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ORIGINAL ARTICLE

The efficacy and safety of varenicline for smoking cessation using a flexible dosing strategy in adult smokers: a randomized controlled trial

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ABSTRACT

Objective: To determine whether self-regulated flexible dosing with varenicline tartrate is safe and effective for smoking cessation.

Research design and methods: 320 healthy, motivated-to-quit smokers (≥10 cigarettes/day) aged 18–65 years, entered a multicenter, randomized, double-blind, placebo-controlled study – conducted between December 26, 2001 and June 24, 2003 – with a 12-week treatment phase and 40-week, double-blind, non-treatment follow-up. Treatment consisted of varenicline or placebo in fixed doses (Week 1: titrated from 0.5 to 1.0 mg/day) followed by a self-regulated flexible schedule (Weeks 2–12: 0.5–2.0 mg/day).

Main outcome measures: Primary outcomes included carbon monoxide-confirmed continuous abstinence rate (CAR) from smoking for Weeks 4 through 7, 9 through 12, and 9 through 52. Secondary outcomes included CAR from Weeks 9 through 24, 7-day point prevalence of abstinence, safety assessments, and measures of craving, withdrawal, and smoking reward.

Results: Superior CARs were observed in varenicline-treated ($n = 157$) versus placebo participants ($n = 155$) for Weeks 4 through 7 (38.2 vs. 11.6%), 9 through 12 (40.1 vs. 11.6%), 9 through 24 (28.0 vs. 9.0%), and 9 through 52 (22.3 vs. 7.7%) (all $p < 0.001$). Seven-day point prevalence was higher in varenicline-treated than placebo participants at Weeks 12 (46.5 vs. 14.2%; $p < 0.001$), 24 (32.5 vs. 13.5%; $p < 0.001$), and 52 (28.0 vs. 13.5%; $p = 0.001$). Overall, medication compliance was high, although varenicline-treated, but not placebo, participants tended to taper down their dosage over time. Total treatment-emergent AEs were 77.1% (varenicline: 121/157) and 65.8% (placebo: 102/155). Few AEs led to treatment discontinuation (varenicline: 11/157, 7.0% and placebo: 7/155, 4.5%). Participants were primarily healthy Caucasians, so more research is necessary to determine how applicable these findings are to other populations.

Conclusions: A self-regulated, flexible dosing regimen of varenicline is well tolerated, with superior effectiveness versus placebo for smoking cessation.

Introduction

Approximately 1.3 billion people worldwide smoke[1]. In 2000, smoking contributed to an estimated 4.9 million premature deaths[2]. If the current trend continues, this death count could reach 6.4 million people annually by the year 2015 and 8.3 million by 2030[3,4]. Moreover, by 2015, smoking is projected to be responsible for 10% of all deaths globally[3,4].

Varenicline tartrate is a selective partial agonist at $\alpha 4\beta 2$ nicotinic acetylcholine receptors and it is the most recent pharmacotherapy to gain regulatory approval for smoking cessation. As a partial agonist, varenicline stimulates low levels of dopamine release in the nucleus accumbens, while as an antagonist, it blocks the ability of nicotine to bind to these receptors[5]. Thus, varenicline may replace the rewarding properties, and simultaneously prevent the positive reinforcement, of nicotine. In this way, varenicline may reduce craving and withdrawal symptoms following smoking cessation, which could promote abstinence in smokers motivated to quit.

The first dose-ranging study conducted with varenicline examined doses of 0.3 mg once daily, 1.0 mg once daily, and 1.0 mg twice daily taken for 6 weeks and found that doses of 1.0 mg once daily and 1.0 mg twice daily effectively promoted abstinence from smoking[6]. Furthermore, the 1.0 mg twice-daily dose also increased the rate of continuous abstinence at 52 weeks. In a previous study, the most frequently reported adverse event (AE) among participants receiving varenicline was nausea[6]. Although most of these incidences of nausea were mild or moderate in intensity and seldom resulted in discontinuation of study medication[6], two strategies were investigated for their potential to retain high efficacy rates for smoking cessation with lower incidences of nausea. One study examined the effect of initiating 0.5 mg twice-daily and 1.0 mg twice-daily fixed-dose regimens with gradually increasing doses during the first week of therapy, and found that titrated dosing reduced the incidence of nausea[7]. This study, performed at the same time, evaluated if a self-regulated, flexible dosing strategy would be effective and safe for smoking cessation.

Patients and methods

Design overview

This randomized, double-blind, placebo-controlled study investigated the safety and efficacy of a flexible dosing regimen of varenicline during a 12-week treatment period. Long-term efficacy was examined during a 40-week non-treatment follow-up. The study protocols and amendments were approved by the Institutional Review Board for each of the participating institutions.

Setting and participants

This study was conducted at five US centers between December 2001 and June 2003. Participants were healthy adult cigarette smokers, motivated to quit, aged 18–65 years, who smoked an average of at least 10 cigarettes a day with no period of abstinence longer than 3 months in the past year. Exclusion criteria included any conditions or medications that might interfere with the study drug or drug absorption; treatment with or plans to take another investigational drug within 1 month of study enrollment or completion; unwillingness or inability to follow the study protocol; history of clinically significant allergies (except seasonal); endocrine, gastro-intestinal, hematological, hepatic, neurological, psychiatric, pulmonary, renal, or cardiovascular disease; clinically significant abnormalities on an electrocardiogram (ECG); cancer (except treated basal cell or squamous cell carcinoma); systolic blood pressure of >160 mmHg or diastolic blood pressure of >95 mmHg; history of depression, panic disorder, psychosis, or bipolar disorder; non-nicotine drug or alcohol dependence within 12 months before study enrollment; use of any non-cigarette tobacco products or marijuana within the past month or any nicotine replacement product within the past 3 months; or plans to donate blood components during or within 1 month of study completion. Participants who were enrolled into the study received financial compensation for time and travel.

Randomization

A computer-generated randomization list was created by Pfizer using randomly permuted blocks and a pseudo-random number generator. At the baseline visit, qualified participants were assigned in a 1 : 1 ratio to varenicline treatment or placebo in the numerical order that they were accepted to the study.

Interventions

Participants were supplied with tablets of 0.5 mg of varenicline or placebo in blister packs. Dosing consisted of one tablet once daily (i.e., 0.5 mg/day) for 3 days, followed by one tablet twice daily (i.e., 1.0 mg/day) for 4 days. After the seventh day, participants began a flexible dosing schedule, wherein they were allowed

to modify their own dosage as often as they wished (e.g., in response to AEs); however, they were instructed to take at least one tablet daily but not to exceed two tablets twice daily (i.e., 0.5–2.0 mg/day) through Week 12 of the study. Participants were advised to take all medications after eating and with 240 mL of water. Compliance was assessed by tracking returned blister packs at weekly clinic visits. The daily dose taken by individual participants was recorded and a weekly modal daily dose was determined. Individual weekly modal daily doses over the course of treatment were averaged to calculate the mean modal daily dose for each treatment group.

Participants were given an educational booklet, *Clearing the Air: How to Quit Smoking . . . and Quit for Keeps* at the baseline visit[8]. The target quit date was scheduled to coincide with the Week 1 clinical visit, although participants were permitted to quit earlier if they wished. During the 12-week treatment period, participants attended weekly clinic visits to assess efficacy, safety, and to receive brief (up to 10 min) counseling in accordance with the US Public Health Service guideline[9,10].

Assessment of cigarette usage

At each clinic visit, participants provided verbal 'yes' or 'no' responses to a series of questions about smoking cigarettes and use of other products containing nicotine since the previous visit or during the past 7 days. Exhaled carbon monoxide (CO) concentrations were measured and levels $\leq$10 ppm confirmed self-reported abstinence. Participants also kept a daily smoking diary through Week 12 (i.e., the treatment phase) that was collected at each clinic visit.

Missing data imputation rules

Participants with missing data for a single clinic visit were considered abstinent from smoking for the visit if they were CO-confirmed abstinent for the visits immediately preceding and following the missed visit. Participants missing data for more than one visit in a 4-week endpoint evaluation period (Weeks 4–7 or 9–12) during the treatment phase were coded as smokers for that endpoint. Participants who withdrew from the study or were lost to follow-up were considered smokers for the remainder of the study, regardless of their smoking status at their last recorded visit. For the 7-day point prevalence of abstinence, participants with a missing response were considered smokers for that 7-day period and missing CO confirmation was imputed as above.

Assessment of craving, withdrawal, and smoking reward

Participants completed the Minnesota Nicotine Withdrawal Scale (MNWS)[11,12] weekly from baseline through Week 7, and again at Week 12 or at early termination of study medication. Items from this questionnaire yielded an urge to smoke score (item 1) and a composite score of withdrawal symptoms (items 2–9). The desirable and aversive effects of smoking were assessed with the modified cigarette evaluation questionnaire (mCEQ)[13], which was completed daily from baseline through the first week of treatment, and at each subsequent clinic visit through Week 7, but only by participants who had reported smoking since the previous assessment.

Safety and tolerability

All observed or reported AEs were documented. Treatment-emergent AEs included any adverse drug reactions, illnesses with onset during the study, exacerbation of previous illnesses, and symptoms that may have been from nicotine withdrawal that occurred up to 7 days after the end of treatment. A serious AE (SAE) was an event that resulted in death, was life threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability, or resulted in a birth defect. Specified laboratory tests were performed during certain visits (e.g., blood chemistry and complete blood count). ECGs were obtained at baseline, Week 2, and Week 12. Vital signs and weight were documented at all clinic visits.

Outcomes and follow-up

Study endpoints

The primary efficacy endpoints were the CO-confirmed continuous abstinence rate (CAR) for Weeks 4 through 7, 9 through 12, and 9 through 52. CAR was defined as the proportion of participants who reported abstaining from smoking during the specified periods as confirmed by exhaled CO $\leq$10 ppm at each clinic visit. To be considered abstinent from smoking during the treatment period, participants also had to report that they did not use any other products containing nicotine. During the follow-up period, use of nicotine replacement therapy did not disqualify participants from being considered abstinent.

Secondary endpoints were the CO-confirmed CAR from Weeks 9 through 24; the CO-confirmed 7-day point prevalence of abstinence, which was defined as the proportion of participants who had abstained from smoking during the preceding week; and MNWS and

mCEQ assessments of nicotine withdrawal and smoking reward.

Non-treatment follow-up

Participants were encouraged to remain in the study to provide smoking status evaluations even if they discontinued medication early, and those who completed the 12-week treatment phase were asked to continue into the non-treatment phase of the study to assess long-term efficacy. During the post-treatment follow-up period, long-term abstinence was assessed with clinic visits at Weeks 13, 24, and 52, and participants were contacted by telephone at 4-week intervals between clinic visits.

Statistical analysis

The primary analysis population for both efficacy and safety comparisons was defined as all participants who were randomized and received at least one dose of study medication.

A sample size of 150 per group would have ≥90% power to detect the difference in 4-week CARs between varenicline treatment (estimated response rate 38%) and placebo (estimated response rate 20%), as determined by a two-group, continuity-corrected χ^2 test with a 0.05 two-sided significance level (odds ratio [OR] of 2.452). Since dropouts were coded as smokers, no adjustments for sample size calculation were made for dropouts.

All reported significance tests were two-tailed, using an overall significance level of $\alpha = 0.05$. Additionally, a step-down procedure was used for the primary endpoints (Weeks 9–12 CAR, then Weeks 4–7 CAR) to preserve family-wise error rate, $\alpha = 0.05$. Abstinence rates (i.e., CARs and 7-day point prevalence) were expressed as binary data and analyzed with a logistic regression model including treatment and center, with testing carried out with a likelihood ratio χ^2 test. ORs with 95% confidence intervals (CIs) presented are least square estimates from the logistic regression model. Inferential statistics of self-administered rating scales MNWS and mCEQ were carried out using an analysis of covariance model, including baseline value as a covariate and fixed effects of treatment and center.

Results

Subject disposition and baseline characteristics

Figure 1 summarizes the subject disposition. Demographic characteristics and smoking history at baseline were comparable between treatment groups (Table 1). A total of 434 participants were screened and of these, 320 participants were randomized to receive study medication, with 157 and 155 receiving treatment in the varenicline and placebo groups, respectively. A total of 232 participants completed the treatment phase (122 varenicline-treated and 110 placebo). Some participants elected to withdraw from the study between the treatment and non-treatment phases, leaving 120 varenicline-treated and 100 placebo participants to enter into the non-treatment phase, with 100 varenicline-treated and 89 placebo participants completing the study. The median duration of treatment for both groups was 83 days. The ranges were 5–92 days for the group receiving varenicline and 1–90 days for the group receiving placebo.

Average doses taken

The mean modal dose through the 12-week treatment phase was 1.35 mg/day for varenicline treatment and 1.63 mg/day for placebo treatment (expressed in milligram equivalents based on the number of tablets taken). The number of subjects taking each modal dose by week is shown for the varenicline-treated (Figure 2A) and placebo (Figure 2B) groups. Medication compliance was generally high with few participants failing to take at least one dose of medication each week (Figures 2A and 2B). Varenicline-treated participants exhibited a trend of decreasing weekly modal daily dose over the treatment period (Figure 2A). A similar pattern of dose reduction was not observed in the placebo group (Figure 2B).

Efficacy results

CO-confirmed CAR was significantly higher in varenicline-treated versus placebo participants from Weeks 4 through 7 (varenicline: 60/157, 38.2% vs. placebo: 18/155, 11.6%; $p < 0.001$) and 9 through 12 (varenicline: 63/157, 40.1% vs. placebo: 18/155, 11.6%; $p < 0.001$) (Figure 3). CO-confirmed CAR during Weeks 9 through 24 and Weeks 9 through 52 also were significantly greater in the varenicline group than in the placebo group (44/157, 28.0% vs. 14/155, 9.0%; $p < 0.001$ and 35/157, 22.3% vs. 12/155, 7.7%; $p < 0.001$, respectively) (Figure 3). Among the subjects who had achieved long-term (Weeks 9–52) abstinence, 1 of 35 participants in the varenicline group and 1 of 12 in the placebo group had used nicotine replacement therapy (NRT) during the post-treatment follow-up period.

The 7-day point prevalence of abstinence was significantly higher in the varenicline group than in

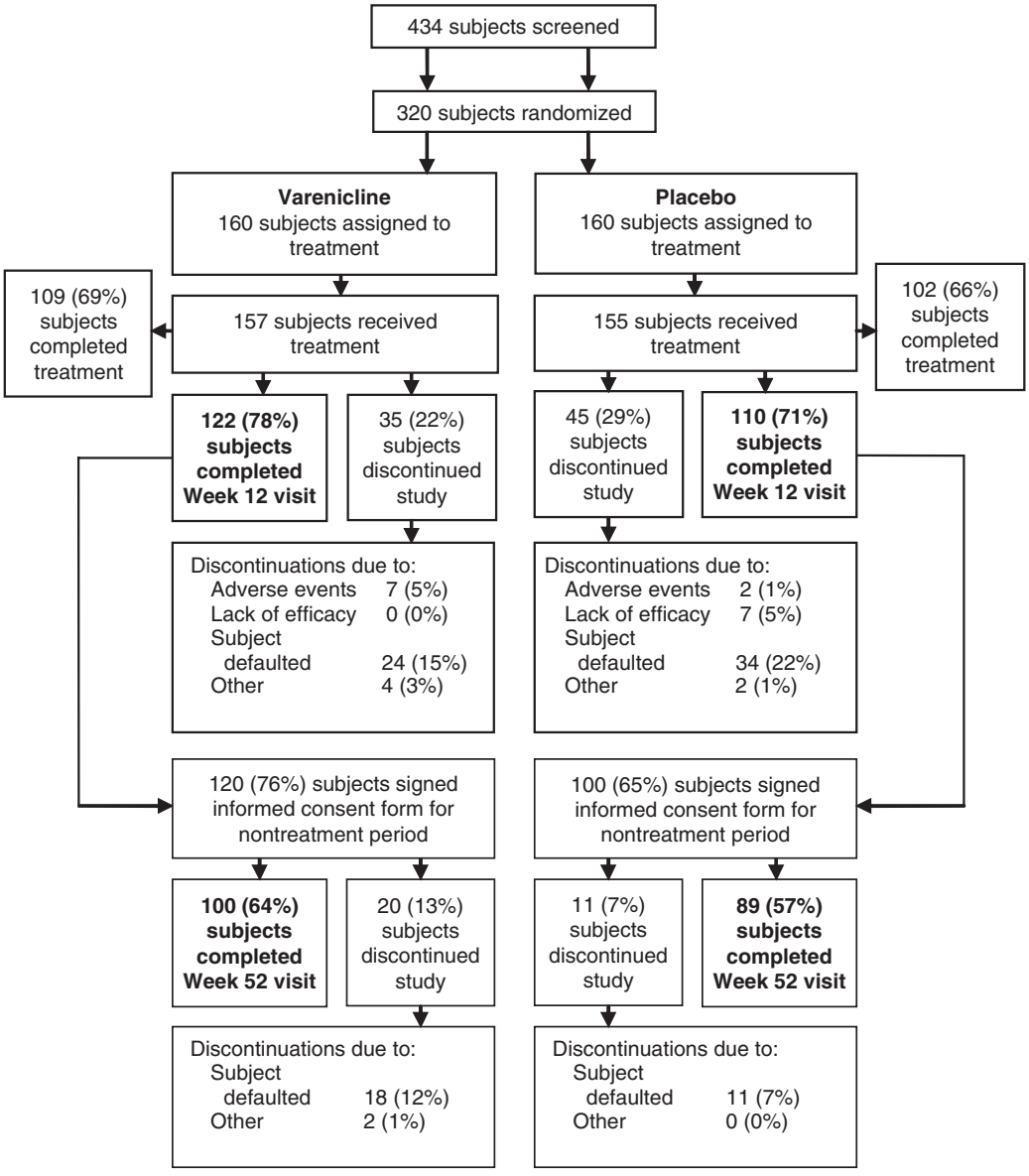

Figure 1. *Subject disposition. Subject defaulted = subject withdrew consent or was lost to follow-up; Other = protocol violations or noncompliance*

the placebo group at Weeks 12 (73/157, 46.5% vs. 22/155, 14.2%; $p < 0.001$), 24 (51/157, 32.5% vs. 21/155, 13.5%; $p < 0.001$), and 52 (44/157, 28.0% vs. 21/155, 13.5%; $p = 0.001$) (Figure 4).

Minnesota Nicotine Withdrawal Scale

Varenicline reduced the urge to smoke (MNWS Item 1) significantly more than placebo at every time point assessed (Weeks 1–7 and Week 12; all $p < 0.01$) (Table 2). The composite score for withdrawal effects (MNWS items 2–9) showed that, for both treatment groups, withdrawal symptoms peaked at Week 2 and declined steadily thereafter, but did not return to baseline. At all weekly time points, the composite score for withdrawal symptoms was numerically greater among placebo participants than among varenicline-treated participants. Among a subpopulation of abstinent subjects defined as 'non-lapsing quitters' – participants who had abstained from smoking from the target quit date of the Week 1 visit through the time point of interest – composite scores for withdrawal effects on the MNWS demonstrated that varenicline-treated subjects experienced significantly fewer withdrawal effects than placebo subjects during the first 6 weeks of treatment (Table 3).

Modified cigarette evaluation questionnaire

At the initial time point (Week 1), there were no significant treatment differences for any of the

Table 1. *Baseline demographic characteristics and smoking history*

	Varenicline $n = 157$	Placebo $n = 155$
Sex, *n* (%)		
Male	79 (50.3)	83 (53.5)
Female	78 (49.7)	72 (46.5)
Age (years)		
Mean (SD)	41.5 (11.3)	42.1 (11.7)
Range	19–65	18–65
Race, *n* (%)		
White	146 (93.0)	137 (88.4)
Black	8 (5.1)	14 (9.0)
Asian	3 (1.9)	0
Hispanic	0	3 (1.9)
Other	0	1 (0.6)
Fagerström score*		
N	157	153
Mean	5.40	5.35
Number of years subject smoked		
Mean	24.9	25.7
Range	4–50	2–46
Average number of cigarettes per day over the past month		
Mean	22.2	22.3
Range	10–60	6–60†
Number of lifetime serious quit attempts (any method), *n* (%)		
None	17 (10.8)	19 (12.3)
≥1	140 (89.2)	136 (87.7)
Longest period of abstinence in past year (days)		
Mean	8.38	8.59
Range	0–90	0–90

* Fagerström score can range from 0 to 10, with higher scores indicating greater nicotine dependence
† One subject smoked 6 cigarettes per day over the past month, but reported a lifetime cigarette per day average of 30

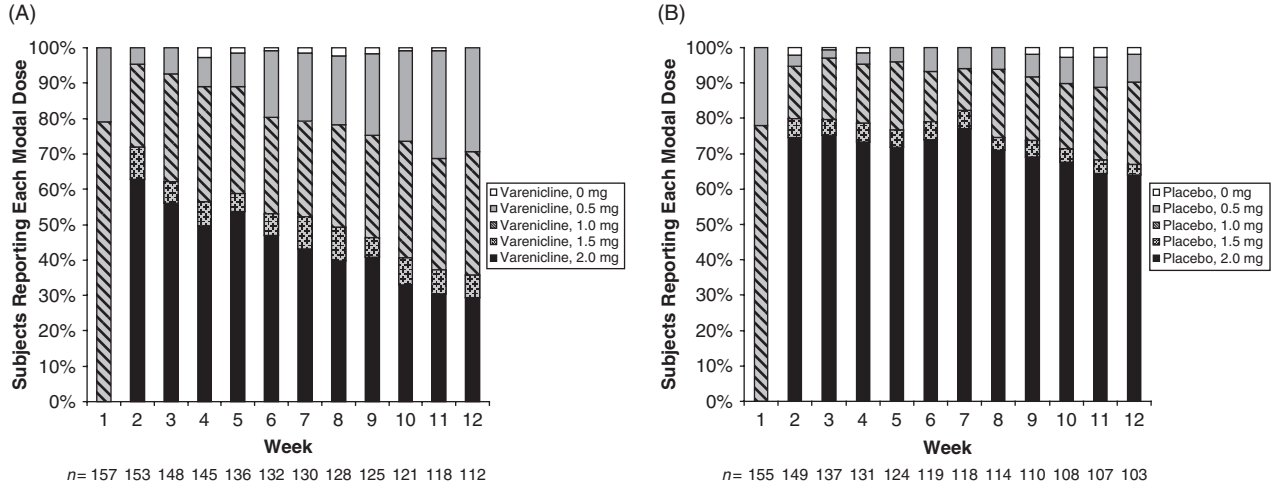

Figure 2. *Percentage of participants for each modal dose by week. The percentage of subjects that reported taking a modal dose of 0 mg, 0.5 mg, 1.0 mg, 1.5 mg, or 2.0 mg – or mg equivalent for placebo – are presented for each week of treatment in the (A) varenicline-treated or (B) placebo group*

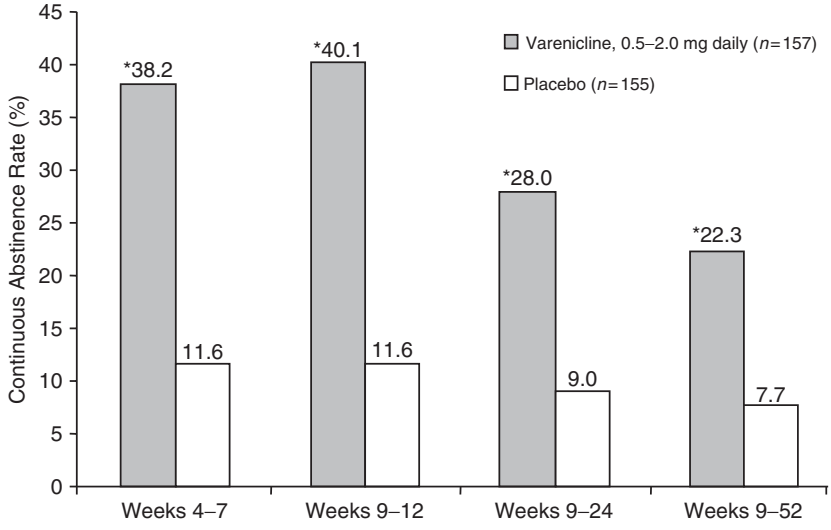

Figure 3. *Continuous abstinence rates for Weeks 4–7, 9–12, 9–24, and 9–52. *p < 0.001. The odds ratios and 95% confidence intervals (CIs) for Weeks 4–7 were 5.52 (95% CI, 2.95–10.30), 9–12 were 5.66 (95% CI, 3.08–10.40), 9–24 were 4.39 (95% CI, 2.23–8.66), and 9–52 were 3.75 (95% CI, 1.82–7.76)*

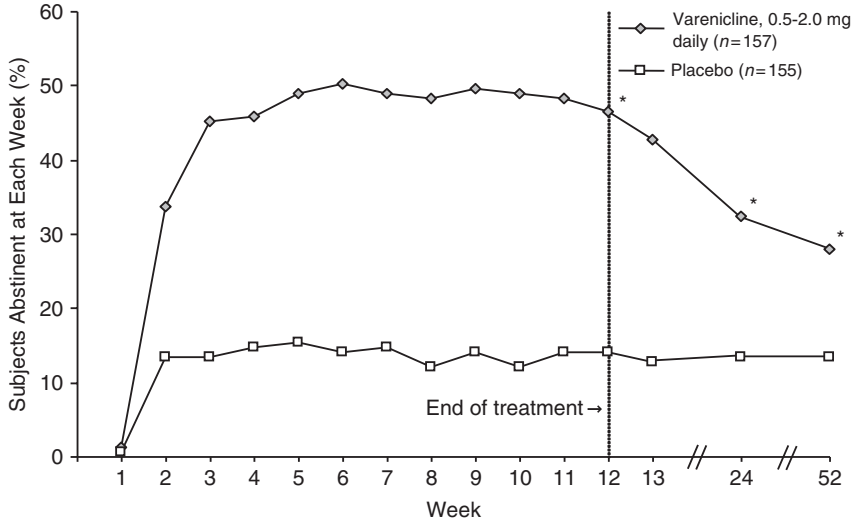

Figure 4. *Carbon monoxide-confirmed 7-day point prevalence of abstinence. *p ≤ 0.001 versus placebo. No inferential statistics were performed for any time points besides Weeks 12, 24, and 52*

mCEQ subscales. From Week 2, satisfaction subscale scores showed that varenicline was significantly more effective than placebo in reducing the satisfaction of smoking ($p < 0.05$ at Weeks 2, 3, 4, and 5) (Table 4). Also, varenicline scores were numerically lower than placebo for enjoyment of respiratory tract sensations (Table 4).

Safety results

The incidence of treatment-emergent AEs with varenicline treatment was 77.1% (121/157) and with placebo was 65.8% (102/155). Most of these AEs were mild or moderate in intensity; only seven AEs of severe intensity were observed in the varenicline-treated and five in the placebo group. Discontinuations of study medication owing to treatment-emergent AEs were low in both groups (varenicline: 11/157, 7.0% and placebo: 7/155, 4.5%).

The most frequent AEs in the varenicline and placebo groups were insomnia, headache, respiratory tract infection, and nausea (Table 5). Examination of nausea AEs revealed only one case of severe-intensity nausea in the varenicline group. All other cases were of mild or moderate intensity. Only two varenicline-treated participants discontinued treatment because of nausea. No events that met the pre-specified criteria of an SAE were reported in either group during the treatment phase.

In the post-treatment phase, three participants in the varenicline group experienced SAEs (myocardial

Table 2. *MNWS scores for urge to smoke† and withdrawal‡ effects (all participants)*

Week	Urge to smoke†				Withdrawal‡			
	Varenicline		Placebo		Varenicline		Placebo	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	156	2.6 (0.8)	155	2.7 (0.8)	155	4.3 (4.2)	154	4.2 (4.6)
1	153	2.0 (1.1)***	151	2.4 (1.0)	149	6.3 (5.5)	148	6.7 (5.4)
2	149	1.6 (1.2)**	143	2.0 (1.1)	146	7.1 (6.3)	142	7.8 (6.3)
3	145	1.4 (1.2)***	130	2.0 (1.1)	139	6.3 (5.8)	128	7.0 (5.7)
4	135	1.4 (1.3)***	129	1.9 (1.0)	133	6.0 (5.4)*	127	7.1 (5.6)
5	135	1.3 (1.2)***	122	1.9 (1.1)	133	5.9 (5.5)	121	6.2 (5.7)
6	130	1.4 (1.3)**	118	1.9 (1.2)	129	5.7 (5.2)	117	6.1 (5.8)
7	130	1.4 (1.1)**	113	1.8 (1.1)	129	5.7 (5.5)	111	5.9 (5.7)
12	119	1.1 (1.2)***	110	1.7 (0.9)	117	4.5 (4.8)	107	5.4 (5.0)

Scores ranged from 0 to 4 with higher scores indicating greater symptom intensity
SD = standard deviation
†Item 1 of the Minnesota Nicotine Withdrawal Scale (MNWS): Q1 = urge to smoke
‡Items 2–9 of the MNWS: Q2 = depressed mood; Q3 = irritability, frustration, or anger; Q4 = anxiety; Q5 = difficulty concentrating; Q6 = restlessness; Q7 = increased appetite; Q8 = difficulty going to sleep; Q9 = difficulty staying asleep
These analyses were performed using analysis of covariance (ANCOVA) with baseline as a covariate and treatment and center as fixed effects
* $p \leq 0.05$ versus placebo
** $p < 0.01$ versus placebo
*** $p < 0.001$ versus placebo

Table 3. *MNWS scores for urge to smoke† and withdrawal‡ effects (non-lapsing quitters)*

Week	Urge to smoke†				Withdrawal‡			
	Varenicline		Placebo		Varenicline		Placebo	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
2§	53	1.4 (1.5)	21	1.6 (1.0)	53	7.6 (6.2)*	21	10.1 (5.4)
3	46	1.1 (1.2)*	16	1.6 (1.0)	44	5.8 (5.2)*	16	8.4 (4.6)
4	42	1.0 (1.4)	15	1.5 (0.8)	41	6.0 (4.7)*	15	9.1 (4.3)
5	45	1.0 (1.3)	15	1.3 (1.0)	45	5.6 (5.2)*	15	8.2 (3.9)
6	42	1.0 (1.4)	13	1.3 (1.2)	42	5.9 (5.6)	13	8.5 (6.0)
7	40	1.1 (1.1)	14	1.0 (0.6)	40	6.0 (5.7)	13	6.2 (3.1)
12	33	0.6 (1.2)	13	0.8 (0.6)	33	5.0 (5.9)	13	6.2 (3.4)

Scores ranged from 0 to 4 with higher scores indicating greater symptom intensity
Non-lapsing quitters are defined as participants who had abstained from smoking from the target quit date of the Week 1 visit through the timepoint of interest
SD = standard deviation
† Item 1 of the Minnesota Nicotine Withdrawal Scale (MNWS): Q1 = urge to smoke
‡ Items 2–9 of the MNWS: Q2 = depressed mood; Q3 = irritability, frustration, or anger; Q4 = anxiety; Q5 = difficulty concentrating; Q6 = restlessness; Q7 = increased appetite; Q8 = difficulty going to sleep; Q9 = difficulty staying asleep
§ Week 2 is the first week after the target quit date (set at the Week 1 visit)
These analyses were performed using analysis of covariance (ANCOVA) with baseline as a covariate and treatment and center as fixed effects
* $p < 0.05$ versus placebo

infarction, ventricular fibrillation, and spontaneous abortion) within 30 days of the last dose of study medication, but none of these events was considered related to study medication by the investigator.

Treatment-emergent elevations of hepatic enzymes (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, or lactate dehydrogenase) led to discontinuations in two participants in each of the varenicline-treated and placebo groups. The elevations were clinically significant (three times the upper limit of normal) in one subject in each group. Overall, the frequency of clinically-significant

Table 4. *mCEQ scores for satisfaction[†] and enjoyment of respiratory tract sensations[‡] subscales*

Week	Satisfaction[†]				Enjoyment of respiratory tract sensations[‡]			
	Varenicline		Placebo		Varenicline		Placebo	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	157	12.9 (3.8)	155	13.6 (4.0)	155	2.6 (1.6)	155	3.0 (1.6)
1	146	9.8 (3.6)	145	10.1 (3.5)	143	2.3 (1.3)	146	2.4 (1.6)
2	95	7.8 (4.4)**	119	9.6 (4.3)	93	1.9 (1.6)	118	2.2 (1.7)
3	75	7.9 (3.9)*	104	9.6 (4.4)	73	2.0 (1.7)	104	2.4 (1.6)
4	65	8.0 (4.1)*	104	9.6 (3.9)	64	1.8 (1.7)*	104	2.3 (1.5)
5	57	7.5 (4.2)*	97	9.5 (4.1)	56	1.8 (1.6)	96	2.3 (1.6)
6	53	7.4 (3.7)	95	9.4 (4.0)	52	1.8 (1.2)	95	2.3 (1.6)
7	57	7.6 (3.7)	90	9.5 (4.2)	56	1.9 (1.5)	89	2.3 (1.5)

These evaluations were completed only by participants who reported smoking during the previous week
[†] Satisfaction – Items 1, 2, and 12 of the modified cigarette evaluation questionnaire (mCEQ)
Q1: was smoking satisfying? Q2: did cigarettes taste good? Q12: did you enjoy smoking?
Satisfaction scores ranged from 3 to 21 with higher scores representing greater intensity
[‡] Enjoyment of respiratory tract sensations – Q3: did you enjoy the sensations in your throat and chest?
Enjoyment of respiratory tract sensations scores ranged from 1 to 7 with higher scores representing greater intensity
None of the other subscales were significantly different
These analyses were performed using an analysis of covariance (ANCOVA) with baseline as a covariate and treatment and center as fixed effects
* $p < 0.05$ versus placebo
** $p < 0.01$ versus placebo

Table 5. *Treatment-emergent adverse events occurring in ≥5% of participants receiving varenicline*

Adverse event COSTART preferred term	Varenicline, $n = 157$ *n* (%)	Placebo, $n = 155$ *n* (%)
Insomnia	34 (21.7)	17 (11.0)
Headache	25 (15.9)	20 (12.9)
Respiratory tract infection	25 (15.9)	15 (9.7)
Nausea	21 (13.4)	8 (5.2)
Asthenia	11 (7.0)	7 (4.5)
Dyspepsia	10 (6.4)	3 (1.9)
Accidental injury	9 (5.7)	3 (1.9)
Irritability	8 (5.1)	6 (3.9)
Flu syndrome	8 (5.1)	7 (4.5)
Abnormal thinking	8[†] (5.1)	6* (3.9)
Pharyngitis	8 (5.1)	2 (1.3)

*The preferred term 'abnormal thinking' was coded from a variety of verbatim investigator terms all related to reduced or lack of concentration

laboratory abnormalities was low and similar between groups.

In both treatment groups, participants who abstained from smoking from the target quit day gained more weight than those who smoked, although no inferential statistics were performed. Mean (SD) weight gain from baseline to Week 12 was 4.0 kg (4.5) in the varenicline group ($n = 32$) and 3.8 kg (1.9) in the placebo group ($n = 9$). Among those who smoked at any time since the Week 1 visit during the treatment period, mean (SD) weight gain was 1.9 kg (2.9) in the varenicline group ($n = 78$) and 0.4 kg (2.9) in the placebo group ($n = 91$).

Discussion

Varenicline administered in flexible, self-regulated doses (0.5–2.0 mg/day) for 12 weeks was significantly more efficacious than placebo for short-term smoking

abstinence during Weeks 4 through 7 and Weeks 9 through 12, and for prolonged abstinence during Weeks 9 through 24 and 9 through 52. The 7-day point prevalence of abstinence rates was also consistently higher for varenicline than placebo at all time points. Varenicline was also well tolerated and demonstrated an acceptable safety profile.

In addition, varenicline significantly reduced the urge to smoke among the overall subject population, but did not significantly alter overall withdrawal effects as assessed by the MNWS. However, among subjects defined as 'non-lapsing quitters', varenicline treatment did reduce withdrawal effects for the first 6 weeks after quitting. In participants who continued to smoke, varenicline was significantly better than placebo in reducing satisfaction from smoking as measured by the mCEQ subscale. Enjoyment of respiratory tract sensations scores were also numerically lower in varenicline-treated patients.

The most frequently reported AE for varenicline in this trial was insomnia. In contrast, other trials of varenicline consistently have found nausea as the most frequent AE. The incidence of nausea in varenicline-treated participants observed in this study (13.4%) was lower than in other dose–response studies using non-titrated doses (17.5% at 0.3 mg once daily for 6 weeks, 22.6% at 0.5 mg twice daily for 12 weeks, 37.3% at 1.0 mg once daily for 6 weeks, 41.9% at 1.0 mg twice daily for 12 weeks, or 52.0% at 1.0 mg twice daily for 6 weeks)[6,7], or titrated doses of varenicline (16.3% at 0.5 mg twice daily for 12 weeks and 34.9% at 1.0 mg twice daily for 12 weeks)[7]. Presumably this reduced incidence of nausea is due to the lower total daily dose, as previous evidence supports that the nausea effect is dose-dependent. However, the incidence of nausea in the placebo group also was lower in this flexible dosing study (5.2%) than in the fixed-dose dose–response studies (14.9–18.7%).

One limitation of this study was that participants were physically and psychologically healthy and primarily Caucasian. This raises the question of whether these findings can be generalized to other populations. Further research is needed to fully address these issues, however, initial studies have shown that 1.0 mg twice-daily dose of varenicline is more effective than placebo and is well tolerated in Japanese[14], as well as Korean and Taiwanese participants[15].

Also, participants were not required to reach a dose of 1.0 mg twice-daily immediately following the first week dose-titration period. The most effective dose of varenicline for smoking cessation in other dose–response studies was 1.0 mg twice daily[6,7], and it is possible that the effectiveness in this study may have been greater, if all participants had begun the flexible dosing period after achieving a target dose of 1.0 mg twice-daily at the start of the 2nd week.

Another limitation was that the MNWS analysis included all participants, even those who continued to smoke. Because the symptoms experienced by smokers can be highly variable (e.g., due to varying success in the reduction of pre-study levels of smoking), mean withdrawal effects as measured by the MNWS could be affected by the inclusion of these participants. Additionally, because varenicline is effective in reducing the number of smokers, the proportion of smokers is higher in the placebo group than in the varenicline group. This unequal distribution of smokers may affect the ability to detect a treatment effect because withdrawal symptoms may be lower among placebo participants who continued to smoke in greater numbers. This bias was addressed in this study by analysis of the non-lapsing quitters' population.

In this flexible dosing study, the 4-week CAR increased from 38.2% for Weeks 4 through 7 to 40.1% for Weeks 9 through 12, supporting the 12-week treatment duration. The treatment effect for end-of-treatment (Weeks 9–12) and long-term (Weeks 9–52) abstinence, measured as the OR for varenicline versus placebo, was 5.66 (95% CI, 3.08–10.40) and 3.75 (95% CI, 1.82–7.76), respectively. Even with the lower modal daily doses of varenicline in this study, the 1-year treatment effect of varenicline (vs. placebo) was higher than treatment effects of other FDA-approved smoking cessation agents (vs. control) such as bupropion (OR: 2.06, 95% CI, 1.77–2.40)[16] or NRT (OR: 1.77, 95% CI, 1.66–1.88)[17], determined in *Cochrane Database Systematic Reviews*.

In another study, conducted concurrently with this flexible dosing study, participants were treated for 12 weeks with a varenicline fixed-dose regimen of 1.0 mg twice daily and CARs rose from 39.8% for Weeks 4 through 7 to 49.4% for Weeks 9 through 12[7]. In that study, the varenicline versus placebo OR for the CAR from Weeks 9 through 12 was 8.07 (95% CI, 4.42–14.70)[7], which was higher than this study (Weeks 9–12 CAR OR: 5.66, 95% CI, 3.08–10.40). However, the flexible dosing regimen described in this study resulted in lower incidences of AEs, suggesting that smokers who did not tolerate the 1.0 mg twice-daily fixed-dose regimen, may have benefited from self-directed, flexible dosing.

Conclusion

From this study and other dose–response studies[6,7], the dosing regimen for varenicline taken forward into

confirmatory clinical trials was 1.0 mg twice daily. The results of those trials demonstrated that varenicline at 1.0 mg twice daily led to significantly greater CARs at the end of 12 weeks of treatment than those seen in participants given either bupropion 150 mg twice daily or placebo[18,19]. Additional research would be required to ascertain whether a flexible dosing regimen of varenicline also would yield higher CARs than bupropion.

Our findings suggest that a self-regulated, flexible dosing schedule of varenicline taken for 12 weeks is efficacious both for end-of-treatment and long-term smoking abstinence and is well tolerated with an acceptable safety profile.

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