Notice of correction 5/24/2012: *In the Safety and Tolerability section, the percentage for 52/84 patients has been corrected to 61.9%.*

A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Varenicline for Smoking Cessation in Patients With Schizophrenia or Schizoaffective Disorder

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ABSTRACT

Objective: Effective smoking cessation treatments are needed for patients with schizophrenia, who, compared with the general population, have high rates of cigarette smoking and more difficulty quitting. We evaluated the safety and efficacy of varenicline for smoking cessation in outpatients with stable schizophrenia or schizoaffective disorder.

Method: In this 12-week, randomized, double-blind, multicenter trial (May 8, 2008, to April 1, 2010), 127 smokers (≥ 15 cigarettes/d) with *DSM-IV*–confirmed schizophrenia or schizoaffective disorder received varenicline or placebo (2:1 ratio). The primary outcome was safety and tolerability of varenicline assessed by adverse events frequency and changes in ratings on the Positive and Negative Syndrome Scale and other psychiatric scales from baseline to 24 weeks. Abstinence was defined as no smoking 7 days prior to weeks 12 and 24, verified by carbon monoxide level.

Results: Eighty-four participants received varenicline; 43, placebo. At 12 weeks (end of treatment), 16/84 varenicline-treated patients (19.0%) met smoking cessation criteria versus 2/43 (4.7%) for placebo ($P = .046$). At 24 weeks, 10/84 (11.9%) varenicline-treated and 1/43 (2.3%) placebo-treated patients, respectively, met abstinence criteria ($P = .090$). Total adverse event rates were similar between groups, with no significant changes in symptoms of schizophrenia or in mood and anxiety ratings. Rates of suicidal ideation adverse events were 6.0% (varenicline) and 7.0% (placebo) ($P = 1.0$). There was 1 suicide attempt by a varenicline patient with a lifetime history of similar attempts and no completed suicides.

Conclusions: Varenicline was well tolerated, with no evidence of exacerbation of symptoms, and was associated with significantly higher smoking cessation rates versus placebo at 12 weeks. Our findings suggest varenicline is a suitable smoking cessation therapy for patients with schizophrenia or schizoaffective disorder.

Trial Registration: ClinicalTrials.gov identifier: NCT00644969

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The prevalence of smoking in individuals with schizophrenia or schizoaffective disorder (70%–80%) is higher than in the general population (~ 20%),[1] and they exhibit greater nicotine intake per cigarette[2] and greater severity of nicotine dependence.[3,4] Unsurprisingly, smoking-related cardiovascular and respiratory diseases contribute markedly to reduced life expectancy.[5,6] Smoking cessation rates are also lower in individuals with schizophrenia or schizoaffective disorder than in the general population,[7,8] even when nicotine replacement therapy[9] or sustained-release (SR) bupropion is used.[10–12] Therefore, this population requires more effective cessation therapies.

Varenicline tartrate is a selective, partial agonist that binds $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors[13] with lower efficacy than nicotine, simultaneously preventing nicotine binding. Several trials demonstrate that varenicline is an efficacious smoking cessation aid,[14,15] increasing quit rates nearly 3-fold versus placebo and by 50% versus bupropion-SR.[16–18] Postmarketing case reports indicated a possible association between varenicline and neuropsychiatric symptoms (depressed mood, psychosis, agitation, suicidal behavior/ideation).[19] However, the contribution of varenicline is unclear, because smoking cessation, with or without treatment, causes nicotine withdrawal symptoms that can be difficult to distinguish from those of psychiatric conditions.[20] Moreover, higher rates of lifetime psychiatric illnesses in smokers versus nonsmokers complicate interpretation of some neuropsychiatric adverse events.[7] Furthermore, nicotine dependence is known to be a significant risk factor for suicide.[21] Post hoc analyses of neuropsychiatric safety data from 10 placebo-controlled studies[22] and the United Kingdom General Practice Research Database[23] lend little support to a causal relationship between varenicline and neuropsychiatric adverse events. Although there is a published case report of 1 individual who experienced clinical worsening of schizophrenia while taking varenicline,[24] other reports indicate good tolerability with no clinical worsening.[25–30]

The primary objective of this study was to assess the safety and tolerability of varenicline through measurement of adverse-event frequency and changes in ratings on the Positive and Negative Syndrome Scale (PANSS)[31] and other psychiatric scales from baseline to 24 weeks in stable outpatients with schizophrenia or schizoaffective disorder who wished to stop smoking. Second, efficacy measures were used to assess smoking cessation and reduction.

METHOD

Study Design

This randomized, double-blind, placebo-controlled trial was conducted at 12 research centers in the United States and Canada

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between May 8, 2008, and April 1, 2010. The study comprised a 2-week screening period, 12-week treatment period, and 12-week posttreatment follow-up period. Written informed consent was obtained from all participants. Consent forms and procedures were approved by institutional review boards at each site. The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization. The study was registered on ClinicalTrials.gov (identifier: NCT00644969).

Screening and Eligibility

Participants were outpatients aged 18–75 years with schizophrenia or schizoaffective disorder confirmed by the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition (SCID-I/P).[32] Participants smoked 15 or more cigarettes/d, had no period of smoking abstinence of over 3 months during the previous year, had a baseline motivation to quit score on the Contemplation Ladder[33] of at least 7 (indicating willingness to quit in 30 days), and were clinically stable (ie, without hospitalization/acute exacerbation and receiving psychiatric treatment for at least the past 6 months), with a total PANSS score of less than 70. Female participants of childbearing age were required to have a negative serum pregnancy test at baseline and to use birth control during the study.

Exclusion criteria included psychiatric hospitalization, serious suicidal ideation/behavior, history of drug or alcohol abuse/dependence, or clinically significant cardiovascular/cerebrovascular disease in the previous 6 months; serious/unstable medical disease; prior use of varenicline; uncontrolled hypertension; body mass index (kg/m^2) under 15 or over 38; use of another investigational drug within 30 days of baseline visit or study completion; use of other smoking cessation aids; and use of marijuana or other noncigarette tobacco products during study participation.

Study Procedures

Screening procedures included medical history, physical examination, vital signs, electrocardiogram (ECG), serum pregnancy test, blood chemistry, hematology, and urinalysis. Subjects were randomized (2:1) to varenicline or placebo (starting the evening of the baseline visit) and were stratified according to antipsychotic medication type (typical vs atypical). Patients taking a combination of typical and atypical agents were included in the atypical stratum. The sample size (varenicline, n = 80; placebo, n = 40) was based on enrollment feasibility and was considered adequate for assessing safety in this population. Although assessment of efficacy was not a primary consideration, we estimated that a sample size of 120 participants would be sufficiently large to detect a between-group difference in 7-day point prevalence of abstinence rates for a medium effect size.[10,11]

Participants were asked to cease smoking completely on the target quit date (8 days following baseline visit). The 12-week treatment period included weekly clinic visits for safety and efficacy assessments and smoking cessation counseling (≤ 30 minutes), during which cigarette and other tobacco use since the previous contact and over the previous 7 days, vital signs, expired carbon monoxide, and changes in concomitant medications were assessed. Study drug was discontinued at the week-12 visit. A 12-week follow-up period ensued, with clinic visits at weeks 13, 16, 20, and 24, supplemented with brief telephone contact at weeks 14, 18, and 22. All follow-up sessions assessed tobacco use and included brief (≤ 10 minutes), one-to-one smoking cessation counseling, tailored to individual needs.[34] Whenever possible, counseling was conducted by the same counselor to add value. Spontaneously reported adverse events (from randomization through 30 days after the last dose of study medication) were recorded during each weekly visit. Neuropsychiatric adverse events were collected to week 24.

Clinical Points

- Individuals with schizophrenia exhibit high rates of smoking and more difficulty with quit attempts compared with the general population, and effective smoking cessation treatments are needed.
- Varenicline has proven efficacy for smoking cessation in the general population; however, postmarketing reports have revealed neuropsychiatric symptoms in some patients.
- The findings of this study suggest that varenicline may be a well-tolerated and efficacious smoking cessation therapy for patients with schizophrenia or schizoaffective disorder.

Assessments

Nicotine dependence was assessed at screening using the Fagerström Test for Nicotine Dependence.[35] Expired carbon monoxide levels were assessed; participants took a deep breath, held it for 10 seconds, and exhaled into a hand-held carbon monoxide monitor (Vitalograph Inc, Lenexa, Kansas). Psychotic symptom severity was assessed with the PANSS,[33] which captures positive and negative symptoms of schizophrenia and general psychopathology. Extrapyramidal signs associated with antipsychotic medication were assessed with the Simpson-Angus Rating Scale.[36] The Columbia Suicide Severity Rating Scale (C-SSRS) was used to assess suicidal thinking and behavior; answers were mapped to Columbia Classification Algorithm of Suicide Assessment codes.[37] Global assessment of functioning was determined at baseline using the 7-point Clinical Global Impressions-Severity of Illness scale (CGI-S; higher scores correspond to greater severity).[38] The CGI-Improvement scale (CGI-I) was utilized at all subsequent visits for comparison with the CGI-S score from the prior visit. The PANSS, Simpson-Angus Rating Scale, C-SSRS, CGI-S, and CGI-I were completed at baseline and at all clinic visits. As a secondary objective, self-reported smoking cessation and reduction of cigarette use were assessed by timeline follow-back verified with expired carbon

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monoxide. The study was blinded to subjects, sponsors, investigators, and raters.

Study Medication

Varenicline dosing began with a 1-week titration period comprising one 0.5-mg oral tablet/d (evening) on days 1–3 of week 1, followed by two 0.5-mg tablets/d (1 morning, 1 evening) for the next 4 days. From the week 2 to the week 12 visit, patients took two 1-mg tablets daily (1 morning, 1 evening). Subjects were asked to return blister packs at each visit. A dosing record and drug accountability form was completed. Reasons for missed doses and/or patterns of missed doses were incorporated into counseling.

Outcome Measures and Statistical Methods

The primary analysis was safety, including general safety (assessed by adverse events and changes in physical examination, ECG, clinical laboratory measures), changes in psychiatric symptoms or illness severity, and suicidal ideation. Secondary outcomes included 7-day point prevalence of abstinence at weeks 12 and 24, verified by a carbon monoxide measure of 10 ppm or less. An intention-to-treat approach was used for all analyses.

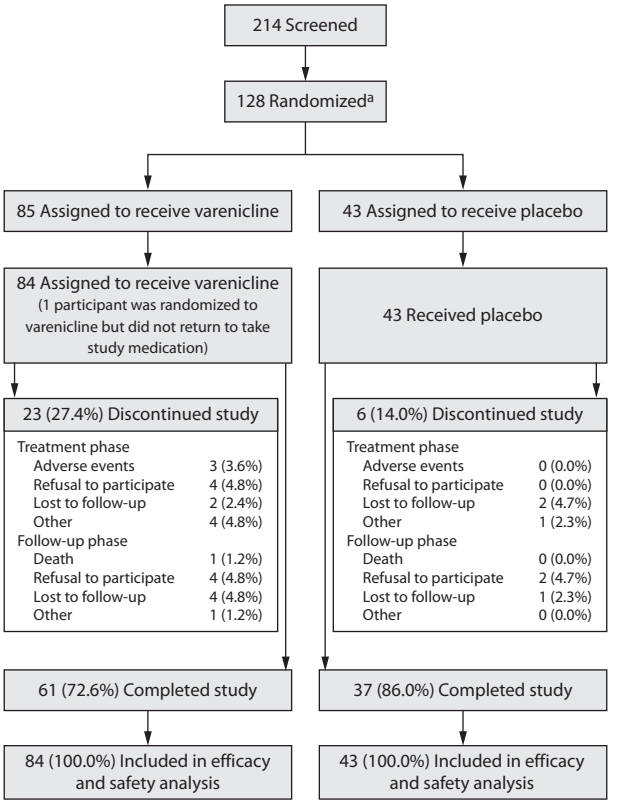
Reduction of smoking in patients who did not meet abstinence criteria was determined by assessment of participants with a 50% or greater reduction from baseline in mean number of cigarettes/d over the past 7 days at weeks 12 and 24 and change from baseline in mean number of cigarettes/d over the previous 7 days at weeks 12 and 24. Seven-day point prevalence of abstinence and 50% or greater reductions were analyzed using a logistic regression model with strata, region, and treatment arm as factors. Treatment arms were compared using the χ^2 test. Change from baseline in mean number of cigarettes/d was assessed by using analysis of covariance, with baseline value, treatment group, stratum, and study site region included in the model. Treatment differences were analyzed by using the Wald test. Comparison of demographic characteristics and adverse event rates was performed by Fisher exact test or Wald test as appropriate. Statistical tests were 2-tailed, and differences were considered significant when $P < .05$. While P values are provided, they should be interpreted with caution because of the small sample size and lack of adjustment for multiplicity, which can result in incorrect conclusions regarding risk by increasing the likelihood of false-positive outcome when many risks are evaluated or by failing to identify a real risk due to lack of statistical power.

RESULTS

Patient Disposition

Patient disposition is shown in Figure 1. In total, 128 patients were randomized; 127 received 1 or more doses of study medication and were reported as the intention-to-treat sample. Patients lost to follow-up were counted as smokers. Study discontinuation rates were 27% and 14% in the varenicline and placebo groups, respectively. Overall, 98 of 127 patients completed the study, with no statistically significant difference between the treatment groups (varenicline, 73%; placebo, 86%; $P = .12$).

Figure 1. Patient Disposition



[a]Eighty-six patients were excluded for the following reasons: medical problem/abnormal laboratory value (n = 21); substance abuse/positive urine toxicology screen (n = 16); clinically unstable at screening (n = 11); body mass index requirement not met (n = 8); taking an excluded medication (n = 4); absence of SCID-I/P diagnosis of schizophrenia or schizoaffective disorder (n = 4); smoking less than 15 cigarettes/d or using other tobacco products (n = 4); and other reasons, including no longer interested (n = 18).

Abbreviation: SCID-I/P = Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition.

Baseline Characteristics

There were no significant differences between treatment groups in baseline smoking variables (Table 1). All patients except 1 were receiving antipsychotic medications (84%, atypical). No significant differences were detected between groups on most illness characteristics, including psychiatric diagnosis, symptom severity, or antipsychotic medication type. Most patients were mildly or moderately ill according to CGI-S, and more than half had a lifetime history of suicidal ideation/behavior, as assessed by the C-SSRS. A slightly higher proportion of patients in the varenicline group had a positive lifetime history of suicidal ideation/behavior versus the placebo group.

Safety and Tolerability

A similar proportion of patients reported adverse events during the treatment phase (and within 30 days of the last dose) in both treatment groups (varenicline, 86.9%; placebo,

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Table 1. Baseline Participant Characteristics and Smoking History

Characteristic	Varenicline (n = 84)	Placebo (n = 43)
Male sex, n (%)	65 (77.4)	33 (76.7)
Age, mean (SD), y	40.2 (11.9)	43.0 (10.2)
Race, n (%)		
White	50 (59.5)	25 (58.1)
African American	25 (29.8)	13 (30.2)
Asian	4 (4.8)	2 (4.7)
Other	5 (6.0)	3 (7.0)
BMI (kg/m^2), mean (SD)	30 (4.6)	28.7 (4.8)
Current psychiatric diagnosis, n (%)		
Schizophrenia	59 (70.2)	32 (74.4)
Schizoaffective disorder	25 (29.8)	11 (25.6)
Atypical antipsychotic use, n (%)	74 (88.1)	35 (81.4)
PANSS score, mean (SD)		
Positive	13.4 (3.2)	13.5 (4.2)
Negative	14.8 (4.1)	14.8 (5.0)
Total	55.9 (9.5)	54.5 (10.7)
CGI-S, n (%)		
Normal	1 (1.2)	0 (0.0)
Borderline	3 (3.6)	3 (7.0)
Mild	34 (40.5)	19 (44.2)
Moderate	44 (52.4)	21 (48.8)
Marked	2 (2.4)	0 (0.0)
Severe	0 (0.0)	0 (0.0)
Extreme	0 (0.0)	0 (0.0)
C-SSRS		
Lifetime suicidal ideation and behavior, n (%)	52 (61.9)	22 (51.2)
Smoking history		
Age of first smoking, mean (range), y	16.0 (8–28)	17.8 (9–40)
No. of years smoking, mean (range)	23.7 (2–48)	24.9 (3–44)
FTND score, mean (SD)	6.6 (1.7)	6.3 (1.6)
Baseline carbon monoxide level, mean (SD), ppm	23.9 (12.9)	27.8 (13.2)
Cigarettes/d, mean (range)	23.5 (15–50)	22.3 (15–50)
Lifetime serious quit attempts (any method), n (%)		
None	5 (6.0)	3 (7.0)
1	19 (22.6)	9 (20.9)
2	17 (20.2)	4 (9.3)
≥ 3	43 (51.2)	27 (62.8)

Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions-Severity of Illness scale, C-SSRS = Columbia Suicide Severity Rating Scale, FTND = Fagerström Test for Nicotine Dependence, PANSS = Positive and Negative Syndrome Scale.

Table 2. Adverse Events Reported in 5% or More of Patients in Either Treatment Group

Adverse Event	Varenicline (n = 84), n (%)	Placebo (n = 43), n (%)
Gastrointestinal disorders	40 (47.6)	16 (37.2)
Abdominal pain upper	7 (8.3)	1 (2.3)
Diarrhea	7 (8.3)	2 (4.7)
Nausea	20 (23.8)	6 (14.0)
Vomiting	9 (10.7)	4 (9.3)
General disorders and administration site conditions	15 (17.9)	9 (20.9)
Fatigue	5 (6.0)	2 (4.7)
Irritability	5 (6.0)	3 (7.0)
Infections and infestations	16 (19.0)	5 (11.6)
Upper respiratory tract infection	6 (7.1)	1 (2.3)
Metabolism and nutrition disorders	6 (7.1)	4 (9.3)
Decreased appetite	2 (2.4)	3 (7.0)
Musculoskeletal and connective tissue disorders	9 (10.7)	6 (14.0)
Back pain	3 (3.6)	3 (7.0)
Nervous system disorders	24 (28.6)	10 (23.3)
Headache	9 (10.7)	8 (18.6)
Psychiatric disorders	31 (36.9)	14 (32.6)
Abnormal dreams	6 (7.1)	4 (9.3)
Anxiety	4 (4.8)	4 (9.3)
Depression	4 (4.8)	3 (7.0)
Insomnia	8 (9.5)	2 (4.7)
Suicidal ideation	5 (6.0)	3 (7.0)

83.7%). Those adverse events reported in 5% or more of patients in either treatment group are shown in Table 2. The most common adverse events in participants taking varenicline versus placebo were nausea (23.8% vs 14.0%, $P = .25$), headache (10.7% vs 18.6%, $P = .27$), and vomiting (10.7% vs 9.3%, $P = 1.00$). No significant difference was shown between the varenicline and placebo groups in permanent study discontinuation due to adverse events (13.1% vs 9.3%, respectively; $P = .77$) or neuropsychiatric adverse events (36.9% vs 32.6%, respectively; $P = .70$; insomnia, abnormal dreams, anxiety, and suicidal ideation were most frequently reported). A total of 13 serious adverse events was reported by 10 patients (varenicline, 9; placebo, 4). In the varenicline group, 2 patients had 3 serious adverse events considered related to the study drug. One patient with depression and suicidal ideation had a prior lifetime suicide attempt by overdose and was hospitalized after 6 days of study dosing; no additional treatment was prescribed, and he was discharged the next day. Another patient with a history of 4 prior suicide attempts overdosed and suffered a seizure for which he was hospitalized. No treatment-related serious adverse events were reported in the placebo group. There was 1 death during the post-therapy follow-up period that was unrelated to study treatment (accidental drowning 51 days after last dose of varenicline). There were no clinically significant changes in ECG or laboratory results in either group.

Total, positive, and negative PANSS scores remained stable or slightly decreased from baseline to weeks 12 and 24 in both groups, indicating no worsening of psychotic symptoms (Figure 2). There was no significant difference between treatment groups in the number of patients who experienced a 10% or greater change in PANSS scores during the study (week 12: varenicline, 8.8% [n = 6]; placebo, 10.2% [n = 4]). At week 12, forty-four percent of patients had an improvement in PANSS scores compared with baseline (varenicline, n = 30; placebo, n = 17).

In both treatment groups, the majority (> 75%) of patients had no change in CGI-I score from baseline to week 12 or 24. Only 1.9% had worsening on the CGI-S at week 12 (varenicline, 1.4%; placebo, 2.6%). To account for patients who discontinued the study, PANSS, CGI-I, and CGI-S score change analyses were repeated using last-observation-carried-forward methodology. The results (not shown) were similar to those above. Mean Simpson-Angus Rating Scale scores decreased modestly from baseline to weeks 12 and 24 in both the placebo (1.14, 1.10, and 0.76, respectively; mean changes = −0.10 and −0.29) and the varenicline (1.45, 1.03, and 0.97, respectively; mean changes = −0.42 and −0.37) groups, suggesting an improvement in extrapyramidal signs, although overall scores were low throughout the study.

Suicidal ideation adverse events in the treatment phase (and 30 days after last dose) were reported in 5 and 3 subjects in the varenicline and placebo groups,

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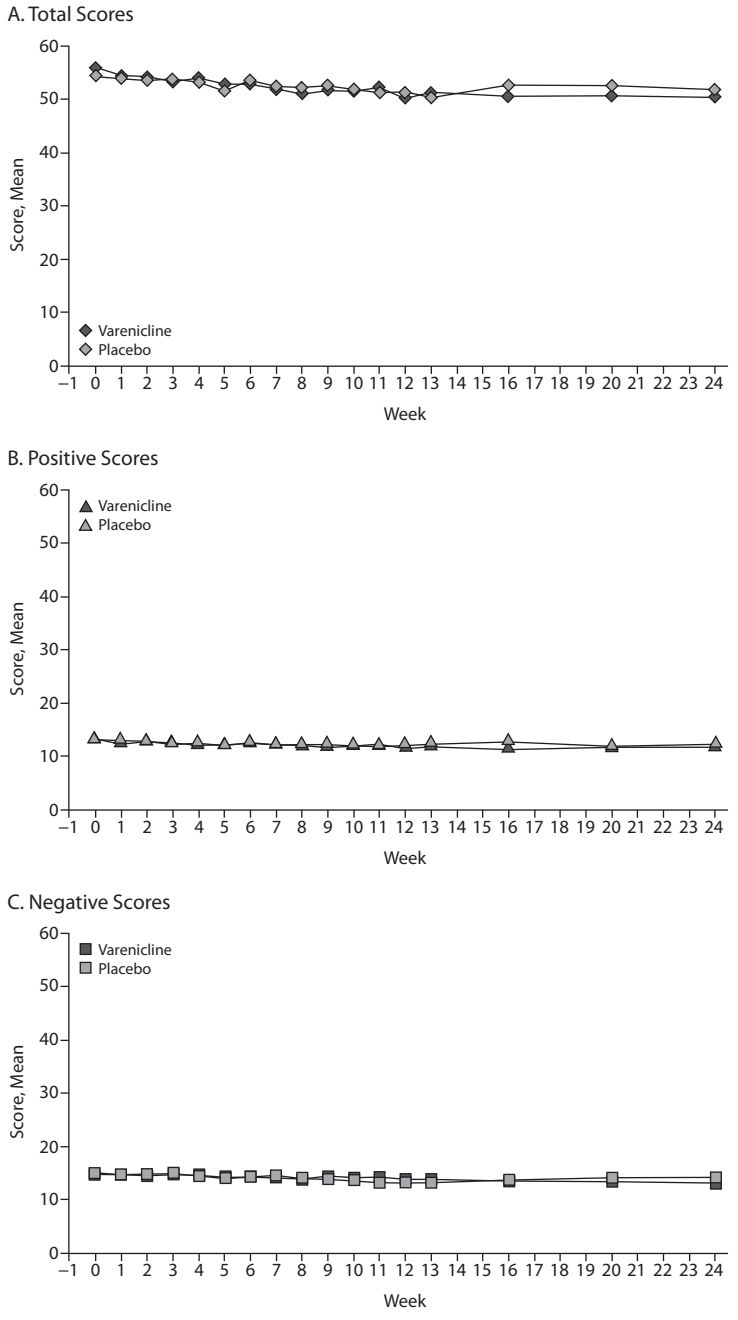
Figure 2. Mean PANSS Scores (total and subscale) by Week



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

respectively (overall figures: 6.0% and 7.0%; $P = 1.0$). In addition, 1 suicide attempt adverse event was reported in the varenicline group. There were no completed suicides. Responses on the C-SSRS captured more instances of ideation because not all yes answers were considered adverse events by the investigators or they occurred outside of the time frame for reporting. History of lifetime suicidal behavior/ideation on the C-SSRS was reported in 61.9% (52/84) and 51.2% (22/43) of patients in the varenicline and placebo groups, respectively. At baseline, no patients in the varenicline arm and 2.4% (1/42) in the placebo arm had suicidal ideation/behavior. During the treatment phase, these figures were 11.0% (9/82) and 9.3% (4/43), respectively ($P = 1.0$). All patients reporting suicidal ideation had a positive history of prior suicidal ideation or attempt on the C-SSRS. In the placebo group, fewer patients with C-SSRS data answered yes during the follow-up phase than the treatment phase (5.1% vs 9.3%, respectively). There was no difference in the proportion of patients in the varenicline group experiencing suicidal ideation/behavior during the treatment versus follow-up phase (11.0% vs 11.4%, respectively); 6 subjects had yes answers for the first time during the follow-up period (in all instances, more than 30 days after the last treatment dose). The subject who made a suicide attempt during treatment with varenicline (and whose lifetime history included several similar attempts) did not report any yes answers on the C-SSRS completed 1 day prior to the attempt. No clear pattern was shown between smoking status and suicidal ideation/behavior. Some, but not all, patients had periods of smoking abstinence when they reported suicidal thoughts or behaviors, making interpretation in this small sample complex.

Efficacy Results

A statistically significantly higher percentage of patients randomized to varenicline versus placebo abstained from smoking at week 12 (7-day point prevalence of abstinence: 19.0% vs 4.7%, respectively; $P = .046$). At week 24, a numerical but not a statistically significant difference favoring varenicline was shown (11.9% vs 2.3%, respectively; $P = .090$; Figure 3). During the treatment phase, 7-day point prevalence of abstinence was higher every week for the varenicline group. Although initially low (weeks 1–3), 7-day point prevalence of abstinence increased to 11.9% at week 4 (vs 2.3% for placebo) and remained stable (15%–20%) during weeks 5–12. In patients who did not meet 7-day point prevalence of abstinence criteria, similar trends were observed in mean number and change from baseline in average number of cigarettes/d. Although patients in both groups reduced their cigarette consumption from baseline, a statistically significant reduction was shown in favor of the varenicline group at week 12 (least squares means = −13 vs −9.7, respectively; difference = −3.2 [95% CI, −6.1 to −0.4], $P = .030$), but not week 24. There was a trend for more patients in the varenicline versus placebo group to have a 50% or greater reduction in the number of cigarettes/d at week 12 (73% vs 54%, respectively, $P = .090$). Nonabstainers in both groups had reduced levels of end expiratory carbon monoxide at week 12, but the difference was not statistically significant (least squares means = −11.0 vs −7.1, respectively; difference = −3.9 [95% CI, −8.6 to 0.8], $P = .105$).

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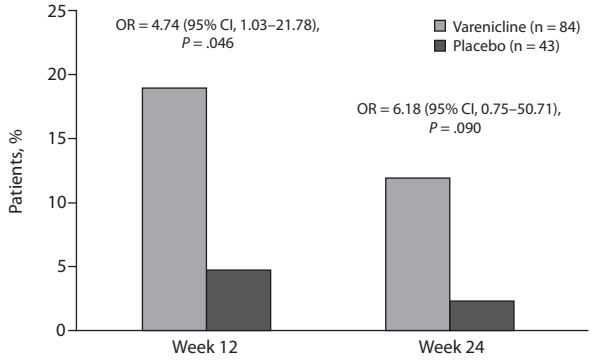
Figure 3. Seven-Day Point Prevalence of Abstinence From Smoking at Weeks 12 and 24[a]



[a]The analysis population was the intention-to-treat population except the 1 patient who was randomized to varenicline but did not receive treatment.
Abbreviation: OR = odds ratio.

DISCUSSION

In this double-blind, placebo-controlled trial evaluating the safety and efficacy of varenicline in smokers with schizophrenia or schizoaffective disorder, cessation rates for varenicline at 12 weeks were less than half those reported in phase 3 trials in nonpsychiatric smokers,[14,15] and those for placebo were approximately one-third. The observed odds ratios at 12 and 24 weeks (~5.0) are comparable with varenicline phase 3 trials and with studies of bupropion-SR in patients with schizophrenia,[17] suggesting that varenicline is an effective cessation aid in smokers with these disorders. This study also demonstrates the safety of varenicline in smokers with stably treated schizophrenia or schizoaffective disorder; no significant changes in symptoms and no evidence of clinical worsening were observed. The overall tolerability of varenicline was favorable, although *P* values should be interpreted with caution due to the relatively small sample size and lack of adjustments for multiplicity. Fewer reports of nausea were recorded in this population compared with other varenicline studies.[17] The exact interpretation of this finding is unknown, but nausea events may have been less frequently reported because of antiemetic properties of antipsychotic medications.[39] Reports of insomnia, abnormal dreams, irritability, and anxiety were common in both groups, suggesting that these events were associated with nicotine withdrawal symptoms and/or the process of trying to quit smoking. The rates of suicidal ideation reported as adverse events or captured by C-SSRS during the treatment phase were similar between treatment arms. Six patients in the varenicline group reported suicidal ideation solicited by the C-SSRS for the first time during the follow-up phase, more than a month after the last dose of study medication. The significance of this finding is unknown; the unequal randomization of patients reporting a higher lifetime incidence of suicidal ideation/behavior at baseline into the varenicline arm and the small sample size make interpretation difficult. Furthermore, the time between administration of the last dose and occurrence of suicidal events was relatively long, particularly considering the elimination period of varenicline (~7 days). Notably, this is one of the first smoking cessation studies to use a structured questionnaire to assess suicidal ideation at each study visit; the implications of this approach are not currently known.

In conclusion, this study provides preliminary information on the use of varenicline in patients with stably treated schizophrenia or schizoaffective disorder, with no new or significant safety risks. The results suggest that varenicline may be a well-tolerated, efficacious aid for smoking cessation in smokers with psychiatric illness and add to the growing literature on the potential utility of this first-line treatment in mentally ill populations.

Drug names: bupropion (Zyban and others), varenicline (Chantix).
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Study investigators: The authors would also like to thank the other investigators involved in this study: Charl Els, MB, ChB, MMed (Psych), Regional Mental Health Services (Capital Health), Edmonton, Alberta, Canada; Sunny Johnson, MD, Medical Research Associates, Mississauga, Ontario, Canada; Gerardo Gonzalez, MD, Department of Psychiatry, University of Massachusetts–Biotech One, Worcester, MA; Deepak Cyril D'Souza, MBBS, MD, Clinical Neuroscience Research Unit, Connecticut Mental Health Center, Yale University, New Haven, CT; Jason Dennis Baron, MD, MedLabs Research of Houston Inc, Houston, TX; Ashwin Anand Patkar, MD, Department of Psychiatry, Duke University Medical Center, Durham, NC; Cheryl Ann Oncken, MD, MPH, Department of Medicine, University of Connecticut Health Center, Farmington, CT; Kadiamada Nanaiah Chengappa, MD, Western Psychiatric Institute and Clinic, Pittsburgh, PA.
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