ORIGINAL RESEARCH | Annals of Internal Medicine

Effects of Varenicline on Smoking Cessation in Adults With Stably Treated Current or Past Major Depression

A Randomized Trial

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Background: Depression is overrepresented in smokers.

Objective: To evaluate smoking abstinence and changes in mood and anxiety levels in smokers with depression treated with varenicline versus placebo.

Design: Phase 4, multicenter, parallel, 1:1 allocation, double-blind, randomization trial. Randomization, stratified by antidepressant use and depression score at baseline, was blocked in sizes of 4. (ClinicalTrials.gov: NCT01078298)

Setting: 38 centers in 8 countries.

Participants: 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events.

Intervention: Varenicline, 1 mg twice daily, or placebo for 12 weeks, with 40-week nontreatment follow-up.

Measurements: Primary outcome was carbon monoxide–confirmed continuous abstinence rate (CAR) for weeks 9 to 12. Other outcomes included CARs assessed during nontreatment follow-up and ratings of mood, anxiety, and suicidal ideation or behavior.

Results: 68.4% versus 66.5% of the varenicline and placebo groups, respectively, completed the study. Varenicline-treated participants had higher CARs versus placebo at weeks 9 to 12 (35.9% vs. 15.6%; odds ratio [OR], 3.35 [95% CI, 2.16 to 5.21]; $P < 0.001$), 9 to 24 (25.0% vs. 12.3%; OR, 2.53 [CI, 1.56 to 4.10]; $P < 0.001$), and 9 to 52 (20.3% vs. 10.4%; OR, 2.36 [CI, 1.40 to 3.98]; $P = 0.001$). There were no clinically relevant differences between groups in suicidal ideation or behavior and no overall worsening of depression or anxiety in either group. The most frequent adverse event was nausea (varenicline, 27.0%; placebo, 10.4%). Two varenicline-group participants died during the nontreatment phase.

Limitations: Some data were missing, and power to detect differences between groups was low in rare events. Smokers with untreated depression, with co-occurring psychiatric conditions, or receiving mood stabilizers and antipsychotics were not included.

Conclusion: Varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety.

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Depression and smoking are among the leading causes of disability (1) and death (2) in the world. The presence of 1 condition increases risk for the other (3) to the extent that roughly half of smokers seeking treatment have a history of depression (4). Depressed smokers are more likely to become nicotine dependent than smokers without psychiatric disorders (5) and have greater difficulty quitting (6). Nicotine replacement therapy (7, 8), bupropion (9–11), and nortriptyline (12) are effective in smokers with a history of depression. However, relapse rates are high (13), and studies testing these agents in depressed patients routinely exclude persons receiving antidepressants and other psychotropic medications who make up an important subgroup of smokers (14).

See also:

Print
Summary for Patients I-36

Web-Only
Supplement

Quit rates in smokers without psychiatric disorders are greater with varenicline than with bupropion (15, 16), with effects persisting up to 1 year. Varenicline's ability to alleviate symptoms of nicotine withdrawal and to block nicotine's rewarding effects (17–20) may be particularly helpful in depressed smokers who experience greater levels of withdrawal symptoms (21). However, case reports (22–24) and postmarketing surveillance data (25–27) have raised concerns about varenicline's neuropsychiatric safety profile in psychiatric patients. Smokers with current psychiatric disorders were generally excluded from the pivotal phase 3 trials that led to varenicline's approval, and few direct empirical data are available to place the surveillance reports in proper perspective.

We conducted what we believe to be the first randomized, controlled trial of varenicline in persons with stably treated current or past major depressive disorder (MDD). We hypothesized that varenicline treatment would increase quit rates versus placebo, maintain smoking abstinence up to 1 year after treatment, and be well-tolerated among depressed smokers without exacerbating neuropsychiatric symptoms.

METHODS

Design Overview

This was a phase 4, multicenter, parallel, randomized, controlled clinical study designed to assess the efficacy and safety of 12 weeks of treatment of varenicline, 1 mg twice daily, or placebo for smoking cessation, with 40 weeks of nontreatment follow-up. Participants, investigators, and research personnel were blinded to randomization until after the last patient's final visit. The study was done between 25 March 2010 and 13 June 2012 in 38 centers across 8 countries.

Consent forms and procedures were reviewed and approved by the institutional review board or independent ethics committee at each site. The trial adhered to the Declaration of Helsinki (28) and the International Conference on Harmonisation Good Clinical Practice guidelines (29).

Setting and Participants

Potential participants were recruited from the investigators' own patients; through television, radio, and newspaper advertising; and posters and flyers. Study sites were academic clinical trial centers and smoking cessation clinics providing outpatient services. Participants signed written informed consent before any screening procedures were done.

Eligible participants were male and female smokers aged 18 to 75 years who smoked at least 10 cigarettes daily, exhaled carbon monoxide more than 10 ppm at screening, were motivated to stop smoking, and were considered suitable for a cessation attempt. Participants were individuals who met current or past *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (30), criteria for unipolar MDD without psychotic features. The diagnosis was confirmed by the Structured Clinical Interview for Axis I Disorders (Research Version, Patient Edition) of the *Diagnostic and Statistical Manual of Mental Disorders* (31) administered by trained mental health professionals. Participants also had been receiving an antidepressant treatment for MDD at a stable dose (at least 2 months without dosing changes anticipated during study treatment) and/or had had a successfully treated major depressive episode in the past 2 years. Women of childbearing potential agreed to practice effective contraception.

Key exclusion criteria included current or past (previous 6 months) diagnosis of dementia, schizophrenia, schizoaffective disorder, other psychotic disorders, or bipolar disorder (I and II); severe personality disorders compromising the participant's ability to comply with the study requirements; suicidal or homicidal risk; severe chronic obstructive pulmonary disease; clinically significant cardiovascular or cerebrovascular disease in the past 6 months; recent (<5 years) history of cancer; body mass index less than 15 kg/m^2 or greater than 38 kg/m^2 or body weight less than 45.5 kg; or any other severe, acute, or unstable medical or psychiatric condition or laboratory abnormality.

Context

Although varenicline increases quit rates in smokers, some question its efficacy and safety in patients with psychiatric disorders.

Contribution

In this trial, 525 smokers with stably treated current or past major depression and no recent cardiovascular disease were randomly assigned to varenicline, 1 mg twice daily, or placebo for 12 weeks. More participants treated with varenicline than those receiving placebo stopped smoking. Varenicline caused nausea but did not worsen depression or anxiety.

Caution

About one third of the participants did not complete the study.

Implication

Varenicline can increase smoking cessation rates in some smokers with stable depression without exacerbating depression or anxiety.

—The Editors

Use of bupropion, nortriptyline, medications for mania or psychosis, and investigational drugs (<30 days before baseline) during the study or previous use of varenicline was prohibited. Noncigarette tobacco products and marijuana were also excluded.

Randomization and Interventions

Eligible participants were randomly assigned to varenicline or placebo in a 1:1 ratio by using a computer-generated, 4-block randomization scheme at each site. Randomization was stratified by antidepressant medication use at baseline (any vs. none) and baseline Montgomery–Åsberg Depression Rating Scale (MADRS) score (≤11 vs. >11) (32). Investigators obtained participant identification numbers and randomized study drug assignments by using a Web-based or telephone call-in computerized drug management system. The study drug was supplied in blinded bottles by the sponsor to the study sites, where they were dispensed according to computerized instructions.

All participants randomly assigned to varenicline were titrated to full dose during the first week (0.5 mg/d for 3 days, 0.5 mg twice daily for 4 days, then 1 mg twice daily for the following 11 weeks). The dose could be reduced temporarily or permanently to 0.5 mg twice daily for participants with tolerability problems. The placebo tablets were the same as the varenicline tablets except for removal of the active agent; dose titrations and allowable adjustments were the same for both agents. Participants who discontinued study medication were encouraged to remain in the study for all assessments.

Participants set a target quit date to coincide with the week 1 visit. Both treatment groups received the same

manual-guided smoking cessation counseling developed by one of the authors in accordance with Agency for Healthcare Research and Quality guidelines (33) at each clinic and telephone visit starting at baseline through week 52. One-on-one counseling was provided for up to 10 minutes and, whenever possible, was done by the same counselor throughout the study.

Outcomes and Follow-up

Participation included attending clinic visits at screening, baseline, every week during the treatment phase and at weeks 13, 16, 24, 32, 40, and 52 (or at early termination) during the nontreatment follow-up phase. Telephone visits occurred at weeks 14, 20, 28, 36, 44, and 48 during the nontreatment follow-up phase.

Treatment adherence was recorded by weekly pill counts. Investigators ascertained reasons for missed doses with participants and incorporated the issues raised into the smoking cessation counseling.

For participants withdrawing from the study, every effort was made to document outcomes, reasons for withdrawal, and safety status.

Unblinding for safety reasons was available electronically or via a manual backup procedure.

Investigators received sponsor-organized quality control and data management training during an investigator meeting or during regularly scheduled site visits. A central laboratory was used.

The external independent data safety monitoring committee met via teleconference to review safety data after approximately each quartile of participants completed the treatment period.

Efficacy

Consistent with previous varenicline studies (15, 16, 34–40) and the Society for Research on Nicotine and Tobacco recommendations (41), the primary efficacy end point was the carbon monoxide–confirmed (≤10 ppm) continuous abstinence rate (CAR) for the last 4 weeks of treatment (weeks 9 to 12). Secondary efficacy end points included carbon monoxide–confirmed CARs for weeks 9 to 24 and 9 to 52 and 7-day point prevalence of abstinence at weeks 12, 24, and 52. Smoking abstinence was assessed at each clinic and telephone visit by self-report using a standardized set of questions, the Nicotine Use Inventory (15, 16). Carbon monoxide was confirmed at clinic visits with a calibrated Smokerlyzer (Bedfont Scientific, Maidstone, United Kingdom).

Psychiatric Rating Scales

Two valid, reliable psychiatric rating scales were administered at baseline and at each clinic visit during treatment and up to week 16 to measure depressive symptoms (MADRS) (32) and anxiety-related symptoms (Hamilton Rating Scale for Anxiety [HAM-A]) (42). Suicide risk was assessed at screening with the Suicidal Behaviors Questionnaire-Revised (SBQ-R) (43) and the Columbia Suicide Severity Rating Scale (C-SSRS) (44), which was also administered at each clinic visit through week 52. If suicidal ideation was associated with actual intent or plan in the past year, if a history of suicidal behavior in the past 10 years was identified with the C-SSRS, or if SBQ-R scores were greater than 8, then qualified mental health professionals performed risk assessments to determine whether participation in the study was safe. Also, if the participant answered "yes" on items 4 or 5 or any behavioral question on the C-SSRS, a determination was made about whether it was safe to continue dosing. Details of scoring and cutoff points for MADRS, HAM-A, SBQ-R, and C-SSRS are available in **Table 1** of the **Supplement** (available at www.annals.org). Whenever possible, all psychiatric scales were administered by the same trained, experienced rater in the same order at all visits. All assessors were blind to study treatment.

Adverse Events

Study investigators were required to ask whether participants had experienced any adverse events (AEs). In addition to AEs that were observed or voluntarily reported by participants, actively solicited neuropsychiatric AEs of special interest were recorded by using the Neuropsychiatric Adverse Event Interview (NAEI). The NAEI is a semistructured interview designed by the sponsor to specifically probe for psychiatric symptoms during the conduct of a clinical trial. It supplemented the standardized depression and anxiety assessments by asking about agitation, mania, hostility, paranoia, hallucinations, delusions, and derealization or depersonalization. Investigators used the information collected to further report AEs as appropriate. Adverse events were recorded through week 16 and were coded by using the Medical Dictionary for Regulatory Activities.

Statistical Analysis

Sample size was based on the comparison of varenicline, 1 mg twice daily, versus placebo by using a 2-group, continuity-corrected, chi-square test with a 2-sided significance level of 0.05. Two hundred fifty participants in each group provided at least 80% power to detect an odds ratio (OR) of 2.35, assuming the placebo response rate for smoking abstinence from weeks 9 to 52 was 7%.

We performed primary efficacy and safety analyses on all randomly assigned participants who received at least 1 dose of study medication. The a priori data analysis plan used a series of logistic regression models (PROC GENMOD in SAS, version 8.2 [SAS Institute, Cary, North Carolina]) that included treatment condition, pooled center (United States vs. Europe), and stratum as independent variables. Strata 1 through 4 varied by the use of antidepressant medication at baseline (receiving vs. not receiving antidepressants) and MADRS cutoff score (≤11 vs. >11) at baseline. The CAR at weeks 9 to 12 and during weeks 9 to 24 and 9 to 52 were analyzed along with 7-day point prevalence of abstinence at weeks 12, 24, and 52, respectively. Participants who discontinued the study and were lost to follow-up for subsequent visits were assumed

to be smokers for the remainder of the study. (More details about handling missing data are available in **Text 1** of the **Supplement**.)

We also conducted post hoc sensitivity analyses that used a longitudinal logistic regression model with the same assumptions as the primary analysis about postdiscontinuation responder status and a longitudinal logistic regression model with no imputation for postdiscontinuation visits. These models included the same fixed effects and covariates as the primary analysis but included an effect for time and an interaction for treatment by time. An unstructured covariance structure was used. Additional sensitivity analyses to more thoroughly explore the effect of treatment discontinuation were done and are described in **Text 2**, **Figure 1**, and **Table 2** of the **Supplement**.

For the MADRS and HAM-A scales, mean change from baseline and associated 95% CIs by treatment and visit were calculated. For the C-SSRS, frequency counts and percentages of participants reporting suicidal ideation or behavior were calculated for screening (lifetime), baseline, treatment (up to 30 days after the last dose), and posttreatment (30 days after the last dose to the end of the study).

All statistical analyses were performed by blinded data analysts until the database was locked and treatment codes were released.

Role of the Funding Source

Pfizer funded the study and was involved in study design and in collection, analysis, and interpretation of data with the authors.

RESULTS

Of 646 persons screened, 525 smokers with MDD (aged 19 to 73 years) were randomly assigned into the study and all received study treatment (**Figure 1**). Fewer participants discontinued varenicline than placebo (21.5% vs. 30.9%; $P = 0.017$); however, overall study discontinuation rates were similar across treatment groups (31.6% vs. 33.5%). **Table 3** of the **Supplement** shows study discontinuations by responder status at the time of discontinuation, and **Table 4** of the **Supplement** shows the number of recorded measurements at each visit. No assignment crossovers occurred during the trial.

Baseline Characteristics

Baseline demographic, smoking history, and psychiatric characteristics were similar between groups (**Table 1**). On average, participants had smoked for 26.7 years, smoking 22 cigarettes daily in the past month, and had scores on the Fagerström Test for Nicotine Dependence of 5.9. Mean total scores at baseline were 7.8 for MADRS and 6.3 for HAM-A, both in the remitted or normal range. Approximately 26% of participants had a MADRS score greater than 11, the midpoint between remitted and mildly depressed.

Most participants (varenicline, 70.7%; placebo, 73.2%) were receiving antidepressant medications at study entry, with selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors the predominant choice (varenicline, 61.3%; placebo, 67.7%). The other most common psychotropic treatment was alprazolam (varenicline, 8.6%; placebo, 13.4%).

Efficacy

Varenicline participants were more likely to quit smoking than placebo participants in all 3 periods: CAR weeks 9 to 12, 35.9% vs. 15.6% (OR, 3.35 [95% CI, 2.16 to 5.21]; $P < 0.001$); weeks 9 to 24, 25.0% vs. 12.3% (OR, 2.53 [CI, 1.56 to 4.10]; $P < 0.001$); and weeks 9 to 52, 20.3% vs. 10.4% (OR, 2.36 [CI, 1.40 to 3.98]; $P = 0.001$). Abstinence rates as a function of time are illustrated in **Figure 2**.

Post hoc sensitivity analyses using longitudinal models confirmed the primary analysis results for CARs at weeks 9 to 12 (35.9% vs. 15.6%; OR, 2.38 [CI, 1.68 to 3.36]; $P < 0.001$), 9 to 24 (25.0% vs. 12.3%; OR, 1.87 [CI, 1.36 to 2.57]; $P < 0.001$), and 9 to 52 (20.3% vs. 10.4%; OR, 1.84 [CI, 1.29 to 2.62]; $P = 0.001$) for varenicline versus placebo, respectively. A post hoc sensitivity analysis using a longitudinal model with postdiscontinuation visits assumed missing at random confirmed the primary analysis results for CARs at weeks 9 to 12 (41.6% vs. 18.7%; OR, 2.17 [CI, 1.60 to 2.95]; $P < 0.001$), 9 to 24 (27.9% vs. 14.9%; OR, 1.77 [CI, 1.24 to 2.53]; $P = 0.002$), and 9 to 52 (23.5% vs. 12.7%; OR, 1.65 [CI, 1.12 to 2.41]; $P = 0.010$). See **Text 2** and **Figure 1** of the **Supplement** for results of additional sensitivity analyses done to more thoroughly explore the effect of treatment discontinuation.

As expected, 7-day point-prevalence abstinence rates were higher for the varenicline group than the placebo group at week 12 (46.1% vs. 20.1%; OR, 3.82 [CI, 2.53 to 5.78]; $P < 0.001$), week 24 (31.3% vs. 18.2%; OR, 2.16 [CI, 1.40 to 3.33]; $P < 0.001$), and week 52 (28.5% vs. 17.5%; OR, 1.98 [CI, 1.28 to 3.08]; $P = 0.002$).

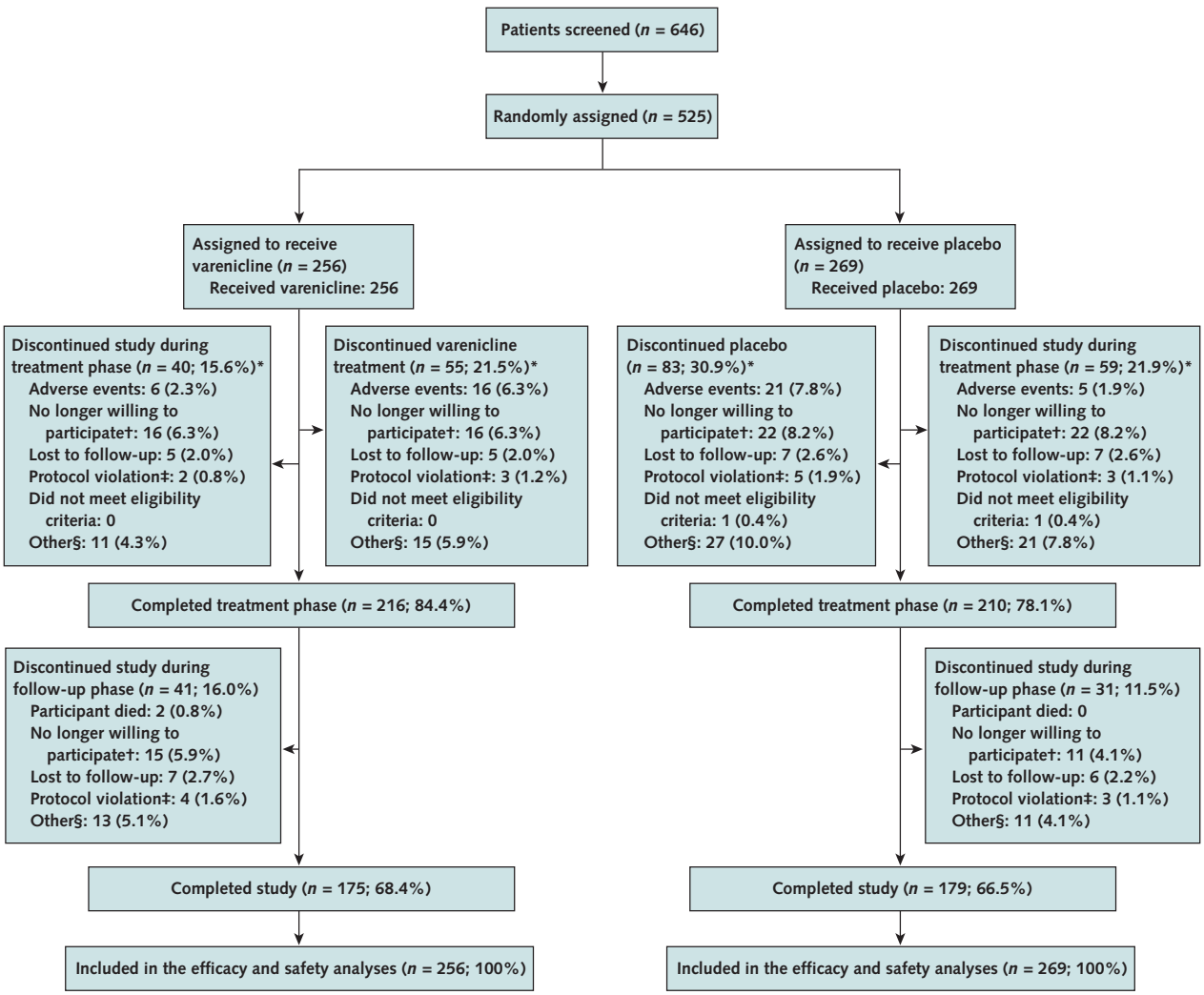
Psychiatric Rating Scales

The mean change from baseline in MADRS is depicted in **Figure 3** (*top*), and HAM-A change scores are depicted in **Figure 4**. Over time, both treatment groups had a similar change in scores, and rating trajectories trended toward slight improvement in mood and anxiety. The trajectories for MADRS scores as a function of medication and smoking status during weeks 9 to 12 are illustrated in **Figure 3** (*bottom*).

Adverse Events

Treatment-emergent AEs (that is, those occurring during treatment and ≤30 days thereafter) occurred in 72.3% of varenicline participants and 66.9% of placebo participants, with most being rated as mild or moderate. Treatment discontinuations due to AEs occurred in 6.3% and 7.8% of varenicline and placebo participants, respectively.

Figure 1. **Study flow diagram.**



* Participants could discontinue treatment but remain in the study. Treatment phase was weeks 1 through 12.
† Discontinuations from study due to reasons classified by the investigators as "no longer willing to participate" were withdrawal of consent for unknown reasons ($n = 28$), lack of motivation to quit smoking ($n = 12$), lack of clinical response ($n = 9$), new job or schedule change ($n = 7$), moved out of area ($n = 3$), nonadherence to the study protocol ($n = 3$), transportation issues ($n = 1$), and incarceration ($n = 1$).
‡ Discontinuations from study classified by the investigators as "protocol violations" were nonadherence to study visits ($n = 5$), bupropion use ($n = 3$), nonadherence to study medication ($n = 2$), and illicit drug use ($n = 2$).
§ Discontinuations from study due to reasons classified by the investigators as "other" were new job or schedule change ($n = 24$), moved out of area ($n = 24$), nonadherence to study ($n = 3$), lack of motivation to quit smoking ($n = 2$), transportation issues ($n = 2$), and suspicion of alcohol use ($n = 1$).

The most common AEs leading to treatment discontinuation were depression (varenicline, 2.0%; placebo, 1.1%) and depressed mood (varenicline, 0%; placebo, 1.5%). Dose reductions or temporary discontinuations due to AEs occurred in 8.6% and 3.7% of varenicline and placebo participants, respectively. Treatment-emergent, serious AEs occurred in 7 varenicline participants and 7 placebo participants and all were nonfatal. Of these, 2 varenicline participants had psychiatric serious AEs (psychotic disorder, depression, and suicidal ideation) versus 4 placebo participants who reported intentional self-injury, depression with suicidal ideation, agitation, and depression. Two participants receiving varenicline died during the 40-week nontreatment follow-up. Study investigators did not consider either death (an overdose of clonazepam and morphine sulfate 76 days into the posttreatment phase and an accidental fall 234 days into the posttreatment phase) to be related to the study treatment.

The most frequent treatment-emergent AEs in the varenicline versus placebo groups were nausea (27.0% vs. 10.4%), headache (16.8% vs. 11.2%), abnormal dreams (11.3% vs. 8.2%), irritability (10.9% vs. 8.2%), and insomnia (10.9% vs. 4.8%). Treatment-emergent psychiatric AEs occurring in 1% or more of either treatment group by

Table 1. **Patient Characteristics at Baseline**

Characteristic	Varenicline (*n* = 256)	Placebo (*n* = 269)
Demographic		
Sex, *n (%)*		
Male	97 (37.9)	99 (36.8)
Female	159 (62.1)	170 (63.2)
Age, *y*		
Mean (SD)	45.4 (10.9)	47.1 (10.8)
Range	19–73	20–73
Body mass index, kg/m^2		
Mean (SD)	26.8 (4.6)	27.3 (5.0)
Range	17.3–38.0	17.9–38.1
Country, *n*		
Bosnia and Herzegovina	10	10
Croatia	10	13
Germany	27	27
Hungary	24	29
Romania	13	11
Russian Federation	30	34
Spain	16	16
United States	126	129
Smoking		
Fagerström total score*		
Mean (SD)	5.9 (1.9)	5.9 (2.0)
Range	1–10	1–10
Total duration of smoking, *y*		
Mean (SD)	26.0 (11.7)	27.3 (11.8)
Range	1–55	2–56
Cigarettes/d in the past month		
Mean (SD)	21.9 (7.5)	21.5 (8.7)
Range	10–50	10–70
Psychiatric		
MADRS total score		
Mean (SD)	7.6 (7.4)	7.9 (7.5)
Median	6.0	6.0
Range	0–37	0–37
Total score ≤11, *n*	196	193
Total score >11, *n*	60	76
HAM-A total score		
Mean (SD)	6.1 (5.2)	6.4 (5.2)
Median	5.0	6.0
Range	0–24	0–29
Participants taking any antidepressant medication, *n (%)*	181 (70.7)	197 (73.2)

HAM-A = Hamilton Rating Scale for Anxiety; MADRS = Montgomery–Åsberg Depression Rating Scale.
* Fagerström Test for Nicotine Dependence score ranges from 0–10. Scores ≥6 indicate greater levels of nicotine dependence.

Medical Dictionary for Regulatory Activities (version 15.0) High-Level Group Terms are depicted in **Table 2**.

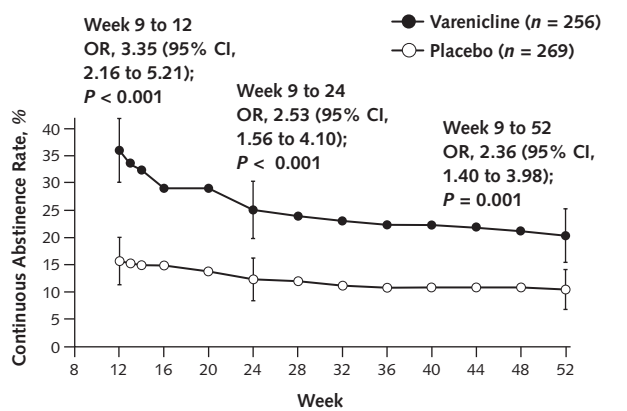
Lifetime history of suicidal ideation or behavior endorsed in the C-SSRS was similar in both groups (**Table 3**), with roughly equal proportions of participants reporting a history of suicide attempts (varenicline, 7.4%; placebo, 7.8%). Suicidal ideation at pretreatment baseline was present in more varenicline participants than placebo participants (2.3% vs. 0.4%), whereas differences between groups in suicidal ideation or behavior were minimal during treatment (6.0% vs. 7.5%) and in the posttreatment phase (6.2% vs. 5.8%). Most reports on the C-SSRS during the study were suicidal ideations. One event of intentional self-injury or a possible suicide attempt occurred on day 73 of treatment in a placebo participant. One death by overdose occurred in the varenicline group during follow-up, 76 days after the last dose of study treatment. A possible suicide could not be ruled out; therefore, the event was included in **Table 3**.

Discussion

Smokers in the varenicline group who were stably treated for or remitted from MDD were about twice as likely to quit throughout the last 4 weeks of treatment than were those in the placebo group. These beneficial effects persisted throughout the 40-week, nontreatment follow-up. Standardized assessments of mood and anxiety levels showed no clinically relevant differences between groups and no overall worsening of depression in either group. The most frequent AEs in the varenicline group were nausea, headache, abnormal dreams, irritability, and insomnia. Suicidal ideation or behavior as captured by the C-SSRS during study treatment occurred in 6.0% of the varenicline group versus 7.5% of the placebo group.

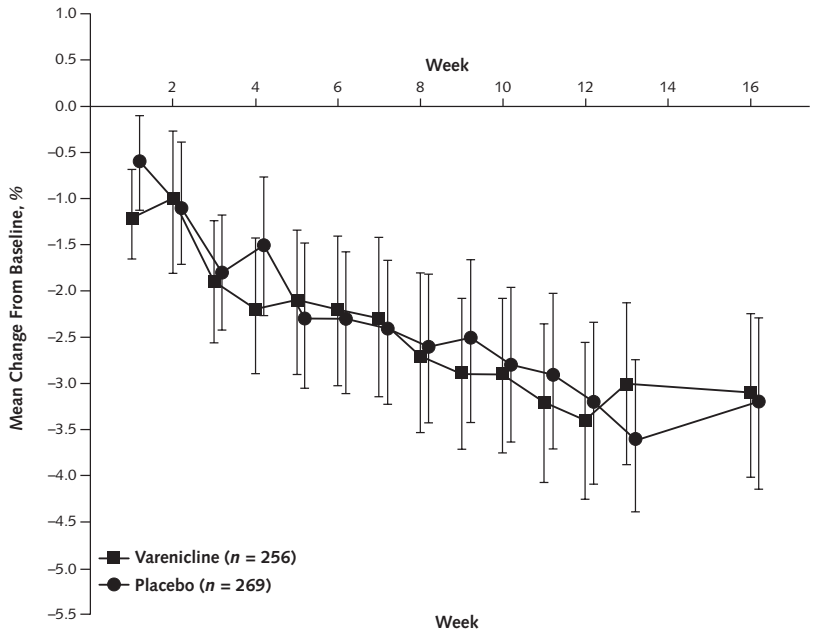
Comparing our results with relevant studies obtained via a PubMed search through April 2013 reveals several consistent themes. First, FDA-approved smoking cessation aids effective in nonpsychiatrically ill smokers have similarly beneficial effects in smokers with histories of depression (9, 14). Our study extends this observation to varenicline, but unlike those previous studies we evaluated a population in which most participants were receiving commonly prescribed antidepressant medications. Second, consistent with other findings that smoking cessation aids in

Figure 2. **Continuous abstinence rates defined as percentage of abstinent participants, from week 9 to each clinic visit through week 52.**

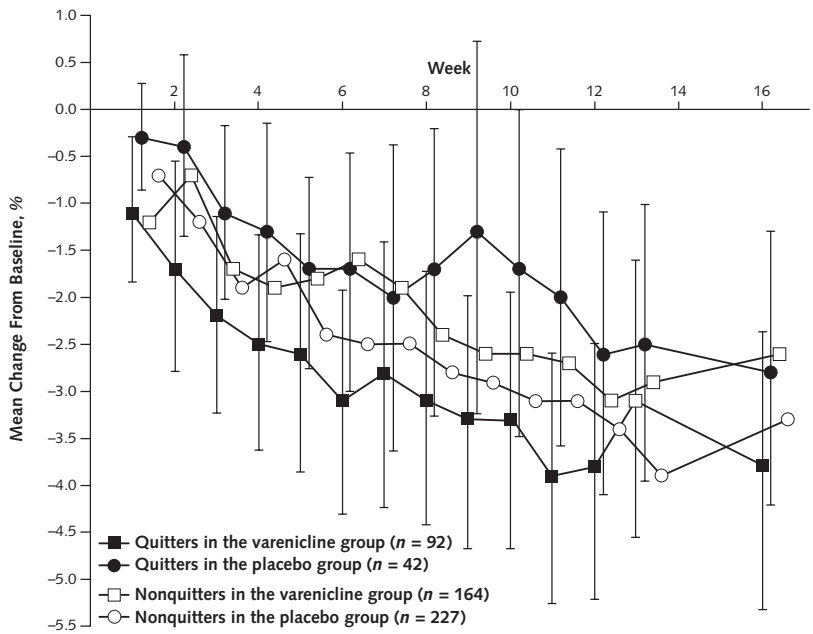


Data shown are observed data. Vertical bars show 95% CIs. Odds ratios shown are for CARs during weeks 9 to 12 (primary end point), 9 to 24, and 9 to 52 (secondary end points) and were calculated under the assumption that those who discontinued the study and were lost to follow-up were smokers for the rest of the study. CAR = continuous abstinence rates; OR = odds ratio.

Figure 3. **MADRS total scores mean change from baseline.**



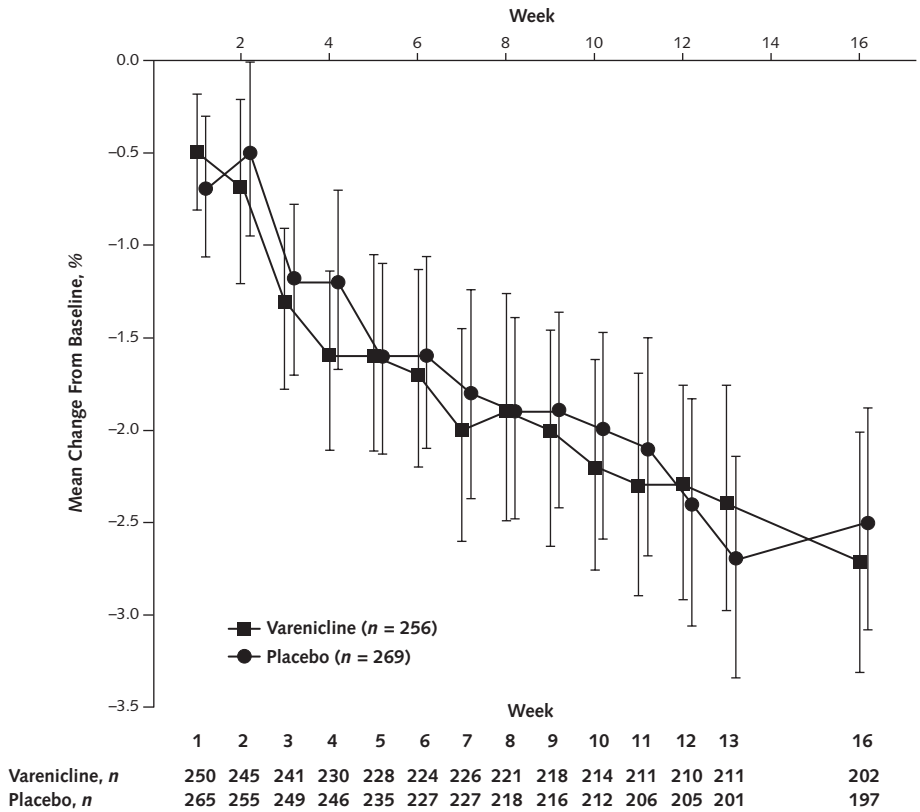
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	16
Varenicline, *n*	250	245	241	230	228	224	226	221	218	214	211	210	211	202
Placebo, *n*	265	255	249	246	235	227	227	218	216	212	206	205	201	197



Week	1	2	3	4	5	6	7	8	9	10	11	12	13	16
Quitters in the varenicline group, *n*	92	91	92	92	92	92	92	92	92	92	92	92	91	90
Quitters in the placebo group, *n*	41	42	42	42	42	42	42	42	42	42	42	42	42	40
Nonquitters in the varenicline group, *n*	158	154	149	138	136	132	134	129	126	122	119	118	120	112
Nonquitters in the placebo group, *n*	224	213	207	204	193	185	185	176	174	170	164	163	159	157

Vertical bars show 95% CIs. MADRS = Montgomery–Åsberg Depression Rating Scale. **Top**. Mean change from baseline overall. **Bottom**. Mean change from baseline by responder status; 95% CIs for quitters only.

Figure 4. **HAM-A total scores mean change from baseline.**



Vertical bars show 95% CIs. HAM-A = Hamilton Rating Scale for Anxiety.

psychiatric patients generally do not exacerbate psychiatric illness (45, 46), trajectories of mood and anxiety ratings trended toward slight improvement across time in both treatment groups. Third, our findings extend a consistent body of evidence showing that varenicline is an effective smoking cessation aid in smokers without current psychiatric illness (34, 36, 39), including those with other common, serious medical illnesses, such as chronic obstructive pulmonary disease (38) and cardiovascular disease (37).

Although not directly tested in this trial, we speculate that varenicline's effectiveness in smoking cessation results from its proposed dual mechanism of action. Varenicline is a partial agonist of brain $\alpha 4\beta 2$ nicotinic acetylcholine receptors and is believed to alleviate nicotine withdrawal while simultaneously blocking its rewarding effects (17–20). Because depressed smokers are prone to more severe nicotine withdrawal than nonpsychiatric smokers (5, 6), mitigating withdrawal symptoms may be important in this population. Speculating further, depressed smokers who lapse into smoking while attempting to regulate mood may find cigarettes less reinforcing when receiving varenicline or other smoking cessation aids, facilitating prolonged abstinence.

Although this study was not adequately powered to detect differences in rare events, these results in a vulnerable population of smokers with currently treated or remitted depression are reassuring from a neuropsychiatric safety perspective. By conducting a blinded, placebo-controlled trial, we reduced the potential for stimulated overreporting of adverse events that might occur in the context of the postmarketing surveillance process (47, 48). We combined reliable and valid mood and anxiety rating scales with a thorough AE collection, facilitated by the NAEI (which probed different types of psychiatric symptoms) and found no new clinically relevant safety signals. Although 2 participants who had received varenicline died in the 40-week nontreatment follow-up, neither death was considered treatment-related by the treating investigators. Moreover, retrospective reviews by the authors of the MADRS, HAM-A, C-SSRS, and NAEI results for these participants did not indicate any worsening of depressive illness that would portend such an outcome. Although the possibility of misclassification cannot be ruled out completely, the lengthy duration between drug discontinuation and these events makes linkage between the two unlikely. The neuropsychiatric safety findings reported here are consistent with other clinical trial results in nonpsychiatric (49) and psychiatric (40) populations, retrospective observational studies in smokers treated with varenicline (50–55), human laboratory findings (35), and pooled analyses of safety

Table 2. **Solicited and Volunteered Treatment-Emergent AEs***

High-Level Group Term From MedDRA	Varenicline (*n* = 256), *n (%)*	Placebo, (*n* = 269), *n (%)*
Sleep disorders and disturbances		
Abnormal dreams	29 (11.3)	22 (8.2)
Insomnia	28 (10.9)	13 (4.8)
Sleep disorder	7 (2.7)	4 (1.5)
Nightmare	4 (1.6)	3 (1.1)
Middle insomnia	3 (1.2)	3 (1.1)
Initial insomnia	1 (0.4)	4 (1.5)
Sleep talking	1 (0.4)	0
Terminal insomnia	1 (0.4)	0
Dyssomnia	0	1 (0.4)
Hypnagogic hallucination	0	1 (0.4)
Total	63 (24.6)	47 (17.5)
Anxiety disorders and symptoms		
Anxiety	18 (7.0)	25 (9.3)
Agitation	17 (6.6)	11 (4.1)
Tension	9 (3.5)	8 (3.0)
Nervousness	2 (0.8)	1 (0.4)
Panic attack	2 (0.8)	1 (0.4)
Stress	0	3 (1.1)
Total	39 (15.2)	41 (15.2)
Depressed mood disorders and disturbances		
Depression	17 (6.6)	13 (4.8)
Depressed mood	7 (2.7)	10 (3.7)
Depressive symptom	2 (0.8)	1 (0.4)
Depression suicidal	1 (0.4)	1 (0.4)
Anhedonia	1 (0.4)	0
Major depression	1 (0.4)	0
Negative thoughts	1 (0.4)	0
Total	28 (10.9)	25 (9.3)
Mood disorders and disturbances NEC		
Apathy	3 (1.2)	2 (0.7)
Affect lability	2 (0.8)	2 (0.7)
Altered mood	2 (0.8)	2 (0.7)
Elevated mood	1 (0.4)	1 (0.4)
Anger	1 (0.4)	0
Total	8 (3.1)	7 (2.6)
Personality disorders and disturbances in behavior		
Hostility	5 (2.0)	1 (0.4)
Aggression	2 (0.8)	1 (0.4)
Social avoidant behavior	1 (0.4)	0
Total	8 (3.1)	2 (0.7)
Changes in physical activity		
Restlessness	5 (2.0)	5 (1.9)
Total	5 (2.0)	5 (1.9)
Suicidal and self-injurious behaviors NEC		
Suicidal ideation	0	3 (1.1)
Intentional self-injury	0	1 (0.4)
Self-injurious ideation	0	1 (0.4)
Total	0	5 (1.9)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities, version 15.0; NEC = not elsewhere classified.
* Adverse events occurred in 1% or more of either treatment group and were classified by psychiatric High-Level Group Terms from MedDRA. Treatment-emergent AEs are those that occurred during treatment and up to 30 days after the last dose of study treatment. Participants were counted only once per row but could be counted several times per column.

data (56)—all finding no clear, untoward effects of varenicline on psychiatric AEs.

Our study has several limitations. First, we selected a population of smokers who were stably treated for or remitted from depression for this trial. Thus, our findings may not extrapolate to untreated or actively depressed smokers whom many consider to be poor candidates for smoking cessation until their condition stabilizes (57). Second, we excluded participants with psychotic features, bipolar disorder, current substance use disorders, and other conditions frequently associated with MDD, further limiting the generalizability of our results. Third, although selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, benzodiazepines, and nonbenzodiazepine sedative hypnotics were commonly used among nearly three quarters of participants, we excluded those receiving medications prescribed for mania or psychosis. Finally, although we made concerted efforts to retain and follow all randomly assigned participants throughout the 52-week study, attrition occurred across both treatment groups, and missing data could have affected outcomes.

In conclusion, our findings suggest that varenicline may be suitable for smoking cessation in smokers with stably treated current or past depression. With 350 million individuals having the disease worldwide (1) and because many smokers who seek treatment have a lifetime history

Table 3. **Participants With Positive Responses on the C-SSRS***

Suicidal Ideation or Behavior	Varenicline, *n (%)*	Placebo, *n (%)*
Lifetime		
Participants	256	269
Suicidal ideation or behavior	88 (34.4)	89 (33.1)
Suicidal behavior	23 (9.0)	28 (10.4)
Suicidal ideation	86 (33.6)	87 (32.3)
Baseline		
Participants	256	269
Suicidal ideation or behavior	6 (2.3)	1 (0.4)
Suicidal behavior	0	0
Suicidal ideation	6 (2.3)	1 (0.4)
During treatment†		
Participants	251	268
Suicidal ideation or behavior	15 (6.0)	20 (7.5)
Suicidal behavior	0	1 (0.4)
Suicidal ideation	15 (6.0)	19 (7.1)
During follow-up		
Participants	209	207
Suicidal ideation or behavior	13 (6.2)‡	12 (5.8)
Suicidal behavior	1 (0.5)‡	0
Suicidal ideation	12 (5.7)	12 (5.8)

C-SRSS = Columbia Suicide Severity Rating Scale.
* Percentages are based on the number of participants without missing values for a given time point or with at least 1 assessment during a given period. Positive responses on the C-SSRS might not have been deemed as an adverse event when evaluated by the study investigator. Participants were counted only once per row but could be counted multiple times per column.
† Treatment-emergent responses were those occurring between the date of first dose of study medication and the date of the last dose of study medication plus 30 d.
‡ One participant died by overdose; however, the reason for death was noted as possible suicide. Therefore, the participant is included in this table as a suicide during follow-up.

of MDD (4), these results have the potential to reduce morbidity and mortality in many smokers. Varenicline was generally well-tolerated, with the common AEs similar to those of smokers without psychiatric disorders. Depression and anxiety rating scales did not show any overall deterioration in these variables in either treatment group during treatment or at 4 weeks or fewer after treatment concluded. However, clinicians should remain vigilant when treating depressed smokers with more complex psychiatric presentations for smoking cessation.

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