

Effect of Maintenance Therapy With Varenicline (SmokeLESS) on Smoking Cessation

/A Randomized Controlled Trial Performed by Serena Tonstad (PhD) et al/

Full Text

INTRODUCTION

- One of the most striking features of attempts to stop smoking is the discrepancy between early success rates and long-term outcomes.

In most studies, as well as in large-scale treatment services for dependent smokers, more than 50% of smokers manage to achieve abstinence for at least a few initial weeks.

For the majority of smokers, this is the most difficult period of the quit attempt, and at the end of it, they report diminishing withdrawal discomfort and increasing confidence in the possibility of remaining smoke-free.

Nevertheless, 50% to 60% of initially successful quitters go on to relapse within a year.

- Among the numerous interventions proposed to prevent relapse is that of Marlatt and Gordon, who recommend that patients should learn to identify situations likely to lead to relapse and be provided with cognitive and behavioral strategies to cope with these situations.

This approach is by far the most widely used.

Despite the importance of this area of research, few controlled studies have examined such interventions.

A recent comprehensive review of existing studies concluded that currently there is no evidence-based relapse prevention intervention available.

- Varenicline is a highly selective $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist developed specifically for smoking cessation.

The efficacy of a 12-week course of varenicline surpasses that of bupropion and placebo. The odds of quitting are nearly quadrupled at the end of treatment compared with placebo and nearly tripled at 1-year follow-up.

We report herein the results of a randomized, double-blind, placebo-controlled trial evaluating the efficacy of an additional 12 weeks of varenicline used for relapse prevention in smokers who successfully achieved abstinence following an initial 12-week open-label varenicline treatment.

METHODS

Participants

Cigarette smokers between the ages of 18 and 75 years were recruited between April 13, 2003, and February 17, 2004, at 6 US and 18 international medical clinics experienced in smoking cessation.

Entry criteria included men and women who smoked an average of 10 or more cigarettes per day during the past year and over the month prior to the screening visit, with no period of abstinence longer than 3 months in the past year and who were motivated to quit.

Women with childbearing potential were required to be actively practicing effective contraception.

Participants were excluded if they had a serious or unstable disease within the past 6 months; required treatment for depression within the past 12 months; had a history of or current panic disorder, psychosis, or bipolar disorder; had severe chronic obstructive pulmonary disease, a history of cancer, evidence or history of clinically significant allergic reactions, laboratory abnormalities, cardiovascular disease within the past 6 months, uncontrolled hypertension, or a history of drug or alcohol abuse or dependence within the past 12 months; used a smoking cessation aid (ie, nicotine replacement therapy [NRT], bupropion, clonidine, or nortriptyline) within the previous month; used tobacco products other than cigarettes or marijuana within the past month and did not agree to abstain from use of these products during study participation; had a body mass index of less than 15 or more than 38 (calculated as weight in kilograms divided by height in meters squared); or used any of the following medications: NRT, antidepressants, antipsychotics, mood stabilizers/anticonvulsants, naltrexone, steroids, or insulin.

Study Design

- This was a 52-week, multicenter trial approved by the institutional review board at each site, and all participants provided written informed consent prior to any procedures.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices Guidelines.

- Following 12 weeks of open-label treatment with varenicline, 1 mg twice daily, participants who had successfully abstained from smoking and use of tobacco and NRT for at least the last 7 days of the treatment period were randomly assigned to receive either varenicline or placebo and continued into a 12-week, double-blind treatment phase. Thereafter, participants continued into a nontreatment follow-up phase for an additional 28 weeks (for a total of 52 weeks in the study).

Following a 3- to 21-day screening period, participants returned for a baseline visit, which was the start of the 12-week open-label phase.

Sociodemographic data were obtained; race and ethnicity were assessed by self-report. Participants received varenicline, 0.5 mg daily for 3 days, 0.5 mg twice daily for 4 days, then 1 mg twice daily for 11 weeks.

At each visit, participants received up to 10 minutes of smoking cessation counseling in accordance with US Public Health Service guidelines.

Participants were advised to take study medication for 1 week before attempting to quit smoking but could attempt to quit earlier if they wished.

From their target quit date, participants attempted to remain abstinent from smoking and other nicotine use.

Participants attended clinic visits weekly from weeks 1 through 8 and at weeks 10 and 12. At the end of the open-label treatment phase, participants were eligible for randomization into the double-blind treatment phase if they reported that they had not smoked or used tobacco or NRT during the last 7 days, had an end-expiratory carbon monoxide (CO) level of 10 ppm or less, were adherent to the study drug, and were deemed appropriate for study participation according to the protocol.

- The study used a single centralized, computer-generated randomization sequence (stratified by center with a block size of 4) to assign participants to receive varenicline or placebo during the 12-week double-blind phase in a ratio of 1:1.

Participants were to continue to abstain from smoking or nicotine use and attended clinic visits at weeks 13, 14, 16, 20, and 24.

During the double-blind treatment phase, participants who discontinued study medication or began smoking could continue participation in the study provided they attended the remaining visits and completed all assessments.

At the end of the double-blind treatment phase, all participants continued in the 28-week nontreatment follow-up phase, regardless of whether they had completed the full 12 weeks of double-blind treatment or had stopped smoking.

The participant blinding was maintained during this phase.

Participants attended follow-up visits at weeks 25, 28, 36, 44, and 52 and were contacted by telephone at weeks 26, 32, 40, and 48.

Assessments

At each contact (clinic visit or telephone call), participants were asked questions regarding use of cigarettes and other nicotine-containing products (during the treatment periods) or tobacco products (during posttreatment follow-up) since the last contact and during the past 7 days.

At each clinic visit, exhaled CO was measured.

Safety Evaluations

Complete physical examinations were conducted at the screening or baseline visit and at weeks 12 and 24.

Visits at screening, baseline, and weeks 2, 12, and 24 included a 12-lead electrocardiogram and blood laboratory measurements.

Efficacy Evaluations

- The primary efficacy end point was the CO-confirmed continuous abstinence rate from week 13 through week 24 (double-blind treatment phase).

A key secondary efficacy end point was the continuous abstinence rate from week 13 through week 52.

Continuous abstinence rates were also summarized for each clinic visit or telephone contact.

The continuous abstinence rate from week 13 through a given time point was defined as the proportion of participants who were abstainers from smoking and from nicotine or tobacco-containing products from the randomization visit through the time point of interest.

Participants were considered to be abstainers from smoking since the prior clinic visit or telephone contact if they responded "no" to the question of smoking any cigarettes (even a single "puff") since the last study visit or contact and had not used any other nicotine-containing products (during the double-blind treatment phase) or tobacco products (during the nontreatment follow-up phase) since the previous study visit or contact. Additionally, participants whose CO value was more than 10 ppm were classified as smokers.

- Those missing a CO value but meeting other abstinence criteria were considered nonsmokers, with the exception of the week 52 visit, at which time participants with a missing CO value were considered smokers.

Participants were considered nonsmokers at missed visits if, at the next nonmissed visit, they reported not smoking or using nicotine or tobacco products since the last study visit.

- Point prevalence of abstinence was defined as a self-report of no smoking or other tobacco use (or other nicotine product use during the treatment phases) in the previous 7 days, confirmed by an expired CO value of not more than 10 ppm at clinic visits. Participants with a missing smoking assessment were considered smokers for that 7-day period.

- Time to first lapse was calculated from the date of first randomized therapy to the date of the first cigarette smoked (even a puff).

- The Minnesota Nicotine Withdrawal Scale (MNWS) was used to assess the experience of craving and withdrawal after the end of treatment with varenicline. The MNWS was self-administered by participants at weeks 13 and 25 to assess symptoms during the previous week.

RESULTS

- Demographic and smoking characteristics of the participants are shown in [Table 1](#). Of 1927 who participated in the first 12 weeks of open-label treatment, 1236 (64.1%) met the point prevalence criterion for abstinence during week 12. Twenty-six chose not to continue or had other reasons for not being eligible to continue, and 1210 were randomized and were included in efficacy evaluations. Participant disposition is shown in [Figure 1](#).

Table 1. Baseline Participant Characteristics

Characteristics	Open-Label Varenicline Phase (n = 1927)	Double-Blind Phase	
		Varenicline (n = 603)	Placebo (n = 607)
Age, mean (SD), y	44.2 (10.7)	45.4 (10.4)	45.3 (10.4)
Male, No. (%)	941 (48.8)	303 (50.2)	293 (48.3)
Race/ethnicity, No. (%)			
White	1853 (96.2)	583 (96.7)	589 (97.0)
Black	35 (1.8)	9 (1.5)	10 (1.6)
Asian	14 (0.7)	3 (0.5)	4 (0.7)
Other	25 (1.3)	8 (1.3)	4 (0.7)
Fagerström score, mean (SD)*	5.55 (2.04)	5.43 (1.96)	5.35 (1.98)
No. of years of smoking, mean (SD) [range]	27.2 (10.7) [2-59]	28.2 (10.4) [3-58]	28.1 (10.5) [2-58]
No. of cigarettes per day in past month, mean (SD) [range]	21.6 (8.3) [3-99]	20.7 (7.3) [8-60]	20.7 (7.5) [10-65]
Previous serious quit attempts, No. (%)			
0	341 (17.7)	88 (14.6)	89 (14.7)
≥1	586 (82.3)	515 (85.4)	518 (85.3)
Longest period of abstinence in past year, d			
Mean (SD)	7.4 (18.4)	8.3 (19.6)	7.6 (18.3)
Median (range)	0 (0-200)	0 (0-90)	0 (0-90)

*The possible range is from 1 to 10, with higher scores indicating greater dependence on nicotine. The numbers of participants completing all questions of the Fagerström test were as follows: open-label varenicline, n = 1922; double-blind varenicline, n = 602; double-blind placebo, n = 605.

Table 1. Baseline Participant Characteristics

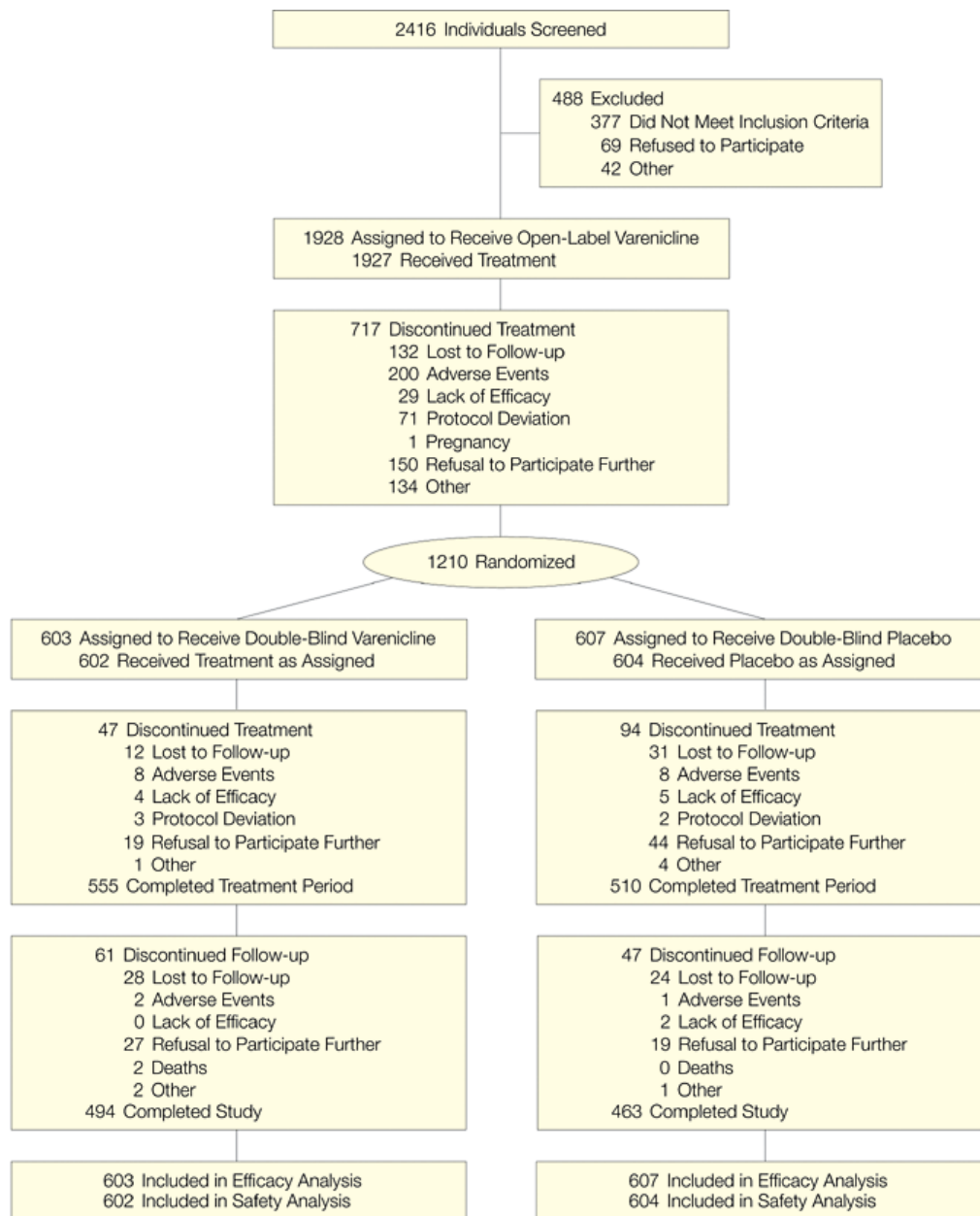


Figure 1. Participant Flow Through the Study

Continuous Abstinence Rates

The continuous abstinence rate for weeks 13 to 24 was higher for participants randomized to varenicline than for participants randomized to placebo (odds ratio, 2.48; 95% CI, 1.95-3.16; $P < .001$) (Table 2).

The continuous abstinence rate for weeks 13 to 52 was also higher for the varenicline group than for the placebo group (odds ratio, 1.34; 95% CI, 1.06-1.69; $P = .02$) (Table 2).

The number needed to treat for the continuous abstinence rate of varenicline relative to placebo was 5 (95% CI, 4-7) for weeks 13 to 24 and 14 (95% CI, 8-71) for weeks 13 to 52.

Table 2. Carbon Monoxide–Confirmed Continuous Abstinence Rate at Clinic Visits

	No. (%) of Participants	
	Double-Blind Varenicline (n = 603)	Double-Blind Placebo (n = 607)
Double-blind treatment phase, wk*		
13	576 (95.5)	537 (88.5)
14	551 (91.4)	476 (78.4)
16	509 (84.4)	413 (68.0)
20	454 (75.3)	331 (54.5)
24	425 (70.5)	301 (49.6)
Nontreatment follow-up phase, wk†		
25	408 (67.7)	293 (48.3)
28	361 (59.9)	282 (46.5)
36	306 (50.7)	257 (42.3)
44	280 (46.4)	239 (39.4)
52	263 (43.6)	224 (36.9)

*Weeks 13-24: odds ratio, 2.48; 95% confidence interval, 1.95-3.16; $P < .001$.

†Weeks 13-52: odds ratio, 1.34; 95% confidence interval, 1.06-1.69; $P = .02$.

Table 2. Carbon Monoxide–Confirmed Continuous Abstinence Rate at Clinic Visits

Point Prevalence of Abstinence

The 7-day point prevalence of abstinence at week 24 (odds ratio, 2.82; 95% CI, 2.18-3.64; $P < .001$) and at week 52 (odds ratio, 1.33; 95% CI, 1.06-1.67; $P = .01$) was significantly higher for participants who received varenicline than for participants who received placebo (Figure 2).

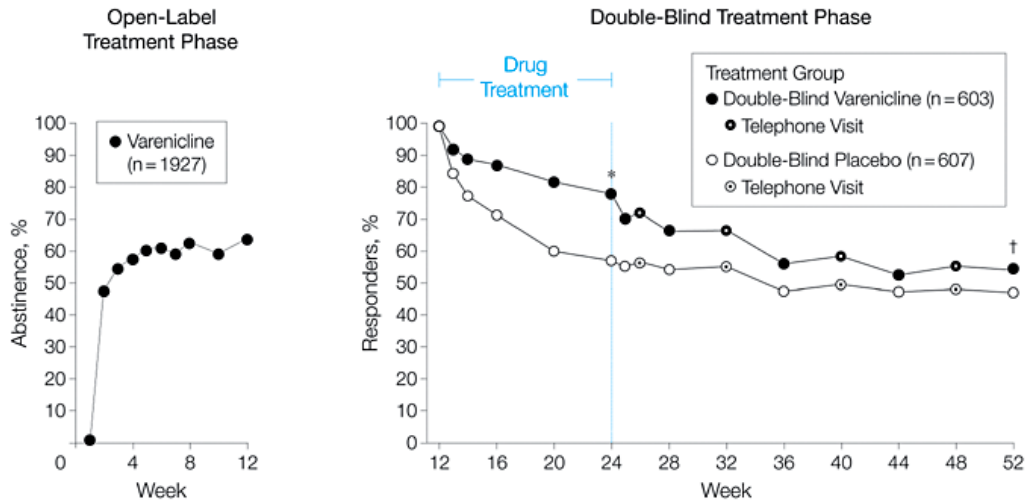


Figure 2. Seven-Day Point Prevalence of Abstinence

* $P < .001$.

† $P = .01$.

Time to First Lapse

The median time to the first lapse (postrandomization to double-blind treatment) was significantly longer for participants receiving double-blind varenicline than for participants treated with double-blind placebo (198 [95% CI, 159-260] days vs 87 [95% CI, 58-143] days, respectively; log-rank $P < .001$) (Figure 3).

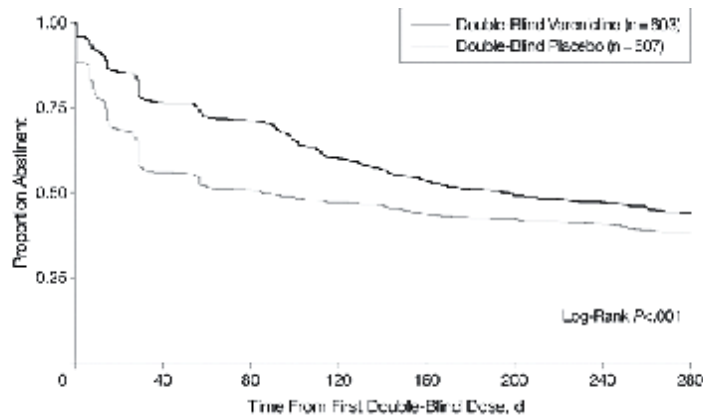


Figure 3. Time to First Lapse

Weight Change

For participants who were continuously abstinent from smoking during weeks 13 to 24, mean weight change from open-label varenicline baseline to week 24 was 3.62 kg (SD, 3.29 kg) for participants who received double-blind varenicline vs 4.03 kg (SD, 3.30 kg) for the double-blind placebo participants.

The mean change in body weight between weeks 12 and 24 for these abstinent participants was 0.80 kg (SD, 2.13 kg) for those treated with double-blind varenicline vs 1.51 kg (SD, 2.31 kg) for the placebo group. Among all participants, the mean weight change from open-label baseline to week 24 for double-blind varenicline-treated participants was 3.41 kg (SD, 3.27 kg) vs 3.53 kg (SD, 3.20 kg) for placebo-treated participants.

The mean change in body weight for the double-blind varenicline-treated participants between weeks 12 and 24 was 0.71 kg (SD, 2.18 kg) vs 1.02 kg (SD, 2.35 kg) for placebo-treated participants.

MNWS Scores

In this study, the MNWS was used to assess experience of craving and withdrawal after treatment with varenicline was discontinued at the end of the open-label and double-blind treatment periods.

At weeks 13 and 25, the withdrawal symptoms tended on average to be low (between "slight" and "not at all" in the 5-point rating scale).

The differences in the mean urge-to-smoke subscale scores between the placebo and varenicline groups are shown in [Figure 4](#).

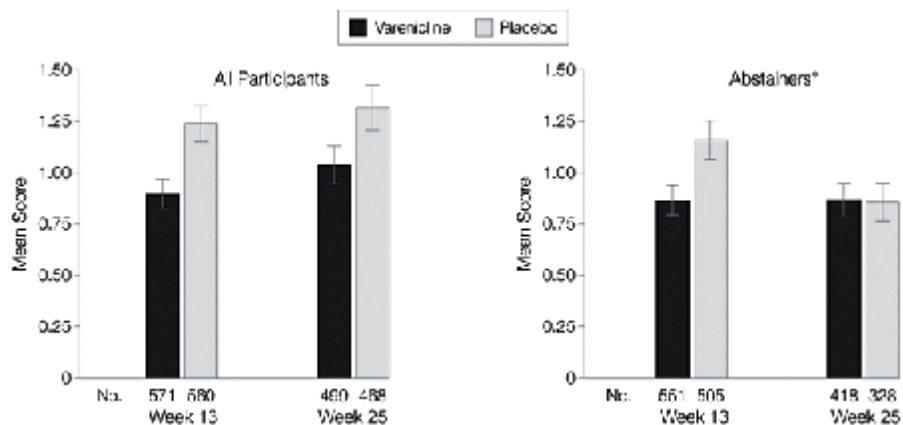


Figure 4. Mean Scores on the Urge to Smoke Subscale of the MNWS

Error bars indicate 95% confidence intervals.

*Defined by the 7-day point prevalence abstinence prior to the week of Minnesota Nicotine Withdrawal Scale (MNWS) evaluation, weeks 13 and 25.

Safety and Tolerability

- Table 3 shows the most frequent adverse events.

During the open-label phase, 229 participants (11.9%) experienced adverse events that led to treatment discontinuation.

Events that contributed most frequently to treatment discontinuation were nausea (3.2% of participants), headache (1.0%), insomnia (0.9%), depression (0.8%), and fatigue (0.6%).

The median onset to nausea was 8 days (interquartile range, 3-15 days) and the median duration was 20 days (interquartile range, 6-54 days).

Vomiting was reported in 56 participants (2.9%).

Table 3. Most Frequent Adverse Events*

Adverse Events	No. (%) of Participants Taking ≥1 Dose of Study Medication		
	Open-Label Varenicline Phase (n = 1927)	Double-Blind Treatment Phase	
		Varenicline (n = 602)	Placebo (n = 604)
Gastrointestinal disorders			
Nausea	645 (33.5)	7 (1.2)	4 (0.7)
Flatulence	234 (12.1)	2 (0.3)	0
Constipation	168 (8.7)	0	3 (0.5)
Dyspepsia	133 (6.9)	9 (1.5)	6 (1.0)
Psychiatric disorders			
Insomnia	377 (19.6)	16 (2.7)	17 (2.8)
Abnormal dreams†	276 (14.3)	6 (1.0)	0
Irritability	97 (5.0)	16 (2.7)	27 (4.5)
Headache	304 (15.8)	17 (2.8)	12 (2.0)
Nasopharyngitis	145 (7.5)	29 (4.8)	32 (5.3)
Fatigue	162 (8.4)	9 (1.5)	11 (1.8)

*All-cause adverse events that occurred in 5% or more of participants in the open-label treatment phase or in the double-blind phase in varenicline-treated participants at a frequency greater than that for placebo; adverse events that began or increased in severity during study drug treatment or up to 7 days after the last dose.
†"Abnormal dreams" is the MedDRA (Medical Dictionary for Regulatory Activities) for several descriptions, including vivid dreams and increased frequency of dreams.

Table 3. Most Frequent Adverse Events*

- The incidence of adverse events during the double-blind treatment phase was similar for the varenicline and placebo groups (46% and 45%, respectively).
A total of 10 varenicline-treated participants (1.7%) and 8 placebo participants (1.3%) discontinued because of adverse events.
No adverse event resulted in discontinuation in more than 1 participant in either treatment group.

- Three participants died in this study. None of these deaths was considered related to the study drug.

One man with a history of depression that was not revealed at the time of enrollment died of suicide 27 days after completing double-blind treatment.

Another man died of complications related to lung cancer 19 days after completing double-blind treatment.

A third man discontinued the open-label phase of the study on day 25 because of an adverse event of back pain and died of a rectal sarcoma 197 days after last varenicline dose.

Nonfatal serious adverse events were reported for 20 participants during or after treatment with open-label varenicline.

Ten participants randomized to double-blind varenicline and 5 participants randomized to double-blind placebo experienced nonfatal serious adverse events during or after treatment.

- During the double-blind treatment phase, changes from baseline in blood pressure did not differ between the varenicline and placebo groups.

The mean pulse rate remained approximately the same from the double-blind period baseline in participants treated with varenicline and decreased by approximately 2/min in placebo participants.

COMMENT

- In this randomized clinical trial, smokers who successfully quit after taking open-label varenicline for an initial 12 weeks experienced a significantly reduced rate of relapse when taking an additional 12 weeks of varenicline, 1 mg twice per day, compared with placebo.

There was a substantial difference in continuous validated abstinence rates at the end of treatment and a smaller but significant difference 6 months later.

In this study, varenicline was safe and well tolerated for prolonged use, and most adverse events were characterized as mild or moderate in intensity.

In the field of relapse prevention—in which there is a notable lack of positive findings—these results represent an important new development.

- A recent review of relapse prevention literature identified a need for studies randomizing abstaining smokers and using strict outcome criteria.

The present trial used stringent methods, setting standards of rigor in this difficult area.

In particular, the use of continuous rather than point prevalence abstinence rates as the primary outcome criterion, with self-reports validated by frequent CO monitoring, contributes to the robust results.

Study participants in the open-label phase attended 10 clinic visits.

During the double-blind phase, participants attended 5 clinic visits during the treatment period, as well as another 5 visits and 4 telephone contacts during the 6-month posttreatment follow-up.

The visits were brief but were still likely to provide a level of motivational support not available in routine care.

However, the level of support would not be expected to contribute to differences between the active drug and placebo.

Since intensive support is probably of particular benefit to participants taking placebo, the support could in fact have reduced the effect size.

- It is important to note that the 43.6% rate of continuous abstinence achieved at week 52 reflects only participants who were abstinent for at least 7 days at the end of the first 12 weeks of treatment.

We included only participants who had made progress in cessation to understand whether prolonged treatment would help these participants to remain abstinent.

The week 12 point prevalence rate of abstinence was unusually high (64.1%), and it surpassed the rates of about 50% that were observed in 2 smoking cessation studies of 12 weeks of treatment with varenicline vs bupropion or placebo.

This difference is probably due to the open-label design of the first phase of the present study compared with the double-blind design of the 2 smoking cessation studies.

- A temporary acceleration of the rate of relapse (as measured by the strict criterion of a single "puff") occurred in the varenicline group after the withdrawal of medication. Toward week 52, the relapse rates of the 2 study groups did not show any further signs of converging ([Table 2](#)).

A statistically and clinically significant difference remained in place through the follow-up period.

- At the end of this trial, as in all existing literature on smoking cessation with 1 year of follow-up, more than 50% of participants in each group returned to smoking.

Thus, an examination of longer medication periods is warranted.

Discontinuation of varenicline in participants randomized to placebo at week 12 was followed by a mean urge-to-smoke value that was small and only modestly higher than that of participants continuing to receive double-blind varenicline.

Similarly, at week 24, discontinuation of varenicline was not followed by a large difference in urge to smoke than discontinuation of placebo, both for all participants and for abstainer groups.

- In this study, varenicline was safe and well tolerated.

Some of the adverse events recorded in the open-label phase of the trial are known tobacco withdrawal effects (eg, constipation and sleep disturbance).

The only notable drug effect was nausea, which was mostly mild and tolerable.

Although 32% of participants reported some nausea, only 3% discontinued the medication because of it.

During the second 12-week course of varenicline, there were no adverse events reported more frequently in the varenicline group than in the placebo group.

- The study population included a generally healthy sample because of the number of exclusion criteria, as many clinical trials of new medications do, so there may be limits to its generalizability.

During the double-blind treatment phase, the Nicotine Use Inventory did not distinguish among participants who used NRT or tobacco products other than cigarettes.

Thus, in the analysis of the primary end point, 2 participants in the placebo group were counted as smokers because of the use of other nicotine-containing products.

During the nontreatment period, NRT use did not disqualify the participants from being considered abstinent at these visits.

- The number of participants classified as lost to follow-up or who refused further participation differed between the varenicline and placebo groups.

The differences are explainable by dropouts due to inability to stop smoking.

All participants were encouraged to remain in the study and participate in assessments even if they discontinued treatment.

Nonetheless, there were some participants who discontinued the study for adverse events or protocol deviations.

The numbers were small and similar between treatment groups.

Although CO only has a 4-hour half-life and does not provide a complete check on the smoker's self-report of abstinence from smoking, regular CO monitoring is in accordance with established standards.

The follow-up period ended 1 year from the initial quit date but 40 weeks from the start of the double-blind phase.

Six months is the accepted minimum for long-term follow-up, but future studies may consider extended follow-up periods.

- In conclusion, extended use of varenicline helps recent ex-smokers to maintain their abstinence and prevent relapse.

Varenicline is the first smoking cessation treatment to demonstrate a significant long-term relapse prevention effect.