Varenicline Versus Bupropion SR or Placebo for Smoking Cessation: A Pooled Analysis

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***Objectives*: To evaluate varenicline's efficacy for smoking cessation versus bupropion SR and placebo and to explore whether factors typically predictive of abstinence influence varenicline's efficacy versus placebo, as measured by the week 9-12 continuous abstinence rate (CAR9-12). *Methods*: Smokers in 2 randomized, placebo-controlled trials received varenicline 1 mg BID (n=696), bupropion SR 150 mg BID (n=671), or placebo (n=685) for 12 weeks. Nontreatment follow-up lasted 40 weeks. *Results*: CAR_{9-12} was greater for varenicline (44.0%) versus bupropion SR (29.7%; P<0.0001) and placebo (17.7%; P<0.0001). CAR_{9-12} for varenicline versus placebo was not affected by age, gender, or nicotine dependence level. *Conclusions*: Varenicline was more efficacious than bupropion SR or placebo. Varenicline's efficacy versus placebo was not influenced by factors predictive of abstinence.**

***Key words*: varenicline, smoking cessation, nicotine partial agonist, tobacco dependence**

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Tobacco smoking is the leading preventable cause of death and disease and is responsible for more than 400,000 premature deaths per year in the United States alone.[1] About 1 in 5 (20.9%) adults in the United States are current smokers, and 70% of these indicate a desire to quit smoking.[1]

The pervasive health effects of smoking place a huge burden on healthcare budgets due to smoking-related diseases. The US Centers for Disease Control and Prevention reported that from 1997 to 2001, cigarette smoking caused more than $167 billion in health-related economic losses and resulted in 5.5 million years of potential life lost annually in the United States alone.[2]

Several pharmacologic therapies are available to aid smoking cessation. Nicotine replacement therapy (NRT) and sustained release (SR) bupropion are approved by the US Food and Drug Administration (FDA) for smoking cessation and are currently recommended as first-line therapies in the US Department of Health and Human Services guidelines.[3,4] Other phar-

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macologic interventions include nortriptyline or clonidine, which are recommended as second-line therapies.[3,4]

The use of pharmacologic aids to smoking cessation can double or triple the odds of successfully quitting, yet many patients relapse to smoking within a year.[5] The need exists for safe and more efficacious compounds for smoking cessation. Varenicline, a selective $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, is the first prescription pharmacologic agent for smoking cessation to be approved by the FDA in the United States in almost a decade.

It is thought that the agonist properties of varenicline lead to reduced craving and withdrawal symptoms by stimulating dopamine release, while the antagonist properties prevent inhaled nicotine from binding to the receptors and may reduce the rewarding effects of continued smoking.[6] The potentially reduced nicotine craving, withdrawal, and reward with varenicline may stimulate initial quitting and lower the likelihood of a slip becoming a full relapse. In clinical trials, varenicline has demonstrated superior efficacy versus both placebo and bupropion SR.[7-11]

Here we present the pooled results of 2 identically designed, randomized, double-blind, previously published, studies[9,10] comparing the efficacy and safety of varenicline 1 mg twice daily (BID) versus bupropion SR 150 mg BID and placebo taken for 12 weeks followed by 40 weeks of nontreatment follow-up.

The primary objective of this pooled analysis was to evaluate the efficacy of varenicline for smoking cessation versus both bupropion SR and placebo and to take advantage of the larger subject pool from the 2 studies combined, to additionally explore whether varenicline's effect versus bupropion SR or placebo was influenced by age, gender, smoking level, or degree of nicotine dependence at baseline. A further objective was to assess the safety of varenicline using the pooled data.

MATERIALS AND METHODS

The design and methodology of these trials have also been described in full detail previously.[9,10]

Subjects

Adult cigarette smokers aged 18 to 75 years were eligible for the studies if they were motivated to quit smoking, had smoked an average of at least 10 cigarettes per day during the previous year, and had no period of abstinence exceeding 3 months in the past year. To prevent bias, previous use of bupropion SR for any indication was exclusionary as was participation in a previous varenicline clinical trial.

Females of childbearing potential were included only if they were not pregnant, not nursing, and were practicing effective contraception. Also ineligible for the trials were those who were not candidates for bupropion SR therapy; those who had clinically significant cardiovascular disease in the previous 6 months or uncontrolled hypertension, severe chronic obstructive pulmonary disease, a history of cancer, significant allergic reactions, elevated liver function tests, a body mass index <15 or >38 kg/m^2, weight <45 kg, active depression requiring treatment, history of panic disorder, psychosis, bipolar disorder, eating disorders, alcohol or drug abuse/dependency within the previous year; those who used NRTs, clonidine, or nortriptyline within 1 month of study entry or used medications that might interfere with the evaluation of the study drug.

Subjects who used tobacco products other than cigarettes had to agree to abstain from these products for the duration of the study.

Study Design

Both studies were 52-week, double-blind, double-dummy, placebo-controlled, randomized, multicenter trials. Following a screening visit, qualified subjects were scheduled for a baseline visit at which they were randomized in a 1:1:1 ratio to receive varenicline 1 mg BID, bupropion SR 150 mg BID, or placebo. Randomization was accomplished by a computer-generated random code.

Subjects in all treatment groups were given an educational booklet on smoking cessation (*Clearing the Air: How to Quit Smoking*[12]) at baseline and were provided with up to 10 minutes of counseling in accordance with the Agency for Healthcare Research and Quality (AHRQ) guidelines[3,4] at baseline and each subsequent clinic visit (weeks 1 through 13, 24, 36, 44, and 52). Study drugs were dispensed at the baseline visit, and subjects were instructed to take their first dose on the following day.

The duration of active treatment was 12 weeks followed by a nontreatment follow-up phase of an additional 40 weeks. Varenicline was titrated to full dosage over 1 week (varenicline: 0.5 mg once daily (OD) for days 1-3; 0.5 mg BID for days 4-7; then 1 mg BID through week 12). Bupropion SR was titrated to full dosage over 3 days (150 mg OD for days 1-3; then 150 mg BID through week 12). Clinic visits at which efficacy and safety assessments were conducted occurred weekly during the active treatment phase (weeks 1-12). Subjects were instructed to attempt to quit on the target quit date (TQD) at the week 1 visit and to remain abstinent from smoking thereafter. During the nontreatment phase, subjects returned to the clinic at weeks 13, 24, 36, 44, and 52 for scheduled assessments; subjects also received telephone calls at weeks 16, 20, 28, 32, 40, and 48. Smoking status was assessed at clinic visits and during telephone follow-up calls using a standardized questionnaire to record self-reported use of cigarettes and other nicotine- and tobacco-containing products since the last visit or during the previous 7 days.

Study Endpoints

For both studies, the primary endpoint was carbon monoxide (CO)-confirmed 4-week continuous abstinence rate (CAR) during weeks 9-12, which was defined as no reported smoking (not even a puff), as verified by CO levels ≤10 ppm.

Secondary endpoints included the CAR for weeks 9-24 and weeks 9-52 (no reported smoking, verified by CO levels ≤10 ppm) and the 7-day point prevalence of abstinence during the treatment and nontreatment phases. Point prevalence of smoking abstinence was determined by subjects' reporting no smoking or use of other nicotine-containing products during the treatment period (or tobacco products during follow-up) for the last 7 days and confirmed by CO measurements at clinic visits.

The primary endpoint, week 9-12 CAR was further examined within subgroups of demographic characteristics: age (<45 or ≥45 years) and gender; and baseline smoking history: number of cigarettes smoked per day (10 to <20; 20 to <30; or ≥30 cigarettes); total score on the Fagerström Test for Nicotine Dependence (FTND; scores of 0-3; 4-6; or 7-10), and time to first cigarette of the day (≤30 minutes or >30 minutes after waking; based on Question 1 of the FTND). These post hoc subanalyses were conducted in all 3 treatment groups.

Other efficacy endpoints have been published separately elsewhere.[9,10]

Safety and Tolerability

Safety evaluations, including adverse event (AE) reporting, clinical laboratory tests, vital signs, body weight, physical examinations, and electrocardiograms were conducted throughout the treatment period. Safety evaluations have been described in full for each trial separately elsewhere.[9,10]

Vital signs and weight were documented at all clinic visits; specified laboratory tests were performed during certain visits (blood chemistry, complete blood count, urinalysis, serum cotinine, C-reactive protein, and serum pregnancy tests for females). Electrocardiograms were obtained at baseline, week 2 and week 12. All observed or self-reported AEs were documented and included adverse drug reactions, illnesses with onset during the study, exacerbation of previous illnesses, and symptoms that may have been due to nicotine withdrawal. Treatment-emergent AEs included those that occurred up to 7 days after the end of treatment. A serious adverse event (SAE) was an event up to 28 days after the last dose that resulted in death, was life threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability, or resulted in a birth defect.

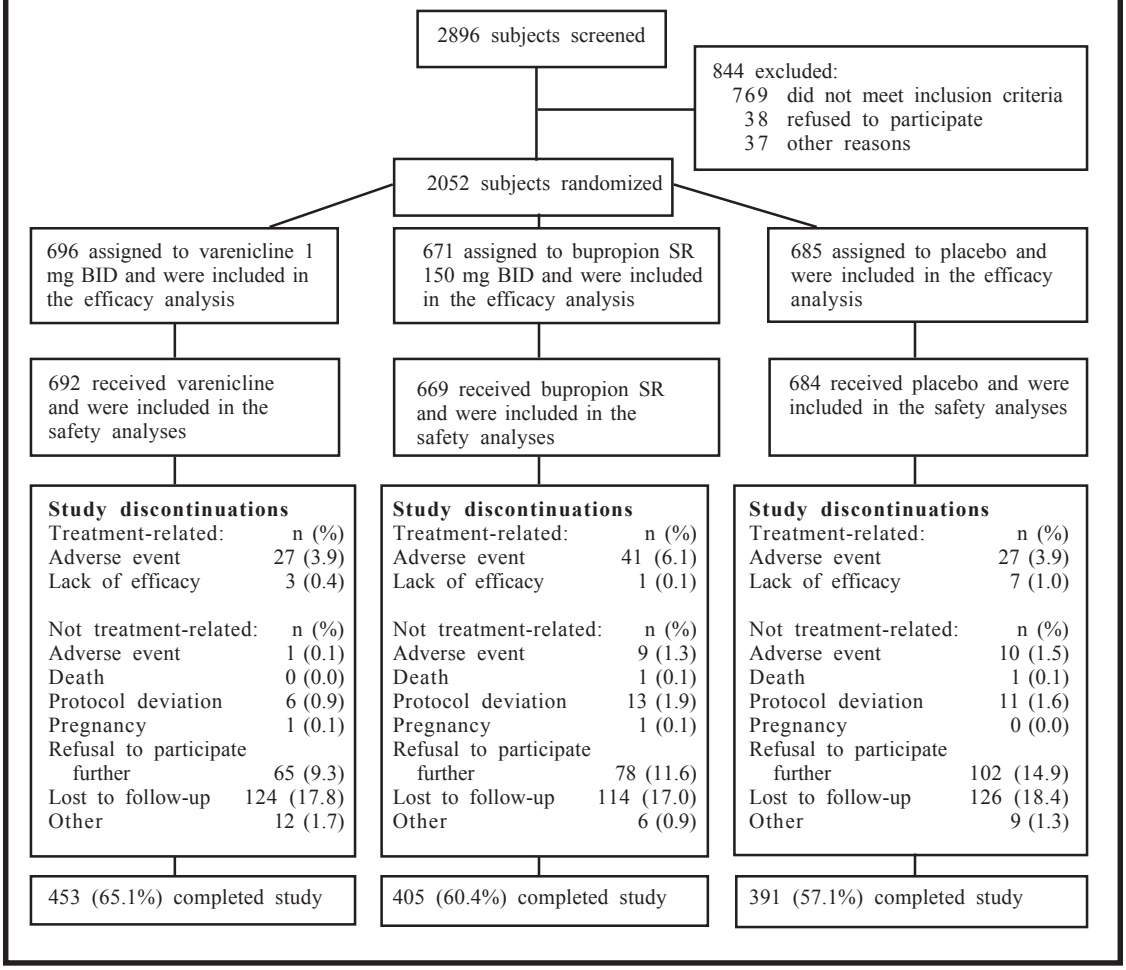
As a post hoc evaluation, the most frequently occurring AE in subjects treated with varenicline, nausea, was further explored for onset and prevalence over the 12 weeks of treatment.

Statistical Methods

The primary analysis population for efficacy parameters consisted of all randomized subjects. The primary analysis population for safety comparisons consisted of all randomized subjects who also took at least 1 dose of study medication.

The pooled data for CAR binary endpoints were modeled using logistic regression with treatment group and study as the main effects. Hypothesis testing was carried out using the likelihood ratio chi-square statistic. Response rates with corresponding odds ratios (ORs), 95% con-

Figure 1
Subject Disposition



fidence intervals (CIs), and P-values comparing treatment groups were obtained.

The subgroup analyses for week 9-12 CAR by subgroups based on age, gender, smoking level, and degree of nicotine dependence at baseline were not prespecified and were conducted as post hoc analyses. An expanded logistic regression model including effects of treatment, study, subgroup, and treatment by subgroup interaction was used to perform these analyses.

RESULTS

Subject Disposition

A total of 2052 subjects were randomized to receive study medication (varenicline, n=696; bupropion SR, n=671; or placebo, n=685; Figure 1) and formed the primary analysis population for measures of efficacy. Of these, 2045 subjects received at least 1 dose of study medication (varenicline, n=692; bupropion SR, n=669; or placebo, n=684; Figure 1) and were included in the analyses for measures of safety. Overall, discontinuations from the study during the treatment and nontreatment phases of the study were 34.9% for varenicline, 39.6% for bupropion SR, and 42.9% for placebo (Figure 1).

Baseline characteristics were similar between the treatment groups (Table 1).

Table 1
Baseline Characteristics

	Varenicline (N=696)	Bupropion SR (N=671)	Placebo (N=685)
Age (years), mean (SD)	43.5 (11.3)	42.5 (11.8)	42.5 (11.7)
Gender, n (%)			
Men	366 (52.6)	398 (59.3)	384 (56.1)
Women	330 (47.4)	273 (40.7)	301 (43.9)
Race, n (%)			
White	574 (82.5)	547 (81.5)	552 (80.6)
Black	67 (9.6)	64 (9.5)	75 (10.9)
Asian	12 (1.7)	9 (1.3)	15 (2.2)
Other	43 (6.2)	51 (7.6)	43 (6.3)
# years smoked			
n	695	670	685
Mean (range)	25.7 (2-59)	24.8 (2-61)	24.5 (0-61)
# cigarettes/day past month			
n	695	670	685
Mean (range)	21.8 (10-70)	21.4 (10-65)	21.5 (10-80)
FTND score[a]			
n	693	670	681
Mean (SD)	5.28 (2.19)	5.29 (2.14)	5.27 (2.09)
≥1 Prior quit attempt			
n/n (%)	585/695 (84.2)	575/670 (85.8)	579/685 (84.5)
Prior quit attempt with nicotine replacement therapies			
Nicotine patch, n/n (%)			
1 attempt	180/695 (25.9)	184/670 (27.5)	191/685 (27.9)
≥2 attempts	77/695 (11.1)	84/670 (12.5)	75/685 (10.9)
Nicotine gum, n/n (%)			
1 attempt	101/695 (14.5)	107/670 (16.0)	102/685 (14.9)
≥2 attempts	40/695 (5.8)	23/670 (3.4)	29/685 (4.2)
Nicotine lozenge, n/n (%)			
1 attempt	11/695 (1.6)	10/670 (1.5)	11/685 (1.6)
≥2 attempts	2/695 (0.3)	2/670 (0.3)	1/685 (0.1)
Nicotine inhaler, n/n (%)			
1 attempt	5/695 (0.7)	16/670 (2.4)	17/685 (2.5)
≥2 attempts	0/695 (0.0)	1/670 (0.1)	0/685 (0.0)

Note.
FTND Fagerström Test for Nicotine Dependence
a Range 0-10. Higher scores indicate greater dependence

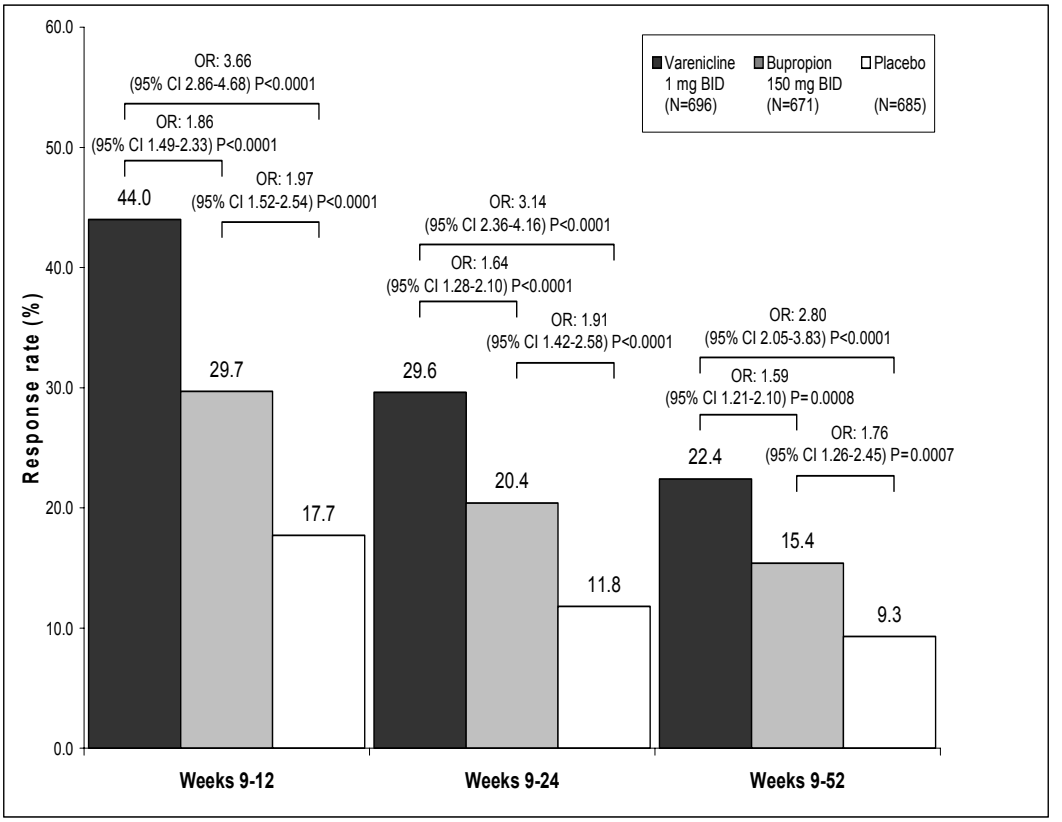
Smoking history at baseline was comparable between groups with subjects having smoked for approximately 25 years, with average daily cigarette consumption in the previous month about 21 cigarettes (Table 1). The FTND score across groups was very similar and more than 84% of subjects had previously made at least 1 serious quit attempt (Table 1).

Efficacy Outcomes

Continuous abstinence rate (weeks 9-12). Carbon monoxide-confirmed 4-week CAR for weeks 9-12 was higher for varenicline versus bupropion SR (44.0% vs 29.7%; OR 1.86; 95% CI: 1.49-2.33; P<0.0001) and varenicline versus placebo (44.0% vs 17.7%; OR 3.66; 95% CI: 2.86-4.68; P<0.0001; Figure 2). Similarly, 4-week CAR was greater with bupropion SR than with placebo (29.7% vs 17.7%; OR 1.97; 95% CI: 1.52-2.54; P<0.0001; Figure 2).

Continuous abstinence rate (weeks 9-24). For weeks 9-24, CAR was higher for varenicline compared with bupropion SR

Figure 2
Carbon Monoxide-Confirmed Continuous Abstinence Rate, Weeks 9-12, 9-24, and 52

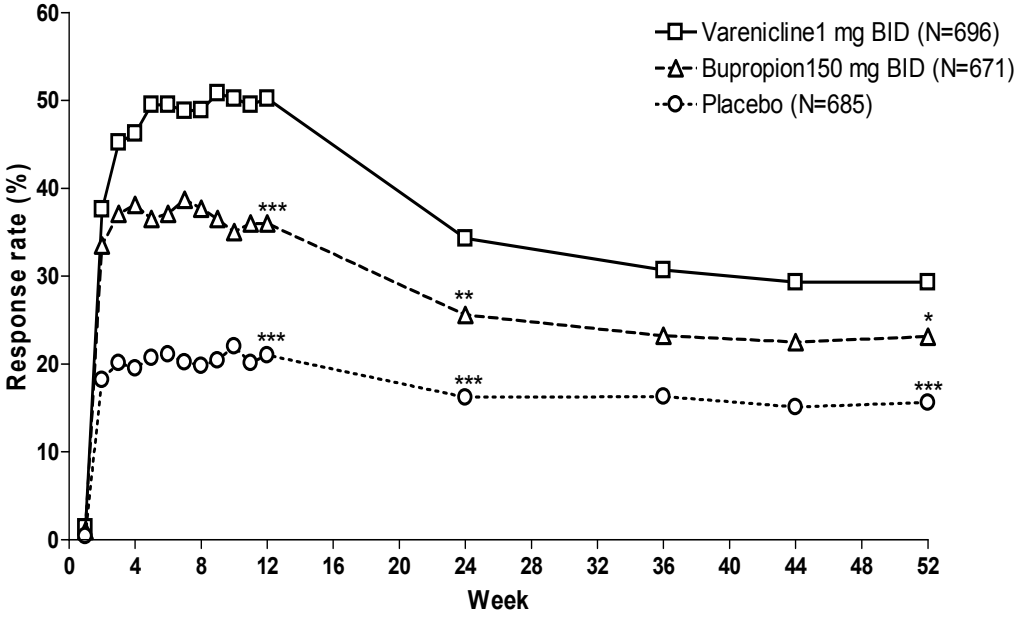


(29.6% vs 20.4%; OR 1.64; 95% CI: 1.28-2.10; P<0.0001) and placebo (29.6% vs 11.8%; OR 3.14; 95% CI 2.36-4.16; P<0.0001; Figure 2). In addition, the CAR with bupropion SR was greater than for placebo (20.4% vs 11.8%; OR 1.91; 95% CI: 1.42-2.58; P<0.0001; Figure 2).

Continuous abstinence rate (weeks 9-52). The CAR for weeks 9-52 was greater for varenicline compared with bupropion SR (22.4% vs 15.4%; OR 1.59; 95% CI: 1.21-2.10; P=0.0008) and placebo (22.4% vs 9.3%; OR 2.80; 95% CI: 2.05-3.83; P<0.0001; Figure 2); and bupropion SR was better than placebo (15.4% vs 9.3%; OR 1.76; 95% CI: 1.26-2.45; P=0.0007; Figure 2).

7-day point prevalence of abstinence. The 7-day point prevalence of abstinence for all weeks from week 2 through to the end of the treatment period at week 12 is shown in Figure 3. Varenicline was higher than bupropion SR from week 3 onwards (week 3: P=0.0020; week 4: P=0.0021; and P<0.001 thereafter) and higher than placebo (P<0.0001, at all time points). Similarly, the 7-day point prevalence of abstinence through the post-treatment period to week 52 was better for varenicline compared with bupropion SR (week 12: P<0.0001; week 24: P=0.0004; and week 52: P=0.0079) and placebo (P<0.0001, at all time points; Figure 3). Bupropion SR was better than placebo at all time points (P<0.0001 for all weeks except week 52 for which P=0.0005).

Figure 3
Carbon Monoxide-Confirmed 7-day Point Prevalence of Abstinence



Note.
P values are shown for weeks12, 24, and 52 only but were calculated at all time points. Versus bupropion SR, 7-day point prevalence of abstinence with varenicline was significantly higher from week 3 onwards (Week 3: P=0.0020; week 4: P=0.0021; and P<0.001 thereafter) and significantly higher than placebo (P<0.0001, at all time points).
*** P<0.01 vs varenicline**
**** P<0.001 vs varenicline**
***** P<0.0001 vs varenicline**

Subgroup Analyses

The week 9-12 CARs for varenicline, bupropion SR, and placebo by subgroups (age, gender, daily cigarette consumption, FTND score, and time to first cigarette of the day) are displayed in Table 2, and the ORs for varenicline versus placebo are shown in Figure 4. Similar patterns were observed in the CARs for weeks 9-24 and weeks 9-52 (data not shown).

CARs were higher in older patients but showed little difference between males and females (less than 2% difference in any of the treatment groups). The observed CARs were higher in those subjects who smoked fewer than 20 cigarettes per day at baseline, in those with a baseline FTND score of 0-3, and in those who waited longer than 30 minutes for the first cigarette of the day. These differences were evident in all treatment groups.

The ORs of varenicline versus placebo (Figure 4) showed the higher odds of quitting with varenicline compared with placebo for all the defined subgroups. The post hoc assessment of treatment by subgroup interaction, which evaluated whether treatment effects were different across the subgroups, yielded no nominal P-values below 0.15 for any of the 5 subgroups (Table 2).

Table 2
Subgroup Analyses of Continuous Abstinence Rates for Weeks 9-12

	Varenicline (N=696) % (n/N)	Bupropion SR (N=671) % (n/N)*	Placebo (N=685) % (n/N)*	P-value treatment by subgroup interaction[a]
Subgroup	**Continuous Abstinence Rates Week 9-12**			
Age				
<45 years	39.5 (144/365)	24.7 (94/380)	16.9 (68/402)	0.2835
≥45 years	48.9 (162/331)	36.1 (105/291)	18.7 (53/283)	
Gender				
Male	43.2 (158/366)	30.4 (121/398)	18.0 (69/384)	0.7786
Female	44.8 (148/330)	28.6 (78/273)	17.3 (52/301)	
Baseline daily cigarette consumption				
10 to <20 cigarettes	48.7 (113/232)	33.0 (73/221)	24.6 (52/211)	0.1633
20 to <30 cigarettes	44.7 (138/309)	31.0 (92/297)	13.8 (46/333)	
≥30 cigarettes	35.7 (55/154)	22.2 (34/153)	16.4 (23/140)	
Baseline FTND score[b]				
0-3	56.1 (83/148)	39.3 (55/140)	20.3 (30/148)	0.2558
4-6	44.0 (147/334)	29.9 (97/324)	21.3 (71/334)	
7-10	35.1 (74/211)	22.8 (47/206)	9.6 (19/199)	
First cigarette of the day at baseline[c]				
≤30 mins after waking	41.2 (222/539)	28.5 (148/520)	15.3 (81/530)	0.3967
>30 mins after waking	53.5 (83/155)	33.8 (51/151)	25.5 (39/153)	

Note.
FTND, Fagerström Test for Nicotine Dependence
*** All subjects comparison in all subgroups versus varenicline P<0.0001**
a Obtained from a logistic regression model including treatment, study, subgroup, and treatment by subgroup interaction
b Range 0-10. Higher scores indicate greater dependence
c Response to Question 1 of the FTND

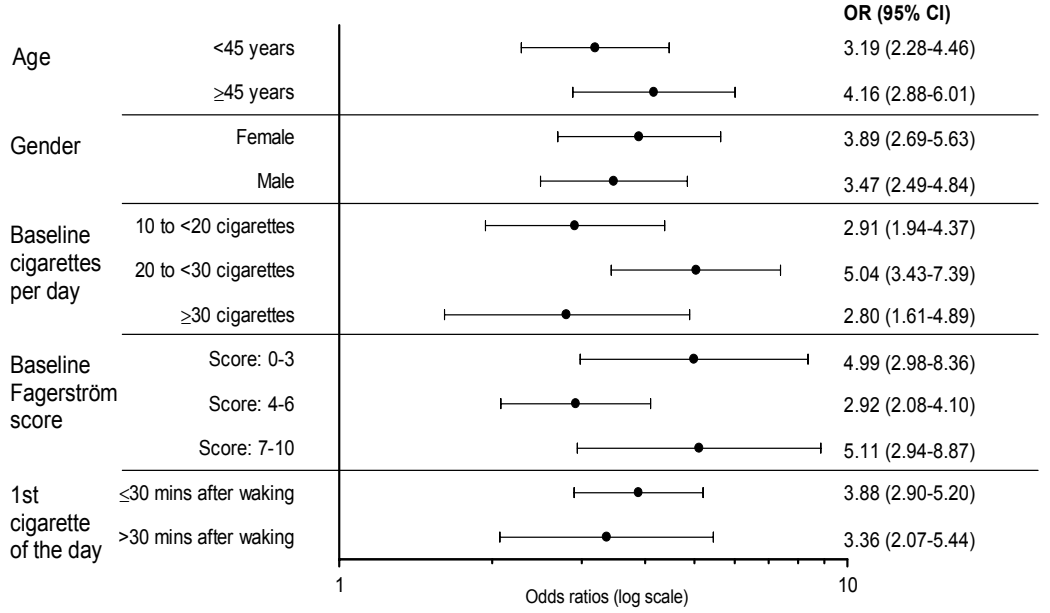
Safety and Tolerability

The safety and tolerability results for these 2 trials have been reported in full elsewhere.[9,10]

Treatment-emergent AEs that were reported in ≥5% of participants taking varenicline and occurred more often than in the placebo group are summarized in Table 3. The most frequently reported AEs in the varenicline group were nausea (28.8%), insomnia (14.2%), and headache (14.2%). Overall discontinuations from study treatment due to AEs were highest in the bupropion SR group for all causality AEs (13.9% vs 9.5% for varenicline and 8.2% for placebo) and for AEs considered related to study medication (12.1% vs 7.9% for varenicline and 6.4% for placebo). Rates of treatment discontinuation due to AEs, including AEs considered treatment related as well as AEs considered not related to treatment, were comparable between varenicline and placebo.

Most cases of nausea in the varenicline group were mild or moderate in intensity, and nausea resulted in treatment discontinuation in only 2.5% of subjects (Table 4). Treatment discontinuations related to nausea were also reported in subjects in the other treatment groups, although at a lower percentage (bupropion SR: 1%; placebo: 0.3%). The median time

Figure 4
Odds Ratios for Continuous Abstinence Rates Weeks 9-12 for Varenicline Group Versus Placebo Group



to onset of the first nausea episode was comparable across groups although the median duration of all nausea episodes was longer in the varenicline group (Table 4).

The temporal pattern of nausea was examined in the varenicline treatment group. Figure 5 shows the weekly point prevalence of nausea onset and the weekly point prevalence of nausea presence by week over the 12 weeks of varenicline treatment. Initial onset of nausea occurred primarily in the first week of treatment and less commonly in the following

Table 3
Adverse Events Occurring in ≥5% of Subjects Treated With Varenicline

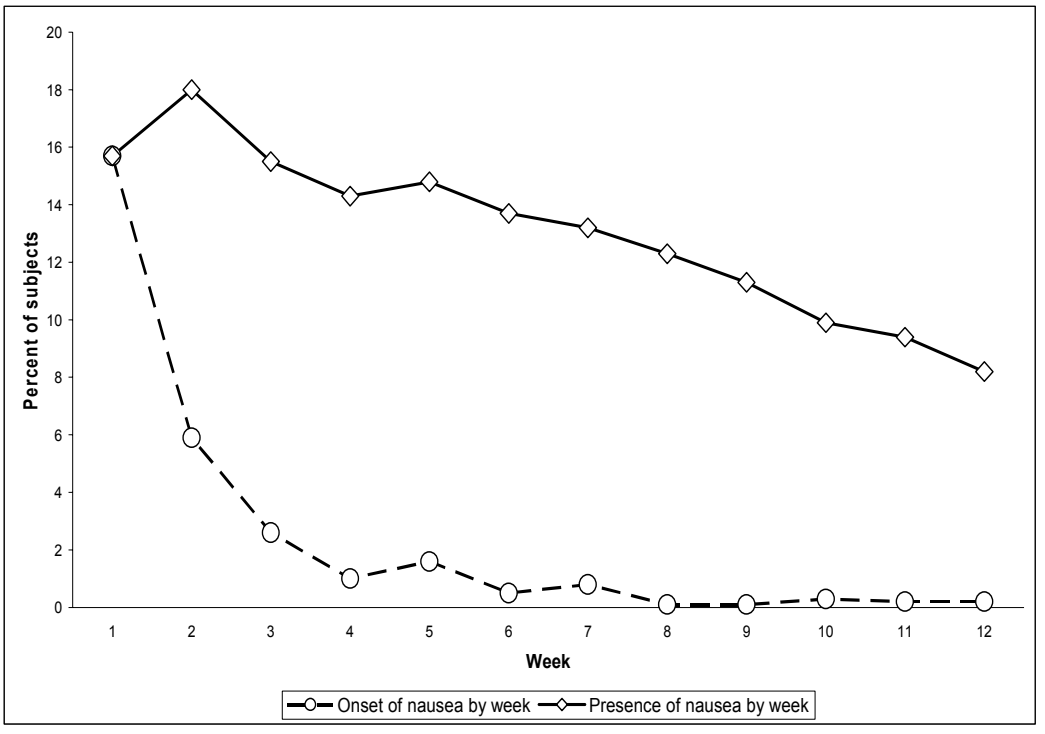
	Varenicline (N=692) n (%)	Bupropion SR (N=669) n (%)	Placebo (N=684) n (%)
Nausea	199 (28.8)	66 (9.9)	62 (9.1)
Headache	98 (14.2)	74 (11.1)	85 (12.4)
Insomnia	98 (14.2)	144 (21.5)	86 (12.6)
Abnormal dreams	81 (11.7)	38 (5.7)	31 (4.5)
Constipation	50 (7.2)	45 (6.7)	18 (2.6)
Dry mouth	42 (6.1)	55 (8.2)	30 (4.4)
Flatulence	40 (5.8)	21 (3.1)	18 (2.6)

Table 4
Descriptive Analyses of Nausea Events

	Varenicline (N=692)	Bupropion SR (N=669)	Placebo (N=684)
Number of individuals with maximum nausea intensity			
Mild, n (%)	142 (20.5)	41 (6.1)	52 (7.6)
Moderate, n (%)	50 (7.2)	22 (3.3)	8 (1.2)
Severe, n (%)	7 (1.0)	3 (0.4)	2 (0.3)
Treatment discontinuation due to nausea, n (%)	17 (2.5)	7 (1.0)	2 (0.3)
Nausea episodes:			
Median time to onset of first episode, days	6	7	7
Median duration of episodes, days	10	5	5

weeks, as shown by the sharp decline in weekly occurrence of new nausea onsets. The presence of nausea peaked at 18.0% in week 2 and then declined during the remainder of the treatment period. This is lower than the 28.8% overall preva-

Figure 5
Weekly Point Prevalence of First Onset and Weekly Point Prevalence of Presence of Nausea in the Varenicline Group for Weeks 1-12



lence because the latter represents the cumulative nausea experience over the 12-week treatment period. The weekly prevalence data reflect the occurrence of nausea in any particular week but do not distinguish between continuous nausea and episodic nausea that may have occurred for only a short time after dosing or just on 1 or a few days of the week.

DISCUSSION

In this pooled analysis, varenicline demonstrated greater efficacy than placebo and bupropion SR with significantly higher abstinence rates at the end of 12 weeks' treatment and sustained through 52 weeks of follow-up. At the end of treatment, the odds of quitting with varenicline were increased by almost 4-fold compared with placebo (OR 3.66) and almost 2-fold compared with bupropion SR (OR 1.86).

For the 7-day point prevalence of abstinence, varenicline similarly demonstrated higher rates of abstinence from week 3 through week 52 compared with bupropion SR and with placebo. Although a less stringent measure than CO-confirmed CARs, the 7-day point prevalence of abstinence has several advantages because this measure of smoking cessation reflects the dynamic process of quitting and is frequently reported in other studies.[3,13] Lapses (brief returns to smoking) that occur during treatment and follow-up can be accommodated within the point prevalence measure without classifying the smoker as a permanent failure, unlike measures of continuous abstinence.[3,13]

An important clinical question regarding smoking cessation is whether there are any factors that may predict a smoker's individual odds of quitting smoking. Factors that have previously been reported to be predictive of successful quit attempts include older age,[14-16] male gender,[15,16] lower daily cigarette consumption,[16] longer time to the first cigarette of the day,[16] and lower level of nicotine dependence.[15,17] In the present analysis, varenicline's effect relative to placebo - as measured by week 9-12 CAR - was demonstrated to be independent of several baseline parameters, including age, gender, number of cigarettes per day, level of nicotine dependence, and time to first cigarette of the day after waking. So, although some of the predictors evaluated in this post hoc analysis might impact the outcome in the general population, the results reported here indicate that the varenicline treatment effect versus placebo is independent of these influential factors. The absence of treatment by subgroup interactions suggests that the effect of varenicline versus placebo at the end of treatment is not influenced by age, gender, baseline daily cigarette consumption, FTND score, or time to first cigarette of the day after waking.

The safety profile of varenicline was acceptable and it was generally well tolerated, with the overall rate of discontinuation from treatment due to AEs similar to placebo. Nausea, the most common AE reported for varenicline, was generally mild or moderate and resulted in few discontinuations from treatment. Nausea occurred more frequently in the varenicline group than the bupropion SR and placebo groups and is also recognized as a transient symptom of nicotine withdrawal.[18] For the majority of subjects who experienced nausea in the varenicline group, the onset of nausea occurred in the first week of treatment, with fewer subjects having an initial onset in subsequent weeks. The prevalence of nausea in the varenicline group was at its highest in the second week of treatment, and the percentage of subjects reporting nausea declined in the weeks thereafter.

CONCLUSION

Varenicline is a safe and well-tolerated agent for smoking cessation, which demonstrated superior efficacy compared with bupropion SR and with placebo both at the end of treatment and up to 52 weeks after quitting.

The effect of varenicline versus placebo for continuous abstinence at the end of treatment is independent of factors that have previously been suggested in the literature to be predictive of successful quit attempts (age, gender, and nicotine dependence level). This information may be useful to physicians and patients when assessing treatment options for smokers wanting to quit.

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Appendix

Abbreviations

AE, adverse event; AHRQ, Agency for Healthcare Research and Quality; BID, twice daily; CAR, continuous abstinence rate; CI, confidence interval; CO, carbon monoxide; FDA, Food and Drug Administration; FTND, Fagerström Test for Nicotine Dependence; OD, once daily; OR, odds ratio; SAE, serious adverse event; SR, sustained release; TQD, target quit date; US, United States