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# Depressive Symptoms Among Patients Receiving Varenicline and Bupropion for Smoking Cessation ☆

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ABSTRACT

While the combination therapy of varenicline and sustained release bupropion (bupropion SR) for cigarette smoking cessation can increase smoking abstinence rates, it has also been associated with increases in self-reported depressive symptoms. We conducted an analysis of the Beck Depression Inventory, second edition (BDI-II), data completed by 505 patients from a large randomized clinical trial, evaluating the efficacy of 12 weeks of combination therapy (varenicline + bupropion SR) compared to varenicline alone. At medication treatment week 2 (1 week after target quit date [TQD]), increased depressive symptoms were observed in patients receiving combination therapy (effect estimate = 0.61, 95% CI [0.03, 1.19], $P = .039$) and those with a history of depression (effect estimate = 0.82, 95% CI [0.07, 1.57], $P = .033$). For treatment weeks 2 to 4, smokers with a history of depression on combination therapy had a greater decline in depressive symptoms compared to those on varenicline alone (effect estimate = −1.99, 95% CI [−3.99, 0.00], $P = .050$). After treatment week 4, no significant effects of treatment or depression history on BDI-II scores were observed. A history of depression did not moderate the efficacy of combination therapy for smoking abstinence. Our study suggests that for combination therapy with varenicline and bupropion SR, an increase in depressive symptoms over the first 2 weeks may be observed; however, the effects on depressive symptoms do not last beyond 4 weeks. We conclude that among smokers without active moderate or severe depression, the decision to use this combination treatment approach should not be based upon a self-reported history of depression.



## 1. Introduction

Despite reductions in the prevalence of cigarette smoking in western nations over the last several decades, smoking continues to be a leading cause of preventable disease, disability, and death worldwide. Aggressive treatment approaches should continue to be explored to further reduce smoking rates.

Available evidence suggests that combination pharmacotherapy may increase smoking abstinence rates, compared to single-agent therapy. The combination treatment of bupropion sustained-release (SR)[1] and the nicotine patch has been shown to be more effective for increasing smoking abstinence than nicotine patch therapy alone (Jorenby et al., 1999). Also, the combination therapy of varenicline, a nicotinic acetylcholine receptor (nAChR) partial agonist (Coe et al., 2005), and bupropion SR is more effective than varenicline alone in promoting prolonged smoking abstinence among heavier and more dependent smokers (Ebbert et al., 2014). However, participants receiving combination therapy with bupropion SR and varenicline reported higher rates of depressive symptoms compared to participants randomized to varenicline alone (3.6% vs. 0.08%; $P = .03$). Adverse events were unprompted and self-reported, but these data raised important questions regarding the emergence of mood symptoms with the use of combination pharmacotherapy in patients attempting to quit smoking.

In order to evaluate the effect of combination pharmacotherapy on depressive symptoms among motivated smokers attempting to quit, we performed an analysis of depression scores from our clinical trial of combination pharmacotherapy with varenicline and bupropion SR.

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[1] Abbreviations: nAChR, nicotinic acetylcholine receptor; BDI-II, Beck Depression Inventory, second edition; SR, sustained release; TQD, target quit date.

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We sought to determine whether: 1) combination therapy worsens objective measures of depressive symptoms in smokers attempting to quit, and 2) combination therapy leads to different rates of prolonged abstinence among those with and without a history of depression.

## 2. Methods

### 2.1. Study overview

Data were collected from participants in a randomized, double-blind, placebo-controlled, multicenter clinical trial (Ebbert et al., 2014). This study evaluated the efficacy of combination therapy with bupropion SR and varenicline compared to varenicline and placebo in 506 cigarette smokers. Of these, 505 provided depression information. Eligible subjects were adult smokers without active moderate or severe depression or other active psychiatric illness, who had not previously attempted suicide, and who were not actively abusing other substances. A history of depression was self-reported at baseline visit. Specifically, the survey asked study participants, "Have you ever been diagnosed and or treated for depression? Yes/No." Participants with BDI-II scores in the moderate to severe range (score > 20) were excluded. Participants were randomized to varenicline and bupropion SR or varenicline and matching bupropion SR placebo. The medication was started the day after the baseline visit (week 0), and the target quit date (TQD) was on the eighth day of therapy. Both medication groups received treatment for a total of 12 weeks.

### 2.2. Depression assessment

The Beck Depression Inventory, second edition (BDI-II) (Beck, Steer, & Brown, 1996) was used to assess depressive symptoms. Each question on the BDI-II is scored 0, 1, 2, or 3 with higher total scores indicating more severe depressive symptoms. The BDI-II was administered at baseline and then at regular intervals during the medication phase (weeks 2, 4, and 8) and during the follow-up phase (weeks 14 and 26).

### 2.3. Statistical analysis

Baseline subject characteristics were compared across treatment arms (varenicline + bupropion SR vs. varenicline + placebo) and history of depression (depression vs. no depression) using 2-way analysis of variance (ANOVA) for continuous variables and binary or multinomial logistic regression for categorical variables. Post-baseline BDI-II scores were analyzed using analysis of covariance (ANCOVA), with treatment (varenicline + bupropion SR vs. varenicline + placebo) and history of depression (depression vs. no depression) as explanatory variables and baseline BDI-II score included as a covariate. An initial analysis that included all follow-up scores was performed using mixed linear models to account for the multiple post-baseline measures within subjects. Supplemental analyses were performed separately for each follow-up time point. Prolonged smoking abstinence at the end of treatment (week 12) was analyzed using logistic regression. Previous analyses from this trial have found that the effect of combination treatment varied with heaviness of smoking and was more effective for heavier smokers (Ebbert et al., 2014). Therefore, in addition to an overall analysis, the end-of-treatment abstinence outcome was analyzed separately for light (≤19 cigarettes per day [cpd]) and heavy (≥20 cpd) smokers. In all cases, two-tailed tests were used, with $P$ values ≤ .05 denoting statistical significance.

## 3. Results

### 3.1. Participant characteristics

Of the 506 study participants, 505 provided depression history information. Of these, 101 reported a history of depression. Treatment assignment was well balanced among those with depression (n = 50, varenicline + bupropion SR; n = 51, varenicline + placebo) and those without depression (n = 198 varenicline + bupropion SR; n = 206 varenicline + placebo). Baseline demographics and smoking history are presented in the Table 1, according to depression history and treatment assignment. Gender ($P < .001$) and marital status ($P = .029$) differed significantly between those with and without a history of depression; participants with a history of depression were more likely to be female and less likely to be married. No other characteristics differed significantly between depression groups, and no characteristics differed significantly between treatment groups.

### 3.2. BDI-II scores

Baseline BDI-II was significantly higher ($P < .001$) in those with a history of depression, but was similar between the treatment groups ($P = .198$). Mean BDI-II scores over time are presented in our Fig. 1, according to depression history and treatment. There were 470 (93%) participants who completed at least one post-baseline BDI-II assessment during the 6 month period following the start of medication. Of these 470, 7 had a BDI-II score ≥20, indicating moderate or severe depression at some point between baseline and 26 weeks. Of these, 2 (1 varenicline + bupropion SR, 1 varenicline + placebo) had a history of depression, the other 5 (3 varenicline + bupropion SR, 2 varenicline + placebo) did not.

From an overall repeated measures analysis of post-baseline BDI-II scores, a significant ($P = .045$) treatment-by-depression-by-visit interaction effect was detected. For this reason, subsequent analyses were performed separately for each time period. For these analyses, the BDI-II score was the independent variable, while a history of depression and treatment assignment were the explanatory variables, and the baseline BDI-II score was a covariate. Two weeks after the start of medication (1 week after the TQD), significant main effects were detected for both history of depression (effect estimate = 0.82, 95% CI [0.07, 1.57], $P = .033$) and treatment (effect estimate = 0.61, 95% CI [0.03, 1.19], $P = .039$), indicating that both a history of depression and the combination therapy were associated with an increase in depressive symptoms. At week 4, a significant ($P = .032$) treatment-by-depression interaction was detected, indicating that the effect of combination treatment on the change in depressive symptoms was dependent on depression history.

Supplemental analyses were performed for each depression group to compare the change in BDI-II scores between treatment groups from week 2 to week 4. Among those with a history of depression, the change in BDI-II from week 2 to week 4 differed significantly between treatment groups. Participants with a history of depression receiving combination therapy experienced a significantly greater decline in depressive symptoms compared to those receiving varenicline alone (effect estimate = −1.99, 95% CI [−3.99, 0.00], $P = .050$). Among those without a history of depression, the change in BDI-II from week 2 to week 4 was similar between treatment groups (effect estimate = −0.19, 95% CI [−0.80, 0.43], $P = .55$). After week 4, there were no significant effects of treatment assignment or depression history on BDI-II scores.

### 3.3. Abstinence rates

We assessed abstinence rates overall, as well as separately, for light and heavy smokers. In all cases, there was no evidence to suggest that a history of depression moderated the efficacy of combination treatment (treatment-by-history of depression interaction $P = .305$, .210, and .637 for overall, light, and heavy smokers, respectively). Among participants without a history of depression, prolonged smoking abstinence rates at week 12 were 53.7% with combination therapy and 37.5% with varenicline monotherapy among heavy smokers and 61.0% and 53.5% among light smokers, respectively. Among participants with a history of depression, heavy smokers had prolonged smoking