

# Efficacy and Safety of the Novel Selective Nicotinic Acetylcholine Receptor Partial Agonist, Varenicline, for Smoking Cessation

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**Background:** The selective nicotinic acetylcholine receptor partial agonist, varenicline tartrate, represents a novel type of therapy for smoking cessation. This study evaluated the efficacy, safety, and tolerability of 4 varenicline dose regimens, 2 with progressive dosing over the first week (eg, titrated) and 2 with a fixed dosing schedule (eg, nontitrated), for promoting smoking cessation.

**Methods:** This multicenter, double-blind, placebo-controlled study randomized healthy smokers (aged 18-65 years) to varenicline tartrate, 0.5 mg twice daily nontitrated (n=129), 0.5 mg twice daily titrated (n=130), 1.0 mg twice daily nontitrated (n=129), 1.0 mg twice daily titrated (n=130), or placebo (n=129) for 12 weeks to aid in smoking cessation. A 40-week follow-up period assessed long-term efficacy. The primary efficacy measures were the carbon monoxide-confirmed 4-week continuous quit rates by pooled dosage group for weeks 4

through 7 and 9 through 12 and the continuous abstinence rates for weeks 9 through 52.

**Results:** Weeks 9 through 12 continuous quit rates were greater in the 1.0-mg group (49.4%) and the 0.5-mg group (44.0%) vs placebo (11.6%;  $P < .001$  vs both doses). Weeks 9 through 52 abstinence rates were greater in the 1.0-mg group (22.4%;  $P < .001$ ) and the 0.5-mg group (18.5%;  $P < .001$ ) vs placebo (3.9%). Varenicline was generally well tolerated, with nausea occurring in 16% to 42% of varenicline-treated subjects. Reports of nausea were lower for the titrated vs nontitrated dosing and infrequently led to medication discontinuation.

**Conclusion:** Varenicline tartrate, 0.5 mg and 1.0 mg twice daily, is efficacious for smoking cessation.

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**T**OBACCO USE CAUSES CANCER, heart disease, chronic obstructive pulmonary disease, and premature death.<sup>1,2</sup> More than one third of the world's population older than 15 years smokes,<sup>3,4</sup> making tobacco addiction the leading cause of preventable death worldwide. Although currently available therapies can help some smokers quit, their efficacy is modest. Therefore, development of new therapies to treat tobacco dependence is crucial.

*See also pages 1547, 1553, and 1561*

Varenicline tartrate represents the first nicotinic acetylcholine receptor partial agonist to be developed specifically for smoking cessation. A partial agonist has lower intrinsic efficacy than a full agonist and may act as an antagonist by competing with an agonist for receptor binding. Varenicline is highly selective for the  $\alpha_4\beta_2$  nicotinic acetylcholine receptor, which is responsible for

mediating the reinforcing properties of nicotine in the brain.<sup>5</sup> As a partial agonist with higher affinity and less functional effect than nicotine, varenicline may alleviate craving and withdrawal during smoking cessation. With nicotine exposure, the receptor occupancy of varenicline would be expected to block the reinforcing effects of smoking. This may lead to an extinction of smoking behavior prior to a quit attempt and prevent a slip from becoming a relapse after a quit attempt.

Varenicline tartrate is well tolerated in doses up to 3 mg/d.<sup>6</sup> Nausea, a common adverse experience, is reduced when varenicline is divided into 2 doses rather than administered as a single dose (unpublished data, 2005). The primary objective of this study was to evaluate the efficacy and safety of 4 varenicline tartrate dose regimens (0.5 mg and 1.0 mg twice daily; titrated and nontitrated) for smoking cessation. A secondary objective was to evaluate the effects of dose titration on nausea and overall tolerability.

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The overall study included 2 phases: a 12-week, multicenter, double-blind, placebo-controlled, randomized study with weekly visits, followed by a 40-week assessment after discontinuation of the regimen. The study was conducted in compliance with the Declaration of Helsinki at 10 sites in the United States. Each center's institutional review board approved the study. Subjects provided written informed consent before participation.

Subjects were healthy cigarette smokers, aged 18 to 65 years, who smoked at least 10 cigarettes per day. Smoking history, including the Fagerström Test for Nicotine Dependence, was assessed at the screening visit.<sup>7</sup> Exclusion criteria included treatment with an investigational drug within the previous month; major depression within the prior year; panic disorder, psychosis, or bipolar disorder; use of nicotine replacement or bupropion within the previous 3 months; cardiovascular disease; clinically significant medical disease; drug or alcohol abuse or dependence within the past year; and use of tobacco products other than cigarettes or marijuana use within the previous month.

### TREATMENT PERIOD

Eligible subjects were randomly assigned to 1 of 5 groups at the baseline visit: 0.5 mg twice daily nontitrated (ie, 0.5 mg twice daily for 12 weeks); 0.5 mg twice daily titrated (ie, 0.5 mg once daily for 7 days, then 0.5 mg twice daily for 11 weeks); 1.0 mg twice daily nontitrated (ie, 1.0 mg twice daily for 12 weeks); 1.0 mg twice daily titrated (ie, 0.5 mg once daily for 3 days, then 0.5 mg twice daily for 4 days, then 1.0 mg twice daily for 11 weeks); or placebo (ie, 2 placebo tablets twice daily for 12 weeks). Subjects and investigators were blinded to the study drug treatment assignment. Subjects were not encouraged to guess their treatment assignment and were encouraged to eat prior to varenicline intake and to take the medication with 240 mL of water.

Subjects received a smoking cessation booklet<sup>8</sup> at the baseline visit and brief smoking cessation counseling (up to 10 minutes) at each visit. Subjects were instructed to take their first dose of varenicline beginning the evening of the baseline visit. The target quit date was planned 7 days later (week 1 visit). Subjects received brief telephone counseling (up to 5 minutes) 3 days after the target quit date. Subjects were instructed to complete a daily smoking diary while taking the study drug.

Self-reported smoking status, use of nicotine-containing products since the last visit and in the past 7 days, and exhaled carbon monoxide measurement were assessed at each weekly visit. The Minnesota Nicotine Withdrawal Scale (MNWS) was assessed weekly from baseline to week 7 and at week 12. Withdrawal symptoms (urge to smoke, depressed mood, irritability, anxiety, difficulty concentrating, restlessness, increased appetite, difficulty going to sleep, and difficulty staying asleep) were rated from 0 (not at all) to 4 (extreme).<sup>9,10</sup> The modified Cigarette Evaluation Questionnaire (mCEQ)<sup>11</sup> was completed by all subjects at baseline and daily for the first week of medication treatment and weekly through week 7 by subjects who continued to smoke. The mCEQ comprised 12 items, which yielded 5 subscales: smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations, craving relief, and aversion. Each item is rated from 1 (not at all) to 7 (extremely).

Vital signs, weight, and adverse event information were collected at each visit. A physical examination was performed prior to randomization and at the final visit. Urine and blood were collected at screening, baseline, and at weeks 1, 2, 4, 7, and 12 for biochemical analysis. Electrocardiograms were under-

taken at screening, baseline, and at weeks 1, 4, 7 and 12 throughout the study.

### FOLLOW-UP PERIOD

Subjects were encouraged to participate in a 40-week assessment without the study drug. Smoking status (verified by exhaled carbon monoxide) was assessed at weeks 13, 24, and 52. Self-reported smoking status was assessed by telephone at weeks 16, 20, 28, 32, 36, 40, and 44.

### OUTCOME MEASURES

The primary efficacy measures, based on the combination of titrated and nontitrated subjects for each dosing group (pooled dosage groups), were the carbon monoxide-confirmed 4-week continuous quit rate for weeks 4 through 7 and 9 through 12 during treatment and the continuous abstinence rates for weeks 9 through 52 for each dose relative to placebo. Continuous abstinence was defined as self-report of no cigarette use during the specified time period confirmed by an exhaled carbon monoxide measurement of 10 ppm or lower. To be considered abstinent from smoking during the treatment period, subjects also had to report that they did not use any other nicotine-containing products. During the follow-up period, use of nicotine replacement therapy did not disqualify subjects from being considered abstinent. If an exhaled carbon monoxide measurement was missing during a clinic visit, or if a study subject missed 1 visit, the subject was counted as a nonsmoker as long as at the preceding and following visit had confirmatory evidence of not smoking by self-report and exhaled carbon monoxide measurement. Subjects who withdrew or were lost to follow-up were assumed to be smokers for the remainder of the study.

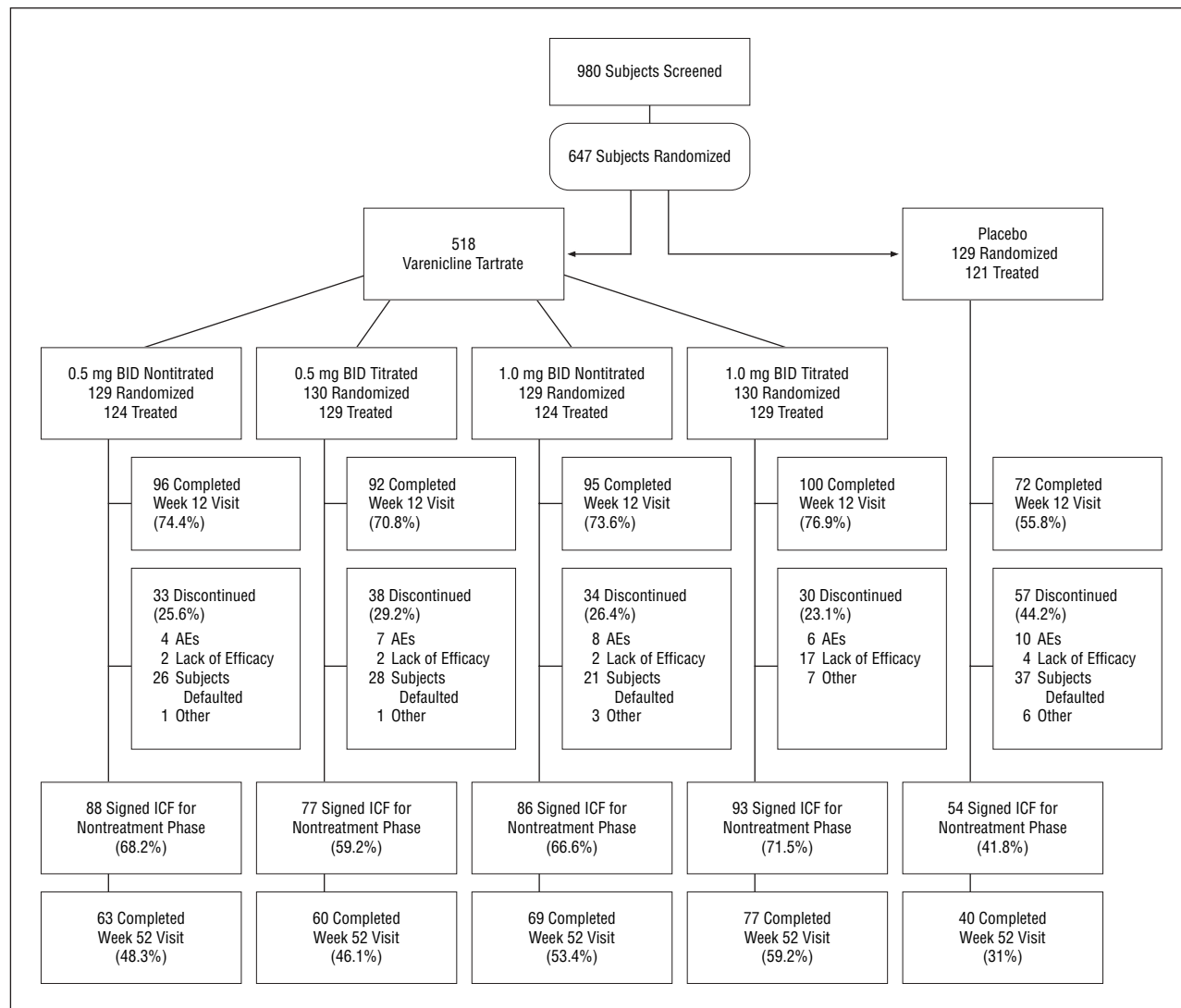
Secondary efficacy end points during the treatment period included the carbon monoxide-confirmed 7-day point prevalence abstinence (abstaining from smoking during the preceding 7 days) and changes in the MNWS and the mCEQ by treatment group. Secondary long-term outcomes also included the carbon monoxide-confirmed 7-day point prevalence abstinence at weeks 24 and 52.

### STATISTICAL ANALYSES

Sample size ( $n=125$  for each group) was determined assuming 4-week continuous quit rates of 38% for active treatment and 20% for placebo (odds ratio, 2.45). A 2-group continuity-corrected  $\chi^2$  test with a 2-sided significance level of .05 would have at least 90% power to detect the difference between active treatment and placebo for the sample sizes of 250 and 125, respectively.

Efficacy analyses were conducted using pooled dosage groups and as separate analyses of each treatment group vs placebo. A step-down procedure was used for the multiple contrasts of active groups to placebo for the primary end point to preserve the family-wise error rate,  $\alpha=.05$ . Binary data were analyzed using a logistic regression model that included treatment and center as independent variables. Testing was carried out using the likelihood ratio  $\chi^2$  test statistic. Odds ratios reported for each treatment group vs placebo are the least squares mean estimates from the logistic model.

For the MNWS and mCEQ, inferential analyses were carried out using an analysis of variance model, including baseline value of the end point as a covariate and the fixed effects of treatment and center. Inferential analyses compared the incidence of nausea for each treatment group with placebo using a logistic regression model that included treatment as the independent variable.



**Figure 1.** Subject disposition. AEs indicates adverse events (including laboratory abnormalities considered AEs, treatment-emergent AEs, and non-treatment emergent AEs); BID, twice daily; and ICF, informed-consent form. "Other" reasons for discontinuation included protocol violations, subject failed to meet entry criteria, noncompliance, and personal reasons.

## RESULTS

The disposition of study subjects is outlined in **Figure 1**. Of the 980 subjects screened, 647 were eligible and randomized to treatment. Subjects completing the 12-week study ranged from 70.8% to 76.9% for the varenicline groups compared with 55.8% for placebo. Of subjects completing the treatment phase, 87.5% (n=344 from the varenicline groups and n=54 from the placebo group) signed another consent to enter the 40-week extension study. Of these, 309 (n=269 from the varenicline groups and n=40 from the placebo group) completed the week 52 visit.

Demographic characteristics and smoking variables were similar across treatment groups, with subjects smoking an average of 21 cigarettes per day for an average of 25 years (**Table 1**).

### ABSTINENCE FROM SMOKING

The 4-week continuous quit rates for weeks 4 through 7 and 9 through 12 were significantly greater in the varenicline treatment groups vs placebo (**Figure 2**) ( $P < .001$ ).

The continuous quit rates for weeks 4 through 7 were significantly higher for the 0.5-mg twice-daily nontitrated and titrated groups (37.2% and 35.4%, respectively) ( $P < .001$ ) and for the 1.0-mg twice-daily nontitrated and titrated groups (38.8% and 40.8%, respectively) ( $P < .001$ ) varenicline groups vs placebo (10.9%). During weeks 9 through 12, continuous quit rates were significantly higher for the 0.5-mg twice-daily nontitrated and titrated groups (47.3% and 40.8%, respectively) ( $P < .001$ ) and for the 1.0-mg twice-daily nontitrated and titrated groups (44.2% and 54.6%) ( $P < .001$ ) varenicline groups vs placebo (11.6%).

The continuous quit rates from the target quit date to week 12 were significantly higher for all varenicline doses compared with placebo ( $P \leq .001$ ). At week 12, 20.8% to 24.0% of subjects in the varenicline groups were continuously abstinent compared with 7% for the placebo group. At each weekly time point, continuous quit rates were similar across the varenicline

**Table 1. Subject Demographics and Smoking History at Screening\***

Characteristic	Placebo (n = 129)	Varenicline Tartrate			
		0.5 mg BID Nontitrated (n = 129)	0.5 mg BID Titrated† (n = 130)	1.0 mg BID Nontitrated (n = 129)	1.0 mg BID Titrated‡ (n = 130)
Age, y	43.0 ± 9.4	42.9 ± 10.1	43.5 ± 10.5	43.7 ± 10.0	42.2 ± 10.7
Men	51.9	45.0	53.1	48.8	48.5
White	72.1	85.3	80.8	83.7	80.8
BMI	27.0 ± 4.6	27.1 ± 5.0	26.6 ± 4.5	27.6 ± 5.5	26.6 ± 4.5
Fagerström§	5.8 ± 2.3	5.5 ± 2.0	5.4 ± 1.9	5.5 ± 2.0	5.3 ± 2.1
Duration of smoking, y	25.3 ± 9.5	26.0 ± 10.8	25.0 ± 10.8	25.7 ± 10.6	24.0 ± 11.1
Cigarettes smoked per day	20.4 ± 7.2	20.9 ± 8.1	21.3 ± 8.1	20.8 ± 10.1	20.9 ± 7.0
Previous serious quit attempts					
None	8.5	10.1	10.8	6.2	3.8
At least 1	91.5	89.9	89.2	93.8	96.2

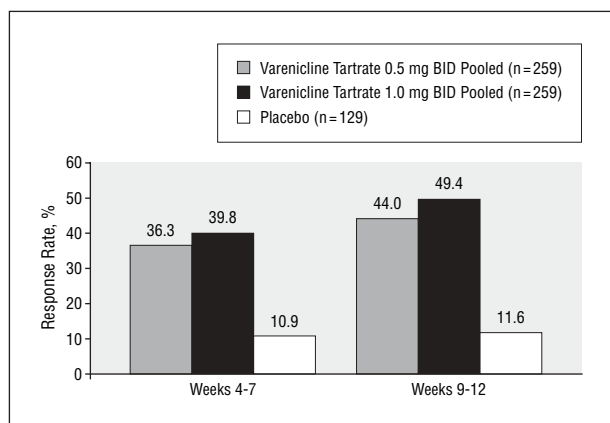
Abbreviations: BID, twice daily; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); QD, once daily.

\*Data are reported as mean ± SD or percentage of subjects.

†Initial dose of 0.5 mg QD for 7 days then 0.5 mg BID for 11 weeks.

‡Initial dose of 0.5 mg QD for 3 days, then 0.5 mg BID for 4 days, then 1.0 mg BID for 11 weeks.

§Fagerström score assesses the severity of nicotine addiction ranging from 0 (minimum dependence) to 10 (maximum dependence).

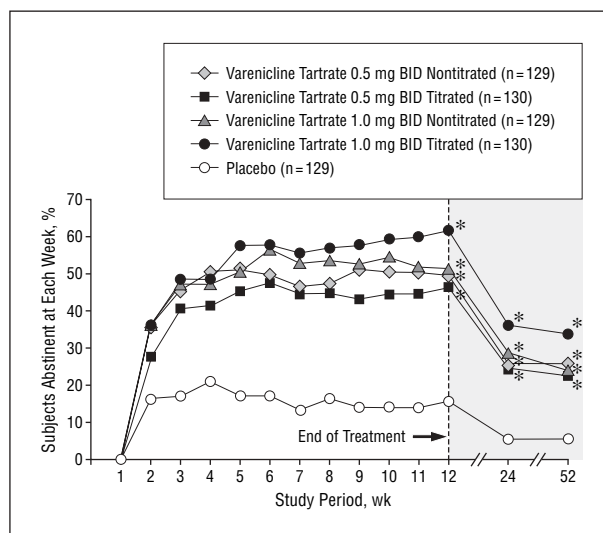


**Figure 2.** Continuous quit rates.  $P < .001$  for each treatment group vs placebo. BID indicates twice daily. The odds ratios (ORs) and 95% confidence intervals (CIs) for the weeks 4 through 7 evaluation were 4.96 (95% CI, 2.66-9.22) for the 0.5-mg group and 5.86 (95% CI, 3.16-10.90) for the 1.0-mg group; for the weeks 9 through 12 evaluation, 6.32 (95% CI, 3.47-11.50) and 8.07 (95% CI, 4.42-14.70), respectively.

groups, which were 2 to 3 times greater than those for placebo.

The weeks 9 through 52 abstinence rates were higher in the pooled 0.5-mg varenicline tartrate twice-daily group (18.5%) ( $P < .001$ ) and in the pooled 1-mg twice-daily group (22.4%) ( $P < .001$ ) relative to placebo (3.9%). The individual continuous abstinence rates were 18.6% for the 0.5-mg twice-daily nontitrated group, 18.5% for the 0.5-mg twice-daily titrated group, 19.4% for the 1.0-mg twice-daily nontitrated group, and 25.4% for the 1.0-mg twice-daily titrated group. Subjects who were abstinent during weeks 9 through 12 but did not continue in the follow-up study (11 [12%] of 94 subjects in the varenicline 0.5-mg group, 4 [5%] of 80 subjects in the 1.0-mg group, and 3 [4%] of 75 subjects in the placebo group) were considered smokers for weeks 9 through 52 analyses.

**Figure 3** demonstrates that the carbon monoxide–confirmed 7-day point prevalence abstinence rates generally increased from weeks 2 through 12. At week 12,

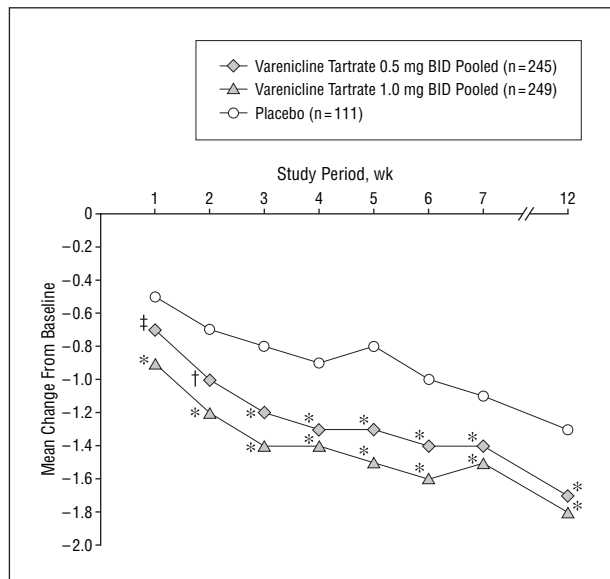


**Figure 3.** Carbon monoxide–confirmed weekly point prevalence abstinence rates. BID indicates twice daily.  $*P < .001$  vs placebo.

rates were significantly higher for each varenicline dose regimen vs placebo ( $P < .001$ ). At weeks 24 and 52, the rates decreased to approximately 1/3 to 1/2 of the rates observed at week 12 and remained significantly higher for varenicline vs placebo.

#### EFFECTS ON OTHER MEASURES

Varenicline significantly reduced the urge to smoke compared with placebo (**Figure 4**). Other measures of withdrawal, including the MNWS composite score, were mild in all groups. The rewarding effects of smoking were assessed only in subjects who continued to smoke since their last clinic visit. In those subjects, varenicline significantly reduced the reinforcing effects of smoking (**Figure 5A**). Compared with placebo, the reduction from baseline for the psychological reward subscale of the mCEQ was significantly greater for the 1-mg BID group



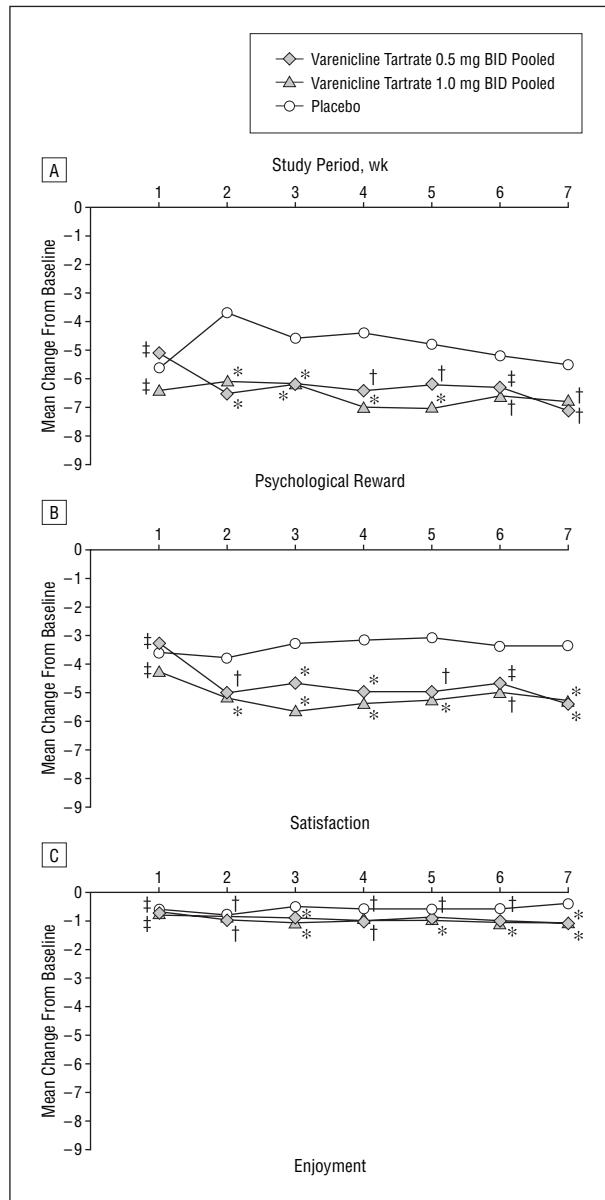
**Figure 4.** Mean changes in Minnesota Nicotine Withdrawal Scale "urge to smoke" scores from week 1 to week 12 for all subjects. BID indicates twice daily. In comparison with placebo, asterisk indicates  $P < .001$ ; dagger,  $P < .01$ ; and double dagger,  $P < .05$ .

at all follow-up time points. Significant reductions were also demonstrated for 2 other subscales: smoking satisfaction and enjoyment of respiratory tract sensations (Figure 5B and C).

Weight was summarized separately for all subjects and cessators (subjects who did not smoke any cigarettes from the target quit date to the day of measurement). Inferential analyses were not performed. Mean weight gain from baseline to week 7 was generally greater among cessators than among smokers. For cessators, mean (SE) weight changes for the varenicline tartrate 0.5-mg twice-daily nontitrated, 0.5-mg twice-daily titrated, 1.0-mg twice-daily nontitrated, 1.0-mg twice-daily titrated, and placebo groups were 3.00 (0.48), 2.88 (0.59), 2.79 (0.57), 1.92 (0.48), and 2.14 (0.63) kg, respectively, at week 12.

### SAFETY AND TOLERABILITY

Adverse events that occurred in 10% of subjects or more in any 1 treatment group are listed in **Table 2**. The denominator for each group is treated subjects (eg, subjects who took at least 1 dose of medication as indicated by a recorded treatment start date in the dosing record). The most frequent adverse events were neurologic (insomnia, headache, abnormal dreams, and/or somnolence) and gastrointestinal (nausea, dyspepsia, constipation, and/or flatulence). Nausea was a common adverse event. The incidence of nausea was significantly higher in the 1.0-mg twice-daily titrated (34.9%) and nontitrated (41.9%) groups vs placebo (14.9%) ( $P < .001$  for both). In the 0.5-mg twice-daily nontitrated group, the incidence of nausea was 22.6% ( $P = .12$  compared with placebo). In the 0.5-mg twice-daily titrated varenicline tartrate group, the incidence of nausea was comparable to placebo (16.3%) ( $P = .86$ ). Titration appeared to reduce the overall incidence of nausea. The discontinua-



**Figure 5.** Mean changes in modified Cigarette Evaluation Questionnaire scores in the "psychological reward" (A), "satisfaction" (B), and "enjoyment" (C) subscales from week 1 to week 12. BID indicates twice daily. In comparison with placebo, asterisk indicates  $P < .001$ ; dagger,  $P < .01$ ; and double dagger,  $P < .05$ .

tion rate owing to nausea was low ( $< 5\%$  of subjects in each treatment group).

No deaths occurred during the study. Serious adverse events (SAEs) that occurred within 30 days of the last dose were reported in 2 subjects treated with placebo (1 syncope and 1 suicide attempt) and 9 subjects treated with varenicline: 1 subject in the 0.5-mg twice-daily nontitrated group had a syncopal episode; 4 SAEs occurred in the 0.5-mg twice-daily titrated group (1 duodenal ulcer, 1 right ear cholesteatoma, 1 unstable angina, and 1 seizure following a car crash); and 4 SAEs occurred in the 1.0-mg twice-daily group (1 paroxysmal supraventricular tachycardia, 1 aseptic meningitis, 1 multiple sclerosis, and 1 carcinoid colon cancer). In addition, 2 SAEs that occurred more than 30 days after

**Table 2. Adverse Events Among Subjects\***

Adverse Event	Treatment Group				
	Placebo (n = 121)	Varenicline Tartrate			
		0.5 mg BID Nontitrated (n = 124)	0.5 mg BID Titrated (n = 129)	1.0 mg BID Nontitrated (n = 124)	1.0 mg BID Titrated (n = 129)
Any adverse event	86.3	81.4	90.3	85.3	79.3
Discontinuation due to adverse event	17.4	7.3	14.0	13.7	21.7
Any nausea	14.9	22.6	16.3	41.9	34.9
Mild	11.6	20.2	11.6	23.4	24.8
Moderate	2.5	2.4	3.9	18.5	8.5
Severe	0.8	0	0.8	0	1.6
Discontinuation from nausea	2.5	1.6	0	4.8	3.9
Median nausea duration, †	4.0	3.0	7.0	9.0	4.0
Insomnia	11.6	33.9	20.9	21.8	37.2
Headache	17.4	27.4	19.4	24.2	22.5
Abnormal dreams	5.0	16.9	11.6	16.9	19.4
Taste perversion	4.1	16.1	7.8	13.7	11.6
Dyspepsia	7.4	8.9	6.2	9.7	14.7
Flatulence	5.8	15.3	8.5	11.3	10.1
Constipation	2.5	6.5	4.7	10.5	10.9
Somnolence	1.7	5.6	5.4	10.5	9.3

Abbreviations: BID, twice daily; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); QD, once daily.

\*Adverse events were reports of symptoms that began after treatment or were exacerbated by treatment; only adverse events occurring in 10% of subjects or more in any group are listed. Unless otherwise noted, data are reported as percentage of subjects.

†If more than 1 event occurred, the median duration of the first nausea event was used for the duration calculation.

the last study medication dose were reported (diabetes mellitus in the 0.5-mg twice-daily titrated group and cholelithiasis in the 1-mg twice-daily nontitrated group). Measured vital signs and results of clinical laboratory tests and electrocardiograms demonstrated no clinically meaningful differences between varenicline and placebo.

#### COMMENT

In this study, treatment with varenicline tartrate at doses of 0.5 mg and 1.0 mg twice daily, was associated with significantly higher smoking cessation rates compared with placebo. Varenicline reduced craving and the reinforcing effects of smoking. Varenicline was generally well tolerated, and nausea was a frequent adverse event. Titration during the first week of treatment appeared to reduce the incidence of nausea.

The pooled analyses for the 0.5- and 1.0-mg groups demonstrate quit rates of approximately 4 times that observed with placebo during weeks 9 through 12 and at the 1-year follow-up. Interestingly, the continuous quit rate for each varenicline dose regimen increased from weeks 4 to 7 to weeks 9 to 12. A similar pattern was observed with the 7-day point prevalence quit rates. When administered for 12 weeks, other smoking cessation pharmacotherapies demonstrate a decrease in abstinence rates or a stabilization of abstinence rates during the latter part of medication treatment.<sup>12-16</sup> Since quit rates appear to increase with continued varenicline treatment, repeated quit attempts with treatment and a longer treatment duration may be beneficial. Moreover, since many subjects relapsed between weeks 12 and 24, future research should examine whether a longer treatment with varenicline

and/or continuation of behavioral counseling also reduces smoking relapse.

The novel mechanism of action of varenicline may be responsible for the relatively high quit rates compared with placebo and the relative increase in quit rates over the medication treatment period. The agonist properties of varenicline may alleviate craving and withdrawal during smoking cessation. Each varenicline tartrate pooled dosage group significantly reduced craving compared with placebo at each weekly visit during the study. Moreover, varenicline reduced the reinforcing effects of smoking (ie, smoking satisfaction, psychological reward, and enjoyment of respiratory tract sensations), which suggests a clinical response to the antagonistic properties of the medication.

Varenicline has an acceptable safety and tolerability profile. The higher rate of completion in the varenicline groups vs placebo group suggests perceived benefit to the subject. Although discontinuation of study medication owing to adverse events was highest in the 1.0-mg twice-daily titrated group (21.7%), this rate was comparable to placebo (17.4%). It seems likely that most of the adverse effects are drug related; however, it is possible that some of the adverse events in the placebo and varenicline groups were signs and symptoms of tobacco withdrawal and were more frequent in the varenicline groups because of higher smoking cessation rates. The basis is unclear for the finding that discontinuation of treatment owing to an adverse event appeared to be greater in the titrated vs nontitrated groups, especially since the incidence rates of adverse events did not follow a similar pattern. Very few subjects (ie, <5%) discontinued medication

because of nausea. The incidence of nausea was consistent with the pharmacologic effects of cholinergic agents and could be centrally or locally mediated. Our results suggest that nausea is dose related and that titration reduced the incidence of nausea.

A limitation of the study is the optional follow-up study design. Subjects who abstained from smoking during weeks 9 through 12 and who did not enter the follow-up phase were counted as smokers, which may have lowered the true long-term efficacy rates (particularly in the 0.5-mg twice-daily group). However, even if the subjects who did not enter the follow-up truly remained abstinent from smoking at 1 year, this would have underestimated the true long-term quit rate by only 4% in the 0.5-mg twice-daily group, 1.5% in the 1.0-mg twice-daily group, and 2.3% in the placebo group. Since approximately 90% of subjects who completed treatment continued in the follow-up phase, the analyses conducted likely represents a reasonable estimation of long-term quit rates.

In summary, varenicline tartrate (0.5-mg and 1.0-mg doses taken twice daily for 12 weeks) significantly improved short- and long-term abstinence rates compared with placebo. Titration of the drug over the first week reduced the incidence of nausea. Future studies are warranted to compare the efficacy of varenicline to other smoking cessation pharmacotherapies and to determine whether a longer duration of medication treatment improves smoking cessation rates.

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**Role of the Sponsor:** Pfizer Inc was involved in all elements of this study, including, but not limited to, the study design and monitoring.

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