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Original Investigation

Effect of Varenicline on Smoking Cessation Through Smoking Reduction

A Randomized Clinical Trial

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IMPORTANCE Some cigarette smokers may not be ready to quit immediately but may be willing to reduce cigarette consumption with the goal of quitting.

OBJECTIVE To determine the efficacy and safety of varenicline for increasing smoking abstinence rates through smoking reduction.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled, multinational clinical trial with a 24-week treatment period and 28-week follow-up conducted between July 2011 and July 2013 at 61 centers in 10 countries. The 1510 participants were cigarette smokers who were not willing or able to quit smoking within the next month but willing to reduce smoking and make a quit attempt within the next 3 months. Participants were recruited through advertising.

INTERVENTIONS Twenty-four weeks of varenicline titrated to 1 mg twice daily or placebo with a reduction target of 50% or more in number of cigarettes smoked by 4 weeks, 75% or more by 8 weeks, and a quit attempt by 12 weeks.

MAIN OUTCOMES AND MEASURES Primary efficacy end point was carbon monoxide–confirmed self-reported abstinence during weeks 15 through 24. Secondary outcomes were carbon monoxide–confirmed self-reported abstinence for weeks 21 through 24 and weeks 21 through 52.

RESULTS The varenicline group ($n = 760$) had significantly higher continuous abstinence rates during weeks 15 through 24 vs the placebo group ($n = 750$) (32.1% for the varenicline group vs 6.9% for the placebo group; risk difference (RD), 25.2% [95% CI, 21.4%-29.0%]; relative risk (RR), 4.6 [95% CI, 3.5-6.1]). The varenicline group had significantly higher continuous abstinence rates vs the placebo group during weeks 21 through 24 (37.8% for the varenicline group vs 12.5% for the placebo group; RD, 25.2% [95% CI, 21.1%-29.4%]; RR, 3.0 [95% CI, 2.4-3.7]) and weeks 21 through 52 (27.0% for the varenicline group vs 9.9% for the placebo group; RD, 17.1% [95% CI, 13.3%-20.9%]; RR, 2.7 [95% CI, 2.1-3.5]). Serious adverse events occurred in 3.7% of the varenicline group and 2.2% of the placebo group ($P = .07$).

CONCLUSIONS AND RELEVANCE Among cigarette smokers not willing or able to quit within the next month but willing to reduce cigarette consumption and make a quit attempt at 3 months, use of varenicline for 24 weeks compared with placebo significantly increased smoking cessation rates at the end of treatment, and also at 1 year. Varenicline offers a treatment option for smokers whose needs are not addressed by clinical guidelines recommending abrupt smoking cessation.

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Forty percent of cigarette smokers make an average of 2 quit attempts annually.¹ In a telephone survey of 1000 current daily cigarette smokers, 44% reported a preference to quit through reduction in the number of cigarettes smoked, and 68% would consider using a medication to facilitate smoking reduction.² However, US clinical practice guidelines³ recommend that smokers quit abruptly even though only 8% of smokers report being ready to quit in the next month.⁴ Developing effective interventions to achieve tobacco abstinence through gradual reduction could engage more smokers in quitting.⁵⁻⁷

Among cigarette smokers not ready to quit, tobacco reduction incorporating nicotine replacement therapy and behavioral interventions decreases cigarettes smoked and increases future smoking abstinence.^{6,7} Population-based studies suggest that quitting gradually may be less successful than quitting abruptly.⁸ However, a systematic review comparing both approaches suggests that reducing cigarettes before the quit date and quitting abruptly without prior reduction yields comparable quit rates.⁹

Almost all prior studies of pharmacotherapy-aided reduction have examined nicotine replacement therapies. Varenicline is a partial agonist binding with high affinity and selectivity at $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors.¹⁰ Varenicline significantly increases smoking abstinence rates among smokers seeking treatment and quitting abruptly.^{11,12} Among smokers not trying to stop, varenicline significantly reduces cigarette consumption¹³ and may increase quit attempts.¹⁴

Varenicline may be an effective intervention for smokers who are not willing or able to make an immediate quit attempt but who would be willing to reduce their smoking in preparation for a quit attempt in the future (ie, a “reduce-to-quit” approach). A prior reduce-to-quit study of varenicline was small, provided only 8 weeks of varenicline, and obtained equivocal results.¹⁴ We conducted a larger, randomized, placebo-controlled clinical trial providing varenicline for 6 months to evaluate a “reduce-to-quit” approach.

Methods

Study Design

Written consent forms and study procedures were approved by the institutional review boards or ethics committees of participating institutions and each enrolled participant voluntarily signed the consent form. A randomized, double-blind, placebo-controlled trial was conducted at 61 centers in 10 countries (Australia, Canada, Czech Republic, Egypt, Germany, Japan, Mexico, Taiwan, United Kingdom, and United States) between July 2011 and July 2013. Study sites included clinical trial centers, academic centers, and outpatient clinics. Study site training was provided at an investigator meeting with training materials maintained and accessible through a shared website. The study consisted of a 24-week treatment period followed by a 28-week nontreatment follow-up phase (protocol in Supplement 1). The first 12 weeks of treatment were the reduction phase and the next 12 weeks were the abstinence phase. Participants were

recruited through advertising. Recruitment advertisements included the following language: “Want to quit smoking but prefer to cut down first?” and “Are you ready to quit but prefer to do it gradually?” and “Want to quit smoking, but hate the idea of going cold turkey?” Enrollment ended when recruitment goals were achieved. Participants received financial compensation for time spent for clinic and phone visits as well as travel time; the amount of remuneration was determined by each clinical trial site.

Screening and Eligibility Criteria

Eligible participants were 18 years or older, smoked an average of 10 or more cigarettes per day with no continuous abstinence period longer than 3 months in the past year, had an exhaled carbon monoxide level higher than 10 ppm, and were not willing or able to quit smoking within the next month but were willing to reduce their smoking and make a quit attempt within the next 3 months.

Exclusion criteria included a history of a suicide attempt or suicidal behavior in the previous 2 years as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)¹⁵ and the Suicide Behavior Questionnaire-Revised (SBQ-R)¹⁶; major depressive or anxiety disorder assessed by a physician as severe (lifetime or current) or unstable (ie, medication dose change or exacerbations in the last 6 months); lifetime diagnosis of psychosis, panic disorder, posttraumatic stress disorder, or schizophrenia; alcohol or substance abuse in the last 12 months; a diagnosis of severe chronic obstructive pulmonary disease; clinically significant cardiovascular or cerebrovascular disease in the previous 2 months; taking more than a limited number of doses of varenicline previously; and self-reported inability to abstain from noncigarette tobacco products, marijuana, or smoking cessation aids (including electronic cigarettes). Women were excluded if pregnant, lactating, or likely to become pregnant and unwilling to use contraception.

Study Procedures

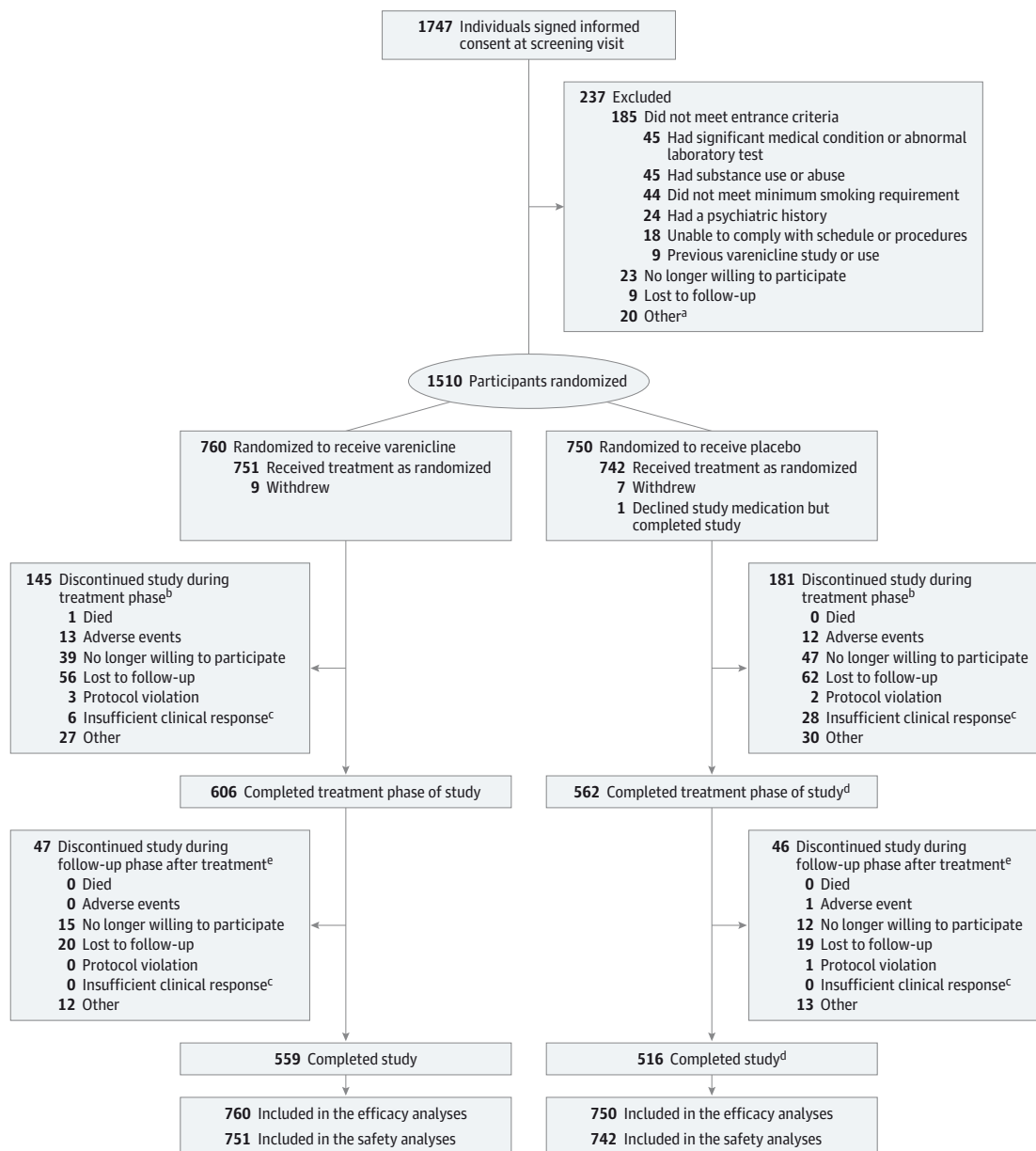
Participants were randomized to receive varenicline or placebo for 24 weeks of treatment in a 1:1 ratio using a computer-generated block randomization schedule within site (Figure 1). Investigators obtained participant identification numbers and treatment group assignments through a web-based or telephone call-in drug management system. Participants, investigators, and research personnel were blinded to randomization until after the database was locked.

Race/ethnicity was self-reported. At each clinic visit and telephone contact, information was collected on cigarette or other nicotine product use. Exhaled carbon monoxide measurements were obtained at all clinic visits. Tobacco dependence was assessed with the Fagerström Test for Nicotine Dependence.¹⁷ Study design is shown in the eFigure in Supplement 2.

Adverse events and US Food and Drug Administration defined serious adverse events (adverse events resulting in death, hospitalization, or other important medical events) were collected during study visits during the treatment phase and up to 1 month after last treatment dose. A semistructured interview solicited information about psychiatric adverse events. Suicidal ideation and behavior were assessed using the C-SSRS

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Figure 1. Varenicline vs Placebo for Smoking Cessation Through Smoking Reduction Trial Flow Diagram



^a Participants excluded due to reasons classified by the investigators as "other" included not attending randomization visit; unable to commit to attending study visits; change in work schedule; change in concomitant medications; change in personal circumstances; and unavailability of urine drug screening kits.

^b Treatment phase was weeks 1 through 24. Discontinuations from study during treatment phase due to reasons classified by the investigators as "other" included new job or change in work schedule; moved out of area; change in personal or family circumstances; and unwilling or unable to attend visits.

^c Insufficient clinical response was a prepopulated option chosen by the investigators on the case report forms.

^d Includes 1 participant in the placebo group who declined study medication but completed study participation.

^e The follow-up phase after treatment was weeks 25 through 52. Discontinuations from study during follow-up phase after treatment due to reasons classified by the investigators as "other" included new job or change in work schedule; moved out of area; change in personal or family circumstances; and unwilling or unable to attend visits.

at baseline and all study visits. Participants completed the Patient Health Questionnaire (PHQ)-9¹⁸ to assess the frequency and severity of potential depression-related events every other week during the treatment phase and at clinic visits during the follow-up phase.

Interventions

Participants were asked to reduce their baseline smoking rate by 50% or more by week 4 with further reduction to 75% or more from baseline by week 8 with the goal of quitting by week 12. Counseling training was provided at the investigator meet-

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ing. Smoking cessation counseling was provided consistent with the recommendations of the US Department of Health and Human Services “Treating Tobacco Use and Dependence” clinical practice guideline.³ Participants received the *Clearing the Air: Quit Smoking Today* booklet from the National Cancer Institute. Advice on reduction techniques was provided such as systematically increasing the amount of time between cigarettes and rank-ordering and then eliminating cigarettes from easiest to hardest to give up.¹⁴ Counseling was tailored to the participant’s needs during the reduction, abstinence, and post-treatment phases. Counsellors were urged to be consistent and brief, to focus on problem solving (eg, what triggers the urge to smoke) and skills training (eg, practical actions to avoid smoking), and to highlight successes not failures. Individual counseling lasted 10 minutes or less per visit during 18 clinic and 10 telephone visits. The last cigarette was to be smoked prior to midnight on the day before the week 12 visit. Participants could reduce their smoking faster and could make a quit attempt before week 12. Participants who had not reduced or made a quit attempt by week 12 were encouraged to continue medications and visits and make quit attempts, and participants who relapsed after week 12 were encouraged to make new quit attempts. After the 24-week treatment phase (ie, 12 weeks of reduction and 12 weeks after a quit attempt) participants were followed up through week 52 (28-week nontreatment follow-up phase).

Participants started with a recommended varenicline (or matching placebo) dosage of 0.5 mg once daily for 3 days, increasing to 0.5 mg twice daily for days 4 to 7, and then to the maintenance dose of 1 mg twice daily.

Study End Points

The primary efficacy end point was the carbon monoxide-confirmed continuous abstinence rate (CAR) during the last 10 weeks of treatment (ie, weeks 15-24). A participant was considered abstinent from tobacco if he or she self-reported tobacco abstinence throughout the period and had an exhaled carbon monoxide level of 10 ppm or less at each visit. In the case of a missing visit, participants were considered abstinent if they were abstinent at the next nonmissed visit and also reported not smoking during the missed visit. A missing carbon monoxide measurement did not disqualify a participant from meeting the end point if they self-reported not smoking. Secondary efficacy end points were the CARs during weeks 21 through 24 and during weeks 21 through 52. We also calculated the nonprespecified end point of the CAR for weeks 15 through 52.

Statistics

The efficacy analysis was based on the intent-to-treat population (all randomized participants). Participants who dropped out of the study were treated as smokers. A sample size of 1404 randomized participants in a 1:1 ratio (702 in each group) was estimated to provide 90% or more power to detect a difference between varenicline and placebo of 10.3% in the primary end point of CAR during weeks 15 through 24, assuming a CAR of 17.2% for varenicline and 6.9% for placebo using a 2-group, continuity-corrected, 2-sided χ^2 test. A *P* value of .05 or less was considered significant.^{9,19,20}

A logistic regression model included treatment effect as the explanatory variable and investigative center as a covariate. In addition, an expanded logistic regression model including the treatment-by-center interaction was used to test for the interaction effect. However, as prespecified in the statistical analysis plan, the inferences were based solely on the predesignated logistic regression model including only the main effects of treatment and center, regardless of the significance of the treatment-by-center interaction (with *P* \leq .05 considered significant). Relative risks (RRs) and risk differences (RDs) calculated using Proc Freq (SAS Institute) with option RELRISK (for RRs) and RISKDIFF (for RDs) are reported for efficacy end points. We conducted a sensitivity analysis for the primary end point in which participants who were missing a carbon monoxide measurement during weeks 15 through 24 were classified as smokers.

To preserve the type I familywise error rate of .05, a fixed-sequence procedure was used. The treatment comparison was performed first for weeks 15 through 24, then for weeks 21 through 24, and then for weeks 21 through 52. A post hoc analysis was conducted in the same manner for the end point of the CAR for weeks 15 through 52. Each test used a 2-sided *P* value of .05 or less for significance. We used SAS (SAS Institute), version 9.2, for statistical analyses.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.1.²¹ Adverse events occurring during treatment and up to 30 days after receiving the last dose of study drug are reported. All safety analyses included all randomized participants who received any dose of study medication. Our study was not powered to detect significant differences in adverse events between groups.

Results

Enrollment and Follow-up

Of 1747 potentially eligible participants screened, 1510 (86%) were randomly assigned to receive varenicline (*n* = 760) or placebo (*n* = 750). Overall study completion was defined as completion of the week 52 visit and was 73.6% (559 of 760 participants) in the varenicline group and 68.8% (516 of 750 participants) in the placebo group (Figure 1). Participants assigned to study groups were similar in demographic and smoking characteristics at baseline (Table 1). Participants who discontinued treatment were encouraged to remain in the study.

Smoking Abstinence

The varenicline group (*n* = 760) had significantly higher continuous abstinence rates during weeks 15 through 24 than the placebo group (*n* = 750) (32.1% for the varenicline group vs 6.9% for the placebo group; RD, 25.2% [95% CI, 21.4%-29.0%]; RR, 4.6 [95% CI, 3.5-6.1]) (Table 2). The varenicline group had significantly higher continuous abstinence rates vs the placebo group during weeks 21 through 24 (37.8% for the varenicline group vs 12.5% for the placebo group; RD, 25.2% [95% CI, 21.1%-29.4%]; RR, 3.0 [95% CI, 2.4-3.7]) and weeks 21 through 52 (27.0% for the varenicline group vs 9.9% for the placebo group; RD, 17.1% [95% CI, 13.3%-20.9%]; RR, 2.7 [95% CI, 2.1-3.5]). No

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significant treatment-by-center interaction for the primary end point was observed in the logistic regression model.

Among the 244 participants receiving varenicline who were counted as abstinent for the primary end point, there were 25 participants with at least 1 missing carbon monoxide measurement (including those with missing visits) during weeks 15 through 24; among the 52 participants receiving placebo who met the primary end point, there were 4 participants with at least 1 missing carbon monoxide measurement. We conducted a sensitivity analysis with participants who were missing a carbon monoxide measurement being classified as smokers for the weeks 15 through 24 continuous abstinence rate (219 participants [28.8%] for varenicline vs 48 participants [6.4%] for placebo). The RR for this analysis was 4.5 (95% CI, 3.4-6.1). This value approximates the value we observed using the prespecified imputation (RR, 4.6 [95% CI, 3.5-6.1]). Among participants meeting the primary end point (abstinent during weeks 15-24), the median time from baseline to the beginning of the continuous abstinence period was 50 days for varenicline and 85 days for placebo ($P < .001$). The varenicline group also had a significantly higher 7-day point prevalence smoking abstinence rate compared with placebo at weeks 12, 24, and 52 (Figure 2). Varenicline significantly increased the 4-week point prevalence smoking abstinence rate compared with placebo at week 52 (32.8% for varenicline vs 17.3% for placebo; RD, 15.4% [95% CI, 11.1%-19.7%]; RR, 1.9 [95% CI, 1.6-2.3])

Smoking Reduction (Weeks 1 to 12)

At week 4, 47.1% of participants treated with varenicline (358 of 760 participants) reduced the number of cigarettes smoked per day (ie, average number of cigarettes during days on which smoking occurred over the last week) compared with baseline by 50% or more or abstained completely compared with 31.1% of participants treated with placebo (233 of 750 participants) (RD, 16.0% [95% CI, 11.2%-20.9%]; RR, 1.5 [95% CI, 1.3-1.7]). After 8 weeks, 26.3% participants in the varenicline group (200 of 760 participants) reduced smoking by 75% or more from baseline or abstained compared with 15.1% participants in the placebo group (113 of 750 participants) (RD, 11.3% [95% CI, 7.2%-15.3%]; RR, 1.8 [95% CI, 1.4-2.2]).

Safety

The percentage of participants with adverse events was higher in the varenicline group than in the placebo group (618 of 751 participants [82.3%] in the varenicline group vs 538 of 742 participants [72.5%] in the placebo group). Adverse events with the greatest risk difference between varenicline and placebo (>2%) were nausea, abnormal dreams, insomnia, constipation, vomiting, and weight gain (Table 3). Adverse event incidence resulting in permanent treatment discontinuation was not significantly different between the 2 groups (63 of 751 participants [8.4%] in the varenicline group vs 52 of 742 participants [7.0%] in the placebo group; $P = .27$). Percentages of participants with serious adverse events were not significantly different between varenicline and placebo (28 of 751 participants [3.7%] in the varenicline group vs 16 of 742 participants [2.2%] in the placebo group; $P = .07$). During treatment and up to 30 days after the last dose, suicidal ideation or behavior was

Table 1. Participant Characteristics

	Varenicline Group (n = 760)	Placebo Group (n = 750)
Demographic Characteristics		
Sex, No. (%)		
Men	425 (55.9)	426 (56.8)
Women	335 (44.1)	324 (43.2)
Age, mean (SD) [range], y	44.7 (11.8) [19-79]	44.4 (12.0) [18-78]
Race/ethnicity, No. (%)		
White	476 (62.6)	463 (61.7)
Black	36 (4.7)	47 (6.3)
Asian	175 (23.0)	177 (23.6)
Other	73 (9.6)	63 (8.4)
Smoking characteristics, mean (SD)		
Fagerström Test for Nicotine Dependence score ^a	5.5 (2.1)	5.6 (2.0)
Age started smoking, y	17.3 (4.3)	17.3 (4.4)
No. of cigarettes per day in past month	20.6 (8.5)	20.8 (8.2)
Longest Period of Abstinence		
Since started smoking, d		
Median (IQR)	30 (3-240)	21 (2-180)
Mean	272	206
In past year, d		
Median (IQR)	0 (0-1)	0 (0-0)
Mean	4	3
No. of Serious Quit Attempts by Any Method		
Since started smoking, No. (%)		
None	130 (17.1)	159 (21.2)
1	191 (25.1)	188 (25.1)
2	139 (18.3)	110 (14.7)
≥3	300 (39.5)	293 (39.1)

Abbreviation: IQR, interquartile range.

^a Fagerström Test for Nicotine Dependence measures the degree of cigarette dependence with scores ranging from 0 to 10 with higher scores indicating a higher degree of dependence.¹⁷

recorded on the C-SSRS in 6 of 751 participants (0.8%) in the varenicline group and 10 of 742 participants (1.3%) in the placebo group. Any increases in PHQ-9 depression scores from baseline to any time point after baseline occurred in 169 of 751 participants (22.5%) treated with varenicline compared with 145 of 742 participants (19.5%) treated with placebo ($P = .16$).

Discussion

Among cigarette smokers not willing or able to quit smoking in the next month but willing to reduce with the goal of quitting in the next 3 months, varenicline produced a statistically and clinically significant increase in the CARs at the end of treatment and at 28 weeks after treatment. Varenicline produced greater smoking reduction than placebo prior to quitting. Varenicline was not associated with significant increases in treatment discontinuations due to adverse events.

Smokers enrolled in the current study were not ready to quit in the next month, and overall smoking abstinence rates would

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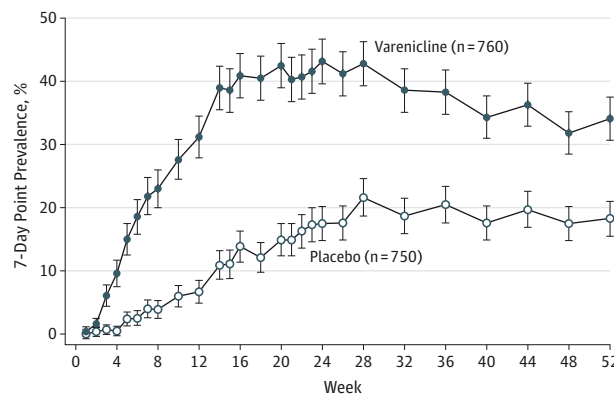
Table 2. Continuous Carbon Monoxide–Confirmed Smoking Abstinence Rates for Periods of the Study^a

	Continuous Abstinence, No. of Participants (%)		Risk Difference, % (95% CI)	Relative Risk (95% CI)
	Varenicline Group (n = 760)	Placebo Group (n = 750)		
Primary End Point^b				
Weeks 15-24	244 (32.1)	52 (6.9)	25.2 (21.4-29.0)	4.6 (3.5-6.1)
Secondary End Points^b				
Weeks 21-24	287 (37.8)	94 (12.5)	25.2 (21.1-29.4)	3.0 (2.4-3.7)
Weeks 21-52	205 (27.0)	74 (9.9)	17.1 (13.3-20.9)	2.7 (2.1-3.5)
Post Hoc End Point^b				
Weeks 15-52	182 (24.0)	45 (6.0)	18.0 (14.5-21.4)	4.0 (2.9-5.4)

^a All randomized participants were included at all time points. For nonmissed visits, a carbon monoxide level higher than 10 ppm disqualified participants from meeting the end point. Participants with missing carbon monoxide measurements met the end point if they self-reported not smoking. Participants with missing visits were considered abstinent if they self-reported not smoking and did not have a carbon monoxide measurement higher than 10 ppm at the next nonmissed visit and also reported not smoking during the missed visit. Participants who withdrew from the study were considered smokers after the time of withdrawal.

^b The primary end point was carbon monoxide–confirmed self-reported abstinence during weeks 15 through 24; secondary end points, carbon monoxide–confirmed self-reported abstinence for weeks 21 through 24 and weeks 21 through 52; post hoc end point, carbon monoxide–confirmed self-reported abstinence for weeks 15 through 52.

Figure 2. Seven-Day Point Prevalence Smoking Abstinence for Participants Receiving Varenicline vs Placebo



RD indicates risk difference; RR, relative risk. Week 12: RD, 24.5% (95% CI, 20.8%-28.3%), RR, 4.7 (95% CI, 3.5-6.2); week 24: RD, 25.7% (95% CI, 21.2%-30.1%), RR, 2.5 (95% CI, 2.1-3.0); week 52: RD, 15.8% (95% CI, 11.5%-20.2%), RR, 1.9 (95% CI, 1.6-2.2).

All randomized participants were included at all time points. For nonmissed visits, carbon monoxide level higher than 10 ppm disqualified participants from meeting the end point when abstinence was self-reported. Participants with missing carbon monoxide measurements met the end point if they self-reported smoking abstinence. Participants with missing visits were considered smokers for that visit. Participants who withdrew from the study were considered smokers from the time of withdrawal. Error bars indicate 95% CIs.

have been expected to be low. Although overall smoking abstinence rates were low in the placebo group, varenicline increased the rates of achieving abstinence such that the absolute abstinence rates were similar to those observed in studies of varenicline in smokers motivated to quit after 1 week of treatment.^{11,12}

The mechanism of varenicline action as an aid to gradual cessation could relate to a reduction in cigarette craving or a blockade of the reinforcing action of nicotine through partial agonist activity at the nicotinic acetylcholine receptors.¹⁰ Ancillary effects from varenicline may exist with respect to con-

fidence in ability to quit. However, this should have been controlled through study blinding and any effect via this route is likely to be small given limited evidence that confidence plays a causal role in sustaining quitting attempts.²²

Adverse events caused by varenicline were similar to previous observations. In the present study, varenicline was associated with an increased rate of constipation and weight gain. However, both are established effects of smoking cessation,^{23,24} and it is possible that the greater incidence of abstinence with varenicline and not the direct effect of varenicline was the cause. The incidence of bronchitis was lower in those treated with varenicline, an effect which is possibly mediated by an increased rate of smoking cessation.²⁵ Varenicline did not increase the risk of suicidal ideation or behavior or other psychiatric adverse events.

Major strengths of this study include the randomized design, large sample size, and convergent validity of the findings across multiple outcomes and measures. One limitation of this study relates to the exclusion of potential participants if they had severe psychiatric, pulmonary, cardiovascular, or cerebrovascular disease. As a result, the generalizability of this treatment approach to a broader population of smokers who need to quit smoking but may want to achieve it through reduction is unknown. In addition, participants in the current study were provided with significant support with counseling from trained staff occurring during 18 clinic and 10 telephone visits. Because of this, the observed abstinence rates with varenicline in actual clinical practice might be expected to be less than that observed in the current trial. We did not test whether varenicline would be more effective for the reduce-to-quit cessation approach than other tobacco treatments such as nicotine replacement therapy.

Uncertainty remains as to the prevalence of smokers in the general population who meet the definition of smokers enrolled in this study. In a cross-sectional study collecting data via telephone or face-to-face interview with daily smokers responding to the Current Population Survey, the prevalence of contemplators (ie, interested in quitting smoking in next 6

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Table 3. Adverse Events Occurring During Treatment Plus 30 Days in 2% or More of Participants Who Received 1 or More Doses of Study Drug in Either Treatment Group^a

Adverse Events	No. (%)		Risk Difference, % (95% CI)
	Varenicline Group (n = 751)	Placebo Group (n = 742)	
Nausea	209 (27.8)	67 (9.0)	18.80 (14.99 to 22.61)
Nasopharyngitis	98 (13.0)	89 (12.0)	1.05 (-2.30 to 4.41)
Abnormal dreams	86 (11.5)	43 (5.8)	5.66 (2.83 to 8.49)
Insomnia	80 (10.7)	51 (6.9)	3.78 (0.92 to 6.64)
Upper respiratory tract infection	63 (8.4)	63 (8.5)	-0.10 (-2.92 to 2.72)
Headache	62 (8.3)	54 (7.3)	0.98 (-1.74 to 3.69)
Anxiety	52 (6.9)	65 (8.8)	-1.84 (-4.56 to 0.89)
Fatigue	46 (6.1)	34 (4.6)	1.54 (-0.74 to 3.82)
Irritability	39 (5.2)	30 (4.0)	1.15 (-0.98 to 3.28)
Constipation	38 (5.1)	13 (1.8)	3.31 (1.48 to 5.14)
Increased appetite	37 (4.9)	30 (4.0)	0.88 (-1.22 to 2.98)
Sleep disorder	37 (4.9)	29 (3.9)	1.02 (-1.06 to 3.10)
Dizziness	32 (4.3)	27 (3.6)	0.62 (-1.35 to 2.60)
Vomiting	31 (4.1)	13 (1.8)	2.38 (0.67 to 4.08)
Back pain	28 (3.7)	29 (3.9)	-0.18 (-2.12 to 1.76)
Weight increased	28 (3.7)	12 (1.6)	2.11 (0.48 to 3.74)
Diarrhea	27 (3.6)	23 (3.1)	0.50 (-1.33 to 2.32)
Depressed mood	26 (3.5)	27 (3.6)	-0.18 (-2.05 to 1.70)
Depression	25 (3.3)	35 (4.7)	-1.39 (-3.38 to 0.61)
Decreased appetite	20 (2.7)	19 (2.6)	0.10 (-1.52 to 1.72)
Agitation	20 (2.7)	14 (1.9)	0.78 (-0.74 to 2.29)
Dyspepsia	19 (2.5)	9 (1.2)	1.32 (-0.05 to 2.69)
Abdominal pain upper	18 (2.4)	7 (0.9)	1.45 (0.16 to 2.75)
Middle insomnia	17 (2.3)	11 (1.5)	0.78 (-0.59 to 2.16)
Flatulence	17 (2.3)	6 (0.8)	1.46 (0.21 to 2.70)
Influenza	16 (2.1)	12 (1.6)	0.51 (-0.86 to 1.89)
Dry mouth	16 (2.1)	11 (1.5)	0.65 (-0.70 to 2.00)
Abdominal distention	16 (2.1)	8 (1.1)	1.05 (-0.22 to 2.32)
Somnolence	15 (2.0)	10 (1.3)	0.65 (-0.65 to 1.95)
Initial insomnia	15 (2.0)	9 (1.2)	0.78 (-0.49 to 2.06)
Cough	14 (1.9)	23 (3.1)	-1.24 (-2.81 to 0.34)
Disturbance in attention	13 (1.7)	17 (2.3)	-0.56 (-1.98 to 0.86)
Sinusitis	12 (1.6)	16 (2.2)	-0.56 (-1.94 to 0.82)
Bronchitis	10 (1.3)	23 (3.1)	-1.77 (-3.26 to -0.28)

^a All participants had been randomized and had received at least 1 dose (including partial doses) of study drug; and includes all participants who had experienced an adverse event from the date of first dose of study drug and up to 30 d after the last dose of study drug. Adverse events were recorded in the clinical report form (volunteered and observed adverse events) and, in addition, neuropsychiatric adverse events were solicited in a semistructured neuropsychiatric adverse event interview. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA).²¹ Participants were counted for each type of adverse event but were counted only once for multiple occurrences of the same type of event.

months but not in the next 30 days) was 33.2%.⁴ We were not attempting to fit smokers into a specific stage of readiness for behavior change.²⁶ Instead, our approach aimed to reduce barriers to engaging in the quitting process by allowing and facilitating smoking reduction in a precessation phase.²⁷ Our sample most closely resembles the 33% of smokers who want to quit sometime between 1 and 6 months in the future. The approach used in this study would be expected to be of interest to 14 million of the 42 million current smokers.

The US Public Health Service³ and other guidelines recommend smokers set a quit date in the near future and quit abruptly. However, many smokers may be unwilling to commit to a quit date at a clinic visit. Because most clinicians are likely to see smokers at times when a quit date in the next month is not planned, the current study indicates that prescription of varenicline with a recommendation to reduce the

number of cigarettes smoked per day with the eventual goal of quitting could be a useful therapeutic option for this population of smokers. The approach of reduction with the goal of quitting increases the options for a clinician caring for a smoker.

Conclusions

Among cigarette smokers not willing or able to quit within the next month but willing to reduce cigarette consumption and make a quit attempt at 3 months, use of varenicline for 24 weeks compared with placebo significantly increased smoking cessation rates at the end of treatment, and also at 1 year. Varenicline offers a treatment option for smokers whose needs are not addressed by clinical guidelines recommending abrupt smoking cessation.

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ARTICLE INFORMATION

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Study concept and design: Hughes, West, Rennard, Russ, Treadow, Yu, Park.

Acquisition, analysis, or interpretation of data: Ebbert, Hughes, West, Rennard, Russ, McRae, Treadow, Yu, Dutro.

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Obtained funding: Park.

Administrative, technical, or material support: Treadow, Dutro, Park.

Study supervision: Ebbert, Russ, McRae, Treadow, Park.

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REFERENCES

- Borland R, Partos TR, Yong HH, Cummings KM, Hyland A. How much unsuccessful quitting activity is going on among adult smokers? *Addiction*. 2012; 107(3):673-682.
- Shiffman S, Hughes JR, Ferguson SG, Pillitteri JL, Gitchell JG, Burton SL. Smokers' interest in using nicotine replacement to aid smoking reduction. *Nicotine Tob Res*. 2007;9(11):1177-1182.
- Fiore MC, Jaen CR, Baker TB, et al. Treating tobacco use and dependence: 2008 update. <http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html>. Accessed December 31, 2014.
- Wewers ME, Stillman FA, Hartman AM, Shopland DR. Distribution of daily smokers by stage of change: Current Population Survey results. *Prev Med*. 2003;36(6):710-720.
- Asfar T, Ebbert JO, Klesges RC, Relyea GE. Do smoking reduction interventions promote cessation in smokers not ready to quit? *Addict Behav*. 2011;36(7):764-768.
- Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D. "Cut down to quit" with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis. *Health Technol Assess*. 2008;12(2):iii-iv; ix-xi; 1-135.
- Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ*. 2009;338:b1024.
- Cheong Y, Yong HH, Borland R. Does how you quit affect success? *Nicotine Tob Res*. 2007;9(8): 801-810.
- Lindson N, Aveyard P, Hughes JR. Reduction vs abrupt cessation in smokers who want to quit. *Cochrane Database Syst Rev*. 2010;(3):CD008033.
- Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an $\alpha_4\beta_2$ nicotinic receptor partial agonist for smoking cessation. *J Med Chem*. 2005; 48(10):3474-3477.
- Gonzales D, Rennard SI, Nides M, et al; Varenicline Phase 3 Study Group. Varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296(1):47-55.
- Jorenby DE, Hays JT, Rigotti NA, et al; Varenicline Phase 3 Study Group. Efficacy of varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296(1):56-63.
- Ashare RL, Tang KZ, Mesaros AC, Blair IA, Leone F, Strasser AA. Effects of 21 days of varenicline vs placebo on smoking behaviors and urges among nontreatment seeking smokers. *J Psychopharmacol*. 2012;26(10):1383-1390.
- Hughes JR, Rennard SI, Fingar JR, Talbot SK, Callas PW, Fagerstrom KO. Efficacy of varenicline to prompt quit attempts in smokers not currently trying to quit: a randomized placebo-controlled trial. *Nicotine Tob Res*. 2011;13(10):955-964.
- Posner K. Suicidality issues in clinical trials: Columbia suicide adverse event identification in FDA safety analyses. <http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4306s1-01-CU-Posner.ppt>. Accessed January 20, 2015.
- Osman A, Bagge CL, Gutierrez PM, Konick LC, Kopper BA, Barrios FX. The Suicidal Behaviors Questionnaire-Revised (SBQ-R): validation with clinical and nonclinical samples. *Assessment*. 2001; 8(4):443-454.
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict*. 1991;86(9): 1119-1127.
- Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.
- Hatsukami DK, Rennard S, Patel MK, et al. Effects of sustained-release bupropion among persons interested in reducing but not quitting smoking. *Am J Med*. 2004;116(3):151-157.
- Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2008;(3):CD006103.
- Medical Dictionary for Regulatory Activities website. <http://www.meddra.org/>. Accessed December 31, 2014.
- Vangeli E, Stapleton J, Smit ES, Borland R, West R. Predictors of attempts to stop smoking and their success in adult general population samples: a systematic review. *Addiction*. 2011;106(12):2110-2121.
- Hajek P, Gillison F, McRobbie H. Stopping smoking can cause constipation. *Addiction*. 2003; 98(11):1563-1567.
- Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. *BMJ*. 2012;345:e4439.
- Willemsse BW, Postma DS, Timens W, ten Hacken NH. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness, and inflammation. *Eur Respir J*. 2004;23(3):464-476.
- Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. *J Consult Clin Psychol*. 1983;51(3):390-395.
- Baker TB, Mermelstein R, Collins LM, et al. New methods for tobacco dependence treatment research. *Ann Behav Med*. 2011;41(2):192-207.