Depressive Symptoms and Smoking Cessation After Hospitalization for Cardiovascular Disease

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Background: Although smoking cessation is essential for prevention of secondary cardiovascular disease (CVD), many smokers do not stop smoking after hospitalization. Mild depressive symptoms are common during hospitalization for CVD. We hypothesized that depressive symptoms measured during hospitalization for acute CVD would predict return to smoking after discharge from the hospital.

Methods: This was a planned secondary analysis of data from a placebo-controlled, double-blind, randomized trial of bupropion hydrochloride therapy in 245 smokers hospitalized for acute CVD. All subjects received smoking counseling in the hospital and for 12 weeks after discharge. Depressive symptoms were measured during hospitalization with the Beck Depression Inventory (BDI), and smoking cessation was biochemically validated at 2-week, 12-week, and 1-year follow-up. The effect of depressive symptoms on smoking cessation was assessed using multiple logistic regression and survival analyses.

Results: Twenty-two percent of smokers had moderate to severe depressive symptoms (BDI ≥16) during hospitalization. These smokers were more likely to resume smoking by 4 weeks after discharge (P = .007; incidence rate ratio, 2.40; 95% confidence interval, 1.48-3.78) than were smokers with lower BDI scores. Smokers with low BDI scores were more likely to remain abstinent than were those with high BDI scores at 3-month follow-up (37% vs 15%; adjusted odds ratio, 3.02; 95% confidence interval, 1.28-7.09) and 1-year follow-up (27% vs 10%; adjusted odds ratio, 3.77; 95% confidence interval, 1.31-10.82). We estimate that 27% of the effect of the BDI score on smoking cessation was mediated by nicotine withdrawal symptoms.

Conclusions: Moderate to severe depressive symptoms during hospitalization for acute CVD are independently associated with rapid relapse to smoking after discharge and lower rates of smoking cessation at long-term follow-up. The relationship was mediated in part by the stronger nicotine withdrawal symptoms experienced by smokers with higher depressive symptoms.

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symptoms were less likely to quit smoking. However, to our knowledge, there are no data demonstrating that depressive symptoms measured during a hospital stay predict relapse to smoking after discharge from the hospital.

The purpose of this study was to determine the effect of depressive symptoms measured during hospitalization for acute CVD on the likelihood of quitting smoking after discharge from the hospital. We hypothesized that smokers with depressive symptoms during hospitalization would be more likely to resume smoking during the year after hospital discharge compared with smokers without depressive symptoms. We also explored whether treatment with bupropion hydrochloride was more effective for smoking cessation in smokers with depressive symptoms compared with those without depressive symptoms.

METHODS

We performed a planned secondary analysis of data from a randomized, double-blind, placebo-controlled trial that tested the safety and efficacy of sustained-release bupropion, a smoking cessation aid and antidepressant, when added to cognitive-behavioral counseling for smoking cessation in smokers hospitalized for acute CVD. The methods have been described in detail elsewhere. Subjects were randomly assigned to receive sustained-release bupropion or identical placebo for 12 weeks. All subjects participated in a multicomponent cognitive-behavioral smoking cessation and relapse prevention counseling program that began during hospitalization and was continued by telephone 5 times after discharge (at 2 days and at 1, 3, 8, and 12 weeks). Subjects were recruited from 5 hospitals. Institutional review boards at each site approved the study, and all study participants provided written informed consent. An external data safety and monitoring board monitored the trial.

PARTICIPANTS

We recruited patients admitted for acute CVD who were 18 years old or older, who had smoked 1 cigarette or more in the past month, and who had an expected stay of more than 24 hours. Eligible admission diagnoses included acute coronary syndromes (myocardial infarction or unstable angina), coronary artery bypass graft surgery, or other cardiovascular conditions in subjects with documented coronary artery disease. Subjects were excluded if they were unwilling to consider smoking cessation. Other reasons for exclusion included a contraindication to bupropion therapy, risk of seizure, an in-hospital blood pressure higher than 160/100 mm Hg, heavy alcohol use (>3 drinks per day or binge drinking), severe hepatic or renal disease, major depression, psychosis, cognitive impairment, or lack of access to a telephone.

MEASUREMENTS

Depressive symptoms were assessed at baseline and at 2-, 4-, and 12-week follow-ups using the Beck Depression Inventory (BDI), a 21-item self-report scale for assessing depressive symptoms. Total scores range from 0 to 63. In patients with medical illness, a score of 16 or higher indicates moderate to severe depressive symptoms. For the main analyses, we categorized smokers into 2 groups: those with a BDI score of 16 or higher (BDI) and those with a BDI score lower than 16 (low BDI). We also performed some analyses categorizing smokers by BDI scores 10 or higher and lower than 10 to determine whether including smokers with mild depressive symptoms produced similar results.

Smoking cessation was measured as 7-day point-prevalence tobacco abstinence (no smoking in the previous 7 days) at 2 weeks, 3 months, and 1 year after hospital discharge. Self-reported abstinence was validated by expired carbon monoxide at 2 weeks and by saliva cotinine concentration at 3 months and 1 year. Subjects were considered smokers if they were unavailable for follow-up or failed to provide a carbon monoxide or cotinine sample. Subjects having an expired carbon monoxide level greater than 8 ppm at 2 weeks or a saliva cotinine concentration greater than 20 ng/mL (to convert to nanomoles per liter, multiply by 0.331) at 3 months or 1 year were considered to be smoking.

Duration of abstinence after discharge was determined by a subject’s self-reported date of having the first cigarette after discharge from the hospital. During the first 4 weeks, smoking status was assessed at nurse counseling calls placed 2 days, 1 week, 2 weeks, and 4 weeks after discharge. If the subject did not know the exact date or was lost to follow-up, we made a conservative estimate, using the day after the last date of validated abstinence.

Nicotine withdrawal symptoms were assessed at baseline with the Minnesota Nicotine Withdrawal Scale. Smokers rated the severity of 10 symptoms during the last 24 hours using a scale of 0 (not present) to 3 (severe). The symptoms assessed in the scale included irritability/anger, impatience, anxiety, difficulty concentrating, restlessness, excessive hunger, trouble sleeping, depressed mood, craving, and physical symptoms (tremor, racing heart, sweating, or bowel problems). The distribution of withdrawal scores was not normally distributed, and we applied a square root transformation of this measure in all analyses. Because the withdrawal scale includes 1 item for depressed mood, we excluded this item in the analyses that assessed the relationship between depressive symptoms and nicotine withdrawal symptom scores.

Nicotine dependence was assessed with the Fagerström Test for Nicotine Dependence. Scores range from 0 to 10, with higher scores indicating more severe nicotine dependence. The number of cigarettes smoked per day was determined by asking the smoker, “On average, in the past month, how many cigarettes did you smoke per day?” Smokers were asked to rate their confidence in their ability to abstain from smoking cigarettes in the next year on a scale of 0% to 100%.

ASSESSMENTS

A baseline questionnaire during the hospitalization was used to assess depressive symptoms, demographic data, smoking history, nicotine withdrawal symptoms, nicotine dependence, past attempts to quit smoking, craving, self-efficacy for smoking cessation, and alcohol use. An expired carbon monoxide sample was requested at 2 weeks, and a saliva sample was requested from self-reported nonsmokers at 3 months and at 1 year. Self-reported date of resuming smoking after hospital discharge was assessed at nurse counseling calls placed at 2 days, 1 week, 2 weeks, and 4 weeks after discharge.

STATISTICAL ANALYSIS

Statistical analysis was conducted using commercially available software (version 8.0; StataCorp LP, College Station, Texas). A χ² test compared tobacco abstinence rates between the 2 BDI groups (BDI score ≥16 vs BDI score <16) at each follow-up. The relationship between BDI score and nicotine withdrawal symptoms was analyzed with multiple linear regression. Duration of abstinence in the first 4 weeks after discharge was assessed by
We enrolled 245 smokers admitted to the hospital for acute cardiovascular disease (CVD) between October 1, 1999, and October 31, 2002. During the hospital admission, 22% of subjects had a Beck Depression Inventory (BDI) score of 16 or higher, indicating moderate to severe depressive symptoms, and 18% of subjects had a BDI score of 10 or higher but lower than 16, indicating mild depressive symptoms.26,27 The median BDI score was 7, with an interquartile range of 4 to 13; scores ranged from 0 to 50. Subjects with a baseline BDI score of 16 or higher were significantly less likely to follow up at 1 year (66% vs 70%; P = .05).

Table 1 gives the characteristics of smokers with low BDI scores (<16) and high BDI scores (≥16) at baseline (during hospitalization). The BDI scores were higher in smokers who were women, nonwhite, and living alone, but did not differ by age, educational achievement, or alcohol use. Compared with smokers with low BDI scores, subjects with high BDI scores had higher nicotine dependence scores, more craving, and higher nicotine withdrawal scores even though the difference in their daily cigarette consumption was small and not statistically significant. Smokers with a high BDI score also had less confidence in their ability to quit smoking in the next 30 days.

The BDI score was not associated with 2 markers of a smoker’s severity of illness. First, the hospital length of stay was similar for smokers with high BDI scores compared with those with low scores (Table 1). Second, smokers with high BDI scores were no more likely to have a subsequent cardiac event (myocardial infarction, unstable angina, or hospitalization for another cardiovascular diagnosis) than were those with low scores during the 3 months after discharge from the hospital (15% vs 19%; P = .46). The BDI measured during the hospitalization declined during 12 weeks of follow-up, from a median of 7 in the hospital to 4 at 12 weeks. Among smokers with a high baseline BDI score, the median BDI score declined from 21 at baseline to 15 at 2 weeks and 12 at 12 weeks. The median in-hospital BDI score for smokers with a low baseline BDI score was 6, and this score decreased to 4 at 2 weeks and to 1 at 12 weeks.

### WITHDRAWAL SYMPTOMS

The relationship between a high BDI score and more nicotine withdrawal symptoms in the hospital persisted after linear regression analysis adjusted for sex, race/ethnicity, number of cigarettes smoked per day, and Fagerström Test for Nicotine Dependence score.

We assessed the role of nicotine withdrawal symptoms as a mediator of the effect of BDI score on confirmed quit status at 3 months. We used a joint test of significance of the mediated effect, that BDI is a significant predictor of withdrawal and that withdrawal is a significant predictor of 3-month quit rates, while controlling for BDI score, at the P = .05 level. We tested the significance of the product of these coefficients using 95% confidence intervals derived from a bootstrapped sampling distribution using the method described by Mallinckrodt et al.31 We estimated the proportion of the effect of BDI score on quit status that was mediated by withdrawal symptoms.32 All coefficients were standardized for these analyses.32,33

We explored the relationship between BDI score and the drug treatment arm on smoking cessation by creating an interaction term between baseline BDI score and the bupropion treatment arm. We performed logistic regression with smoking cessation as the outcome, and BDI score, drug treatment arm, and the interaction term as dependent variables.

### SMOKING CESSATION

#### Figure 1 shows the relationship between baseline BDI score of 16 or higher and self-reported duration of tobacco abstinence in the first 4 weeks after hospital discharge. Smokers with a BDI score of 16 or higher while in the hospital relapsed to smoking more frequently than did smokers with a BDI score less than 16 (P = .007; incidence rate ratio, 2.40; 95% confidence interval, 1.48-3.78), and this difference was maintained for the remainder of the 1-year follow-up (Table 2). The effect of

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**Table 1. Characteristics of Smokers Hospitalized With Cardiovascular Disease by BDI Score**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low: &lt;16 (n=192)</th>
<th>High: ≥16 (n=53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects, %</td>
<td>78</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>56</td>
<td>55</td>
<td>.31</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>25</td>
<td>45</td>
<td>.005</td>
</tr>
<tr>
<td>Married or with partner, %</td>
<td>67</td>
<td>44</td>
<td>.002</td>
</tr>
<tr>
<td>Educational level ≥12 y, %</td>
<td>52</td>
<td>64</td>
<td>.13</td>
</tr>
<tr>
<td>White race, %</td>
<td>97</td>
<td>86</td>
<td>.002</td>
</tr>
<tr>
<td>Alcohol use ≤1 drink/wk, %</td>
<td>28</td>
<td>20</td>
<td>.22</td>
</tr>
<tr>
<td>No. of cigarettes smoked/d</td>
<td>21</td>
<td>25</td>
<td>.07</td>
</tr>
<tr>
<td>Nicotine dependence score,a mean</td>
<td>5.0</td>
<td>5.7</td>
<td>.06</td>
</tr>
<tr>
<td>Withdrawal symptom score,a mean</td>
<td>7.7</td>
<td>11.6</td>
<td>.001</td>
</tr>
<tr>
<td>Any craving, %</td>
<td>56</td>
<td>73</td>
<td>.03</td>
</tr>
<tr>
<td>Confidence in ability to quit, mean</td>
<td>74</td>
<td>62</td>
<td>.005</td>
</tr>
<tr>
<td>Any previous attempt to quit lasting ≥24 h, %</td>
<td>91</td>
<td>76</td>
<td>.005</td>
</tr>
<tr>
<td>Length of stay in hospital &gt;3 d, %</td>
<td>65</td>
<td>62</td>
<td>.68</td>
</tr>
</tbody>
</table>

*a BDI indicates Beck Depression Inventory; b Fagerström Test for Nicotine Dependence; c Minnesota Nicotine Withdrawal Scale; d Confidence to quit for the next 30 days was assessed on a scale of 0% (not confident) to 100%.

Kaplan-Meier survival methods and the log-rank test, and the effect size was calculated with an incidence rate ratio. Smoking cessation outcomes were assessed at 2 weeks, 3 months, and 12 months with multiple logistic regression. All multivariate analyses were adjusted for sex, race/ethnicity, number of cigarettes smoked per day, and Fagerström Test for Nicotine Dependence score.

We assessed the role of nicotine withdrawal symptoms as a mediator of the effect of BDI score on confirmed quit status at 3 months. We used a joint test of significance of the mediated effect, that BDI is a significant predictor of withdrawal and that withdrawal is a significant predictor of 3-month quit rates, while controlling for BDI score, at the P = .05 level. We tested the significance of the product of these coefficients using 95% confidence intervals derived from a bootstrapped sampling distribution using the method described by Mallinckrodt et al.31 We estimated the proportion of the effect of BDI score on quit status that was mediated by withdrawal symptoms.32 All coefficients were standardized for these analyses.32,33

We explored the relationship between BDI score and the drug treatment arm on smoking cessation by creating an interaction term between baseline BDI score and the bupropion treatment arm. We performed logistic regression with smoking cessation as the outcome, and BDI score, drug treatment arm, and the interaction term as dependent variables.

#### RESULTS

**DEPRESSIVE SYMPTOMS**

We enrolled 245 smokers admitted to the hospital for acute cardiovascular disease (CVD) between October 1, 1999, and October 31, 2002. During the hospital admission, 22% of subjects had a Beck Depression Inventory (BDI) score of 16 or higher, indicating moderate to severe depressive symptoms, and 18% of subjects had a BDI score of 10 or higher but lower than 16, indicating mild depressive symptoms.26,27 The median BDI score was 7, with an interquartile range of 4 to 13; scores ranged from 0 to 50. Subjects with a baseline BDI score of 16 or higher were significantly less likely to follow up at 1 year (66% vs 70%; P = .05).
baseline depressive symptoms on biochemically validated smoking cessation remained statistically significant at 3-month follow-up (odds ratio, 3.02; 95% confidence interval, 1.28-7.09) and 1-year follow-up (odds ratio, 3.77; 95% confidence interval, 1.31-10.82) after adjusting for sex, race/ethnicity, number of cigarettes smoked per day, and nicotine dependence score. The results were similar when smokers with mild depressive symptoms (BDI score <16) were included in the analyses, but the difference in smoking cessation rates at 3 months and 1 year were not statistically significant.

To determine whether differential loss to follow-up in the BDI groups affected our results, we performed the analysis excluding subjects who did not follow up at 3 months and 1 year. Among subjects who did follow up, those with a BDI score of 16 or higher were more likely to relapse at 3 months ($P=.002$) and 1 year ($P=.02$).

**EFFECT OF BUPROPION THERAPY**

We conducted an exploratory subgroup analysis to compare the benefit of treatment with bupropion vs placebo on cessation rates in the groups with high and low BDI scores at baseline (Figure 2). Smokers with both high and low BDI scores who were assigned to the bupropion group had higher quit rates at 3 months than those assigned to the placebo group. At 1-year follow-up, smokers with high baseline BDI scores assigned to the bupropion group had a higher quit rate compared with the placebo group (19% vs 3%; $P=.07$), but smokers with low baseline BDI scores had similar quit rates in the bupropion and placebo groups (27% vs 27%; $P=.95$). The interaction between baseline BDI score and bupropion therapy predicting quitting at 1 year was not statistically significant ($P=.10$).

The results of this study demonstrate that moderate to severe depressive symptoms occurred frequently among smokers hospitalized for acute CVD. Depressive symptoms were independently associated with early relapse to smoking after hospital discharge. Although these symptoms decreased rapidly after hospitalization, they also predicted lower smoking cessation rates at 1-year follow-up. The association between depressive symptoms and stronger nicotine withdrawal suggests a possible mechanism for the association. Stopping smoking is one of the most important behavioral changes in smokers with acute...
... CVD that can prevent subsequent morbidity and mortality.\(^1\) Our findings may help explain why many smokers with CVD resume smoking after hospitalization even if they receive intensive smoking cessation interventions during and after their hospital stay.\(^6\)\(^8\)

Our study is consistent with previous research showing that outpatient smokers who are depressed or have a history of depression are less likely to quit smoking.\(^15\)\(^-\)\(^20\) A previous study in smokers after admission for acute coronary symptoms found that patients who were persistently depressed for the 3 months after admission were less likely to quit smoking.\(^21\) In our study, the baseline depressive symptoms improved during the 3 months after the hospitalization, but mood during the hospitalization was a major predictor of return to smoking. Depressive symptoms in patients with cardiac disease predict lack of adherence with other recommendations such as exercise, taking medications, and attending cardiac rehabilitation.\(^21\)\(^22\)\(^35\)\(^37\)

In our study, smokers with moderate to severe depressive symptoms experienced more nicotine withdrawal symptoms during hospitalization compared with smokers with mild depressive symptoms, and this may explain, in part, the association between depressive symptoms and early relapse to smoking. A relationship between stronger withdrawal symptoms and craving and depression or history of depression has been observed in other studies.\(^9\)\(^30\)\(^-\)\(^45\) The discomfort associated with more severe withdrawal symptoms combined with the emotional and physical discomfort of the smoker's acute CVD may contribute to the high rates of relapse after hospital discharge. Aggressive pharmacologic treatment of nicotine withdrawal symptoms might improve cessation rates in this group of smokers.

Our data suggest that bupropion therapy might be more effective for smoking cessation in patients with CVD with moderate to severe depressive symptoms than in smokers with no or mild depressive symptoms. Treatment with bupropion had a large, though nonsignificant, effect at 1-year follow-up in smokers with a BDI score of 16 or higher but not in smokers with a BDI score lower than 16. This difference was less pronounced at 3-month follow-up (end of bupropion treatment) than at 1-year follow-up, making it more difficult to attribute the difference to the bupropion therapy. Another study showed a benefit of bupropion therapy in a subgroup analysis of smokers with chronic obstructive pulmonary disease who had a baseline BDI score of 16 or higher.\(^41\) Our data are limited by the few subjects in this subgroup but warrant further study to determine whether bupropion and other smoking cessation medications may have a benefit in this group of smokers with CVD.

This study has limitations. The BDI score measures depressive symptoms but does not provide a diagnosis of major depression. In the setting of an acute hospitalization, it is unclear whether the BDI score reflects the last 2 weeks of symptoms, as it is intended to measure, or symptoms related to the current hospitalization. Some of the physical symptoms measured with the nicotine withdrawal scale such as tremor, racing heart, and sweating could also be attributed to either depression or CVD. The subgroup analysis of bupropion therapy in smokers with severe to moderate and mild depressive symptoms is limited by the relatively small number of subjects with BDI scores of 16 or higher.

Smoking cessation is critical for the secondary prevention of CVD in smokers. However, many smokers with CVD relapse to smoking soon after a cardiovascular event.\(^6\)\(^8\) Our findings implicate moderate to severe depressive symptoms during the hospitalization as a major independent predictor of early relapse to smoking after hospitalization for a cardiovascular event. Higher withdrawal symptoms partially mediate the association between depressive symptoms and relapse to smoking. Our findings further emphasize the clinical importance of identifying and treating depression in patients hospitalized with CVD. Future studies should determine which medications or combinations of medications are safe and effective for smoking cessation in patients with symptoms of depression.

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Author Contributions: Dr Thorndike had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Thorndike, Regan, McKool, Pasternak, and Rigotti. Acquisition of data: Thorndike, McKool, Pasternak, Swartz, Torres-Finnerty, and Rigotti. Analysis and interpretation of data: Thorndike, Regan, Pasternak, and Rigotti. Drafting of the manuscript: Thorndike and Rigotti. Critical revision of the manuscript for important intellectual content: Thorndike, Regan, McKool, Pasternak, and Rigotti. Administrative, technical, and material support: Thorndike and Pasternak. Study supervision: Thorndike, Pasternak, Swartz, and Rigotti.

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Additional Contributions: Our study nurses (Sharon Maginnis, RN, Thalia Metalides, RN, and Nancy McCleary, RN), study staff (Alison Yen, MA, Lee Bullock Schwentker, BA, Alison Keith, BA, Jill Papsdorf, BA, Alexandra Sherman,
REFERENCES