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

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Abstract

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

Background—Varenicline (Chantix) is a nicotinic acetylcholine receptor $\alpha 4\beta 2$ partial agonist and $\alpha 7$ full agonist approved for smoking cessation. Studies of similar compounds have suggested evidence of antidepressant effects.

Methods—Eighteen patients were recruited from a general psychiatric outpatient clinic. Inclusion criteria were 1) primary Axis I depressive disorder, 2) persistent depressive symptoms despite adequate treatment, and 3) current cigarette smoking with nicotine dependence. Patients received varenicline 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 improvement in depressive symptoms.

Results—Fourteen patients (78%) completed the study; 4 discontinued due to side effects, including gastrointestinal ($n = 3$) and worsened mood/irritability ($n = 1$). Patients demonstrated significant improvement in depression at endpoint ($p < .001$), with significant improvement as early as week 2. Eight (44%) patients met criteria for categorical response, and six (33%) reached remission criteria; the overall effect size was large. All patients were interested in smoking cessation, eight (44%) achieved abstinence, and nine (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.

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Keywords

Varenicline; Depression; Smoking

INTRODUCTION

Varenicline (Chantix) is a nicotinic acetylcholine receptor (nAChR) $\alpha 4\beta 2$ partial agonist and $\alpha 7$ full agonist drug that has been 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 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 nonpsychiatrically ill samples,^{3–4} it would be important to clarify whether varenicline has any clinically significant mood effects in smokers requiring treatment of 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 $\alpha 4\beta 2$ 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.^{16–19} Most recently, Hughes²⁰ and Wilhelm et al.²¹ 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.²²

Given these considerations, varenicline could represent a novel therapeutic approach to treat depressive symptoms in smokers with depression. Based on 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 Quick Inventory of Depressive Symptoms-Self Report (QIDS-SR16).²³

METHOD

Eighteen adult patients between the ages of 18–65 were recruited from outpatient clinics at a freestanding psychiatric teaching hospital primarily by poster advertisements and clinician referral. The Butler Hospital Institutional Review Board (IRB) 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, dysthymia, 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 Quick Inventory of Depressive Symptoms-Self Report (QIDS-SR16)²³ 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 breastfeeding 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.^{24–25} Patients agreed not to alter their primary antidepressant or mood stabilizing medications or doses during the trial, although study physicians (N.P., L.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 two weeks for a total of 8 weeks. At each clinic visit, patients filled out self-report ratings, including the QIDS-SR16, the clinician- and patient-rated Clinical Global Impressions scales for illness severity (CGI-S) and improvement (CGI-I).²⁶ Patients also filled out the Snaith-Hamilton Pleasure Scale (SHAPS) for anhedonia²⁷ and the SAFTEE^{28–29} 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, and assessed for side effects. Changes in smoking status were measured based on the patient's report of how many cigarettes a day were smoked on average during the two 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-SR16. Response was defined as a baseline-to-endpoint $\geq 50\%$ improvement in QIDS-SR16 score, and remission was defined as an endpoint QIDS-SR16 score ≤ 5 .²² Secondary outcome variables were mean change in the clinician and patient-rated CGI-S and SHAPS; 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 one 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-SR16 from baseline to endpoint. Data were analyzed with SPSS for Windows, version 11.5 (SPSS, Inc. Chicago, IL). All statistical tests were two-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 dose of varenicline at study endpoint 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 squared = .37). There was a statistically significant improvement in the primary outcome measure, mean QIDS-SR16 score, between baseline and LOCF endpoint (12.9 ± 2.8 vs. 8.2 ± 4.7 , $t = 4.44$, $p < .001$) (Fig. 1), with significant improvement in QIDS-SR16 score beginning at week 2 that was sustained for the full 8 weeks. At study endpoint, 8 (44%) patients achieved response and 6 (33%) achieved remission. While the total sample demonstrated a mean decrease in QIDS-SR16 score of -4.7 , patients achieving response ($n = 8$) and remission ($n = 6$) demonstrated a mean decrease in QIDS-SR16 of -8.6 and -8 , respectively.

On secondary outcome measures, there was significant improvement in clinician-rated CGI-S score from baseline to study endpoint (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 endpoint (Table 2).

On clinician-rated CGI-I scores at endpoint, 10 (56%) patients 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.

On patient-rated CGI-I scores at endpoint, 7 (39%) patients 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 (5%) 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 endpoint (19 ± 16 cigarettes/day, range 10–80, vs. 6 ± 9 cigarettes/day, range 0–40, $p < .001$). Mean percent decrease in cigarette consumption from baseline to endpoint was $68 \pm 33\%$. Percent changes from baseline to weeks 2, 4 and 6 were $44 \pm 32\%$, $57 \pm 36\%$ and $63 \pm 32\%$ respectively. There was a significant correlation between percent decrease in QIDS score and percent decrease in cigarette daily consumption from baseline at week 6 ($r = .48$, $p = .042$), followed by a trend-level association at week 8 ($r = .46$, $p = .053$). 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 ($r = .49$, $p = .038$), followed again by a trend at week 8 ($r = .45$, $p = .06$).

Overall, 8 (44%) patients successfully achieved self-reported abstinence (i.e. zero cigarettes per day by study endpoint) 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 endpoint. 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 (17%) patients.

The most common spontaneously reported side effects were trouble sleeping, nightmares or vivid dreams ($n = 10$, 55%), 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 (22%) patients required the dose of varenicline be lowered to 1 mg/day because of gastrointestinal side effects or sedation. Of the eight patients who demonstrated irritability on the SAFTEE, 37.5% ($n = 3$) reported these symptoms within the first two weeks of the trial, 50% ($n = 4$) within weeks 2–4 of the trial.

Four (22%) patients discontinued the study due to side effects. Of these, 3 were due to gastrointestinal side effects and 1 was 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-SR16 score from baseline to discontinuation endpoint. All primary psychotropic medications taken by patients in the non-completer 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 varenicline,³⁰ a post-hoc analysis was performed to examine changes on the specific core QIDS-SR16 mood and suicidality items (items 5 and 12). There was a significant improvement in core mood score from baseline to endpoint (1.98 ± 0.76 vs. 1.22 ± 0.65 , $t = 4.76$, $p < .001$), but no significant change in suicidality ratings during the study (0.56 ± 0.71 vs. 0.33 ± 0.59 , $t = 1.07$, $p = .30$). When data from the four subjects who discontinued the study were examined separately, no significant change in core mood (2.0 ± 0.82 vs. 1.5 ± 0.56 , $t = 1.73$, $p = .18$) or suicidality (1.0 ± 0.82 vs. 0.25 ± 0.5 , $t = 1.19$, $p = .32$) was seen. The one 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 thirty-three percent achieved remission, with a mean decrease in depression score comparable to that reported for the second tier of the STAR*D³¹ 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 two-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 SHAPS. 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 towards 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 non-completers were taking the stimulant modafinil is notable in this regard. Irritability developed early (i.e., within the first four 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 advisories³⁰), 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 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 cessation²⁰, 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, 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,^{32–34} while other case reports have featured patients with chronic depression.^{35–36}

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 non-smokers are needed to better understand the possible antidepressant properties of varenicline.

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Fig. 1.

QIDS-SR16 scores during varenicline augmentation*

QIDS -SR 16 = Quick Inventory of Depressive Symptoms, Self-Report

p values for post-hoc paired t-tests from baseline

* p = .049, ** p = .004, *** p < .001

Table 1**Baseline clinical characteristics (n = 18)**

Age (years), mean (SD); range	47.8 (10.1); 30–65
Gender, N (%)	
Male	6 (33.3)
Female	12 (66.6)
# Cigarettes/day, mean (SD); range	18.7 (16.1); 10–80
Primary Diagnosis, N (%)	
Major depressive disorder	12 (66.6)
Bipolar I, current episode depressed	2 (16.6)
Bipolar II, current major depressive episode	1 (7)
Depressive disorder not otherwise specified	3 (21)
Comorbid Diagnoses, N (%)	
Generalized anxiety disorder	7 (38.8)
Dysthymic disorder	2 (11.1)
Social phobia	3 (16.6)
Post-traumatic stress disorder	2 (11.1)
Alcohol abuse	2 (11.1)
Body mass index (kg/m ²), mean (SD); range	29.5 (6.8); 18.4–49.7
Blood pressure (mm Hg), mean (SD); range	
Systolic	124 (15); 90–150
Diastolic	75 (10); 60–90
Primary Mood Medication, N (%) ^a	
Selective serotonin reuptake inhibitor	8 (44.4)
Serotonin/norepinephrine reuptake inhibitor	2 (11.1)
Mood stabilizer (lithium, valproate, carbamazepine)	3 (16.6)
Other antidepressant ^b	5 (27.7)
Duration of Primary Mood Medication Trial, weeks	
Mean (SD); range	81 (104); 8–350 ⁺
Number of Previous Primary Mood Medication Trials	
Mean (SD); range	2.3 (1.2); 1–6
Adjunctive Psychotropic Medications/Treatments, N (%)	
Antidepressants	6 (33.3)
Mood stabilizers	1 (5.5)
Atypical antipsychotics	4 (22.2)
Benzodiazepines	5 (27.7)
Other ^c	8 (44.4)
Quick Inventory of Depressive Symptoms-Self-Report (QIDS-SR 16)	
Total score, mean (SD); range	12.9 (2.8); 8–19
Clinical Global Impression – Severity (CGI-S), mean (SD)	3.1 (1.1)
Patient-Rated Global Impression – Severity, mean (SD)	2.7 (1.4)

^aPrimary mood medication based on primary diagnosis (i.e., mood stabilizer for bipolar disorder, antidepressant for depressive disorder). If more than 1 medication was used, the first utilized was designated as primary.

^bOther antidepressants included bupropion (n = 2), mirtazapine (n = 2), amitriptyline (n = 1)

^cOther medications/treatments included lithium (n = 2), gabapentin (n = 2), modafinil (n = 2), prednisone (n = 1), trazodone (n = 4), vagus nerve stimulation (n = 1)

Table 2

Mean (SD) scores and categorical outcomes (N [%]) for intent-to-treat sample (N = 18)

	Baseline	Endpoint	p-value ^a
QIDS-SR16	12.9 (2.8)	8.2 (4.8)	<.001
Clinician-Rated CGI-S	3.1 (1.1)	2.1 (1.4)	.039
Patient-Rated CGI-S	2.7 (1.4)	2.2 (1.3)	.106
Snaith-Hamilton Pleasure Scale	25.3 (6)	24.9 (7.4)	.839
Cigarettes smoked daily	19 (16)	6 (9)	<.001
# Patients discontinuing before completion of week 8 visit		4 (22)	
# Patients with response (50% reduction on QIDS-SR16 score)		8 (44)	
# Patients with remission (endpoint QIDS-SR16 score ≤ 5)		6 (33)	

^a p-value for paired t-test, baseline versus endpoint (LOCF) after significant ($p < .001$) general linear model analysis for within-group effects

QIDS-SR16 = Quick Inventory of Depressive Symptoms, Self-Report

CGI-S = Clinical Global Impression - Severity