Varenicline Augmentation in Depressed Smokers: An 8-Week, Open-Label Study

Noah S. Philip, M.D.; Linda L. Carpenter, M.D.; Audrey R. Tyrka, M.D., Ph.D.; Laura B. Whiteley, M.D.; and Lawrence H. Price, M.D.

Objective: To assess possible antidepressant effects of varenicline augmentation in outpatients with treatment-resistant depressive disorders and nicotine dependence.

Background: Varenicline is a nicotinic acetylcholine receptor α4β2 partial agonist and α7 full agonist approved for smoking cessation. Studies of similar compounds have suggested evidence of antidepressant effects.

Method: Eighteen patients (aged 18 to 65 years) were recruited from a general psychiatric outpatient clinic. Inclusion criteria were (1) primary Axis I depressive disorder (DSM-IV-TR criteria), (2) a stable antidepressant or mood stabilizer regimen, (3) persistent depressive symptoms despite adequate treatment, and (4) current cigarette smoking with nicotine dependence. Patients received varenicline (started at 0.5 mg daily and titrated to 1 mg twice daily) in addition to stable doses of their regular psychotropic medications. Depression symptoms, side effects, clinical global impressions, anhedonia, daily cigarette consumption, and vital signs were assessed every 2 weeks for 8 weeks. Baseline and endpoint ratings were compared, and the relationship between mood improvement and smoking cessation was examined. The primary outcome variable was mean change score in depressive symptoms as assessed by the 16-item Quick Inventory of Depressive Symptomatology–Self-Report. The study was conducted between September 2007 and March 2008.

Results: Fourteen patients (78%) completed the study; 4 discontinued due to side effects, including gastrointestinal effects (n = 3) and worsened mood/irritability (n = 1). Patients demonstrated significant improvement in depression at end point ($p < .001$), with significant improvement as early as week 2. Eight patients (44%) met criteria for categorical response, and 6 (33%) reached remission criteria; the overall effect size was large. All patients were interested in smoking cessation: 8 (44%) achieved abstinence and 9 (50%) had some reduction in smoking. Improvement in depressive symptoms was correlated with smoking cessation. There was no evidence of treatment-emergent suicidality.

Conclusion: Open-label varenicline augmentation was associated with significant improvement in mood in a small sample of outpatient smokers with persistent depressive symptoms. Larger, double-blind studies are needed to investigate potential antidepressant effects of varenicline augmentation.

Trial Registration: clinicaltrials.gov Identifier: NCT00525837

J Clin Psychiatry 2009;70(7):1026–1031

Received May 29, 2008; accepted Dec. 12, 2008. From the Mood Disorders Research Program, Butler Hospital, and the Department of Psychiatry and Human Behavior, The Warren Alpert Medical School at Brown University, Providence, R.I.

This study was supported entirely by internal, clinically generated funds at Butler Hospital.

Dr. Carpenter has received research support from the U.S. Department of the Interior, the U.S. Department of Defense, UCB Pharma, Sepracor, Pfizer, Cephalon, Cyberonics, and Medtronic; has been a consultant for Abbott, Bristol-Myers-Squibb, Cyberonics, Medtronic, Novartis, Pfizer, Wyeth, and Sepracor; and has received speaker honoraria from AstraZeneca, Pfizer, and Cyberonics. Dr. Price has received research support from the U.S. Department of the Interior, U.S. Department of Defense, UCB Pharma, Sepracor, Pfizer, Cephalon, Cyberonics, and Medtronic, and has received speaker honoraria from AstraZeneca and Jazz Pharmaceuticals. Dr. Tyrka has received research support from the U.S. Department of the Interior, U.S. Department of Defense, UCB Pharma, Sepracor, Pfizer, Cephalon, Cyberonics, and Medtronic. Drs. Philip and Whiteley have no interests to disclose.

Corresponding author and reprints: Lawrence H. Price, M.D., Butler Hospital, 345 Blackstone Blvd., Providence, RI 02906 (e-mail: Lawrence_Price_MD@Brown.edu).

Varenicline is a nicotinic acetylcholine receptor (nAChR) α4β2 partial agonist and α7 full agonist drug that was approved recently for smoking cessation. In phase III trials, varenicline attenuated "negative symptoms of nicotine withdrawal," including depression, irritability, anxiety, and sleep disturbances.[1,2] These findings raise the possibility that varenicline may have independent antidepressant effects, but evaluation of such effects has not been systematically undertaken. Clinical trials of varenicline[1,2] included patients with major depression only if they did not require treatment for their depression during the past year before enrolling in the smoking cessation program. Given that patients with depression have higher rates of nicotine use relative to non–psychiatrically ill samples,[3,4] it would be important to clarify whether varenicline has any clinically significant mood effects in smokers requiring treatment for their depression.

Several features of varenicline's pharmacology are consistent with potential antidepressant properties.

Varenicline is structurally related to the plant alkaloid cytisine, which has been found to have antidepressant effects in animal models.[5] Through its actions on α4β2 nicotinic receptors in the nucleus accumbens, varenicline could modulate dopamine neurotransmission,[6,7] dysregulation of which has been linked to the anhedonia characteristic of depression.[8,9] Other lines of evidence have also implicated nicotinic cholinergic systems in the modulation of mood in depression. For example, mecamylamine, an nAChR antagonist, has been shown to have antidepressant properties in preliminary human studies,[10,11] including a recently published placebo-controlled trial of mecamylamine augmentation in treatment-resistant depression.[12] It is important to note that varenicline, an nAChR partial agonist, has a mechanism of action different from that of the nAChR antagonist mecamylamine, and it is unclear as to how these different actions on the nAChR may influence antidepressant effects.[13]

In addition, older research suggests that nAChR modulation may have effects on the hypothalamic-pituitary-adrenal axis,[14,15] which has been strongly implicated in the pathophysiology of depression. Finally, there is a wealth of clinical data on the relationship between nicotine and depression.[4,16–18] Most recently, Hughes[19] and Wilhelm et al.[20] demonstrated that patients with a previous history of depression have a higher rate of depression after quitting smoking, suggesting that modulation of nicotinic systems may affect mood, and a single dose of transdermal nicotine has been shown to increase reward responsiveness, which may be a proxy for hedonic drive.[21]

Given these considerations, varenicline could represent a novel therapeutic approach to treat depressive symptoms in smokers with depression. On the basis of its unique pharmacodynamic profile as an nAChR partial agonist, we hypothesized that varenicline might be particularly effective in relieving symptoms in depressed smokers who had received only limited benefit from standard drugs. We undertook this study to evaluate potential antidepressant effects of varenicline when used as an augmenting agent with conventional antidepressant and mood-stabilizing agents in smokers with treatment-resistant depressive symptoms. The primary outcome variable was mean change score in depressive symptoms, as assessed by the 16-item Quick Inventory of Depressive Symptomatology—Self-Report (QIDS-SR-16).[22]

METHOD

Eighteen adult patients aged 18–65 years were recruited from outpatient clinics at a freestanding psychiatric teaching hospital primarily by poster advertisements and clinician referral. The Butler Hospital Institutional Review Board approved this open-label study, and all subjects gave voluntary written informed consent.

Patients were eligible if they had a DSM-IV-TR mood disorder with predominating depressive symptoms (current major depressive episode [unipolar or bipolar], depressive disorder not otherwise specified, dysthymic disorder, adjustment disorder with depressed mood, or substance-induced mood disorder). Other inclusion criteria were (1) a stable antidepressant or mood stabilizer regimen (i.e., no change in dosage or start/stop of new agents) for at least 6 weeks; (2) persisting depressive symptoms, defined as a QIDS-SR-16[22] score greater than 5; and (3) currently meeting criteria for nicotine (cigarette) dependence. Exclusion criteria were (1) previous adverse events related to varenicline, (2) current breast-feeding or pregnancy, or (3) serious renal disease or dialysis. The study was conducted between September 2007 and March 2008.

Patients were treated with open-label varenicline in addition to their previous medication regimen. Patients were informed that although smoking cessation could occur during the study, the primary objective was assessment of antidepressant effects, and that formal smoking-cessation counseling would not be provided during the study. In accordance with the product labeling, varenicline was started at 0.5 mg daily and titrated to 1 mg twice daily over 1 week, followed by 1 mg twice daily as tolerated for the duration of the trial. Varenicline could be decreased to 1 mg/day if patients were unable to tolerate twice daily dosing, consistent with previous clinical trials.[23,24] Patients agreed not to alter their primary antidepressant or mood stabilizing medications or doses during the trial, although study physicians (N.S.P., L.B.W.) could make changes if medically necessary to avoid significant adverse clinical outcomes. Additionally, study physicians could prescribe adjunctive low-dose benzodiazepines for anxiety or trazodone for insomnia during the trial if needed.

Patients were assessed at baseline and every 2 weeks for a total of 8 weeks. At each clinic visit, patients filled out self-report ratings, including the QIDS-SR-16 and the clinician- and patient-rated Clinical Global Impressions-Severity of Illness (CGI-S) and CGI-Improvement (CGI-I) scales.[25] Patients also filled out the Snaith-Hamilton Pleasure Scale for anhedonia[26] and the Systematic Assessment for Treatment Emergent Events (SAFTEE)[27,28] self-report side-effect scale. At each visit, treating clinicians rated CGI-S and CGI-I scales, assessed for side effects, and recorded tobacco use and use of smoking-cessation resources. Changes in smoking status were measured on the basis of the patient's report of how many cigarettes a day were smoked on average during the 2 weeks since the last study visit. Treatment-emergent side effects recorded as moderate to severe, or those side effects present at baseline that worsened at any time during the varenicline trial, were summarized with simple frequencies. Blood pressure and body mass index (BMI) were determined at each visit. When a follow-up visit could not take place at the

scheduled 2-week study assessment interval, data for that time point were obtained by telephone interviews and mailed-in questionnaires.

The primary outcome variable was mean change score on the QIDS-SR-16. Response was defined as a baseline-to-endpoint ≥ 50% improvement in QIDS-SR-16 score, and remission was defined as an endpoint QIDS-SR-16 score ≤ 5.[22] Secondary outcome variables were mean change in the clinician- and patient-rated CGI-S and Snaith-Hamilton Pleasure Scale; clinician- and patient-rated CGI-I results were reported as simple frequencies. Cigarette consumption was measured by self-report; change in cigarette use over time was analyzed using percent change from baseline in self-report of cigarettes smoked per day.

Data were analyzed on an intent-to-treat (ITT)/last-observation-carried-forward (LOCF) basis. Patients were included in the ITT analysis if they completed baseline ratings, took at least 1 dose of varenicline, and had at least 1 subsequent assessment.

To assess for within-subjects effects of repeated measures over time, a general linear model analysis was performed, followed by post hoc paired t tests to compare baseline scores to LOCF scores at each time point. Pearson correlation coefficients were calculated to evaluate the relationship between the percent change in number of self-reported cigarettes smoked daily and percent change in QIDS-SR-16 from baseline to end point. Data were analyzed with SPSS for Windows, version 11.5 (SPSS, Inc., Chicago, Ill.). All statistical tests were 2-tailed, with significance set at $p < .05$.

RESULTS

Sample characteristics are presented in Table 1. Of the 18 patients enrolled, 14 (78%) completed all 8 weeks and 4 (22%) discontinued due to side effects. Mean ± SD dose of varenicline at study end point was 1.8 ± 0.4 mg/day. There was a statistically significant change in within-subject effects over time ($F = 9.96$; $df = 4, 59$; $p < .001$), with a large effect size (partial $\eta^2 = 0.37$). There was a statistically significant improvement in the primary outcome measure, mean QIDS-SR-16 score, between baseline and LOCF end point (mean ± SD = 12.9 ± 2.8 vs. 8.2 ± 4.7, $t = 4.44$, $p < .001$) (Figure 1), with significant improvement in QIDS-SR-16 score beginning at week 2 that was sustained for the full 8 weeks. At study end point, 8 patients (44%) achieved response and 6 (33%) achieved remission. While the total sample demonstrated a mean decrease in QIDS-SR-16 score of –4.7, patients achieving response (n = 8) and remission (n = 6) demonstrated a mean decrease in QIDS-SR-16 of –8.6 and –8, respectively.

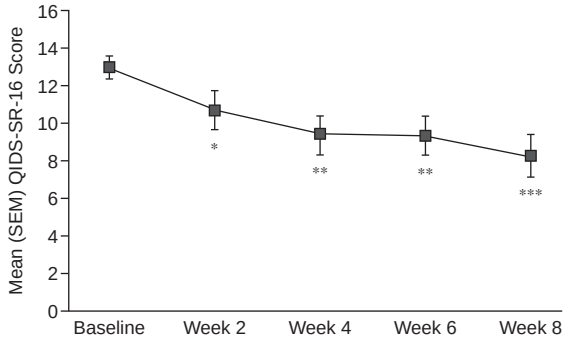
On secondary outcome measures, there was significant improvement in clinician-rated CGI-S score from

Table 1. Baseline Clinical Characteristics of Depressed Smokers (N = 18)

Characteristic	Value
Age, y	
Mean (SD)	47.8 (10.1)
Range	30–65
Gender, N (%)	
Male	6 (33.3)
Female	12 (66.7)
No. of cigarettes/day	
Mean (SD)	18.7 (16.1)
Range	10–80
Primary diagnosis, N (%)	
Major depressive disorder	12 (66.7)
Bipolar I disorder, current episode depressed	2 (11.1)
Bipolar II disorder, current MDE	1 (5.6)
Depressive disorder not otherwise specified	3 (16.7)
Comorbid diagnoses, N (%)	
Generalized anxiety disorder	7 (38.9)
Dysthymic disorder	2 (11.1)
Social phobia	3 (16.7)
Posttraumatic stress disorder	2 (11.1)
Alcohol abuse	2 (11.1)
Body mass index, kg/m^2	
Mean (SD)	29.5 (6.8)
Range	18.4–49.7
Systolic blood pressure, mm Hg	
Mean (SD)	124 (15)
Range	90–150
Diastolic blood pressure, mm Hg	
Mean (SD)	75 (10)
Range	60–90
Primary mood medication, N (%)[a]	
SSRI	8 (44.4)
SNRI	2 (11.1)
Mood stabilizer[b]	3 (16.7)
Other antidepressant[c]	5 (27.8)
Duration of primary mood medication trial, wk	
Mean (SD)	81 (104)
Range	8–350+
No. of previous primary mood medication trials	
Mean (SD)	2.3 (1.2)
Range	1–6
Adjunctive psychotropic medications/treatments, N (%)	
Antidepressants	6 (33.3)
Mood stabilizers	1 (5.6)
Atypical antipsychotics	4 (22.2)
Benzodiazepines	5 (27.8)
Other[d]	8 (44.4)
QIDS-SR-16 total score	
Mean (SD)	12.9 (2.8)
Range	8–19
Clinician-rated CGI-S score, mean (SD)	3.1 (1.1)
Patient-rated CGI-S score, mean (SD)	2.7 (1.4)

[a]Primary mood medication based on primary diagnosis (ie, mood stabilizer for bipolar disorder, antidepressant for depressive disorder). If more than 1 medication was used, the first utilized was designated as primary.
[b]Lithium, valproate, and carbamazepine.
[c]Other antidepressants included bupropion (n = 2), mirtazapine (n = 2), and amitriptyline (n = 1).
[d]Other medications/treatments included liothyronine (n = 2), gabapentin (n = 2), modafinil (n = 2), prednisone (n = 1), trazodone (n = 4), and vagus nerve stimulation (n = 1).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, MDE = major depressive episode, QIDS-SR-16 = Quick Inventory of Depressive Symptomatology–Self-Report, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Figure 1. QIDS-SR-16 Scores During Varenicline Augmentation[a]



[a]p Values for post hoc paired t tests from baseline.
*p = .049.
**p = .004.
***p < .001 (F = 9.96, df = 4,59).
Abbreviation: QIDS-SR-16 = Quick Inventory of Depressive Symptomatology–Self-Report.

Table 2. Outcome Measures (A) and Categorical Outcomes (B) for Intent-To-Treat Sample (N = 18)

A. Outcome Measure	Baseline, Mean (SD)	End Point, Mean (SD)	p Value[a]
QIDS-SR-16 score	12.9 (2.8)	8.2 (4.8)	< .001
Clinician-rated CGI-S score	3.1 (1.1)	2.1 (1.4)	.039
Patient-rated CGI-S score	2.7 (1.4)	2.2 (1.3)	.106
Snaith-Hamilton Pleasure Scale score	25.3 (6)	24.9 (7.4)	.839
No. of cigarettes smoked daily	19 (16)	6 (9)	< .001

B. Categorical Outcome	N (%)
Patients discontinuing before completion of week 8 visit	4 (22)
Patients with response (50% reduction on QIDS-SR-16 score)	8 (44)
Patients with remission (endpoint QIDS-SR-16 score ≤ 5)	6 (33)

[a]p Value for paired t test, baseline versus end point (last observation carried forward) after significant (p < .001) general linear model analysis for within-group effects.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, QIDS-SR-16 = Quick Inventory of Depressive Symptomatology–Self-Report.

baseline to study end point (mean ± SD = 3.1 ± 1.1 vs. 2.1 ± 1.4, t = 2.23, p = .039); there was significant improvement from baseline observed as early as week 4. There were no significant changes in patient-rated anhedonia or patient-rated CGI-S from baseline to end point (Table 2).

On clinician-rated CGI-I scores at end point, 10 patients (56%) showed much or very much improvement, 3 (17%) had minimal improvement, 3 (17%) demonstrated no change, and 2 (11%) had minimally worse symptoms. No patients demonstrated much or very much worse symptoms on the clinician-rated CGI-I scale.

On patient-rated CGI-I scores at end point, 7 patients (39%) reported much or very much improvement, 5 (28%) described minimal improvement, 4 (22%) had no change in symptoms, 2 (11%) described minimally worse symptoms, and 1 (6%) reported much worse symptoms. No patients reported very much worse symptoms on the patient-rated CGI-I. There were no statistically significant changes in BMI or blood pressure observed during the study.

There was a significant decrease in number of cigarettes smoked daily from baseline to end point (19 ± 16 cigarettes/day, range 10–80, vs. 6 ± 9 cigarettes/day, range 0–40, p < .001). Mean ± SD percent decrease in cigarette consumption from baseline to end point was 68% ± 33%. Percent changes from baseline to weeks 2, 4, and 6 were 44% ± 32%, 57% ± 36% and 63% ± 32%, respectively. There was a significant correlation between percent decrease in QIDS-SR-16 score and percent decrease in cigarette daily consumption from baseline at week 6 (r = 0.48, p = .042), followed by a trend-level association at week 8 (r = 0.46, p = .053). For weeks 2–4, no significant correlation was observed. Improvement in patient-rated CGI-I score also correlated with percent decrease in smoking at week 6 (r = 0.49, p = .038), followed again by a trend at week 8 (r = 0.45, p = .06).

Overall, 8 patients (44%) successfully achieved self-reported abstinence (i.e., zero cigarettes per day by study end point) from cigarette smoking during this trial, 9 (50%) had some reduction in smoking, and 1 (6%) had no change. Average duration of abstinence was 4 weeks, and all patients who achieved abstinence remained abstinent until study end point. While not objectively measured, all patients expressed an interest in smoking cessation when starting the trial. No patients used additional nicotine replacement products. One patient utilized the smoking cessation resources provided with the varenicline package insert.

Primary antidepressant or mood-stabilizing medications were not changed during the study, although lorazepam, up to 1 mg/day, or trazodone, up to 50 mg/day, was added in 3 patients (17%).

The most common spontaneously reported side effects were trouble sleeping, nightmares, or vivid dreams (n = 10, 56%); gastrointestinal complaints (n = 7, 39%); and irritability (n = 4, 22%). The most common side effects reported on the SAFTEE rating scale were irritability (n = 8, 44%), trouble sleeping (n = 7, 39%), increased appetite (n = 7, 39%), and nightmares (n = 6, 33%). Four patients (22%) required the dose of varenicline to be lowered to 1 mg/day because of gastrointestinal side effects or sedation. Of the 8 patients who demonstrated irritability on the SAFTEE, 38% (n = 3) reported these symptoms within the first 2 weeks of the trial and 50% (n = 4) within weeks 2–4 of the trial.

Four patients (22%) discontinued the study due to side effects. Of these, 3 discontinued due to gastrointestinal side effects and 1 due to irritability and worsened mood. One patient discontinued at 2 weeks, 2 patients at

4 weeks, and 1 patient at 6 weeks. The patient who discontinued at 6 weeks reported worsened mood and irritability, but did not demonstrate a change in QIDS-SR-16 score from baseline to discontinuation end point. All primary psychotropic medications taken by patients in the noncompleter group were also used by some of the study completers, except modafinil (n = 2), alprazolam (n = 1), and paroxetine (n = 1).

Given recent concerns about possible treatment-emergent depressed mood and suicidality on treatment with varenicline,[29] a post hoc analysis was performed to examine changes on the specific core QIDS-SR-16 mood and suicidality items (items 5 and 12, respectively). There was a significant improvement in core mood score from baseline to end point (mean ± SD score = 1.98 ± 0.76 vs. 1.22 ± 0.65, $t = 4.76$, $p < .001$), but no significant change in suicidality ratings during the study (mean ± SD score = 0.56 ± 0.71 vs. 0.33 ± 0.59, $t = 1.07$, $p = .30$). When data from the 4 subjects who discontinued the study were examined separately, no significant change in core mood (mean ± SD score = 2.0 ± 0.82 vs. 1.5 ± 0.56, $t = 1.73$, $p = .18$) or suicidality (mean ± SD score = 1.0 ± 0.82 vs. 0.25 ± 0.5, $t = 1.19$, $p = .32$) was seen. The 1 patient who discontinued due to report of worsened mood did not report increased suicidality.

DISCUSSION

To our knowledge, this is the first prospective trial investigating varenicline as an adjunctive treatment for primary depression. Our findings suggest that varenicline augmentation may have antidepressant properties in smokers with treatment-resistant depression. Improvement in mood was early and sustained throughout this 8-week open trial, and the effect size was large. Forty-four percent of patients achieved categorical clinical response and 33% achieved remission, with a mean decrease in depression score comparable to that reported for the second tier of the STAR*D[30] study of treatment-resistant depression. Response rates were also similar to those reported in a recent controlled study of mecamylamine augmentation.[12] The mean decrease in depressive symptoms represents a clinically meaningful improvement, reflecting a qualitative change in the severity of illness (i.e., from severe to moderate, mild to remission, etc.). The 2-fold larger decrease in depression symptom ratings in responders and remitters compared to the total sample suggests there may be a subset of patients who demonstrate robust clinical improvement on this medication. There were no significant effects observed in ratings of anhedonia as measured by the Snaith-Hamilton Pleasure Scale. While clinician- and patient-rated CGI-I scores were similar, there was a difference between clinician- and patient-rated CGI-S scores, which may reflect a bias toward rater-assessed improvement during an open-label trial.

Consistent with the data obtained in smokers without depression, varenicline augmentation had no effects on BMI or blood pressure, and there was no evidence of general intolerability when combined with standard antidepressant medications. While most patients tolerated the drug without difficulty, 3 discontinued because of intolerable gastrointestinal side effects. The present sample reported overall rates of gastrointestinal side effects that were comparable to previous trials,[1,2] suggesting that such side effects may be a limiting factor for use in this context. The most commonly reported side effect in this sample was sleep disturbance. Insomnia was reported by 44% of patients, compared with approximately 19% of patients taking varenicline in previously published clinical trial data,[1,2] suggesting an interaction between psychotropic drugs and varenicline with respect to sleep that may require further study. The fact that 2 of our 4 noncompleters were taking the stimulant modafinil is notable in this regard. Irritability developed early (i.e., within the first 4 weeks of varenicline treatment). One patient discontinued due to worsened mood or irritability, without emergent suicidality. In a post hoc analysis of mood and suicidality, we found an improvement in core mood items and no change in suicidality. While we did not specifically measure aggression or homicidality (also included in recent product safety advisories[29]), no patients demonstrated these tendencies during the study.

Improvement in mood significantly correlated with decreases in smoking on patient self-report and clinician rating scales at week 6, with near significance at week 8. This suggests that the relationship between smoking cessation and mood may be modified by varenicline, as our results are different from previous findings demonstrating worsened mood during abstinence-based smoking cessation,[19] although it should be noted that the significant mood changes observed during the first 4 weeks of the study did not correlate with smoking status. Additionally, with regard to the use of varenicline as a smoking-cessation aid, our findings are consistent with previous trials.[1,2]

This study has several limitations. Most prominently, this was an open-label trial, and the placebo effect cannot be evaluated. The open-label nature of the study may also account for some of the discrepant results between clinician- and patient-rated global severity scales. The sample size was small, which makes the results difficult to generalize to larger populations. The patient sample included only smokers, making it impossible to know whether mood effects would be different in nonsmoking populations. Other limitations of the study include diagnostic heterogeneity, use of primary psychotropic medications other than antidepressants, and a patient sample characterized by moderate baseline depression scores and low baseline suicidality scores. Lastly, the study included very few bipolar patients, whereas case reports of worsened symptoms with varenicline have focused on

patients with bipolar disorder and schizophrenia,[31–33] while other case reports have featured patients with chronic depression.[34,35]

In summary, varenicline may represent a novel agent for augmentation in smokers with treatment-resistant depression. Larger, double-blind, placebo-controlled studies in both smokers and nonsmokers are needed to better understand the possible antidepressant properties of varenicline.

Drug names: alprazolam (Xanax, Niravam, and others), bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), gabapentin (Neurontin and others), liothyronine (Triostat, Cytomel, and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), mecamylamine (Inversine), mirtazapine (Remeron and others), modafinil (Provigil), paroxetine (Paxil, Pexeva, and others), valproate (Depacon and others), varenicline (Chantix).

REFERENCES

1. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an α4β2 nicotinic acetylcholine partial agonist, vs sustained-release bupropion and placebo for smoking cessation. JAMA 2006;296(1):47–55
2. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006;296(1):56–63
3. Breslau N, Kilbey M, Andreski P. Nicotine dependence and major depression: new evidence from a prospective investigation. Arch Gen Psychiatry 1993;50:31–35
4. Breslau N. Psychiatric comorbidity of smoking and nicotine dependence. Behav Genet 1995;25(2):95–101
5. Mineur YA, Somenzi O, Picciotto M. Cytisine, a partial agonist of high affinity nicotinic acetylcholine receptors, has antidepressant-like properties in male C57BL/6J mice. Neuropharmacology 2007;52(5): 1256–1262
6. Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at α4β2 and a full agonist at α7 neuronal nicotinic receptors. Mol Pharmacol 2006;70(3):801–805
7. Rollema H, Chambers LK, Coe JW, et al. Pharmacological profile of the α4β2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. Neuropharmacology 2007;52(3): 985–994
8. Stahl SM. Symptoms and circuits, pt 1: major depressive disorder [BRAINSTORMS]. J Clin Psychiatry 2003;64(11):1282–1283
9. Nemeroff CB, Dunlop BW. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 2007;64:327–337
10. Shytle RD, Silver AA, Lukas RJ, et al. Nicotinic acetylcholine receptors as targets for antidepressants. Mol Psychiatry 2002;7:525–535
11. Shytle RD, Silver AA, Sheehan KH, et al. Neuronal nicotinic receptor inhibition for treating mood disorders: preliminary controlled evidence with mecamylamine. Depress Anxiety 2002;16:89–92
12. George TP, Sacco KA, Vessicchio JC, et al. Nicotinic antagonist augmentation of selective serotonin reuptake inhibitor-refractory major depressive disorder. J Clin Psychopharmacol 2008;28:340–344
13. Andreasen JT, Olsen GM, Wiborg O, et al. Antidepressant-like effects of nicotinic acetylcholine receptor antagonists, but not agonists, in the mouse forced swim and mouse tail suspension tests [published online ahead of print June 26, 2008]. J Psychopharmacol. doi: 10.1177/0269881108091587
14. Gilad GM. The stress-induced response of the septo-hippocampal cholinergic system: a vectorial outcome of psychoneuroendocrinological interactions. Psychoneuroendocrinology 1987;12:167–184
15. Janowsky DS, Risch SC. Cholinomimetic and anticholinergic drugs used to investigate an acetylcholine hypothesis of affective disorders and stress. Drug Dev Res 1984;4:125–142
16. Swendson JD, Merikangas KR. The comorbidity of depression and substance use disorders. Clin Psychol Review 2000;20(2):173–189
17. Wilhelm K, Arnold K, Niven H, et al. Grey lungs and blue moods: smoking cessation in the context of lifetime depression history. Aust N Z J Psychiatry 2004;38(11–12):896–905
18. Laje RP, Berman JA, Glassman AH. Depression and nicotine: preclinical and clinical evidence for common mechanisms. Curr Psychiatry Rep 2001;3(6):470–474
19. Hughes JR. Depression during tobacco abstinence. Nicotine Tob Res 2007;9(4):443–446
20. Wilhelm K, Wedgwood L, Niven H, et al. Smoking cessation and depression: current knowledge and future directions. Drug Alcohol Rev 2006;25(1):97–107
21. Barr RS, Pizzagalli DA, Culhane MA, et al. A single dose of nicotine enhances reward responsiveness in nonsmokers: implications for development of dependence. Biol Psychiatry 2008;63(11):1061–1065
22. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C) and Self Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003;54:573–583
23. Nides M, Oncken C, Gonzales D, et al. Smoking cessation with varenicline, a selective α4β2 nicotinic receptor partial agonist. Arch Intern Med 2006;166:1561–1568
24. Oncken C, Gonzales D, Nides M, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. Arch Intern Med 2006;166:1571–1577
25. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept of Health, Education and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
26. Snaith RP, Hamilton M, Morely S, et al. A scale for the assessment of hedonic tone: the Snaith-Hamilton Pleasure Scale. Br J Psychiatry 1995;167:99–103
27. Rabkin JG, Markowitz JS, Ocepek-Welikson K, et al. General versus systematic inquiry about emergent clinical events with SAFTEE: implications for clinical research. J Clin Psychopharmacol 1992;12:3–10
28. Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacol Bull 1986;22: 343–381
29. U.S. Food and Drug Administration. 2008 Safety alerts for human medical products. Dept of Health and Human Services. Feb 1, 2008. Available at: www.fda.gov/medwatch/safety/2008/safety08.htm. Accessed Feb 2008
30. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006;354(12): 1243–1252
31. Freedman R. Exacerbation of schizophrenia with varenicline [letter]. Am J Psychiatry 2007;164(8):1269
32. Kohen I, Kremen N. Varenicline induced manic episode in a patient with bipolar disorder [letter]. Am J Psychiatry 2007;164(8):1269–1270
33. Morstad AM, Kutcsher EC, Kennedy WK, et al. Hypomania with agitation associated with varenicline use in bipolar II disorder [letter]. Ann Pharmacother 2008;42:288–289
34. Popkin MK. Exacerbation of recurrent depression as a result of treatment with varenicline [letter]. Am J Psychiatry 2008;165(6):774
35. Pumariega AJ, Nelson R, Rotenberg L. Varenicline-induced mood and psychotic episode in a patient with a past history of depression. CNS Spectr 2008;14(6):511–514

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Marlene Freeman, M.D., at mfreeman@psychiatrist.com.