Efficacy of Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Placebo or Sustained-Release Bupropion for Smoking Cessation

A Randomized Controlled Trial

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Context Varenicline, a partial agonist at the α4β2 nicotinic acetylcholine receptor, has the potential to aid smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding properties of nicotine.

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

Design, Setting, and Participants A randomized, double-blind, placebo-controlled trial conducted between June 2003 and March 2005 at 14 research centers with a 12-week treatment period and follow-up of smoking status to week 52. Of 1413 adult smokers who volunteered for the study, 1027 were enrolled; 65% of randomized participants completed the study.

Intervention Varenicline titrated to 1 mg twice daily (n=344) or bupropion SR titrated to 150 mg twice daily (n=342) or placebo (n=341) for 12 weeks, plus weekly brief smoking cessation counseling.

Main Outcome Measures Continuous abstinence from smoking during the last 4 weeks of treatment (weeks 9-12; primary end point) and through the follow-up period (weeks 9-24 and 9-52).

Results During the last 4 weeks of treatment (weeks 9-12), 43.9% of participants in the varenicline group were continuously abstinent from smoking compared with 17.6% in the placebo group (odds ratio [OR], 3.85; 95% confidence interval [CI], 2.69-5.50; $P<.001$) and 29.8% in the bupropion SR group (OR, 1.90; 95% CI, 1.38-2.62; $P<.001$). For weeks 9 through 24, 29.7% of participants in the varenicline group were continuously abstinent compared with 13.2% in the placebo group (OR, 2.83; 95% CI, 1.91-4.19; $P<.001$) and 20.2% in the bupropion group (OR, 1.69; 95% CI, 1.19-2.42; $P=.003$). For weeks 9 through 52, 23% of participants in the varenicline group were continuously abstinent compared with 10.3% in the placebo group (OR, 2.66; 95% CI, 1.72-4.11; $P<.001$) and 14.6% in the bupropion SR group (OR, 1.77; 95% CI, 1.19-2.63; $P=.004$). Treatment was discontinued due to adverse events by 10.5% of participants in the varenicline group, 12.6% in the bupropion SR group, and 7.3% in the placebo group. The most common adverse event with varenicline was nausea, which occurred in 101 participants (29.4%).

Conclusions Varenicline is an efficacious, safe, and well-tolerated smoking cessation pharmacotherapy. Varenicline's short-term and long-term efficacy exceeded that of both placebo and bupropion SR.

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CIGARETTE SMOKING REMAINS the leading preventable cause of illness and premature death in the United States, claiming an estimated 438 000 lives per year.[1] Research over the past 3 decades has identified effective treatments for smoking, including counseling, social support, and several pharmacotherapies.[2] However, current pharmacological and nonpharmacological smoking cessation treatments have limited efficacy and are not widely disseminated to the general population of smokers.[3,4] Improvements are needed, both in the efficacy of current treatment and in the dissemination of current therapies.

Six smoking cessation pharmacotherapies are currently approved by the US Food and Drug Administration. Five of these are nicotine replacement products (gum, patch, nasal spray, inhaler, and lozenge). Each delivers nicotine, the agent that is responsible for the development of tobacco dependence,[5] in a way that allows an individual to reduce nicotine withdrawal symptoms

See also pp 47, 64, and 94.

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and cravings for cigarettes when quitting smoking. Since nicotine gum first became available in 1984, hundreds of studies have evaluated the efficacy of nicotine replacement therapies. Recent meta-analyses of this literature reported odds ratios (ORs) in the range of 1.5 to 2.7 compared with placebo for long-term (generally ≥6 months) abstinence, whether the outcome measure was point prevalence abstinence[2] or continuous abstinence.[6]

The other smoking cessation pharmacotherapy approved by the Food and Drug Administration, sustained-release bupropion (bupropion SR), is an aminoketone antidepressant that increases smoking cessation rates compared with placebo[7] and compared with the nicotine patch.[8] In addition, bupropion may delay relapse to smoking.[9] Bupropion is hypothesized to aid smoking cessation by inhibiting dopamine reuptake in the mesolimbic dopamine system (the so-called reward center of the brain). A meta-analysis of bupropion SR efficacy yielded ORs ranging from 1.43 to 2.13 compared with placebo for long-term abstinence.[6]

The dependence-producing properties of nicotine are believed to be mediated by the α4β2 subtype of the nicotinic acetylcholine receptor located in the ventral tegmental area of the brain.[10] Varenicline is a partial agonist at the α4β2 nicotinic acetylcholine receptor.[11] As a partial agonist, varenicline theoretically offers the therapeutic benefit of relieving symptoms of nicotine withdrawal and cigarette craving through its agonist actions while blocking the reinforcing effects of continued nicotine use through an antagonist action. Previous efforts to use nicotinic receptor antagonists, primarily mecamylamine,[12] to aid smoking cessation by removing the reinforcing effects of nicotine have produced inconsistent results.[2] The present study was designed to assess the efficacy and safety of varenicline for smoking cessation compared with placebo and bupropion SR during initial treatment and long-term follow-up.

METHODS

Study Design

A randomized, double-blind, placebo-controlled trial was conducted at 14 research centers between June 2003 and March 2005. The study consisted of a 12-week treatment period with follow-up of smoking status to week 52. Written informed consent was obtained from all participants. Consent forms and procedures were approved by institutional review boards at each site. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki[13] and the standards on good clinical practice developed by the International Conferences on Harmonization.[14]

Screening and Eligibility Criteria

Women and men who were between the ages of 18 and 75 years, had smoked 10 cigarettes/d or more during the previous year, and had no period of smoking abstinence longer than 3 months in the past year were eligible for the study. All participants were screened using a combination of a telephone interview and 2 in-person visits during which medical history, physical examination, vital signs, electrocardiogram, serum pregnancy test (for women of childbearing potential), blood chemistry, hematology, and urinalysis were obtained.

Exclusion criteria included previous use of bupropion in any form; contraindications for use of bupropion (eg, history of seizure, diagnosis of eating disorder, use of a monoamine oxidase inhibitor in the prior 14 days, hepatic or renal impairment, diabetes requiring insulin, oral hypoglycemics); serious or unstable disease within the previous 6 months; clinically significant cardiovascular disease in the previous 6 months; uncontrolled hypertension; baseline systolic blood pressure higher than 150 mm Hg or diastolic blood pressure higher than 95 mm Hg; severe chronic obstructive pulmonary disease; history of cancer; clinically significant allergic reactions; body mass index (calculated as weight in kilograms divided by height in meters squared) of less than 15 or higher than 38; body weight of less than 45 kg; history of alcohol or other drug abuse or dependence in the previous 12 months (nicotine excepted); treatment for major depression in the previous 12 months; history of or current panic disorder, psychosis, or bipolar disorder; use of another investigational drug within 30 days; intention to donate blood or blood products during the treatment phase of the study (12 weeks); previous participation in any varenicline study; use in the previous month or intention to use medications that might interfere with study medication evaluation (eg, nicotine replacement, nortriptyline, clonidine); use of marijuana or other tobacco products during the study; clinically significant abnormalities in the screening laboratory values. Female participants of childbearing potential were required to have a negative serum pregnancy test at baseline and agree to use effective birth control during the treatment phase of the study and for 30 days thereafter.

Study Procedures

Following successful completion of the screening procedures, baseline data were collected. Race and ethnicity was self-reported. The Fagerström Test for Nicotine Dependence was administered. This test is a 6-item measure that is scored between 0 and 10, with higher scores reflecting greater nicotine dependence.[15] Participants were randomly assigned to 1 of the 3 treatment groups in a double-blind manner. Randomization was completed centrally by using a computer-generated list and sites used an electronic system to assign participants to treatment.

Participants were asked to stop smoking completely on their target quit date, which was set at 8 days following their baseline study visit. Brief (≤10 min) smoking cessation counseling, which followed the US Public Health Service guidelines,[2] was provided at the baseline visit and at each weekly visit during the following 12 weeks. Each participant also received a 5-minute telephone call 3 days after the target quit date. At each weekly study visit, participants were asked about their use of cigarettes and other forms of nicotine

since their last study visit and in the past 7 days. Vital signs and expired carbon monoxide were assessed along with reports of adverse events and changes in concomitant medications.

At baseline, weeks 1 through 7, and weeks 12 through 13, all participants completed the Minnesota Nicotine Withdrawal Scale, a 9-item scale in which withdrawal symptoms are rated on a scale of 0 (not at all) to 4 (extreme).[16] The Brief Questionnaire of Smoking Urges is a 10-item scale of craving for which statements are rated on a scale of 1 (strongly disagree) to 7 (strongly agree).[17] Ratings on this scale were completed during weeks 1 through 7. The Modified Cigarette Evaluation Questionnaire is a 12-item scale assessing the reinforcing effects of smoking in which questions are rated on a scale of 1 (not at all) to 7 (extremely)[18]; this questionnaire was administered at baseline to all participants. If a participant smoked during the study, this questionnaire was to be completed during the week preceding the target quit date and at each weekly visit through week 7. At weeks 2 and 12 (or if a participant ended study participation before the end of the treatment period), the electrocardiogram, blood chemistry, hematology, and urinalysis were repeated.

Following the week 12 visit, participants completed a 40-week nontreatment follow-up period. Clinic visits were held at weeks 13, 24, 36, 44, and 52. Each clinic visit included brief smoking cessation counseling, assessment of cigarette and other tobacco use since the previous contact and over the previous 7 days, assessment of vital signs and expired carbon monoxide, and use of medications for smoking cessation. Brief telephone contacts at weeks 16, 20, 28, 32, 40, and 48 assessed cigarette and other tobacco use as well as use of medications for smoking cessation.

Study Medication

Treatment phase doses were 1 mg of varenicline twice daily and 150 mg of bupropion SR twice daily for 12 weeks, with an initial dose titration to full strength during the first week for both drugs. Treatment with the study drug began the day following the baseline visit for a full week before the target quit date. To maintain the study blind, each participant randomized to treatment was dispensed 2 folders of study medication each week. Individuals assigned to active varenicline received a folder of active varenicline and placebo bupropion SR; individuals assigned to active bupropion SR received a folder of placebo varenicline and active bupropion SR; and individuals assigned to placebo received a folder of placebo varenicline and placebo bupropion SR. Folders for all participants (regardless of treatment assignment) were identical throughout the treatment phase including a period of dose titration (week 1) and treatment at the target dose (weeks 2-12).

Outcome Measures and Statistical Methods

The primary end point was the 4-week continuous abstinence rate for the last 4 weeks of study drug treatment (weeks 9-12). Continuous abstinence rates from weeks 9 through 24 and weeks 9 through 52 were evaluated as secondary end points. To facilitate comparisons with the existing literature, 7-day point prevalence abstinence was evaluated at weeks 12 (end of treatment), 24, and 52. Abstinence at each visit was defined as a self-report of no smoking or use of other nicotine-containing products (or other tobacco during follow-up) since the previous visit or contact (or previous 7 days in the case of the point prevalence measure), confirmed by an expired carbon monoxide level of 10 ppm or less.

Participants whose smoking status was unknown or whose carbon monoxide level was higher than 10 ppm were classified as smoking during both the treatment phase and follow-up. The only exception to this rule was for assessing the continuous abstinence end points in the case of missed visits: if at the next visit there was a self-report of no smoking or use of other tobacco products (including other nicotine-containing products during the treatment period), a status of not smoking was imputed for the missed visits. At week 52, only those who met all criteria were classified as abstinent.

All primary and secondary end points were analyzed for the population of all randomized participants. All statistical tests were 2-sided with a type I error rate of .05. A step-down procedure was used for the analysis of the primary and key secondary end points to protect against type I error inflation due to the comparisons of varenicline with placebo and bupropion SR. Abstinence rates were expressed as binary data and were analyzed using a logistic regression model including main effects of treatment group and study center.

A sample size of 335 participants per group was chosen to have 90% power to detect a difference between varenicline and bupropion SR for the primary measure for weeks 9 through 12 based on observed cessation rates in an earlier study (OR of 1.72 referenced to a bupropion SR cessation rate of 28.6%).[19] Statistical significance was declared within each end point first by comparison of varenicline with placebo and then by comparison of varenicline with bupropion SR until a $P>.05$ was attained.

Questionnaire data were analyzed using a repeated-measures model (including treatment group, study center, visit, baseline measure, and treatment × visit interaction) with least-squares means reported for the 2 active treatments (varenicline and bupropion SR) compared with placebo. Adverse events were expressed in Medical Dictionary for Regulatory Activities terms and summarized by system organ class for comparison between groups. Statistical analyses were performed using SAS software version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Enrollment and Follow-up

The flow of participants through the study appears in FIGURE 1. Of 1413 volunteers who were screened, 1027 (72.7%) were enrolled and randomly assigned to 1 of 3 treatment groups: varenicline (n=344), bupropion SR (n=342), or placebo (n=341).

Overall study completion rates at week 52 were 70% (240 participants) in the varenicline group, 65% (221 participants) in the bupropion SR group, and 60% (204 participants) in the placebo group. More participants in the placebo group failed to complete the study. There were no differences in demographic variables or baseline characteristics across the 3 groups. The demographic and smoking history characteristics of all randomized participants appear in TABLE 1.

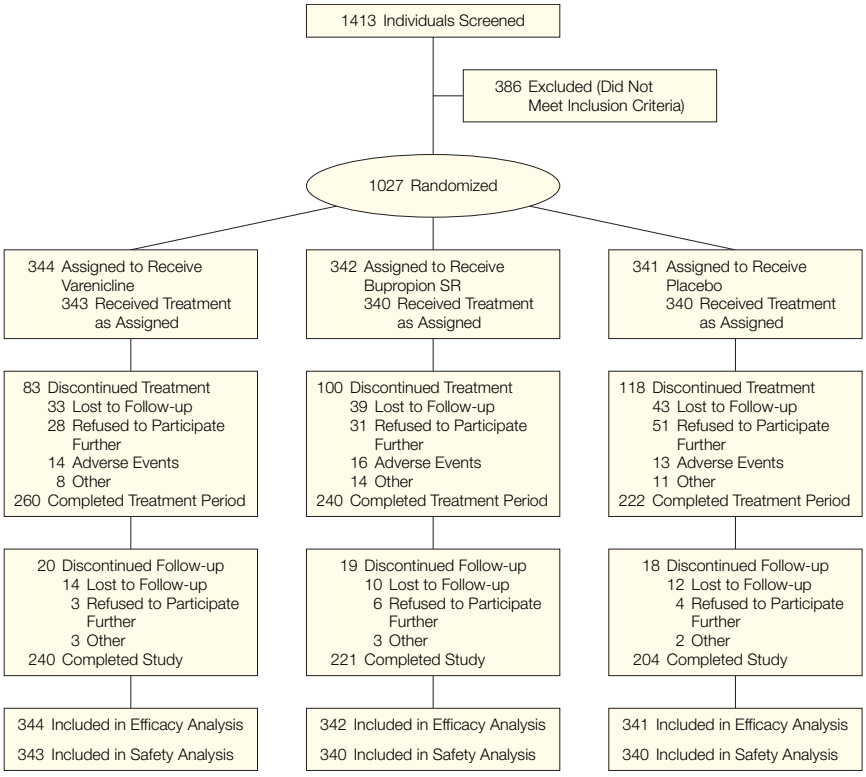
Efficacy

The primary and secondary continuous smoking abstinence outcomes for weeks 9 through 12 at the end of treatment (primary outcome measure) and during follow-up (secondary outcome measures; weeks 9-24 and weeks 9-52) appear in FIGURE 2. Varenicline produced higher continuous abstinence rates than placebo at all time points. During the last 4 weeks of treatment (weeks 9-12), 43.9% of participants in the varenicline group were continuously abstinent from smoking compared with 17.6% in the placebo group (OR, 3.85; 95% CI, 2.69-5.50; $P<.001$) and 29.8% in the bupropion SR group (OR, 1.90; 95% CI, 1.38-2.62; $P<.001$). For weeks 9 through 24, 29.7% of participants in the varenicline group were continuously abstinent compared with 13.2% in the placebo group (OR, 2.83; 95% CI, 1.91-4.19; $P<.001$) and 20.2% in the bupropion group (OR, 1.69; 95% CI, 1.19-2.42; $P=.003$). For weeks 9 through 52, 23% of participants in the varenicline group were continuously abstinent compared with 10.3% in the placebo group (OR, 2.66; 95% CI, 1.72-4.11; $P<.001$) and 14.6% in the bupropion SR group (OR, 1.77; 95% CI, 1.19-2.63; $P=.004$).

Using the 7-day point prevalence measure of abstinence, cessation rates for varenicline were higher at all time points (FIGURE 3). The 7-day point prevalence outcomes for weeks 12, 24, and 52 appear in TABLE 2. In the final week of treatment, 50.3% of participants in the varenicline group were abstinent compared with 20.8% in the placebo group (OR, 4.06; 95% CI, 2.88-5.73). At the end of the study, the 7-day point prevalence for varenicline was 30.5% compared with 17.3% for placebo (OR, 2.14; 95% CI, 1.48-3.09).

Comparisons of continuous abstinence for participants in the varenicline group compared with the bupropion SR group followed a similar pattern (Figure 2). The OR comparing the varenicline group with the bupropion SR group at the end of treatment (week 12) was 1.90 (95% CI, 1.38-2.62; $P<.001$). At the end of the study, the OR was 1.77 (95% CI, 1.19-2.63; $P=.004$).

Figure 1. Participant Disposition



Bupropion SR indicates sustained-release bupropion.

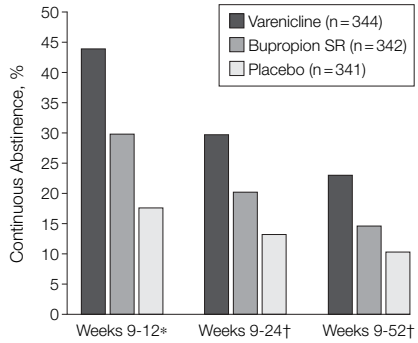
Table 1. Characteristics of Participants*

	Varenicline (n = 344)	Bupropion SR (n = 342)	Placebo (n = 341)
Men	190 (55.2)	206 (60.2)	198 (58.1)
Age, mean (SD), y	44.6 (11.4)	42.9 (11.9)	42.3 (11.6)
Race			
White	294 (85.5)	283 (82.7)	290 (85.0)
Black	31 (9.0)	36 (10.5)	26 (7.6)
Asian	8 (2.3)	4 (1.2)	6 (1.8)
Other	11 (3.2)	19 (5.6)	19 (5.6)
Smoking history, mean (SD), y	27.1 (11.5)	25.4 (12.0)	24.4 (11.6)
Smoking in previous month, mean (SD), cigarettes/d	22.5 (9.5)	21.8 (8.7)	21.5 (8.7)
Fagerström Test for Nicotine Dependence score, mean (SD)†	5.39 (2.21)	5.39 (2.19)	5.16 (2.19)

Abbreviation: Bupropion SR, sustained-release bupropion.
*Values expressed as number (percentage) unless otherwise indicated.
†Scores range from 0 to 10, with higher scores indicating greater nicotine dependence.

Bupropion SR also produced higher rates of continuous abstinence than placebo. At the end of treatment, 29.8% of participants in the bupropion SR group had been continuously abstinent for 4 weeks compared with 17.6% in the placebo group (OR, 2.02; 95% CI, 1.40-2.92). By week 52, 14.6% of participants in the bupropion SR group had been continuously abstinent since week 9. However, the OR comparing bupropion SR with placebo at the end of the study was insignificant (OR, 1.50; 95% CI, 0.94-2.39; $P=.08$). As with varenicline, 7-day point prevalence abstinence rates were higher than placebo at all time points (Figure 3 and Table 2). At the end of treatment, 36.3% of bupropion SR participants were abstinent (OR, 2.21; 95% CI, 1.56-3.13); by the end of the study, this declined to 23.4%. In contrast to the continuous abstinence measure, the point prevalence OR for bupropion SR compared with placebo at the end of the study reached statistical significance (OR, 1.46; 95% CI, 1.00-2.14; $P=.03$).

Figure 2. Continuous Smoking Abstinence Rates



*Carbon monoxide level confirmed at clinic visits.
†Clinic and telephone visits.
Bupropion SR indicates sustained-release bupropion. For weeks 9-12: varenicline vs placebo, $P<.001$; varenicline vs bupropion SR, $P<.001$; and bupropion SR vs placebo, $P=.001$. For weeks 9-24: varenicline vs placebo, $P<.001$; varenicline vs bupropion SR, $P=.003$; and bupropion SR vs placebo, $P=.01$. For weeks 9-52: varenicline vs placebo, $P<.001$; varenicline vs bupropion SR, $P=.004$; and bupropion SR vs placebo, $P=.08$.

Measures of Craving, Withdrawal, and Smoking Reinforcement

Participants in all treatment groups reported changes in mean withdrawal symptom and craving scores, particularly in the first week of treatment. In comparison with participants in the placebo group for the average over weeks 1 through 7, those in the varenicline group reported significantly less of an urge to smoke ($P<.001$) and had less negative affect ($P=.001$) as assessed by the Minnesota Nicotine Withdrawal Scale (TABLE 3). Bupropion SR provided similar relief from urge to smoke and negative affect (compared with placebo), but significantly increased ratings of insomnia ($P<.001$). The results of the Brief Questionnaire of Smoking Urges paralleled those of the Minnesota Nicotine Withdrawal Scale with regard to craving, with both varenicline and bupropion SR reducing total craving compared with placebo ($P<.001$ for both). Varenicline significantly reduced scores on 4 of 5 Modified Cigarette Evaluation Questionnaire subscales (smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations, and craving reduction; range, $P=.04$ to $P<.001$) but did not differ from placebo on the aversion subscale. Only the smoking satisfaction and psychological reward subscales ($P<.001$ for both) were reduced by bupropion SR compared with placebo.

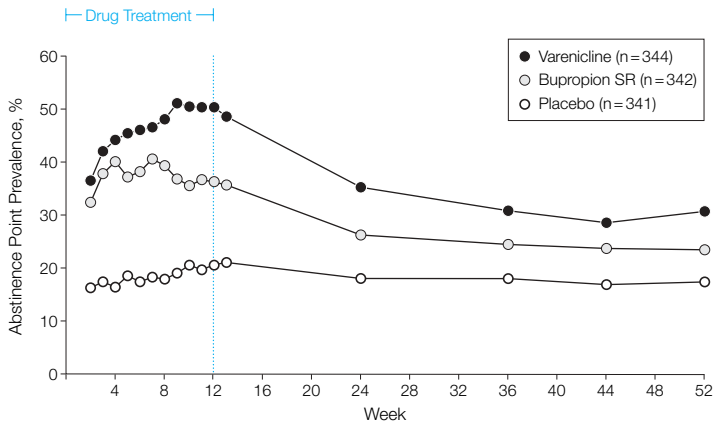
Weight

On average, study participants who completed the 12-week treatment phase gained weight during that period. Those in the varenicline group gained an average of 2.29 kg (SE, 0.18 kg) compared with 1.52 kg (SE, 0.21 kg) in the placebo group and 1.32 kg (SE, 0.22 kg) in the bupropion SR group. Considering only those participants who were continuously abstinent during weeks 9 through 12, weight gain was 3.15 kg (SE, 0.53 kg) in the placebo group, 2.89 kg (SE, 0.24 kg) in the varenicline group, and 1.88 kg (SE, 0.34 kg) in the bupropion SR group.

Safety and Tolerability

No participants died during the 12-week treatment phase of the study or during the subsequent month. Twelve single serious adverse events were reported during the 12 weeks of treatment or within 7 days of the last dose taken. In the varenicline group, these were cancer (lung or brain); acute coronary syndrome; chest pain; dehydration, periorbital cellulitis; acute psychosis, emotional lability; and worsening vertigo, elevated blood pressure, chest pain (judged to be related to study medication). In the bupropion SR group, these were ectopic pregnancy, angioedema (judged to be related to study medication), gunshot wound to left shoulder, postoperative bleeding, right leg pain below knee, and breast cancer (female).

Figure 3. Smoking Abstinence Point Prevance Verified by Carbon Monoxide Level at 7 Days



Bupropion SR indicates sustained-release bupropion.

During follow-up, 5 single serious adverse events were reported. In the varenicline group, these were right arm staphylococcal cellulitis and acute psychosis (same participant as in the treatment phase). In the bupropion SR group, these were occlusion coronary artery, a fatal motorcycle accident, and a miscarriage.

Among the placebo group, 5 participants experienced serious adverse events.

The treatment-emergent adverse events that occurred in 5% or more of the participants treated with varenicline or bupropion SR compared with participants who received placebo appear in TABLE 4. Nausea was the most commonly reported adverse event for varenicline (29.4%). Of those reporting nausea, it was of mild intensity in 72%, moderate in 23%, and severe in 5% of cases. Eight participants in the varenicline group (2.3%) discontinued drug treatment due to nausea. Other common symptoms in the varenicline group were insomnia (14.3%) and abnormal dreams (13.1%). Abnormal dreams were self-described by participants as any change in dreaming, such as vivid dreams or increased frequency of dreaming. Insomnia was the most common adverse event associated with bupropion SR (21.2%), followed by headache (7.9%) and dry mouth (7.6%). Overall, 104 participants had adverse events that resulted in discontinuation of study medication (10.5% in the varenicline group, 12.6% in the bupropion SR group, and 7.3% in the placebo group), but they remained in the study. Adverse events during the treatment period resulted in 43 participants withdrawing from the study. Study withdrawal was distributed evenly across treatment groups (4.1% in the varenicline group, 4.7% in the bupropion SR group, and 3.8% in the placebo group).

COMMENT

This study demonstrated that varenicline, a partial agonist of the α4β2 nicotinic acetylcholine receptor, is an efficacious smoking cessation pharma-

Table 2. Seven-Day Abstinence Point Prevalence at Specified Time Points

Period of Follow-up	Seven-Day Abstinence Point Prevalence Rates, %	OR (95% CI)	*P* Value*	OR (95% CI)	*P* Value†
Week 12‡					
Varenicline	50.3	4.06 (2.88-5.73)	<.001	1.84 (1.34-2.51)	<.001
Bupropion SR	36.3	2.21 (1.56-3.13)	<.001		
Placebo	20.8				
Week 24					
Varenicline	35.2	2.59 (1.80-3.72)	<.001	1.56 (1.11-2.17)	.009
Bupropion SR	26.3	1.67 (1.15-2.42)	.007		
Placebo	17.9				
Week 52					
Varenicline	30.5	2.14 (1.48-3.09)	<.001	1.46 (1.04-2.06)	.05
Bupropion SR	23.4	1.46 (1.00-2.14)	.03		
Placebo	17.3				

Abbreviations: Bupropion SR, sustained-release bupropion; CI, confidence interval; OR, odds ratio.
*Compared with participants receiving placebo.
†Compared with participants receiving bupropion SR.
‡End of treatment.

Table 3. Differences in Withdrawal Symptoms and Cravings Reported by Treatment Participants for Weeks 1 Through 7*

	No. of Participants Providing Response	Difference in Symptoms Compared With Placebo Group (95% CI)	*P* Value
Minnesota Nicotine Withdrawal Scale			
Varenicline			
Urge to smoke	331	–0.48 (–0.59 to –0.37)	<.001
Negative affect	331	–0.13 (–0.21 to –0.05)	.001
Restlessness	331	–0.10 (–0.20 to 0)	.05
Increased appetite	331	0.07 (–0.04 to 0.19)	.22
Insomnia	331	0.10 (–0.01 to 0.20)	.07
Bupropion SR			
Urge to smoke	328	–0.38 (–0.49 to –0.27)	<.001
Negative affect	328	–0.13 (–0.21 to –0.05)	.001
Restlessness	327	–0.07 (–0.17 to 0.03)	.16
Increased appetite	327	–0.07 (–0.19 to 0.05)	.23
Insomnia	327	0.20 (0.09 to 0.30)	<.001
Brief Questionnaire of Smoking Urges			
Varenicline			
Total craving score	330	–0.44 (–0.57 to –0.31)	<.001
Factor 1 (pleasure)	330	–0.56 (–0.71 to –0.40)	<.001
Factor 2 (negative affect relief)	330	–0.27 (–0.38 to –0.16)	<.001
Bupropion SR			
Total craving score	328	–0.34 (–0.47 to –0.21)	<.001
Factor 1 (pleasure)	328	–0.42 (–0.58 to –0.27)	<.001
Factor 2 (negative affect relief)	328	–0.21 (–0.32 to –0.10)	<.001
Modified Cigarette Evaluation Questionnaire			
Varenicline			
Smoking satisfaction	300	–0.44 (–0.61 to –0.25)	<.001
Psychological reward	300	–0.32 (–0.47 to –0.16)	<.001
Enjoyment of respiratory tract sensations	298	–0.22 (–0.39 to –0.05)	.01
Craving reduction	300	–0.25 (–0.49 to –0.02)	.04
Aversion	298	0 (–0.15 to 0.16)	.96
Bupropion SR			
Smoking satisfaction	304	–0.32 (–0.50 to –0.15)	<.001
Psychological reward	304	–0.28 (–0.43 to –0.13)	<.001
Enjoyment of respiratory tract sensations	304	–0.13 (–0.30 to 0.04)	.14
Craving reduction	304	–0.15 (–0.38 to 0.08)	.21
Aversion	302	0.10 (–0.05 to 0.25)	.21

Abbreviations: Bupropion SR, sustained-release bupropion; CI, confidence interval.
*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.

Table 4. Adverse Events Occurring More Frequently in Treatment Participants*

	No. (%) of Adverse Events		
	Varenicline (n = 343)	Bupropion SR (n = 340)	Placebo (n = 340)
Nausea	101 (29.4)	25 (7.4)	33 (9.7)
Constipation	31 (9.0)	22 (6.5)	5 (1.5)
Flatulence	20 (5.8)	7 (2.1)	8 (2.4)
Dry mouth	19 (5.5)	26 (7.6)	11 (3.2)
Dyspepsia	19 (5.5)	10 (2.9)	12 (3.5)
Vomiting	18 (5.2)	7 (2.1)	6 (1.8)
Insomnia	49 (14.3)	72 (21.2)	42 (12.4)
Abnormal dreams†	45 (13.1)	20 (5.9)	12 (3.5)
Sleep disorder	16 (4.7)	23 (6.8)	9 (2.6)
Anxiety	15 (4.4)	18 (5.3)	13 (3.8)
Headache	44 (12.8)	27 (7.9)	43 (12.6)
Dizziness	22 (6.4)	25 (7.4)	24 (7.1)
Fatigue	25 (7.3)	13 (3.8)	22 (6.5)

Abbreviation: bupropion SR, sustained-release bupropion.
*Adverse events occurred at a rate of 5% or higher in participants receiving varenicline or bupropion SR compared with participants receiving placebo. These adverse events began or increased in severity during treatment or up to 7 days after the last dose.
†Self-described by the participants as any change in dreaming, such as vivid dreams or increased frequency of dreaming.

cotherapy. The short-term and long-term cessation rate of varenicline exceeded that of both placebo and bupropion SR, which is a first-line pharmacotherapy for treating tobacco dependence. Because no study participant had ever used bupropion SR prior to this study, it is unlikely that the observed difference in efficacy is attributable to the lower success rates of smokers who have used the same pharmacotherapy in a previously unsuccessful quit attempt.[20,21] At the end of the treatment period, the odds of quitting smoking with varenicline were significantly greater than the odds of quitting with either placebo (OR, 3.85) or bupropion SR (OR, 1.90).

A significant increase in continuous abstinence rates with varenicline treatment compared with the other 2 study groups was sustained through 1 year of follow-up. The OR for 7-day point prevalence abstinence at 6-month follow-up, a commonly used outcome measure, was 2.59 for varenicline compared with placebo. This is near the upper end of comparable measures for first-line pharmacotherapies recommended in the US Public Health Service guidelines.[2] The pattern of results was robust using 2 distinct evaluation strategies: (1) a conservative measure of continuous abstinence during the last 4 weeks of treatment and during follow-up to week 52 and (2) a 7-day point prevalence measure.

In addition to being efficacious, varenicline appeared to be well tolerated by most participants. Nausea, the most common complaint, was reported as being mostly mild to moderate in severity and rarely resulted in discontinuation of study medication. Insomnia was reported less often among varenicline participants than among bupropion SR participants; some form of sleep disturbance is a common symptom of nicotine withdrawal.[16] Analyses of the withdrawal and craving scales suggest that varenicline and bupropion SR each reduced several aspects of the nicotine withdrawal syndrome. The positive results from the Minnesota Nicotine Withdrawal Scale, Brief Questionnaire of Smoking Urges, and Modified Cigarette Evaluation Questionnaire are suggestive of $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist effects of reducing craving and withdrawal and the reinforcing effects from smoking. More detailed modeling of these data will be required to clarify this relationship.

The study results have limitations. First, participants who volunteer for clinical trials of investigational drugs tend to be in better general health and are by definition more motivated than those in a typical primary care population. The external validity of the trial is also limited by the fact that individuals with serious medical illness or current or recent depression were excluded from the trial. Second, all participants received 12 weeks of brief individual smoking cessation counseling along with the study drug. Therefore, this study does not assess the efficacy of varenicline in the context of more minimal counseling support, which is common in health care settings. Because all of the study groups received a counseling component, the ORs reported are likely to remain stable even with differing degrees of counseling support. Third, 35% of participants did not complete the follow-up period. Notably, the dropout rate was higher in the placebo group and the overall rate of treatment discontinuation due to adverse events was 10.1%, providing reassurance of the tolerability of varenicline.

Reducing smoking rates in the US population will require a combination of efforts from individuals, health care systems, insurers, and policy makers as part of a comprehensive tobacco-control strategy.[2] Advances can be made by improving the use of existing smoking cessation treatments and by developing better treatments. Varenicline, with a unique profile of agonist and antagonist properties, has demonstrated a robust ability to increase cessation rates (short-term and long-term) compared with both placebo and a first-line smoking cessation medication (bupropion SR), and may represent an advance in the treatment of tobacco dependence.

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Author Contributions: Dr Jorenby had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Watsky, Williams, Billing, Reeves.
Acquisition of data: Jorenby, Hays, Rigotti, Billing, Gong, Reeves.
Analysis and interpretation of data: Jorenby, Hays, Rigotti, Azoulay, Watsky, Williams, Billing, Gong, Reeves.
Drafting of the manuscript: Jorenby, Hays, Rigotti, Billing.
Critical revision of the manuscript for important intellectual content: Jorenby, Hays, Rigotti, Azoulay, Watsky, Williams, Billing, Gong, Reeves.
Statistical analysis: Jorenby, Watsky, Billing.
Obtained funding: Azoulay, Reeves.
Administrative, technical, or material support: Watsky, Williams.
Study supervision: Gong, Reeves.
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Independent Statistical Analyses: Daniel Bolt, PhD, associate professor of Educational Psychology at the University of Wisconsin, had access to all of the data used in the study and performed an independent analysis in consultation with Dr Jorenby. The independent statistical analyses involved the primary and key secondary outcomes, including participant demographics, self-reported data, and safety as described in this article. The results confirm what is presented in this article. Dr Bolt received compensation from the University of Wisconsin for this reanalysis.
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Role of the Sponsor: Drs Azoulay, Watsky, Williams, Gong, and Reeves, and Mr Billing, employees of Pfizer Inc, were involved in all elements of this study, including but not limited to the study design and monitoring. In addition, the database containing the findings of the 14 investigator sites was maintained by Pfizer Inc, and statistical analyses were performed at Pfizer Inc by Mr Billing and Ann Pennington, MS. All of the authors including those employed by Pfizer Inc, reviewed and edited the manuscript prior to publication of this article.
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Table 2. Hazard Ratios (HRs) for Fracture Associated With a 1-SD Increase in ln-hsCRP, 1-SD Decrease in BMD, and Prevalent Fracture*

Site of BMD Measurement Used in Model	ln-hsCRP		BMD		Prevalent Fracture	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Spine	1.26 (1.03-1.53)	.03	1.52 (1.23-1.89)	<.001	1.68 (1.11-2.54)	.01
Femoral neck	1.27 (1.04-1.55)	.02	1.76 (1.41-2.21)	<.001	1.73 (1.14-2.62)	.01
Ward triangle	1.26 (1.03-1.53)	.03	1.74 (1.38-2.18)	<.001	1.72 (1.13-2.61)	.01
Trochanter	1.30 (1.07-1.58)	.01	1.79 (1.41-2.28)	<.001	1.58 (1.04-2.42)	.03
Ultradistal forearm	1.29 (1.05-1.58)	.01	1.69 (1.35-2.11)	<.001	1.61 (1.05-2.45)	.03
Mid forearm	1.24 (1.02-1.52)	.03	1.53 (1.24-1.89)	<.001	1.65 (1.08-2.52)	.02
Whole body	1.32 (1.08-1.61)	.007	1.76 (1.41-2.29)	<.001	1.52 (0.99-2.33)	.06

Abbreviations: BMD, bone mineral density; CI, confidence interval; ln-hsCRP, log-transformed high-sensitivity C-reactive protein.
*Each model is adjusted for the other 2 risk factors. Separate models were developed for BMD measured at the spine, proximal femur subregions, forearm subregions, and whole body.

tures in mild ankylosing spondylitis and their relationship to bone mineral density. *Rheumatology (Oxford)*. 2000;39:85-89.
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CORRECTION

Additional Study Group Member: In the Original Contribution entitled "Efficacy of Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Placebo or Sustained-Release Bupropion for Smoking Cessation: A Randomized Controlled Trial" published in the July 5, 2006, issue of *JAMA* (2006;296:56-63), the following name should appear. On page 63, under the Varenicline Phase 3 Study Group, "Raymond Niaura, PhD, Transdisciplinary Research, Butler Hospital, Providence, RI" should appear at the end of the list.