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Varenicline for Smoking Cessation in Bipolar Disorder: A Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Objective: Virtually no clinical trials for smoking cessation have been undertaken in bipolar disorder. Varenicline has shown efficacy for smoking cessation, but warnings about neuropsychiatric adverse events have been issued. We assessed the efficacy and safety of varenicline in euthymic bipolar subjects motivated to quit smoking.

Method: Clinically stable adult patients with *DSM-IV* bipolar disorder (n = 60) who smoked ≥ 10 cigarettes per day were randomized to a 3-month, double-blind, placebo-controlled varenicline trial and a 3-month follow-up. Study enrollment was completed from February 2010 through March 2013. Varenicline was dosed using standard titration, and smoking cessation counseling was provided to all patients. The primary outcome was defined as a 7-day point prevalence of self-reported no smoking verified by expired carbon monoxide level < 10 ppm at 12 weeks. Psychopathology and side-effects were assessed at each visit.

Results: At 3 months (end of treatment), significantly more subjects quit smoking with varenicline (n/n = 15/31, 48.4%) than with placebo (n/n = 3/29, 10.3%) (OR = 8.1; 95% CI, 2.03–32.5; $P < .002$). At 6 months, 6 of 31 varenicline-treated subjects (19.4%) remained abstinent compared to 2 of 29 (6.90%) assigned to placebo (OR = 3.2; 95% CI, 0.60–17.6; $P = .17$). Psychopathology scores remained stable. Ten serious adverse events occurred (n = 6, varenicline; n = 4, placebo). Abnormal dreams occurred significantly more often in varenicline-treated subjects (n/n = 18/31, 61.3%) than in those receiving placebo (n/n = 9/29, 31%; Fisher exact test, $P = .04$). Eight varenicline-treated and 5 placebo-assigned subjects expressed fleeting suicidal ideation, a nonsignificant difference.

Conclusions: Varenicline shows efficacy for initiating smoking cessation in bipolar patients, but medication trials of longer duration are warranted for maintaining abstinence. Vigilance for neuropsychiatric adverse events is prudent when initiating varenicline for smoking cessation in this patient population.

Trial Registration: ClinicalTrials.gov identifier: NCT01010204

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Cigarette smoking remains the leading cause of preventable morbidity and mortality in the United States.[1] A recent study[1] reported that 36.1% of adults with mental illness in the United States were current smokers compared to 21.4% of adults without mental illness. Another study[2] concluded that 44% of all cigarettes sold in the United States were smoked by people with mental illnesses. Rates of smoking among people with bipolar disorders or schizophrenia are 2 to 4 times higher than those in the general population.[2–6] In addition to being heavily addicted smokers,[7] patients with bipolar disorder have high rates of ever smoking (88.5%), or being current smokers (69%), but among the lowest rates of cessation (17%) among those with mental illness.[2,8,9] Moreover, standardized mortality rates in bipolar disorder are 2.5- to 2.7-fold higher than in the general population, with cardiovascular disorders (31%), suicide (19%), and cancer (14%) being the leading causes of death.[10] Smoking cessation offers a significant opportunity to diminish the medical burden associated with bipolar disorder.[11,12] Although persons with mental illnesses are the face of smoking in the United States, they are typically excluded from large-scale studies of smoking cessation. While medication trials of smoking cessation agents have begun in earnest for schizophrenia,[13–15] virtually none have been conducted in people with bipolar disorder.

An important question is, Which medications would be the most effective for smoking cessation in bipolar disorder? In the general population, varenicline is far more effective than placebo and bupropion for smoking cessation and relapse prevention.[16–18] In an open study,[19] nicotine replacement therapy was less effective than varenicline in a subgroup of smokers with mental illness. A bupropion trial[20] of 5 bipolar smokers provided suggestive data. Concerns about using bupropion for smoking cessation in persons with bipolar disorder include psychoses or mania induction[21–23] and drug interactions.[24] Similar to smokers with schizophrenia, people with bipolar disorder are highly addicted to nicotine[7] and thus would especially benefit from pharmacotherapies such as varenicline that have shown robust smoking cessation efficacy.[16–18] Moreover, there is recent evidence[25] that patients with bipolar disorder have reduced expression and functional abnormalities in neuronal nicotinic acetylcholine receptors (nAChR). Thus, an agent that stimulates, in part, neuronal nAChRs may be of utility for smoking cessation in these patients. Nevertheless, varenicline, a selective partial agonist that binds to $\alpha_4\beta_2$ nAChRs, has boxed warnings for neuropsychiatric adverse events, and cases of psychoses or mania induction have been reported.[26–28]

The main objectives of this study were to assess the efficacy and safety of varenicline to assist in smoking cessation among patients with bipolar disorder who were euthymic and motivated to quit smoking. We also assessed whether those patients who ceased

smoking in the treatment phase would maintain abstinence during follow-up.

- Virtually no randomized clinical trials for smoking cessation in bipolar disorder have been conducted, in spite of high prevalence of smoking and a patient group that is among the least likely to quit.
- Varenicline has shown robust efficacy for smoking cessation, but warnings about neuropsychiatric side effects have been issued.
- This early clinical trial affirms efficacy for varenicline in initiating smoking cessation among clinically stable bipolar subjects motivated to quit smoking; nevertheless, clinical vigilance toward depression and other emergent psychopathology is prudent.

Clinical Points

METHOD

Study Design and Overview

A randomly assigned, double-blind, placebo-controlled clinical trial of varenicline was conducted at outpatient clinics associated with Western Psychiatric Institute and Clinic, University of Pittsburgh, and Dubois Medical Regional Center, Dubois, both located in Pennsylvania. An investigational new drug application was submitted and approved by the US Food and Drug Administration. Institutional review boards of both hospitals approved the study, and written informed consent was obtained from all subjects. Subjects were randomized starting in February 2010, and the last patient completed the study in March 2013. The study comprised a 1- to 2-week screening period, 12-weeks of treatment, and 12 weeks of follow-up. The clinical trial was registered at ClinicalTrials.gov (identifier: NCT01010204).

Subjects

Male or female outpatients aged 18–65 years of any race with *DSM-IV* bipolar disorder (I, II, or not otherwise specified) were recruited. The diagnoses were affirmed by the Mini-International Neuropsychiatric Interview,[29] supplemented by medical records and clinicians. At study entry, the Montgomery-Asberg Depression Rating Scale (MADRS)[30] and the Young Mania Rating Scale (YMRS)[31] scores were ≤ 8; the maintenance medication for bipolar disorder was used in stable doses for ≥ 8 weeks, and, in the 6 months prior to enrollment, there was no history of psychiatric emergency room visits or hospitalization, suicidal attempts, or aggressive or violent acts. Specific smoking-associated criteria included a willingness to quit smoking in the next 30 days,[32] smoking more than 10 cigarettes per day and having expired carbon monoxide (CO) levels ≥ 10 ppm, and no use of nicotine replacement products, bupropion, or nonpharmacologic treatments for smoking cessation in the 3 months prior to study enrollment. Bupropion was exclusionary only if it was being used for smoking cessation, not if it was prescribed as an antidepressant. Current use or a history of serious adverse effects to varenicline was exclusionary. Females in the reproductive age group were required to have a negative serum pregnancy test and use birth control during the study. Uncontrolled seizure disorder, current or past (3 months) alcohol or substance dependence, and medical conditions that were considered either unstable or uncontrolled were grounds for ineligibility. Subjects receiving heparin, warfarin, lidocaine, or cimetidine were excluded, as were those with moderate to severe renal failure.

Study Procedures and Study Medications

Medical history and review of organ systems were recorded at baseline and at 12 weeks. Vital signs and medication changes (if any) were assessed at each visit. Laboratory parameters (pregnancy test, hematology and blood chemistry, urine analyses, illicit substances) were measured at screening and repeated at 12 weeks, as was an electrocardiogram. Subjects meeting all eligibility criteria proceeded to a 1:1 randomization, stratified by gender, to varenicline or placebo.

Study medications were titrated by using standard package insert guidance (www.Chantix.com), ie, varenicline (or placebo) tablet of 0.5-mg strength orally at bedtime for days 1–3, increasing to 0.5 mg morning and evening (1 mg/d) for the next 4 days. Starting week 2, the dose was increased to 1 mg twice daily (2 mg/d) for the rest of the 12 weeks. Medications for anxiety or insomnia were allowed on an as needed basis. Medications used to treat bipolar disorder or those being used to treat stable medical conditions were continued. Patients experiencing titration-related side effects were permitted to return to a lower dosage, ie, 0.5 mg twice a day (1 mg/d). Pill counts and reconciliation from visit to visit served as the measure of adherence, and study medication was stopped at 12 weeks.

Subjects picked a target quit date after reaching full dosage of study medicine: 2 mg/d. Patients unable to quit smoking were continued in the trial.

Assessments

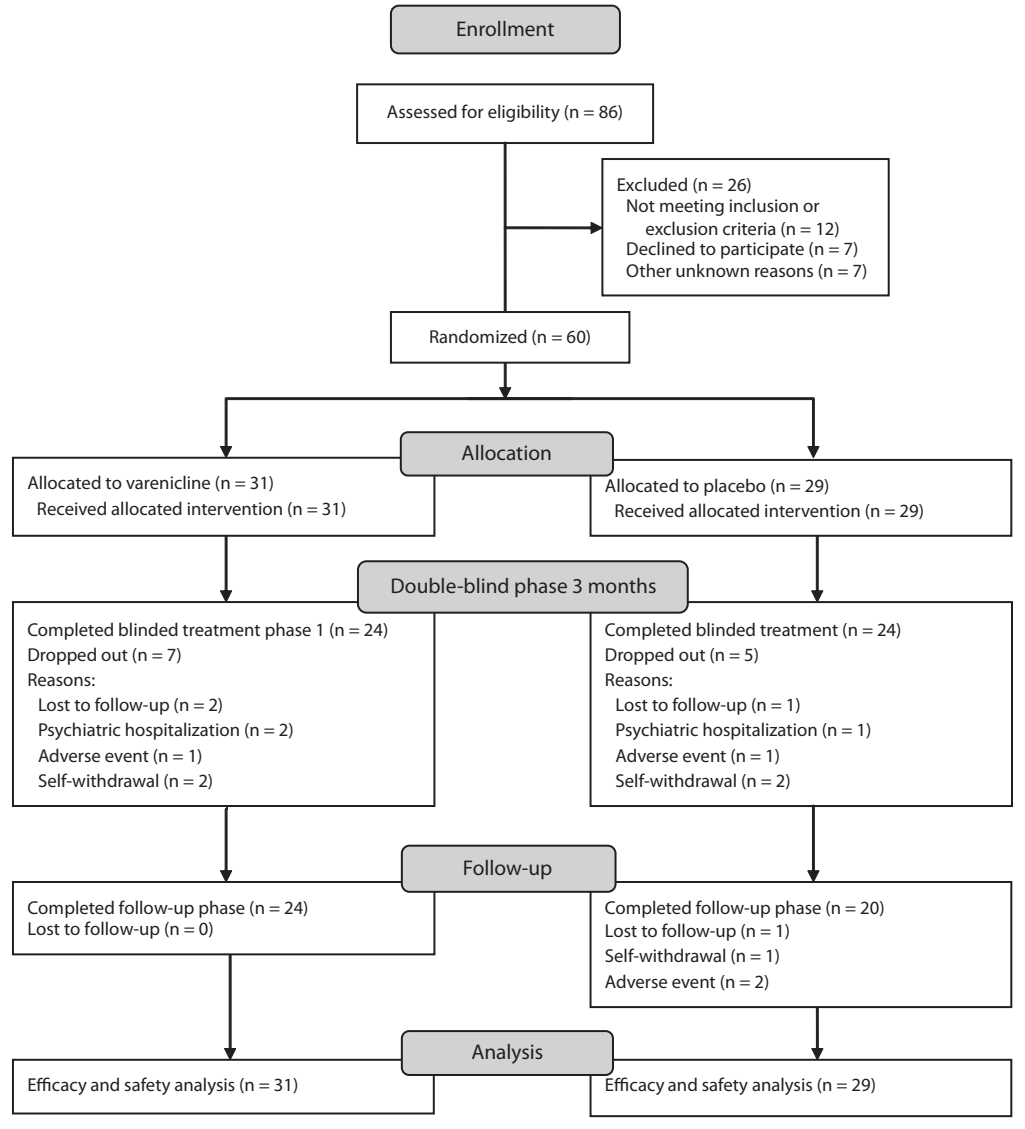
A tobacco use history form was completed at baseline, as was the Fagerström Test for Nicotine Dependence (FTND)[33] to assess the severity of tobacco addiction. Expired CO levels were assessed at every visit. Subjects were instructed to take a deep breath, hold it for 10 seconds, and exhale into a hand-held CO meter (Vitalograph Inc; Lenexa, Kansas). At each visit, mood, anxiety symptoms, illness severity, and suicidal thinking and behavior were evaluated using the MADRS, YMRS, Hamilton Anxiety Rating Scale (HARS),[34] Clinical Global Impressions Scale (CGI),[35] and Columbia Suicide Severity Rating Scale (C-SSRS).[36]

Interrater reliability was established for the MADRS, YMRS, and CGI scales prior to study initiation. Raters were trained to administer the C-SSRS in an earlier study.[15] The treatment assignment was blinded to participating subjects, raters, investigators, and statisticians.

Smoking Cessation Counseling

Fifteen minutes of each visit was utilized for smoking cessation counseling. Prior to study initiation, training for

Figure 1. Patient Disposition in Study



the smoking cessation counseling for the research staff was provided by 1 of the investigators (M.D.L.) based on a prior publication[37] detailing cognitive-behavioral counseling steps.

Data Safety and Monitoring Board

The data safety and monitoring board (DSMB) met via telephone conference calls held monthly. For adverse events or serious adverse events (SAEs), the chair and members of the DSMB took decisions regarding the severity of the event and made causality determinations on relationship of the adverse event or SAE to the study medication without knowledge of the assigned treatment.

Statistical Methods and Outcome Measures

In the absence of controlled clinical trial data for smoking cessation in bipolar patients, we used treatment effects (Φ coefficient) from 2 studies[13,14] that used bupropion for smoking cessation in schizophrenia to estimate a sample size (0.30 to 0.40; ie, medium effects). Sixty subjects with bipolar disorder motivated to quit smoking were expected to provide at least a similarly sized treatment effect with varenicline.

The primary efficacy outcome measure was the initiation of abstinence, defined as a 7-day point prevalence of self-reported no smoking verified objectively by expired CO levels < 10 ppm[13,15] at 12 weeks. An additional smoking outcome at 12 weeks was 4 weeks of continuous abstinence (ie, 4 consecutive weeks of self-reported no smoking verified by expired CO < 10 ppm). We also evaluated whether those who ceased smoking at 12 weeks would maintain abstinence at 24 weeks. Also assessed were treatment-emergent adverse events and SAEs between treatments. Subjects who stopped study participation for any reason were considered as continuing smokers.

An intention-to-treat with the last-observation-carried-forward approach was utilized for data analyses. The Fisher exact test was used to determine statistically significant

Table 1. Demographics, Illness, Treatment, and Smoking Characteristics

Variable	Varenicline (n = 31)	Placebo (n = 29)
Age, mean (SD), y	45.7 (10.3)	46.2 (8.5)
Gender, n		
Male	9	10
Female	22	19
Race, n		
White	20	21
African American	11	8
Bipolar diagnosis, n		
I	26	23
II	3	2
NOS	2	4
Age at onset of first episode, mean, (SD), y	25.9 (9.3)	23.9 (11.6)
No. of lifetime psychiatric hospitalizations, mean (SD)[a]	6.7 (7.6)	6.9 (7.4)
Psychotic symptoms in past episodes, n[a]		
Yes	13	9
No	16	16
Lithium/valproate/lamotrigine/carbamazepine, n (%)	21 (67.7)	16 (55.2)
Second-generation antipsychotic agents, n (%)	21 (67.7)	23 (79.3)
Antidepressants, n (%)	25 (80.6)	18 (62.1)
Lifetime suicidal ideation and behavior, n (%)	30 (96.8)	24 (82.8)
Smoking characteristics		
Age began smoking daily, mean (SD), y	15.7 (3.6)	15.2 (4.7)
Years smoked, mean (SD), y	29.4 (11.5)	29 (10.9)
Lifetime serious quit attempts, mean (SD)	4.8 (7.7)	4.3 (3.1)
Current no. of cigarettes/d, mean (SD)	18.1 (6.2)	18.2 (8.3)
Fagerström Test Score for Nicotine Dependence, mean (SD)	6.4 (1.7)	5.9 (1.9)
Smoking the first cigarette within 5 minutes of waking up, n (%)	20 (64.5)	17 (58.6)
Baseline expired carbon monoxide level, mean (SD), ppm	27.2 (13.5)	25.4 (13.1)

[a]Data not available in all subjects.

differences between treatments in the categorical smoking outcomes, ie, abstinent versus continued smoking, as well as treatment differences in SAEs, adverse events, and suicidal ideation and behavior as assessed by the C-SSRS. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to compute associations between treatments and quitting smoking. Statistical tests were 2-tailed and considered significant at $P < .05$.

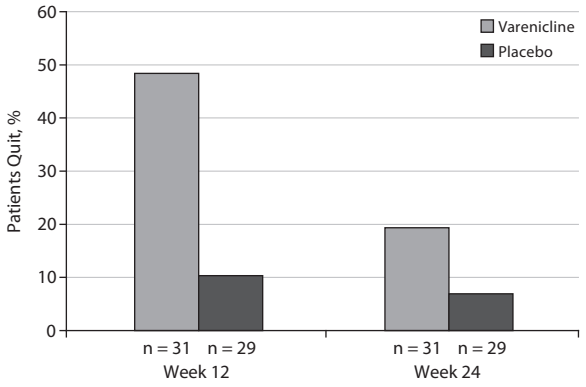
Changes from randomization to end of study in continuous measures (YMRS, MADRS, HARS, and CGI) between treatment groups were assessed with a mixed-model analysis of variance using general linear models. These analyses included 3 time points: baseline, end of week 12 or the end of the active treatment, and week 24 or the last observation at the end of the follow-up. In cases where assumptions of sphericity were violated (a significant Mauchly test), the Huynh-Feldt correction was applied. Similar analyses were used to evaluate changes in vital signs and body weight.

RESULTS

Participant Characteristics

As noted in Figure 1, 86 subjects were screened, and 60 were randomized to varenicline (n = 31) or placebo (n = 29). Forty-eight subjects (80.0%) completed 12 weeks of treatment; 24 (77.4%) varenicline- and 20 (69.0%) placebo-assigned subjects completed the entire study, with no statistically significant differences between treatments. None of the demographic, illness, or treatment characteristics differed significantly between the 2 treatment groups (Table 1). Study subjects comprised a cohort in their 40s, the majority with bipolar I disorder, with approximately 7 lifetime hospitalizations and treated with combinations of medicines. Patients had high baseline lifetime rates of suicidal ideation and/or behavior, with 54 of 60 subjects (90%) endorsing these items on the C-SSRS, with no significant differences between treatment groups. Patients represented a highly addicted group of smokers, as indicated by their smoking characteristics. None of these smoking characteristics differed significantly between treatments (Table 1).

Figure 2. Seven-Day Prevalence of Abstinence From Cigarette Smoking at Weeks 12 and 24[a]



[a]Significant difference was found between groups at 12 weeks (Fisher exact test, $P < .002$) but not at 24 weeks ($P = .26$).

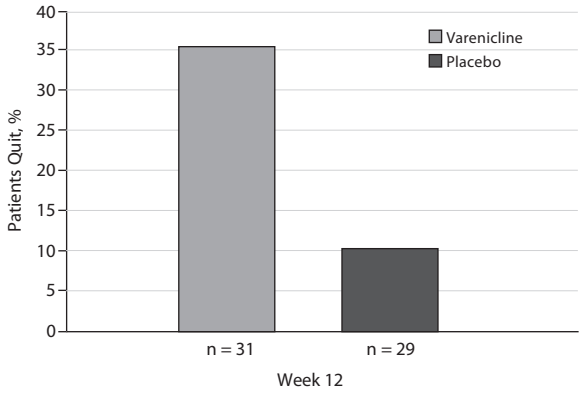
Abstinence Outcomes

On the primary study outcome, at the end of treatment (12 weeks), significantly more varenicline-treated subjects quit smoking (n/n = 15/31, 48.4%) than those assigned to placebo (n/n = 3/29, 10.3%) (OR = 8.13; 95% CI, 2.03–32.53; $P < .002$; Figure 2). The size of the treatment effect was computed as Φ coefficient = 0.415, estimated $P = .001$, number needed to treat = 3 (95% CI, 2–6). At the end of treatment, significantly more varenicline-treated patients (n/n = 11/31, 35.5%) met the 4-week continuous abstinence outcome compared with placebo-assigned subjects (n/n = 3/29, 10.3%) (OR = 4.77; 95% CI, 1.02–25.13; $P = .032$; Figure 3).

At 6 months, 6 of 31 varenicline-treated subjects (19.4%) remained abstinent compared to 2 of 29 subjects (6.9%) assigned to placebo (OR = 3.2; 95% CI, 0.60–17.6; $P = .17$). Among the quitters, 9 of 15 varenicline-treated and 1 of 3 placebo-assigned subjects had relapsed to smoking (Figure 2).

Eight patients (of 60) were treated with bupropion for depression associated with bipolar disorder and had received this medication for several months; 4 were randomized to varenicline, and 4 were allocated to placebo. Among the quitters (n = 18), 3 of 15 varenicline-treated subjects received bupropion, and 1 of 3 placebo-assigned patients received bupropion (Fisher exact test, $P = .45$).

Figure 3. Four Weeks of Continuous Abstinence From Cigarette Smoking at 12 Weeks[a]



[a]Significant difference was found between groups (Fisher exact test, $P = .03$).

There were no statistically significant differences at baseline in either the mean cigarette usage within the last week or the expired CO levels between the 2 treatment groups. By the end of treatment, both groups showed substantial decreases in mean cigarette usage, with an approximately 84% decrease in the varenicline group and a 69% decrease in the placebo group. Similarly, CO levels decreased by approximately 70% in the varenicline group and by 42% in the placebo group. Neither difference was statistically significant.

Adherence as computed by reconciling pill counts at scheduled visits indicated a high rate of adherence, ranging from 87.8% to 100%, with no significant differences between those who received varenicline versus placebo, or those who quit versus those who did not.

Adverse Events

There were 10 SAEs reported during the study: 6 occurred in patients receiving varenicline, and 4 occurred in placebo-assigned subjects (see Supplementary eTable 1 at PSYCHIATRIST.COM). Eight SAEs (varenicline = 5, placebo = 3) occurred during the 12-week treatment phase, 2 SAEs (varenicline = 1, placebo = 1) occurred in the follow-up phase. Seven events were considered "unlikely" to be related to study medicine by the DSMB, and 3 were considered "possibly related" to study medicine (varenicline = 2, placebo = 1); details are provided in Supplementary eTable 1.

Abnormal dreams were reported at significantly higher rates in the varenicline-treated group versus those receiving placebo (Fisher exact test, $P = .04$), and a similar trend was noted for depressed mood (Fisher exact test, $P = .08$; Table 2); none of the other adverse events occurred at significantly different rates between treatments.

During the course of the study, depressed mood was recorded in 10 subjects: 8 received varenicline and 2 were assigned to placebo (Supplementary eTable 2 has details). Depressed mood was experienced by 7 subjects treated with varenicline during the 12-week treatment period and by 1 subject during the follow-up; 4 of 8 subjects met criteria for an episode of major depression and were treated with medication or psychotherapy. The severity of depression and its relationship to study drug were determined by the DSMB. Among the 2 placebo-assigned subjects, depressed mood occurred during the treatment period in 1 subject and during follow-up in the other; 1 subject met criteria for major depression and the dosage of lamotrigine was increased. Three varenicline-treated subjects had quit smoking when depressed mood occurred, and neither of the placebo-assigned subjects had quit.

During the trial, the C-SSRS scale identified 8 instances of suicidal ideation in the varenicline group compared to 5 in the placebo group, and, in every case, patients had experienced such ideation in their lifetime history. Three instances of suicidal ideation recorded as adverse events (varenicline = 2; placebo = 1) were spontaneously reported (Table 2), and, in each subject, suicidal ideation was also identified by the C-SSRS. One placebo-assigned subject experienced suicidal behavior that led to an SAE; details are provided in Supplementary eTable 1.

Table 2. Adverse Events Reported at ≥ 5% in Either Treatment Group

Adverse Event	Varenicline (n = 31), n (%)	Placebo (n = 29), n (%)
Gastrointestinal disorders		
Diarrhea	2 (6.5)	3 (10.3)
Constipation	7 (22.6)	5 (17.2)
Dry mouth	9 (29.0)	9 (31.0)
Flatulence	11 (35.5)	11 (37.9)
Vomiting	3 (9.7)	6 (20.7)
Nausea	13 (41.9)	9 (31.0)
Dyspepsia (heartburn)	7 (22.6)	6 (20.7)
Abdominal pain	6 (19.4)	6 (20.7)
Gastroesophageal reflux	7 (22.6)	2 (6.9)
Psychiatric disorders		
Depressed mood[a]	8 (25.8)	2 (6.9)
Anxiety	2 (6.5)	0
Mood swings	2 (6.5)	1 (3.4)
Insomnia	14 (45.2)	8 (27.6)
Abnormal dreams[b]	18 (58.0)	9 (31.0)
Suicidal ideation	2 (6.5)	1 (3.4)
Nervous system disorders		
Somnolence	2 (6.5)	1 (3.4)
Headache	11 (35.5)	12 (41.4)
Dizziness	2 (6.5)	1 (3.4)
Bad taste	4 (12.9)	2 (6.9)
Musculoskeletal/connective tissue disorders		
Arthralgia/pain	2 (6.5)	2 (6.9)
General disorders		
Fatigue/lethargy	8 (25.8)	5 (17.2)
Asthenia/weakness	1 (3.2)	4 (13.8)
Respiratory disorders		
Rhinorrhea/runny nose	6 (19.4)	6 (20.7)
Shortness of breath	4 (12.9)	1 (3.4)
Skin manifestations		
Rash	3 (9.7)	2 (6.9)
Metabolism and nutrition		
Increased appetite	7 (22.6)	6 (20.7)
Decreased appetite	8 (25.8)	6 (20.7)
Weight gain	2 (6.5)	2 (6.9)
Weight loss	2 (6.5)	1 (3.4)
Renal and urinary disorder		
Urinary tract infection	2 (6.5)	0

[a]Trend between treatments: Fisher exact test, $P = .08$.
[b]Significant difference between treatments: Fisher exact test, $P = .04$.

Table 3. Psychopathology Rating Scale Scores

	Baseline		12 Weeks		24 Weeks	
Scale	Varenicline, Mean (SD) (n = 31)	Placebo, Mean (SD) (n = 29)	Varenicline, Mean (SD) (n = 31)	Placebo, Mean (SD) (n = 28)	Varenicline, Mean (SD) (n = 24)	Placebo, Mean (SD) (n = 22)
MADRS	4.4 (3)	3.1 (2.6)	4 (4.9)	3.3 (4.2)	2.1 (3.2)	1.5 (2)
YMRS	2.4 (2)	2 (2)	1.6 (1.7)	1.6 (2.2)	1.1 (1.5)	1.1 (1.9)
HARS	4.1 (5.2)	4.7 (6.8)	3.5 (2.9)	4.2 (5.7)	3.0 (3.8)	2.1 (2.4)
CGI-Severity of Illness	3.3 (0.6)	3.1 (0.6)	3.2 (0.8)	3.3 (0.5)	3.2 (0.8)	3.1 (0.4)

Abbreviations: CGI = Clinical Global Impressions Scale, HARS = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

Psychopathology and Vital Signs

As a group, the rating scale scores for depression, mania, anxiety, and overall severity reflected a bipolar patient group that was euthymic at study entry and remained stable throughout the study period regardless of treatment assignment (Table 3).

Blood pressure, pulse, respiration, and body temperature remained stable throughout the study, and electrocardiogram and laboratory results did not raise clinical concerns. The mean weight gain from study entry to the end of the follow-up phase was approximately 6 pounds in each treatment arm (Supplementary eTable 3).

DISCUSSION

Although 2 small, controlled studies,[20,38] each with 5 bipolar smokers, have suggested that bupropion or varenicline may be effective for smoking cessation in bipolar disorder, to our knowledge, this is the first adequately powered controlled trial of varenicline in bipolar disorder. Our results affirm the efficacy of varenicline as a smoking cessation aid in outpatients with bipolar disorder who are euthymic. Perhaps surprisingly, these 12-week smoking cessation rates with varenicline in bipolar patients compare favorably to smokers without psychiatric disorders[16,17] and are more than twice that reported in another highly addicted group of smokers: people with schizophrenia.[15] The rates of relapse to smoking after the end of treatment among those given varenicline suggest that a longer duration (≥ 6 months) of varenicline treatment may be required to maintain abstinence in bipolar patients.

The dropout rate in the current 24-week study was 23% in the varenicline arm and 31% among the placebo-assigned subjects. In a multisite smoking cessation study[15] in schizophrenia that used varenicline, a comparable dropout rate was noted in the varenicline arm (27%), whereas the placebo dropout rate was lower (14%). In the present study, 80% completed the 12-week treatment phase and 73% completed the follow-up, findings that are comparable to those in a bupropion study[14] for smoking cessation in schizophrenia, where 81% completed 12 weeks of treatment and 64% completed the 12-week follow-up.

In terms of SAEs, there were no significant differences between the 2 treatment groups in the present study, similar to a recent study[15] of varenicline for smoking cessation in schizophrenia. Furthermore, with the exception of abnormal dreams, there were no significant differences among treatment-emergent adverse events between treatments, including the C-SSRS items for suicidality. A trend was noted for more depressed mood–related events in the varenicline treatment group. Exploratory analyses of the baseline MADRS[30] total and item 1 scores or lifetime hospitalizations for depression did not distinguish the subjects who experienced depressed mood in this study versus those who did not. The risk of neuropsychiatric side effects with varenicline has been debated in the literature.[39–42] Although psychopathology rating scale scores were stable between groups during the trial, individual subjects experienced adverse events and SAEs, and, therefore, clinical vigilance is well advised for treatment-emergent psychiatric events when smoking cessation treatment with varenicline is considered.

Sleep disturbances characterize manic, mixed, and depressive episodes and are also reported when bipolar patients are relatively well.[43] A study[42] that assessed varenicline for smoking cessation in subjects with and without a lifetime history of depression indicated that 46.4% of those with a positive depression history reported difficulty sleeping 21 days after quitting smoking. Moreover, insomnia can complicate nicotine withdrawal and is reported by 18%–19% of subjects receiving varenicline versus 13% assigned to placebo.[44] It is therefore possible that the higher rates of insomnia reported in the placebo and varenicline groups in this study are associated with nicotine withdrawal and higher quit rates (for varenicline) and/or the disease process (bipolar disorder), which is in contrast to the lower rates of insomnia reported in a schizophrenia smoking cessation trial that utilized varenicline.[15] Attention to and management of sleep disturbances may be important during smoking cessation treatment with varenicline or bupropion in bipolar disorder.

Despite similar levels of addiction severity, it remains unclear why bipolar subjects in the present study were able to quit at more than double the rate reported in a recent varenicline study of smokers with schizophrenia.[15] Interestingly, a study of smoking topography indicated that, unlike schizophrenia patients, bipolar patients did not differ from healthy controls in either serum nicotine or cotinine levels.[45] Studies of smokers versus nonsmokers with bipolar disorder have suggested a more severe illness course, worse treatment outcomes, and greater risk of psychotic mood episodes, suicidality, and impulsivity,[5,46–48] and the smoking cohort in the present study affirm similar

illness characteristics. Cardiovascular disease, cancer, and pulmonary disorders are leading contributors to the 2- to 3-fold higher mortality rates among people with bipolar illness.[10] Two recent reports[49,50] indicate that cigarette smoking persists as the most significant public health hazard in the general population; encouragingly, however, smoking cessation at any age offered dramatic lowering of smoking-associated death rates.[51] Similarly, smoking cessation offers a significant opportunity to reverse the alarming mortality statistic in this group of patients.[11]

Limitations of the current study include the recruitment of only bipolar subjects who were relatively stable in their clinical state; moreover, the modest sample size was inadequate to test small to moderate effects for safety (eg, emergence of depressive episodes). Although the illness, treatment and smoking characteristics were balanced between treatment assignments, the present study was not powered to answer clinically important questions regarding subgroups that might benefit less or more from varenicline, eg, bipolar I versus II disorder, those receiving lithium versus other medications, and those with or without past psychotic episodes. Furthermore, important clinical questions such as the impact of smoking cessation on the clearance of medications used in bipolar disorder (eg, antipsychotic or anticonvulsant agents impacted by hepatic cytochrome enzymes) require different study designs but, nonetheless, are highly pertinent for clinical practice.

CONCLUSIONS

This study suggests that use of varenicline in smokers with bipolar disorder is promising for aiding cessation in this highly vulnerable patient population. Future research should examine better maintenance of abstinence with extended treatment (≥6 months), and results from relapse prevention studies are awaited. In highly addicted smokers, a combination of varenicline and bupropion resulted in high rates of continuous abstinence at the end of 52 weeks[52]; therefore, such combinations are worthy of consideration given the levels of addiction severity in patients with bipolar disorder.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetro, and others), cimetidine (Tagamet and others), lamotrigine (Lamictal and others), lidocaine (Xylocaine and others), lithium (Lithobid and others), varenicline (Chantix), warfarin (Jantoven and others).

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Potential conflicts of interest: **Dr Turkin** has served on the speaker's bureau of Forest, Sunovion, and Otsuka; and owns shares of Pfizer stock. **Dr George** has received investigator-initiated and contract research support from Pfizer, served as a consultant to Novartis, and received honoraria from National Institutes of Health (NIH) and American College of Neuropsychopharmacology. **Drs Chengappa, Perkins, Brar,** and **Levine,** and **Mss Schlicht** and **Hetrick** and have no financial disclosures with regards to this study.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Varenicline for Smoking Cessation in Bipolar Disorder: A Randomized, Double-Blind, Placebo-Controlled Study

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List of Supplementary Material for the article

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Supplementary eTable 1 Serious Adverse Events (SAE)								
ID	Age/ Gender/ Race	Description	Varenicline or Placebo	Relationship to Study Medicine	Study Phase	Start and Stop Dates of SAE and Outcome	Smoking Status at time of SAE	Actions Taken
102	55/F/C	Subject exposed to significant stressor (terminally ill brother in hospital). Became very anxious and requested admission to hospital. Denied suicidal/homicidal ideation. Subject had taken only 1 dose of study medication. SAE Terminology: Exacerbation of Anxiety	Varenicline	Unlikely Discussed and confirmed at DSMB meeting 03/12/10	Phase 1	03/12/2010-03/20/2010, Resolved	Smoking at same rate	Study medication stopped. Subject terminated from study and hospitalized. Discharged in 8 days with previous psychotropic medications and mirtazapine was added.
104	48/F/C	After 6 days of study medication, subject developed red, raised maculopapular rash on arms, shoulders and inner thighs. Was also receiving lamotrigine (started 3 months prior to study) SAE Terminology: Development of Rash	Varenicline	Possible Discussed and confirmed with DSMB 06/14/10	Phase 1	06/10/2010-06/14/2010, Resolved - 06/23/2010	Smoking at same rate	Study medication stopped. Subject terminated from study. Lamotrigine was discontinued
10	42/M/C	After receiving an eviction notice, subject became very agitated, began using crack cocaine, heroin, and alcohol, became hostile and expressing homicidal intentions toward roommate. Hospitalized on involuntary commitment. SAE Terminology: Agitation, hostility, alcohol abuse, drug abuse.	Varenicline	Possible Discussed and confirmed via e-mail with DSMB on 08/04/10	Phase 1	7/29/2010-08/4/2010, Resolved	Quit for 3 weeks	Study medication stopped. Hospitalized. Discharged in 6 days on previous psychotropic medication regimen.
17	53/F/C	Subject with history of asthma and COPD. Subject experienced severe breathing difficulty and was admitted to the University hospital	Varenicline	Unlikely Discussed and confirmed at DSMB meeting	Phase 1	10/12/2010-11/03/2010, Resolved	Smoking at reduced rate	Continued on study medication in the hospital and upon discharge.

Supplementary eTable 1 Serious Adverse Events (SAE)								
ID	Age/ Gender/ Race	Description	Varenicline or Placebo	Relationship to Study Medicine	Study Phase	Start and Stop Dates of SAE and Outcome	Smoking Status at time of SAE	Actions Taken
		and treated with steroids, antibiotics, and breathing treatments. SAE Terminology: Hypoxia, asthma with COPD with acute exacerbation		10/27/10				Completed study. Did not quit.
105	56/F/C	Subject contacted via phone after no show for Visit 4. Subject was incoherent and speech was slurred. Admitted to drinking vodka and unsure if she had taken more medications than prescribed. 911 (ambulance) was called and subject admitted to community hospital SAE Terminology: Hospitalization related to alcohol intoxication	Placebo	Unlikely. Discussed and determined at the DSMB meeting 12/22/10	Phase 1	12/22/2010-12/25/2010, Resolved	Smoking at same rate	Study medication stopped and subject terminated from study. Hospitalized. Discharged on previous psychiatric medication regimen.
40	24/F/C	Contacted by subject's mother that subject was experiencing tremors, heaviness in left arm and grogginess. SAE Terminology: Tremulousness, grogginess, upper left arm weakness.	Varenicline	Unlikely Discussed and determined by DSMB Meeting 06/22/2011	Phase 1	06/07/2011-06/13/2011 Resolved	Smoking at a reduced rate	Seen by emergency room MD and by endocrinology. Diagnosis - Reactive hypoglycemia. Subject withdrew from study.
46	45/F/C	Shortness of breath and worsening of asthma symptoms. Admitted to University hospital where she was treated with antibiotics; steroids and breathing treatments. SAE Terminology: Exacerbation of asthma	Placebo	Unlikely Confirmed and decision made to continue subject in study at DSMB meeting 02/29/12	Phase 1	02/25/2012-02/26/2012, Resolved	Smoking at a reduced rate	Subject continued on study medication in hospital and continued in study. Hospitalized and discharged.

Supplementary eTable 1 Serious Adverse Events (SAE)								
ID	Age/ Gender/ Race	Description	Varenicline or Placebo	Relationship to Study Medicine	Study Phase	Start and Stop Dates of SAE and Outcome	Smoking Status at time of SAE	Actions Taken
52	27/F/AA	Laboratory work done at end of treatment phase reported a positive pregnancy test (previous 3 pregnancy tests –were all negative). SAE Terminology: Pregnancy	Placebo	Unlikely Confirmed at DSMB meeting on 08/08/2012	Phase 1	08/07/2012, Resolved	Smoking at reduced rate	Study medication had already been stopped. Subject terminated from study. Subject counseled to stop smoking.
51	61/M/C	Subject hospitalized for c/o gastro intestinal complaints as well as breathing difficulty and nasal congestion. SAE Terminology: Pneumonia	Varenicline	Unlikely Discussed and confirmed at DSMB meeting 09/26/2012	Phase 2	08/23/2012-8/27/2012, Resolved	Quit for nearly 12 weeks	Patient was off study medication for 19 days. Subject continued and completed study. Hospitalized and discharged
54	51/F/AA	Subject went to the hospital after experiencing chest pain and numbness in left hand. Enzymes for myocardial infarction – negative. Pain and numbness subsided. Subject discharged next day. SAE Terminology: Chest pain, left hand numbness	Placebo	Possible Discussed and determined at DSMB meeting on 12/19/2012	Phase 2	12/16/2012-12/17/2012, Resolved	Smoking at a reduced rate	Subject was off study medication for 46 days. Subject continued in study.

Footnote: Phase 1: 12 weeks of Treatment with Varenicline or Placebo, Phase 2: Follow Up (weeks 12 through 24)

Supplementary eTable 2 – Details of Neuropsychiatric Adverse Events – Depressed Mood

ID	Rx	MADRS Baseline	MADRS Scores /Visit #s /# of Days	Episode Of Depression	Specific Rx for Depressive Episode	Quit Status	Severity	Relationship to Study Drug	Study Meds Action Taken
1	V	4	MADRS = 10 Visits 7 (to 8) # Days 11	No	No	No	1	3	1
5	V	8	MADRS = 5 to 10 Visits 10 (to 15) # Days 35	No	No	Yes	1	3	1
21	V	8	MADRS = 10 Visit 14 # Days 11	No	No	Yes	1	3	1
30	V	3	MADRS = 19 Visits 11 (to 12) # Days 14	Yes	Yes, sertraline started	No	2	3	1
40	V	2	MADRS = 18 Visits 6 (to 7) # Days 14	Yes	Yes, Duloxetine increased 60 to 90 mg	No	2	3	4
41	V	1	MADRS = 16 Visit 8 # Days 21	Yes	Yes, escitalopram added	Yes	2	3	1
42	V	8	MADRS = 19 Visits post 14 (to 17) # Days 21	Yes	Yes,↑therapy visits	No	3	3	1
45	V	4	MADRS = 15 Visits 9 (to 10) # Days 5	No	No	No	2	3	1
31	P	1	MADRS = 9 Visit 16 # Days 9	No	No	No	2	4	1
46	P	1	MADRS = 16 Visits 12(to 14) # Days 14	Yes	Yes, lamotrigine increased	No	3	3	1

V = Varenicline, P = Placebo

Severity → 1 = mild, 2 = moderate, 3 = marked
Relationship → 1 = certain, 2 = probable/likely, 3 = possible, 4 = unlikely
Action Taken → 1 = none, 2 = drugs decreased, 3 = drugs stopped temp, 4 = drugs stopped permanently

Supplementary eTable 3 – Vital Signs [a]

Vital Sign	Baseline		12 Weeks		24 Weeks	
	Varenicline Mean (SD) n = 31	Placebo Mean (SD) n= 29	Varenicline Mean (SD) n = 29	Placebo Mean (SD) n = 25	Varenicline Mean (SD) n = 23	Placebo Mean (SD) n = 20
Blood Pressure						
Systolic (mm/hg)	126.2 (15.3)	125.00 (17.9)	123.4 (11.5)	119.6 (13.4)	123.7 (11.8)	128.9 (12.7)
Diastolic (mm/hg)	80.2 (9.6)	79.0 (8.6)	79.4 (8.2)	78.6 (11)	78.7 (8.8)	79.6 (8.6)
Resting Pulse (beats/min)	79.2 (8.1)	75.5 (10.2)	82.8 (9.4)	78.1 (12.3)	82.6 (9.3)	81.6 (11.5)
Respiratory Rate (rate/min)	18.5 (4)	18.8 (2.2)	18.7 (2)	18.2 (1.9)	19.0 (1.9)	18.7 (1.5)
Temperature (◦F)	97.8 (0.6)	98.0 (0.7)	97.7 (0.5)	97.7 (0.7)	97.5 (0.5)	97.8 (0.5)
Body Weight (lbs)	199.2 (47.4)	202.7 (42)	196.8 (47)	204.4 (44.7)	205.3 (49.6)	209 (44.7)

n = number, SD = standard deviation, [a] none of the between group treatment comparisons were statistically significant