigned in a 1:1:1 ratio to receive brief counseling and varenicline titrated to 1 mg twice per day ( $n=352$ ), bupropion SR titrated to 150 mg twice per day ( $n=329$ ), or placebo ( $n=344$ ) orally for 12 weeks, with 40 weeks of nondrug follow-up.

**Main Outcome Measures** Primary outcome was the exhaled carbon monoxide-confirmed 4-week rate of continuous abstinence from smoking for weeks 9 through 12. A secondary outcome was the continuous abstinence rate for weeks 9 through 24 and weeks 9 through 52.

**Results** For weeks 9 through 12, the 4-week continuous abstinence rates were 44.0% for varenicline vs 17.7% for placebo (odds ratio [OR], 3.85; 95% confidence interval [CI], 2.70-5.50;  $P < .001$ ) and vs 29.5% for bupropion SR (OR, 1.93; 95% CI, 1.40-2.68;  $P < .001$ ). Bupropion SR was also significantly more efficacious than placebo (OR, 2.00; 95% CI, 1.38-2.89;  $P < .001$ ). For weeks 9 through 52, the continuous abstinence rates were 21.9% for varenicline vs 8.4% for placebo (OR, 3.09; 95% CI, 1.95-4.91;  $P < .001$ ) and vs 16.1% for bupropion SR (OR, 1.46; 95% CI, 0.99-2.17;  $P = .057$ ). Varenicline reduced craving and withdrawal and, for those who smoked while receiving study drug, smoking satisfaction. No sex differences in efficacy for varenicline were observed. Varenicline was safe and generally well tolerated, with study drug discontinuation rates similar to those for placebo. The most common adverse events for participants receiving active-drug treatment were nausea (98 participants receiving varenicline [28.1%]) and insomnia (72 receiving bupropion SR [21.9%]).

**Conclusion** Varenicline was significantly more efficacious than placebo for smoking cessation at all time points and significantly more efficacious than bupropion SR at the end of 12 weeks of drug treatment and at 24 weeks.

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See also pp 56, 64, and 94.

has been hypothesized that  $\alpha 4\beta 2$  partial agonists could be more efficacious smoking cessation aids than currently available therapies. Partial agonists at this nAChR could stimulate the release of sufficient dopamine to reduce craving and withdrawal while simultaneously acting as a partial antagonist by blocking the binding and consequent reinforcing effects of smoked nicotine. The  $\alpha 4\beta 2$  partial agonist properties reported for cytisine, a natural plant alkaloid, provided a structural starting point for the development of varenicline, a nonnicotine, high-affinity  $\alpha 4\beta 2$  partial agonist<sup>9-11</sup> developed specifically for smoking cessation. In animal studies, the agonist effect of varenicline on dopamine release was 35% to 60% of the maximal nicotine response.<sup>11</sup>

The current phase 3 study evaluated the efficacy of varenicline compared with placebo and sustained-release bupropion (bupropion SR) in generally healthy adult smokers. Two identically designed studies were conducted at different centers. Results of one of these studies are reported here. Results of the other study are reported in a separate article in this issue of *JAMA*.<sup>12</sup>

## METHODS

### Study Design

This study was a randomized, multicenter, double-blind, parallel-group, placebo- and active-treatment-controlled, phase 3 clinical trial, with a 12-week treatment phase and blinded poststudy drug follow-up to week 52. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices Guidelines at 19 centers in the United States from June 19, 2003, to April 22, 2005. The institutional review board at each site approved the study protocol, and all participants provided written informed consent prior to any procedures.

### Study Population

Participants were recruited through media advertising. Those eligible were 18

to 75 years of age, smoked 10 or more cigarettes per day, had fewer than 3 months of smoking abstinence in the past year, and were motivated to stop smoking. Exclusion criteria were any serious or unstable disease within 6 months; seizure risk; diabetes mellitus requiring insulin or oral hypoglycemic medications; hepatic or renal impairment; clinically significant cardiovascular disease within 6 months; uncontrolled hypertension; severe chronic obstructive pulmonary disease; history of cancer (except treated basal cell or squamous cell carcinoma of the skin); and history of clinically significant allergic reactions. Other exclusion criteria were major depressive disorder within the past year requiring treatment; history of panic disorder, psychosis, bipolar disorder, or eating disorders; alcohol or drug abuse/dependency within the past year; use of tobacco products other than cigarettes; use of nicotine replacement therapy, clonidine, or nortriptyline within the month prior to enrollment; and body mass index (calculated as weight in kilograms divided by the square of height in meters) less than 15 or greater than 38 or weight less than 45.5 kg.

Because efficacy of bupropion is reduced in individuals with prior exposure compared with those who are bupropion-naïve,<sup>13</sup> participants with any prior exposure to bupropion were excluded. Those with prior varenicline exposure were also excluded. Females of childbearing potential were eligible if not pregnant or nursing and if they practiced effective contraception (oral, injectable, or implantable contraceptives; intrauterine device; or barrier method with spermicide).

### Interventions

A predefined, central, computer-generated randomization sequence assigned participants in a 1:1:1 ratio to receive varenicline, bupropion SR, or placebo using a block size of 6, and was stratified by center. Participants were randomly assigned to receive active drug or matching placebo administered orally for 12 weeks. Active drugs were titrated as follows: varenicline 0.5

mg/d for days 1 to 3, 0.5 mg twice per day for days 4 to 7, then 1 mg twice per day through week 12; bupropion SR 150 mg/d for days 1 to 3, then 150 mg twice per day through week 12. Participants and investigators were blinded to drug treatment assignments. Participants were not encouraged to guess their treatment assignment and were encouraged to eat prior to dosing and to take doses at least 8 hours apart.

All participants were dispensed study drug at the baseline visit (randomization); given *Clearing the Air: Quit Smoking Today*,<sup>14</sup> a smoking cessation self-help booklet as a guide to the quitting process; and instructed to take their first dose the next day. The target quit date was scheduled for day 8 (week 1 visit). A telephone visit was conducted 3 days following the date. Participants were neither encouraged nor discouraged from making an attempt to quit prior to the target date. During the 12-week drug treatment phase, participants attended weekly clinic visits to assess smoking status, compliance with medications, and safety. Brief ( $\leq 10$ -minute), standardized, individual counseling was provided to assist in problem solving and skills training for relapse prevention following recommendations in the Public Health Service Clinical Practice Guideline.<sup>15</sup> Those discontinuing study drug prematurely were encouraged to remain in the study, attend the remaining study visits, and complete all assessments.

Participants completing the 12-week drug treatment period were continued in a nondrug posttreatment follow-up phase for weeks 13 to 52. Clinic visits were scheduled for weeks 13, 24, 36, 44, and 52, with phone visits at weeks 16, 20, 28, 32, 40, and 48. Use of tobacco products or smoking cessation medications since the prior visit was assessed, and brief smoking cessation counseling was provided at these visits.

### Screening

Screening included a medical history, self-identification of race (white, black, Asian, or other), brief physical examination, electrocardiogram, and mea-

surement of vital signs (blood pressure, resting heart rate, and weight). Laboratory analyses included complete blood cell count, blood chemistry, and urinalysis (dipstick). A smoking history was obtained, and the Fagerström Test for Nicotine Dependence<sup>16</sup> was administered.

### **Postrandomization**

Vital signs were measured at each clinic visit. Electrocardiograms, blood chemistry analyses, and urinalyses were repeated at weeks 2 and 12 or at early termination. A physical examination was performed at week 12 or at early termination.

### **Smoking Status**

Self-report of no smoking and an exhaled carbon monoxide measurement of less than 10 parts per million (ppm), a standard criteria for assessing nonsmoking status used in smoking cessation trials,<sup>13,17</sup> was measured at baseline and each clinic visit to confirm smoking status. A nicotine use inventory was administered at clinic and telephone visits to assess self-reported smoking (even a puff) or other use of nicotine or tobacco products since the previous contact, as well as during the previous 7 days.

### **Study End Points**

The primary end point was exhaled carbon monoxide–confirmed 4-week continuous abstinence rate for weeks 9 through 12, defined as the proportion of participants who reported no smoking (not even a puff) or use of any nicotine-containing products confirmed by an exhaled carbon monoxide measurement of 10 ppm or less. The last 4 weeks of treatment end point was based on the precedent used for previous smoking cessation trials.<sup>13,18</sup>

The 2 secondary end points were continuous abstinence rates from week 9 through week 24, and from week 9 through week 52. These rates were defined as the proportion of participants who met abstinence criteria for weeks 9 through 12 and reported no smoking or use of tobacco products at clinic

or telephone visits through week 24 and separately through week 52, confirmed by exhaled carbon monoxide measurement of 10 ppm or less at clinic visits only.

Other secondary end points were the 7-day point prevalence abstinence rates at weeks 12, 24, and 52. Seven-day point prevalence abstinence was defined as the proportion of participants who met abstinence criteria for the previous 7 days at each visit (verified by measurement of exhaled carbon monoxide at clinic visits). Mean body-weight change from baseline to week 12 was summarized for all participants completing the treatment period and separately for those who were abstinent from weeks 9 through 12.

### **Measures of Craving, Withdrawal, and Reinforcing Effects of Smoking**

Three instruments were used to assess outcomes related to craving, withdrawal, and the reinforcing effects of smoking. The Minnesota Nicotine Withdrawal Scale (MNWS)<sup>19,20</sup> was administered at baseline and at weeks 1 to 7, 12, and 13. The MNWS assesses urge to smoke, depressed mood, irritability, anxiety, difficulty concentrating, restlessness, increased appetite, and sleep. The Brief Questionnaire of Smoking Urges (QSU-brief)<sup>21,22</sup> was administered at baseline and at weeks 1 through 7 and at week 12 to assess craving related to desire to smoke and expectations of positive effects. The Modified Cigarette Evaluation Questionnaire (mCEQ), used to assess the reinforcing effects of smoking,<sup>23-25</sup> was self-administered by all participants at baseline and daily during the first week of treatment (prior to target quit date), and then subsequently at visits during weeks 1 through 7 only by those who had smoked since the last time they had completed the questionnaire.

### **Adverse Events**

All observed or self-reported adverse events were documented in case report forms and followed up to resolution or end of study. Adverse events

at any dose that resulted in death, were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in a persistent or significant disability or incapacity, or resulted in congenital anomaly or birth defect were classified as serious adverse events, documented in case report forms, and reported to the sponsor.

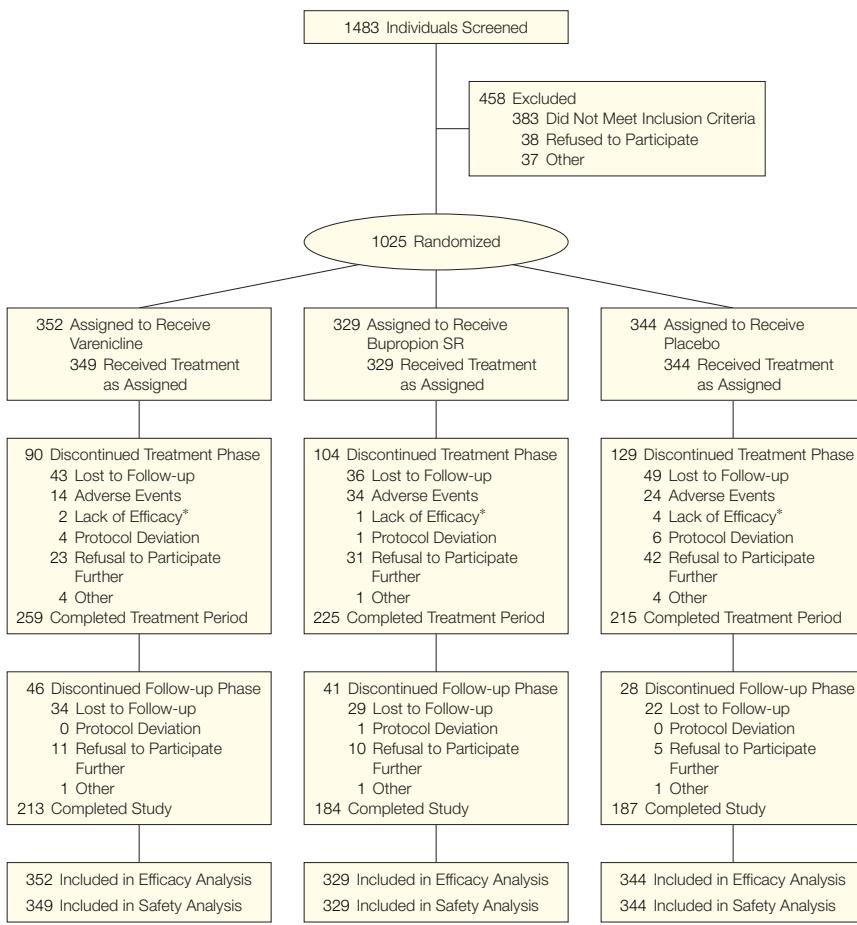
### **Statistical Analysis**

Efficacy data and intent-to-treat comparisons are reported for all randomized participants. A sample size of 335 participants per group was estimated as providing 90% power for a 2-tailed  $\chi^2$  test with  $\alpha = .05$  for the comparison between varenicline and bupropion SR for the 4-week continuous abstinence rate based on an odds ratio (OR) of 1.72 vs a bupropion SR response rate of 28.6%.<sup>26</sup>

Participants who missed visits were considered abstinent if, at the next nonmissed visit, they reported no smoking and no use of nicotine or tobacco products since the prior study visit. Those missing a carbon monoxide value but meeting the other abstinence criteria were considered nonsmokers prior to week 52. At week 52 only those attending the visit and meeting all criteria were considered abstinent. Participants who prematurely withdrew from the study were assumed to be smokers.

The 7-day point prevalence abstinence values were evaluated independently at each clinic or telephone visit. Participants with missed visits were considered smokers for that 7-day period. Missing carbon monoxide values were treated as described above.

Continuous abstinence rates for weeks 9 through 12 (carbon monoxide–confirmed) and for weeks 9 through 52 (carbon monoxide–confirmed at in-clinic visits) were analyzed as randomized using a logistic regression model, including treatment and center, and testing was carried out using the likelihood ratio  $\chi^2$  test. For these analyses, a step-down procedure was used to preserve the family-wise error rate of  $\alpha = .05$  for the 2 varenicline compari-

**Figure 1.** Participant Disposition**Table 1.** Baseline Participant Characteristics

Characteristics	Varenicline (n = 352)	Bupropion SR (n = 329)	Placebo (n = 344)
Age, mean (SD), y	42.5 (11.1)	42.0 (11.7)	42.6 (11.8)
Men, No. (%)	176 (50.0)	192 (58.4)	186 (54.1)
Race, No. (%)			
White	280 (79.5)	264 (80.2)	262 (76.2)
Black	36 (10.2)	28 (8.5)	49 (14.2)
Asian	4 (1.1)	5 (1.5)	9 (2.6)
Other	32 (9.1)	32 (9.7)	24 (7.0)
No. of years smoked, mean (SD)	24.3 (11.5)	24.1 (11.5)	24.7 (12.1)
No. of cigarettes/d in past mo, mean (SD)	21.1 (9.47)	21.0 (8.52)	21.5 (9.51)
Fagerström score, mean (SD)*	5.18 (2.16)	5.19 (2.08)	5.38 (1.99)
≥1 prior attempt to quit, No. (%)	297 (84.4)	284 (86.3)	288 (83.7)
With use of NRT	170 (48.3)	151 (45.9)	151 (43.9)

Abbreviations: bupropion SR, sustained-release bupropion; NRT, nicotine replacement therapy.

\*Range, 0 to 10. Higher scores indicate greater dependence.

sions. The hierarchy of comparisons was varenicline vs placebo followed by varenicline vs bupropion SR. All significance tests were 2-tailed using an overall level of significance of  $\alpha = .05$ . Odds ratios and 95% confidence intervals (CIs) presented are estimates from the logistic regression model reported for each treatment comparison. Treatment comparisons for 7-day point prevalence abstinence were conducted at weeks 12, 24, and 52 using the logistic regression model. Laboratory and other safety data underwent clinical review and were summarized by frequencies of events and mean changes from baseline.

Results for each subscale of the MNWS, the QSU-brief, and the mCEQ were analyzed as continuous variables from data collected at each weekly study visit through the first 7 weeks of treatment. The analysis was based on a repeated-measures model with treatment, baseline measure, center, visit, and treatment  $\times$  visit interaction as factors. Model estimates on the average effect and  $P$  values were obtained by contrasting the average over week 1 through week 7. SAS version 8.2 (SAS Institute Inc, Cary, NC) was used for all analyses.

## RESULTS

### Participant Disposition

Of 1483 participants screened, 1025 were eligible, randomly assigned to receive treatment, and included in the analysis (FIGURE 1). The 52-week study completion rates were 60.5% (213/352) for varenicline, 56% (184/329) for bupropion SR, and 54% (187/344) for placebo. Most study discontinuations occurred during the drug treatment phase. The most common reason for discontinuation for both treatment and nondrug follow-up was loss to follow-up. Compliance with medication dosing was similar across all treatment groups, with a median duration of treatment of 84 days in each of the 3 groups.

Baseline and demographic characteristics were similar across treatment groups (TABLE 1). Overall, 54% of participants were men and 79% were white.

On average, participants were 42 years old, smoked 21 cigarettes per day, and had smoked for 24 years. More than 80% had at least 1 prior attempt to quit, and 46% had previous exposure to nicotine replacement therapy.

### Continuous Abstinence

The carbon monoxide–confirmed 4-week continuous abstinence rate for weeks 9 through 12 was superior for varenicline (44.0%) vs placebo (17.7%) (OR, 3.85; 95% CI, 2.70-5.50;  $P < .001$ ) and vs bupropion SR (29.5%) (OR, 1.93; 95% CI, 1.40-2.68;  $P < .001$ ) (FIGURE 2). Bupropion SR was also superior to placebo (OR, 2.00; 95% CI, 1.38-2.89;  $P < .001$ ). The continuous abstinence rate for weeks 9 to 24 was superior for varenicline (29.5%) vs placebo (10.5%) (OR, 3.68; 95% CI, 2.42-5.60;  $P < .001$ ) and vs bupropion SR (20.7%) (OR, 1.63; 95% CI, 1.14-2.33;  $P = .007$ ). The continuous abstinence rate for weeks 9 through 52 was significantly greater for varenicline (21.9%) than for placebo (8.4%) (OR, 3.09; 95% CI, 1.95-4.91;  $P < .001$ ) but no longer significant compared with bupropion SR (16.1%) (OR, 1.46; 95% CI, 0.99-2.17;  $P = .057$ ) (Figure 2).

### Point Prevalence Abstinence

The 7-day point prevalence abstinence rates were significantly higher for varenicline compared with placebo at weeks 12, 24, and 52 ( $P < .001$  at each assessment) and were significantly higher for varenicline compared with bupropion SR at week 12 ( $P < .001$ ) and week 24 ( $P = .01$ ) (FIGURE 3).

### Sex and Baseline Comparisons

The efficacy of varenicline for smoking cessation as measured by the week 9 through 12 continuous abstinence rate was 42.9% for men and 46% for women, with no differences between them compared with placebo (men: OR, 3.75; 95% CI, 2.30-6.11;  $P < .001$ ; and women: OR, 3.63; 95% CI, 2.21-5.97;  $P < .001$ ). Likewise, analyses of other baseline characteristics by treatment group interactions did not demonstrate significant differences.

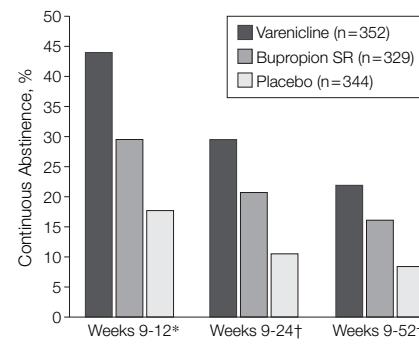
### Effects on Craving, Withdrawal, and Smoking Satisfaction

The effects of varenicline and bupropion SR compared with placebo on craving and withdrawal, measured by the MNWS and QSU-brief, are reported in TABLE 2. As assessed by subscales of the MNWS, both varenicline and bupropion SR significantly reduced urge to smoke and negative affect compared with placebo ( $P < .001$ ). The effect size of the difference from placebo for varenicline was about twice that of bupropion SR on urge to smoke and was similar to bupropion SR for negative affect. Varenicline significantly reduced restlessness ( $P = .01$ ), but the effect size was small.<sup>27</sup> The experience of increased appetite was significantly higher with varenicline than with placebo ( $P = .04$ ), but the effect size was also small. Bupropion SR did not affect restlessness or appetite but significantly increased insomnia compared with placebo ( $P = .048$ ).

Results from the QSU-brief demonstrate that, compared with placebo, the total craving score was significantly less for both varenicline ( $P < .001$ ) and bupropion SR ( $P = .001$ ). The effect size for varenicline was moderate compared with placebo but about double that of bupropion SR.

The mCEQ scores indicate that, compared with placebo, varenicline significantly reduced smoking satisfaction ( $P < .001$ ), psychological reward ( $P < .001$ ), enjoyment of respiratory tract sensations ( $P < .001$ ), and craving relief ( $P < .001$ ) after smoking, with moderate effect sizes. Bupropion SR also

**Figure 2.** Continuous Abstinence Rates

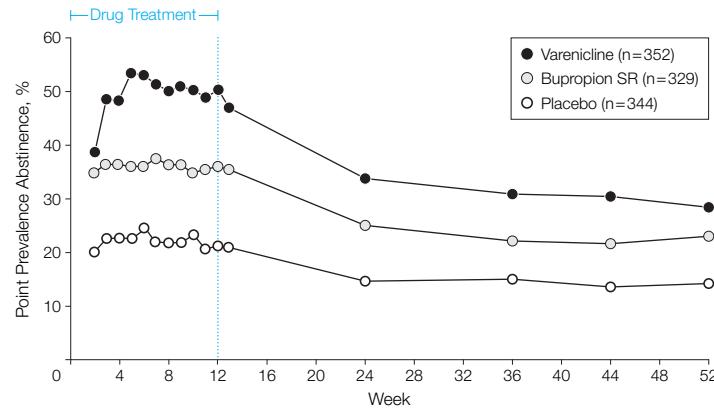


The Ns shown in the key are the denominators used for all 3 periods.  $P < .001$  for all comparisons except varenicline vs sustained-release bupropion (bupropion SR) at weeks 9 through 24 ( $P = .007$ ), varenicline vs bupropion SR at weeks 9 through 52 ( $P = .057$ ), and bupropion SR vs placebo at weeks 9 through 52 ( $P = .001$ ).

\*Abstinence confirmed by measurement of exhaled carbon monoxide.

†Clinic and telephone visits: abstinence confirmed by measurement of exhaled carbon monoxide at clinic visits.

**Figure 3.** 7-Day Point Prevalence Abstinence



The Ns shown in the key are the denominators used for all time points. The 7-day point prevalence rate of abstinence at week 12 was 50.3% for the varenicline group vs 21.2% for the placebo group ( $P < .001$ ) and 35.9% for the sustained-release bupropion (bupropion SR) group ( $P < .001$ ). At week 24, 33.5% of the varenicline group were abstinent vs 14.5% of the placebo group ( $P < .001$ ) and 24.9% of the bupropion SR group ( $P = .01$ ). At week 52, 28.1% of the varenicline group were abstinent vs 14% of the placebo group ( $P < .001$ ) and 22.8% of the bupropion SR group ( $P = .13$ ).

significantly reduced psychological reward compared with placebo ( $P=.004$ ), with an effect size about half that of varenicline (TABLE 3).

### Weight

Because smoking cessation affects weight gain, the effect of drug assignment on change in weight was analyzed separately for participants who completed the treatment period and remained abstinent for weeks 9 through 12. For these participants, mean (SD) weight gains in kilograms from baseline to week 12 were 2.37 (2.76) for varenicline, 2.12 (1.80) for bupropion SR, and 2.92 (3.94) for placebo.

### Safety and Tolerability

Of the 1025 participants, 1022 took at least 1 dose of study drug and were included in the safety analysis. Varenicline was safe and generally well tolerated. Treatment-emergent adverse events

included those that occurred up to 7 days following the end of treatment and were reported in at least 5% of participants taking varenicline and more often than with placebo (TABLE 4). The incidence of adverse events was similar across treatment groups. Study drug discontinuations due to adverse events were 8.6% for varenicline, 15.2% for bupropion SR, and 9.0% for placebo. Nausea, the most common adverse event with varenicline (28.1%), was mostly mild to moderate, diminished over time, and resulted in few treatment discontinuations (2.6%). Insomnia was the most common adverse event with bupropion SR (21.9%).

Fourteen single serious adverse events were reported during the 12 weeks of drug treatment or within 7 days of the last dose taken. For varenicline, these were abdominal pain, atrial fibrillation, pneumonia, and possible stroke; for bupropion SR, these were cholecystitis

and septic shock, headache, and grand mal seizure; and for placebo, these were lung cancer, acute myocardial infarction, schizophrenia (acute exacerbation), chest pain, urinary tract infection, atrial fibrillation, and chest pain (under arms). Two of the 14 serious adverse events were attributed to study drug. A 75-year-old white man receiving varenicline was diagnosed with atrial fibrillation at day 84, with resolution on day 95. A 47-year-old white man receiving bupropion SR experienced a grand mal seizure at day 20. Following evaluation in the emergency department the participant was released and the event considered resolved. No deaths occurred during the drug treatment phase. One participant assigned to placebo died during the 40-week nondrug follow-up.

### COMMENT

In this large phase 3 randomized trial, varenicline was found to be effica-

**Table 2.** Measures of Withdrawal and Craving Using MNWS & QSU-brief: Repeated-Measures Analysis of Data for Week 1 through Week 7

No.*	Least-Square Mean (SE)†	Comparison vs Placebo			
		MNWS			
<b>Varenicline</b>					
Urge to smoke	341 1.11 (0.04)	-0.54 (0.06)	(-0.66 to -0.42)	<.001	-0.67
Negative affect	341 0.59 (0.03)	-0.19 (0.04)	(-0.27 to -0.11)	<.001	-0.30
Restlessness	340 0.70 (0.04)	-0.14 (0.05)	(-0.24 to -0.03)	<.01	-0.16
Increased appetite	341 1.04 (0.05)	0.12 (0.06)	(0.00 to 0.24)	.04	0.15
Insomnia	341 0.69 (0.04)	0.05 (0.05)	(-0.05 to 0.15)	.36	0.06
<b>Bupropion SR</b>					
Urge to smoke	318 1.41 (0.05)	-0.24 (0.06)	(-0.36 to -0.12)	<.001	-0.30
Negative affect	318 0.62 (0.03)	-0.16 (0.04)	(-0.25 to -0.08)	<.001	-0.25
Restlessness	317 0.74 (0.04)	-0.09 (0.05)	(-0.20 to 0.01)	.08	-0.10
Increased appetite	318 0.88 (0.05)	-0.04 (0.06)	(-0.16 to 0.08)	.56	-0.05
Insomnia	318 0.75 (0.04)	0.11 (0.05)	(0.00 to 0.21)	.048	0.13
<b>Placebo</b>					
Urge to smoke	337 1.65 (0.05)				
Negative affect	337 0.78 (0.03)				
Restlessness	337 0.84 (0.04)				
Increased appetite	336 0.92 (0.05)				
Insomnia	337 0.64 (0.04)				
<b>QSU-brief Total Craving Score</b>					
Varenicline	341 1.69 (0.05)	-0.45 (0.06)	(-0.57 to -0.32)	<.001	-0.33
Placebo	337 2.13 (0.05)				
Bupropion SR	318 1.92 (0.05)	-0.21 (0.07)	(-0.34 to -0.08)	.001	-0.15

Abbreviations: bupropion SR, sustained-release bupropion; CI, confidence interval; MNWS, Minnesota Nicotine Withdrawal Scale; QSU-brief, Brief Questionnaire of Smoking Urges.  
\*Includes data for all participants who had an assessment for the subscale both at baseline and at least 1 of the visits for weeks 1 through 7.

†Higher scores on the MNWS (range of possible scores, 0-4) indicate greater intensity of symptoms. Higher scores on the QSU-brief (range of possible scores, 1-7) indicate greater intensity of urge to smoke.

‡Least-square mean difference divided by the pooled SD at baseline.

**Table 3.** Measurement of Smoking Reinforcement Using mCEQ: Repeated-Measures Analysis of Data for Week 1 through Week 7 for Participants Who Smoked

	No.*	Least-Square Mean (SE)†	Comparison vs Placebo				
			Difference (SE)	95% CI	P Value	Effect Size‡	
<b>Varenicline</b>							
Smoking satisfaction	298	2.43 (0.08)	-0.60 (0.10)	(-0.80 to -0.41)	<.001	-0.47	
Psychological reward	298	2.05 (0.06)	-0.50 (0.08)	(-0.65 to -0.34)	<.001	-0.37	
Enjoyment of respiratory tract sensations	298	1.71 (0.07)	-0.34 (0.09)	(-0.52 to -0.16)	<.001	-0.21	
Craving reduction	298	3.47 (0.10)	-0.52 (0.13)	(-0.77 to -0.27)	<.001	-0.33	
Aversion	296	1.86 (0.07)	-0.18 (0.09)	(-0.36 to 0.00)	.053	-0.19	
<b>Bupropion SR</b>							
Smoking satisfaction	290	2.89 (0.08)	-0.13 (0.10)	(-0.32 to 0.06)	.18	-0.10	
Psychological reward	290	2.32 (0.06)	-0.23 (0.08)	(-0.38 to -0.07)	.004	-0.17	
Enjoyment of respiratory tract sensations	289	2.09 (0.07)	0.04 (0.09)	(-0.14 to 0.22)	.67	0.02	
Craving reduction	290	3.99 (0.10)	0.00 (0.13)	(-0.25 to 0.24)	.98	0.00	
Aversion	288	1.86 (0.07)	-0.17 (0.09)	(-0.35 to 0.00)	.056	-0.18	
<b>Placebo</b>							
Smoking satisfaction	319	3.03 (0.07)					
Psychological reward	319	2.55 (0.06)					
Enjoyment of respiratory tract sensations	319	2.05 (0.07)					
Craving reduction	319	3.99 (0.09)					
Aversion	319	2.04 (0.06)					

Abbreviations: bupropion SR, sustained-release bupropion; CI, confidence interval; mCEQ, Modified Cigarette Evaluation Questionnaire.

\*Includes data for all participants who had an assessment for the subscale both at baseline and at least 1 of the visits for weeks 1 through 7.

†Higher scores indicate greater intensity of smoking effects (range of possible scores, 1-7).

‡Least-square mean difference divided by the pooled SD at baseline.

cious for smoking cessation. The end-of-treatment continuous abstinence rate for varenicline was nearly 2.5 times that for placebo, was similar for men and women, and was sustained through 24 and 52 weeks. Varenicline was also more efficacious than bupropion SR through 24 weeks.

The potential role of partial agonists to treat addictions<sup>28,29</sup> and the primary role of the  $\alpha 4\beta 2$  nAChR subtype in nicotine dependence were the theoretical underpinnings for the development of varenicline.<sup>11</sup> Partial agonists may act by 2 mechanisms. First, by partially activating the  $\alpha 4\beta 2$  nAChR, craving and withdrawal symptoms may be mitigated following abrupt cessation or reduction of nicotine consumption. Second, by occupying part of the receptors and blocking nicotine binding, a partial agonist may also act as a partial antagonist to reduce smoking satisfaction prior to quitting or following a slip or relapse. Both of these effects were observed in the current trial. The MNWS and the QSU-brief demonstrated reduced craving and withdrawal symptoms with varenicline. In

**Table 4.** Treatment-Emergent Adverse Events (Including Those Not Necessarily Related to Study Drug)\*

	No. (%)		
	Varenicline (n = 349)	Bupropion SR (n = 329)	Placebo (n = 344)
Any adverse event	275 (78.8)	258 (78.4)	257 (74.7)
<b>Most Frequent Adverse Events*</b>			
Gastrointestinal disorders			
Nausea	98 (28.1)	41 (12.5)	29 (8.4)
Dry mouth	23 (6.6)	29 (8.8)	19 (5.5)
Flatulence	20 (5.7)	14 (4.3)	10 (2.9)
Constipation	19 (5.4)	23 (7.0)	13 (3.8)
Psychiatric disorders			
Insomnia	49 (14.0)	72 (21.9)	44 (12.8)
Abnormal dreams†	36 (10.3)	18 (5.5)	19 (5.5)
Irritability	21 (6.0)	17 (5.2)	20 (5.8)
Sleep disorder	20 (5.7)	13 (4.0)	13 (3.8)
Nervous system disorders			
Headache	54 (15.5)	47 (14.3)	42 (12.2)
Dizziness	21 (6.0)	19 (5.8)	20 (5.8)
Nasopharyngitis	20 (5.7)	17 (5.2)	18 (5.2)
<b>Study Drug Treatment Discontinuations Due to Adverse Events‡</b>			
All causes	30 (8.6)	50 (15.2)	31 (9.0)
Nausea	9 (2.6)	6 (1.8)	1 (0.3)

Abbreviation: bupropion SR, sustained-release bupropion.

\*Treatment-emergent adverse events were defined as adverse events that began or increased in severity during study-drug treatment or up to 7 days after the last dose. Reported events occurred at 5% or more for varenicline and at a higher frequency than reported for placebo.

†Self-described as any change in dreaming, such as vivid dreams or increased frequency of dreaming.

‡Includes participants who discontinued study drug treatment but remained in the study, as well as those who discontinued the overall study.

addition, the mCEQ demonstrated a clear effect of varenicline in reducing some rewarding effects associated with smoking.

These dual effects may be evident in the increase in point prevalence rate for varenicline through week 5. The point prevalence rate for bupropion SR plateaued at 1 to 2 weeks and remained relatively flat during drug treatment. This early plateauing effect for bupropion SR is consistent with observations from earlier trials.<sup>17</sup> The trend of increasing quit rates over time for varenicline may indicate decreased reinforcing effects of smoking.

An important feature of the study design was the inclusion of bupropion, the only previously approved smoking cessation medication not containing nicotine, as an active comparator. Comparison with an active agent is particularly important, as the availability of novel compounds for smoking cessation will create new choices for treatment. To prevent a negative bias against bupropion, individuals who had any prior exposure to bupropion were excluded. A difference between the drugs, therefore, could not be affected by participants who had relapsed while receiving prior bupropion treatment. This approach allows for a clear comparison between the 2 drugs.

This study does not address the effects of varenicline on smokers with a history of bupropion use. Since some smokers may have taken bupropion for smoking cessation or treatment of depression, there may be limitations when interpreting these results for a broader population. Similarly, the generally healthy smokers included in this trial may not be representative of smokers most likely to seek treatment.

The continuous abstinence rate at week 52 for those assigned to receive bupropion SR was somewhat lower than that reported in prior bupropion SR studies reporting 52-week continuous abstinence rates.<sup>17,18</sup> However, study completion rates in this trial were similar across all treatment groups, and placebo response rates were similar to prior investigations of bupropion SR.<sup>17</sup>

It is now recognized that nicotine dependence is a chronic, relapsing disease.<sup>4</sup> Although all participants continued to receive brief counseling throughout the trial, abstinence rates declined in all groups after drug treatment ended, and the differences between the drug treatment groups diminished by 52 weeks. Investigating how to improve longer-term outcomes is an important future step. In a separate trial of participants who achieved abstinence after 12 weeks of open-label varenicline therapy, an additional 12 weeks of double-blinded varenicline therapy led to greater long-term abstinence rates than did placebo.<sup>30</sup>

While varenicline was safe and generally well tolerated, gastrointestinal and sleep disorders were more common with varenicline than with placebo. However, few participants discontinued drug treatment due to nausea, the most common adverse event for varenicline. Overall, the rate of adverse events was similar across all groups. Study drug discontinuations due to adverse events for varenicline were similar to those for placebo (8.6% vs 9.0%) and fewer than those for bupropion SR (15.2%).

## CONCLUSIONS

Varenicline is an efficacious therapy for smoking cessation. In this trial, varenicline was more efficacious than placebo at all time points and more efficacious than bupropion SR at the end of 12 weeks of treatment and at 24 weeks. Additionally, the hypothesis that a partial nAChR agonist would effectively reduce cravings and smoking satisfaction or reinforcement was supported and suggests a new direction for development of smoking cessation therapies.

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**Independent Statistical Analysis:** Barbara Pizacani, PhD, Adjunct Faculty at the School of Nursing at Oregon Health & Science University (OHSU) and Epidemiologist in Program Design and Evaluation Services for Multnomah Health Department and Oregon Department of Human Services, and Clyde Dent, PhD, of the Program Design and Evaluation Services of Multnomah County Health Department and Oregon Department of Human Services, had access to all of the data used in the study and performed an independent analysis in consultation with Dr Gonzales. The independent analysis replicated the analyses of the primary and secondary end points reported in the manuscript using cross tabulations, logistic regression, and mixed-model procedures. Repeat tabulations for other end points were performed. Results for the adverse events were also replicated. Results were comparable with those obtained by the sponsor. While there were several small discrepancies, all were resolved prior to submission of the manuscript and none affected the

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## REFERENCES

1. Centers for Disease Control and Prevention. Cigarette smoking among adults—United States, 2002. *MMWR Morb Mortal Wkly Rep.* 2004;53:427-431.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition, Revised. Washington, DC: American Psychiatric Association; 2000.
3. Shiffman S, West R, Gilbert D. Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. *Nicotine Tob Res.* 2004;6:599-614.
4. Fiore MC, Bailey WC, Cohen SJ, et al. *Treating Tobacco Use and Dependence: Quick Reference Guide for Clinicians*. Rockville, Md: US Dept of Health and Human Services, Public Health Service; 2000.
5. Maskos U, Molles BE, Pons S, et al. Nicotine reinforcement and cognition restored by targeted expression of nicotinic receptors. *Nature.* 2005;436:103-107.
6. Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. *Eur J Pharmacol.* 2000;393:295-314.
7. Tapper AR, McKinney SL, Nashmi R, et al. Nicotine activation of alpha4\* receptors: sufficient for reward, tolerance, and sensitization. *Science.* 2004;306:1029-1032.
8. Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature.* 1996;382:255-257.
9. Papke RL, Heinemann SF. Partial agonist properties of cytisine on neuronal nicotinic receptors containing the beta 2 subunit. *Mol Pharmacol.* 1994;45:142-149.
10. Scharfenberg G, Benndorf S, Kempe G. Cytisine (Tabex) as a pharmaceutical aid in stopping smoking [in German]. *Dtsch Gesundheitsw.* 1971;26:463-465.
11. Coe JW, Brooks PR, Wirtz MC, et al. 3,5-Bicyclic aryl piperidines: a novel class of alpha4beta2 neuronal nicotinic receptor partial agonists for smoking cessation. *Bioorg Med Chem Lett.* 2005;15:4889-4897.
12. Jorenby DE, Hays JT, Rigotti NA, et al; for the Varenicline Phase 3 Study Group. Efficacy of varenicline, an  $\alpha4\beta2$  nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA.* 2006;296:56-63.
13. Gonzales DH, Nides MA, Ferry LH, et al. Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. *Clin Pharmacol Ther.* 2001;69:438-444.
14. National Cancer Institute. *Clearing the Air: Quit Smoking Today*. Washington, DC: National Institutes of Health; 2003. NIH publication 03-1647.
15. Fiore MC. Treating tobacco use and dependence: an introduction to the US Public Health Service Clinical Practice Guideline. *Respir Care.* 2000;45:1196-1199.
16. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict.* 1991;86:1119-1127.
17. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med.* 1999;340:685-691.
18. Tønnesen P, Tonstad S, Hjalmarsen A, et al. A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. *J Intern Med.* 2003;254:184-192.
19. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry.* 1986;43:289-294.
20. Cappelleri JC, Bushmakina AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Revealing the multidimensional framework of the Minnesota nicotine withdrawal scale. *Curr Med Res Opin.* 2005;21:749-760.
21. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res.* 2001;3:7-16.
22. Cappelleri JC, Bushmakina AG, Baker CL, et al. Confirmatory validation of the brief questionnaire of smoking urges. *Value Health.* 2005;8:334.
23. Brauer LH, Behm FM, Lane JD, Westman EC, Perkins C, Rose JE. Individual differences in smoking reward from de-nicotinized cigarettes. *Nicotine Tob Res.* 2001;3:101-109.
24. Rose JE, Behm FM, Westman EC. Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. *Exp Clin Psychopharmacol.* 1998;6:331-343.
25. Cappelleri JC, Bushmakina AG, Baker CL, et al. Confirmatory factor analysis and reliability of the "smoking effects inventory." *Value Health.* 2005;8:333.
26. Nides M, Oncken C, Gonzales D, et al. Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with one-year follow-up. *Arch Intern Med.* In press.
27. Cohen J. *Statistical Power for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.
28. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. *Arch Gen Psychiatry.* 1978;35:501-516.
29. Vocci FJ, Acri J, Elkashaf A. Medication development for addictive disorders: the state of the science. *Am J Psychiatry.* 2005;162:1432-1440.
30. Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR; for the Varenicline Phase 3 Study Group. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA.* 2006;296:64-71.