Sex, Depression, and Risk of Hospitalization and Mortality in Chronic Obstructive Pulmonary Disease

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Background: We sought to determine whether depressive or anxiety symptoms are associated with chronic obstructive pulmonary disease (COPD) hospitalization or mortality. These data were collected as part of the National Emphysema Treatment Trial (NETT), a randomized controlled trial of lung volume reduction surgery vs continued medical treatment conducted at 17 clinics across the United States between January 29, 1998, and July 31, 2002.

Methods: Prospective cohort study among participants in the NETT with emphysema and severe airflow limitation who were randomized to medical therapy. Primary outcomes were 1- and 3-year mortality, as well as COPD or respiratory-related hospitalization or emergency department visit during the 1-year follow-up period. Of 610 patients randomized to medical therapy, complete data on hospitalization and mortality were available for 3 years of follow-up for 603 patients (98.9%).

Results: Depressive symptoms were assessed using the Beck Depression Inventory (BDI) questionnaire, and anxiety was assessed using the State-Trait Anxiety Inventory. Among 610 subjects, 40.8% had at least mild to moderate depressive symptoms. Patients in the highest quintile of BDI score (BDI score, ≥15) had an increased risk of respiratory hospitalization in unadjusted analysis compared with patients in the lowest quintile (BDI score, <5) (odds ratio [OR], 2.26; 95% confidence interval [CI], 1.30-3.93). After adjustment for disease severity, this relationship was no longer statistically significant. The adjusted risk of 3-year mortality was increased among those in the highest quintile of BDI score (OR, 2.74; 95% CI, 1.42-5.29) compared with those in the lowest quintile. Anxiety was not associated with hospitalization or mortality in this population.

Conclusions: Depressive symptoms are common in patients with severe COPD and are treated in few subjects. Depressive symptoms are associated with increased risk for 3-year mortality but not 1-year mortality or hospitalization.

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spective study after adjusting for disease severity. Because there are inconsistent data on the risk of adverse clinical events among patients with COPD with symptoms of depression or anxiety, we sought to determine whether depressive or anxiety symptoms at baseline are associated with subsequent COPD-related hospitalization and mortality in a large prospective cohort of well-characterized patients with severe COPD.

METHODS

SETTING AND DATA COLLECTION

Patients for this prospective cohort study were identified from data collected as part of the National Emphysema Treatment Trial (NETT), a randomized controlled trial of lung volume reduction surgery vs continued medical treatment conducted at 17 clinics across the United States. Details of the study have been published elsewhere. Briefly, between January 29, 1998, and July 31, 2002, subjects with emphysema and severe airflow limitation of 45% or lower predicted were enrolled in the study. All patients were required to complete 6 to 10 weeks of pulmonary rehabilitation before randomization. The primary outcome measures were mortality and maximal exercise capacity 2 years after randomization. Baseline clinical and quality-of-life data were collected after rehabilitation but before randomization.

Information on health care use is based on Medicare claims data provided by the Centers for Medicare and Medicaid Services that were linked to the NETT data. They include inpatient and outpatient care provided by physicians during hospitalizations, ED visits, and outpatient clinic visits. Claims data were not available for 7 subjects because they were not enrolled in Medicare or Medicare+Choice plans. Of 610 patients in the NETT randomized to medical therapy, 603 (98.9%) with complete Medicare data constitute the subjects for the present analyses (Figure 1).

MEASURES OF DEPRESSION AND ANXIETY

Before beginning pulmonary rehabilitation, baseline depressive symptoms were measured using the Beck Depression Inventory (BDI) questionnaire, and general anxiety was measured using the State-Trait Anxiety Inventory (STAI). Baseline antidepressant medication use was assessed at the same visit. The BDI is a self-reported 21-item measure that ranges from 0 and 63. A score of 10 or higher is consistent with mild to moderate depressive symptoms and is associated with risk of adverse outcomes in other medical conditions. To determine whether a cutoff of 10 or higher is appropriate for patients with COPD, the BDI scores were also categorized into quintiles and were entered as indicator variables into the model. During the baseline medical history interview, patients were asked if they were currently prescribed an antidepressant. The type of antidepressant was not recorded.

Anxiety was measured using the STAI, consisting of a 20-item State scale that asks subjects to describe how they feel at a particular point in time and a 20-item Trait scale that describes how they feel in general. Each scale has a range from 20 to 80, with higher scores indicating higher levels of anxiety.

OTHER FACTORS THAT COULD AFFECT HOSPITALIZATION OR MORTALITY

In addition to baseline sociodemographic characteristics, we considered COPD disease severity variables that potentially could affect the relationship between depression and hospitalization or mortality. Because disease severity measures may differ by outcome, we considered variables to predict hospitalization and mortality separately.

For hospitalizations, we included the following factors previously found to predict COPD-related hospitalizations and ED visits in the NETT population: forced expiratory volume in the first second of expiration, partial pressure of oxygen (arterial), prior COPD-related hospitalization, prior COPD-related ED visit, Charlson-Deyo comorbidity score, and University of California, San Diego, Shortness of Breath Questionnaire (SOBQ) total score.

To measure disease severity associated with mortality, we calculated a modified body mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease (BODE index) by replacing the Medical Research Council dyspnea scale with the SOBQ. We divided the SOBQ into quartiles (eg, lowest quartile, 0 points; highest quartile, 3 points). We included the following factors also predictive of mortality in this population: hemoglobin level less than 13.3 g/dL (to convert to grams per liter, multiply by 10), residual vol-
ume greater than 262%, diffusion capacity of carbon monoxide less than 22%, maximal workload on cardiopulmonary exercise test below the 40th percentile, difference in percentage emphysema (upper lung vs lower lung) on chest computed tomography (CT) less than -0.8%, and nuclear perfusion scan perfusion ratio (upper lung vs lower lung) less than 0.14.

Medicare claims data from the year before randomization were used to determine baseline health care use and comorbidity. Chronic obstructive pulmonary disease–specific ED visits and hospitalizations were categorized using the same ICD-9-CM discharge diagnosis codes used to define the primary outcome. Baseline non-COPD comorbidity was determined using the Deyo adaptation of the Charlson comorbidity index, using inpatient and outpatient ICD-9-CM diagnosis codes.

STATISTICAL ANALYSIS

We used F tests from 1-way analysis of variance for continuous variables and the χ2 statistic for categorical variables in bivariate analysis. Multivariate logistic regression analysis was used to predict the hospitalization outcomes of at least 1 COPD or respiratory hospitalization during 1 year of follow-up, as well as mortality at 1 year and 3 years of follow-up. The index date was defined as the date of randomization for the clinical trial. A separate model was developed for each clinical outcome (hospitalization and mortality) to determine the association between depression category after adjusting for sociodemographic factors and disease severity. Potentially confounding variables were added to the model to determine whether there was a statistically significant change (±10%) in the coefficient associated with the depression variable. Sex did not statistically significantly change the relationship between depression and hospitalization or mortality but was included to improve the precision of the estimates in the final models. We assessed whether sex or the use of antidepressants modified the relationship between depression and outcomes using interaction terms. We assessed model fit using the Hosmer-Lemeshow goodness-of-fit test statistic. All continuous variables were modeled as linear terms.

RESULTS

This analysis includes 610 patients initially randomized to medical therapy regardless of subsequent course of treatment. The mean±SD BDI score was 9.3±5.9, and 40.8% had a score of 10 or higher (at least mild to moderate depressive symptoms). Patients with depressive symptoms had worse mean SOBQ and St George’s Respiratory Questionnaire scores (P<.001 for both) and a shorter 6-minute walk distance (P=.003) (Table 1). Only 24.5% of patients with mild to moderate depressive symptoms were taking an antidepressant.

During follow-up, 26.9% were hospitalized or seen in the ED for COPD, and 30.5% were hospitalized for a respiratory reason. The overall 1-year mortality was 7.5%. During the same 1-year period, 25 patients had lung volume reduction surgery outside of the NETT (4 subsequently died the same year), and 3 patients had a lung transplant. One additional patient had non-NETT lung volume reduction surgery, but it is unknown whether it occurred during the 1-year follow-up period. Of 70 patients who had lung volume reduction surgery, lung transplantation, or died, 42.0% had a COPD exacerbation before surgery or death during the follow-up period.

Using a BDI cutoff of 10 or higher, depressive symptoms were not associated with hospitalization in unadjusted analyses (Table 2). Higher proportions of patients with a BDI of 10 or higher had died at 1 year and at 3 years of follow-up. In adjusted analyses, a BDI cutoff of 10 or higher was not associated with risk of hospitalization or 1-year mortality but was associated with a borderline increased risk of 3-year mortality (odds ratio [OR], 1.42; 95% confidence interval [CI], 0.96-2.10).

To determine whether a BDI cutoff of 10 or higher was appropriate for COPD, we repeated the analyses categorizing the BDI score into quintiles. Worsening BDI scores, by quintile, were associated with increasing proportions hospitalized for any reason (P<.03), as well as increasing proportions with a hospitalization or an ED visit for COPD (P<.03) (Figure 2). In adjusted analyses, BDI

Table 1. Baseline Characteristicsa

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;10 (n=361)</th>
<th>≥10 (n=249)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.8 (5.6)</td>
<td>66.0 (6.2)</td>
<td>.07</td>
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<td>Female sex</td>
<td>33.2</td>
<td>39.8</td>
<td>.10</td>
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<td>Nonwhite race/ethnicity</td>
<td>4.7</td>
<td>7.2</td>
<td>.19</td>
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<tr>
<td>Married</td>
<td>65.4</td>
<td>64.3</td>
<td>.78</td>
</tr>
<tr>
<td>Educational achievement</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>16.6</td>
<td>27.7</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>29.1</td>
<td>25.7</td>
<td>.03</td>
</tr>
<tr>
<td>Some college</td>
<td>34.4</td>
<td>34.1</td>
<td></td>
</tr>
<tr>
<td>≥ College</td>
<td>19.9</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Annual income, $</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 000</td>
<td>17.5</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>15 000-29 999</td>
<td>33.3</td>
<td>33.7</td>
<td></td>
</tr>
<tr>
<td>30 000-49 999</td>
<td>28.3</td>
<td>30.5</td>
<td>.49</td>
</tr>
<tr>
<td>≥ 50 000</td>
<td>20.8</td>
<td>16.1</td>
<td></td>
</tr>
<tr>
<td>Forced expiratory volume in the first second of expiration L % Predicted</td>
<td>0.80 (0.25)</td>
<td>0.75 (0.22)</td>
<td>.01</td>
</tr>
<tr>
<td>Partial pressure of oxygen, arterial, mm Hg</td>
<td>26.8 (6.9)</td>
<td>27.5 (7.3)</td>
<td>.65</td>
</tr>
<tr>
<td>Modified BODE score</td>
<td>4.7 (1.6)</td>
<td>5.6 (1.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>University of California, San Diego, Shortness of Breath Questionnaire score</td>
<td>58.8 (18.1)</td>
<td>70.0 (17.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>St George’s Respiratory Questionnaire score</td>
<td>49.9 (11.9)</td>
<td>59.0 (11.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6-min Walk distance, ft [m]</td>
<td>1241 (319)</td>
<td>1165 (306)</td>
<td>.003</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory score</td>
<td>30.5 (9.0)</td>
<td>40.5 (10.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Trait</td>
<td>29.5 (7.2)</td>
<td>41.8 (10.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior COPD-related hospitalization (n=603)</td>
<td>16.2</td>
<td>24.2</td>
<td>.01</td>
</tr>
<tr>
<td>Prior COPD-related ED visit (n=603)</td>
<td>8.6</td>
<td>9.4</td>
<td>.74</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>9.1</td>
<td>24.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Charlson Comorbidity Index &gt; 1 (n=603)</td>
<td>35.4</td>
<td>34.4</td>
<td>.81</td>
</tr>
</tbody>
</table>

Abbreviations: BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity index; COPD, chronic obstructive pulmonary disease; ED, emergency department.

Data are given as mean (SD) or as percentages unless otherwise indicated.

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score quintile was not associated with COPD-related hospitalizations or ED visits (eg, OR, 1.54; 95% CI, 0.81-2.91 for BDI score quintile of ≥15 compared with <5) (Table 3). Similar results were obtained for respiratory-related hospitalization.

There was no association between depressive symptoms and 1-year mortality in adjusted analyses. However, compared with patients with a BDI score in the lowest quintile (BDI score, <5), those with BDI scores of 11 to 14 and 15 or higher had an increased risk of 3-year mortality in adjusted analyses (OR, 1.97; 95% CI, 1.03-3.77; and OR, 2.74; 95% CI, 1.42-5.29; respectively) (Table 4).

There was no association between antidepressant use and mortality. Also, there was no statistically significant interaction between depressive symptoms and antidepressant use to predict 1-year COPD-related hospitalizations or ED visits (P = .6 for interaction term), respiratory hospitalization (P = .98), death at 1 year (P = .4), or death at 3 years (P = .4).

Female sex was associated with an increased risk for respiratory hospitalization after adjustment for disease severity (OR, 1.32; 95% CI, 1.01-2.28). There was no effect modification between sex and depressive symptoms for hospitalization or mortality (data not shown).

In univariate analysis, STAI State (OR per 5-point change, 1.01; P = .8) and STAI Trait (OR per 5-point change, 1.05; P = .3) scores were not associated with risk of hospitalization or mortality (data not shown).

We found a high prevalence of depressive symptoms among patients with severe COPD, with few patients receiving antidepressant treatment. In patients with COPD, a BDI score of 10 or higher was not associated with hospitalization or mortality after adjustment for disease severity. An analysis using BDI divided into quintiles demonstrated a slightly increased risk of 3-year mortality among patients with a score of 11 to 14 and a statistically significantly increased risk among those with a BDI score of 15 or higher compared with those with a score of less than 5. Baseline anxiety was unassociated with risk of hospitalization or mortality.

Most studies that looked at the association between depressive symptoms and adverse outcomes used a BDI score of 10 or higher to identify patients with mild to moderate symptoms; however, existing cutoffs are generally based on non–medically ill patients. Symptoms of depression such as psychomotor slowing or fatigue may overlap notably with COPD. Patients in the present study had a mean ± SD BDI score of 9.3 ± 5.9, suggesting that for COPD a higher threshold for depressive symptoms may be needed compared with ischemic heart disease to identify patients at increased risk for adverse outcomes. This threshold would need to be further tested in other COPD populations.
Respiratory-Related Hospitalization

3-y Mortality

Table 3. Logistic Regression Models for Risk of Hospitalization During 1 Year Associated With Depressive Symptoms

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>COPD-Related Hospitalization or ED Visit</th>
<th>Respiratory-Related Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORb Adjusted ORc</td>
<td>ORb Adjusted ORc</td>
</tr>
<tr>
<td>Beck Depression Inventory score quintile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>5-7</td>
<td>1.60 (0.92-2.81)</td>
<td>1.52 (0.89-2.57)</td>
</tr>
<tr>
<td>8-10</td>
<td>1.66 (0.82-3.33)</td>
<td>1.40 (0.80-2.45)</td>
</tr>
<tr>
<td>11-14</td>
<td>1.23 (0.65-2.32)</td>
<td>1.06 (0.68-1.65)</td>
</tr>
<tr>
<td>≥15</td>
<td>1.86 (1.07-3.19)</td>
<td>1.52 (1.01-2.28)</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>0.86 (0.43-1.69)</td>
<td>0.74 (0.42-1.30)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.83 (0.43-1.69)</td>
<td>0.74 (0.42-1.30)</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department.

Data are given as odds ratio (OR) (95% confidence interval) (n=603).

Unadjusted from univariate logistic regression.

Adjusted for all other variables in the table, as well as age, modified BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity index) score, hemoglobin level, residual volume (percentage predicted), diffusion capacity of carbon monoxide (percentage predicted), maximal cardiopulmonary exercise test workload, difference in percentage emphysema, perfusion ratio, and Charlson-Deyo comorbidity score.

Prior studies found conflicting results as to whether depression in COPD is associated with adverse clinical outcomes such as hospitalization or mortality. Our finding that moderate to severe depressive symptoms are associated with 3-year mortality is consistent with studies that found that depressive symptoms measured during or shortly after hospitalization for COPD were associated with risk of death. In a small study10 of 16 outpatients with COPD, the Minnesota Multiphasic Personality Inventory findings correlated with 4-year mortality. Two other studies11,12 found an increased risk of mortality with emotional function measured using quality-of-life instruments but did not specifically assess depressive symptoms. Our results differ from those of 3 studies of patients with COPD that found that depression, measured using the Brief Assessment Schedule Depression Cards13,14 or by interview15, was unassociated with mortality after adjusting for disease severity.

There are also conflicting data as to whether depression is associated with exacerbations and hospitalizations for COPD. Among outpatients, anxiety and depression measured using the Geriatric Mental State Schedule16 or the Geriatric Depression Scale and Beck Anxiety Inventory7 were associated with prior hospital admissions, although from these studies it was not clear if psychological symptoms contributed to increased health care use or resulted from it. In 2 prospective studies9,17 of patients hospitalized for COPD exacerbations that used the Hospital Anxiety and Depression questionnaire, depressive symptoms were not predictive of readmissions for COPD, although anxiety was predictive in a subgroup.17 In the present prospective study, neither depressive symptoms or anxiety was associated with COPD exacerbations or respiratory hospitalizations.

Because severe COPD may increase the risk of depression and adverse outcomes, statistical adjustment for severity of COPD is essential to detect an independent effect of depression.18 Because of the extensive baseline data collected on patients in this study, we were able to adjust...
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for established measures of disease severity such as spirometry results, prior utilization, the BODE index, and comorbidity.

For hospitalizations and mortality, we adjusted for dyspnea (SOBQ score), 1 of 4 components of the BODE index. Although the BODE index is a well-validated measure of disease severity in COPD, patients with depression may perceive dyspnea differently. Removing dyspnea from the model did not change the lack of association between depressive symptoms and hospitalization but resulted in an association between the highest quintile of depressive symptoms and 1-year mortality (OR for highest vs lowest quintile, 1.60; 95% CI, 1.01-8.35). Therefore, adjusting for dyspnea may have attenuated the relationship between depression and mortality.

We were also able to assess several disease severity factors not generally available in observational studies, including hemoglobin level, lung volumes and diffusion capacity of carbon monoxide, cardiopulmonary exercise test results, and distribution of emphysema by CT and nuclear imaging. This helps to ensure that the association between depression and outcomes in our study is not simply due to a difference in disease severity.

It is estimated that patients with severe COPD have a 2.5-fold increased risk for depression compared with age-matched controls. The prevalence of depressive symptoms in COPD is estimated between 7% and 42%. We also found a high prevalence of depressive symptoms and noted that only 37.0% of patients with moderate to severe symptoms were being treated with an antidepressant. This is similar to the proportion being treated in a 2005 study by Kunik et al and suggests that providers should screen for depression in patients with COPD.
We did not find that the use of an antidepressant reduced the risk of adverse outcomes, although we were unable to ascertain dosage or compliance with therapy. It is unknown whether treatment of depressive symptoms would reduce the risk of mortality or COPD-related exacerbations or hospitalizations, although randomized trials of depression treatment in cardiovascular disease have not yet demonstrated a decreased risk of mortality.\(^\text{66,67}\)

In this study, female sex was associated with an increased risk of respiratory-related hospitalization. Women with COPD may have different clinical presentations for their disease than men and tend to have more symptoms such as dyspnea and shorter 6-minute walk times.\(^\text{48}\) Women differ in their presentation to the ED, more often delaying treatment and using fewer respiratory medications before admission.\(^\text{49}\) This suggests that differences in clinical manifestations of COPD, use of medications, and health care resources in women may account for the difference in risk of hospitalization.

Strengths of our study include a large sample of well-characterized patients with severe COPD for whom complete baseline data were available, including validated measures of depression and anxiety. These data were collected during a period of clinical stability and not during or immediately following an exacerbation. Patients were followed up prospectively, and almost complete data on health care use and mortality are available. Because of the extensive baseline data collected, we were able to adjust for disease severity measures for hospitalization and mortality.

The limitations of data collected as part of a clinical trial are that results might not be generalizable to all patients with COPD. Excluded from this study were patients with multiple comorbidities and the most severe impairment in physical activity, who are at greatest risk for depression and adverse outcomes. However, the prevalence of depression in our study was similar to that in other studies of severe COPD; depressive and anxiety symptoms were only assessed before pulmonary rehabilitation and may have improved after completion of the rehabilitation program.\(^\text{50,51}\) This may have attenuated the relationship between depressive symptoms and outcomes in our study. Also, because COPD exacerbations and hospitalizations were ascertained using administrative data, there may be misclassification of COPD-related hospitalizations, and criteria for hospitalization may vary depending on provider factors. To address this, we combined COPD-related hospitalizations and ED visits into a single outcome.

In conclusion, depressive symptoms are common among patients with COPD, and most subjects are not being treated with antidepressants. Depressive symptoms are associated with an increased adjusted risk for 3-year mortality among patients, and the risk seems to be greatest among those with a BDI score of 15 or higher. Depressive and anxiety symptoms were unassociated with hospitalization among patients with severe COPD. Further understanding of depression in COPD may help to target therapies to reduce mortality.

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