Efficacy of Bupropion and Nortriptyline for Smoking Cessation Among People at Risk for or With Chronic Obstructive Pulmonary Disease

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Background: The observations that smokers with chronic obstructive pulmonary disease (COPD) are at increased risk of depression and that nicotine may have antidepressant effects and regulate mood provide a rationale for the use of antidepressant drugs for smoking cessation in patients with COPD. No clinical trial has studied the efficacy of bupropion hydrochloride and nortriptyline hydrochloride for smoking cessation in this patient population, to our knowledge.

Methods: In a placebo-controlled double-dummy randomized trial, 255 adults at risk for COPD or with COPD were prescribed sustained-release bupropion (bupropion SR) (150 mg twice daily) or nortriptyline (75 mg once daily) for 12 weeks. All patients received smoking cessation counseling. The main outcome measure was prolonged abstinence from smoking from week 4 to week 26 after the target quit date.

Results: The use of bupropion SR and nortriptyline resulted in higher prolonged abstinence rates compared with placebo, although only the difference between bupropion SR and placebo was statistically significant (differences with placebo, 13.1% [95% confidence interval, 1.2%-25.1%] for bupropion SR and 10.2% [95% confidence interval, −1.7% to 22.2%] for nortriptyline). In patients with COPD, bupropion SR and nortriptyline seem efficacious in achieving prolonged abstinence (differences with placebo, 18.9% [95% confidence interval, 3.6%-34.2%] for bupropion SR and 12.9% [95% confidence interval, −0.8% to 26.4%] for nortriptyline). In participants at risk for COPD, no statistically significant differences with placebo in prolonged abstinence rates were found.

Conclusions: Bupropion SR treatment is an efficacious aid to smoking cessation in patients with COPD. Nortriptyline treatment seems to be a useful alternative.

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Research has shown that smoking cessation is the most effective way to reduce the risk of developing chronic obstructive pulmonary disease (COPD). Smoking cessation has also been shown to reduce the rate of decline in forced expiratory volume in 1 second in smokers with COPD. Furthermore, it improves the long-term prognosis and reduces the symptoms of cough and sputum production and airways reactivity.

We conducted a randomized trial to assess the efficacy of sustained-release bupropion hydrochloride (bupropion SR) and nortriptyline hydrochloride for smoking cessation among smokers at risk for COPD and with COPD. Furthermore, we wanted to assess whether time to relapse is different across treatment groups. Compared with healthy smokers, patients with COPD are expected to experience additional barriers to successful smoking cessation, such as higher nicotine addiction scores and a higher prevalence of psychiatric disorders (eg, depression). Therefore, another objective of this trial was to explore the efficacy of bupropion SR and nortriptyline in smokers at risk for COPD compared with smokers with COPD. On the basis of the existing literature (E.J.W. and P.G.K., unpublished data, June 2005), we deemed differences between bupropion SR and nortriptyline treatments unlikely.

Methods

Participants, Screening, and Randomization

The study population consisted of current daily smokers at risk for COPD or with COPD. All participants were aged between 30 and 70 years, had to have a smoking history of at least 5 years, smoked on average at least 10 cigarettes per day during the last year, and were motivated to stop smoking. We defined the severity of COPD according to the definition provided by the Global Initiative for Chronic Obstructive Lung Dis-
We excluded people who reported having used or were still using bupropion SR or nortriptyline, persons who were using nicotine therapy or psychoactive medication at the time of assessment, and patients who had any serious or unstable medical disorders that might affect lung function or for which bupropion SR or nortriptyline was contraindicated.

Participants were randomized between March 1, 2002, and August 27, 2003, with a final 6-month follow-up session before March 2004. Of the 611 people who were screened, 255 met the screening criteria and participated in the study (Figure). Randomization was done according to a computer-generated randomization list provided by the pharmacist of Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands, stratified for COPD severity, using blocks of 33. Patients were stratified based on the definition provided by the European Respiratory Society. However, because the Global Initiative for Chronic Obstructive Lung Disease guideline was subsequently published in 2001 and has been implemented worldwide since then, we decided to present the results of this trial stratified for COPD severity according to the latter classification. No patient, research nurse, counselor, investigator, or any other staff member was aware of the treatment assignments for the duration of the study.

STUDY DESIGN AND MEDICATION

Our study was a blinded, placebo-controlled, double-dummy randomized trial. Participants provided written informed consent during the first visit. The medical ethics committee of the Maastricht University hospital approved the trial.

Eligible individuals were randomly assigned in a 1:1 ratio to receive the following: (1) bupropion SR, 150 mg once daily, for days 1 through 6, followed by 150 mg twice daily for days 7 through 8; (2) nortriptyline, 25 mg once daily, for days 1 through 3, followed by 50 mg once daily for days 3 through 7, and then 75 mg once daily for days 8 through 8; or (3) placebo. Bupropion SR was purchased from GlaxoSmithKline BV, Zeist, the Netherlands. Nortriptyline tablets were produced free of charge by Lundbeck BV, Amsterdam, the Netherlands. Tablets were crushed and reformulated as capsules. Pharmacin BV, Zwiendrecht, the Netherlands, produced placebo bupropion and placebo nortriptyline and film coated the placebo and active bupropion tablets to maintain the patency of the bupropion formulation. At the baseline visit, the target quit date (TQD) was set for the second week, usually day 11 from the start of the medication.

Participants were assessed at baseline and 1, 3, 12, and 26 weeks after the TQD. At the first 3 assessments, participants also attended an individual face-to-face counseling session (approximately 10-20 minutes). The provider was 1 of 3 master’s level counselors trained in counseling smokers who want to quit. In general, participants received counseling from the same person at all 3 sessions. Participants also received supportive telephone calls from a counselor on the TQD and at 2, 4, 6, 8, and 11 weeks after the TQD.

Participants who missed appointments were telephoned at least 3 times to reschedule their visit. At the end of the 26-week follow-up, the study staff tried to contact all participants who did not keep their scheduled visits but did not state that they did not want to participate any more, to collect data regarding their smoking status. To assess adverse effects, we asked participants at every study visit and at each telephone consultation to describe any adverse events they experienced. We did not prepare a checklist of possible symptoms.

The primary outcome measure for the study was prolonged abstinence from smoking from week 4 to week 26 after the TQD. Prolonged abstinence was defined as a participant’s report of 0 cigarettes per day (not even a puff) during weeks 4 through 26, confirmed by urinary cotinine values of 60 ng/mL or less at weeks 4, 12, and 26 after the TQD. Participants were allowed to miss 1 in-person visit but not the last follow-up visit.

Secondary outcome measures included prolonged abstinence during weeks 4 through 12 and 7-day point prevalence abstinence (defined as having smoked 0 cigarettes, not even a puff, for the previous 7 days) at weeks 4, 12, and 26, confirmed by urinary cotinine levels of 60 ng/mL or less.

STATISTICAL ANALYSIS

To have 80% power to detect an absolute difference in biochemically verified prolonged abstinence rates of 15% between active and placebo groups, approximately 100 smokers were to be randomly assigned to each of the 3 groups (bupropion SR, nortriptyline, and placebo). We succeeded in recruiting 255 smokers.

The t test for independent samples and χ² test were used to compare the active treatments (bupropion SR and nortriptyline) with placebo on demographic, behavioral, and clinical characteristics and on primary and secondary outcomes. We performed intention-to-treat and per-protocol analyses. All statistical analyses were done with blinding maintained. Differences in abstinence rates between bupropion SR and placebo and between nortriptyline and placebo were calculated, corresponding 95% confidence intervals (CIs). Participants lost to
follow-up were considered to be smokers in the intention-to-treat analysis.

We conducted Cox proportional hazards regression analysis to compare time to relapse across treatment groups, using failure to achieve abstinence from smoking as the criterion. Survival probabilities were calculated using the Kaplan-Meier method. To assess the relapse probability at the TQD, we used Cox proportional hazards regression analysis.

**BLINDING**

A panel of 3 judges (including P.G.K.) concluded that placebo bupropion and placebo nortriptyline matched the active formulations perfectly in appearance. The panel correctly distinguished bupropion SR and nortriptyline from the corresponding placebo formulations based on differences in taste or texture. A panel of 3 judges (including P.G.K.) concluded that placebo bupropion SR and nortriptyline matched the active formulations perfectly in appearance. The panel correctly distinguished bupropion SR and nortriptyline from the corresponding placebo formulations based on differences in taste or texture.

**RESULTS**

**PARTICIPANT CHARACTERISTICS**

Table 1 lists the baseline characteristics of the study participants. All participants were Dutch Caucasian. The mean±SD age of the participants was 51.0±8.5 years, and 51% were women. The bupropion SR–treated group consisted of more women (60.5%) compared with the nortriptyline- (45%) and placebo-treated (48%) groups. The mean±SD number of cigarettes that participants smoked was 23.0±8.7 cigarettes per day. The nortriptyline-treated group consisted of fewer participants at risk for COPD (stage 0) (35%) compared with the bupropion SR– (49%) and placebo-treated (46%) groups. The number of depressed participants (Beck Depression Inventory score, ≥15) was highest in the bupropion SR–treated group (27%) and lowest in the nortriptyline-treated group (12.5%).

**MEDICATION COMPLIANCE**

We assessed medication compliance by counting the number of pills allotted minus those returned. For 73 participants (29%), medication compliance could not be assessed. Among the others, 82 participants (45%) used more than 80% of the study medication, 33 (18%) used more than 80% of the study medication.
between 50% and 80% of the study medication, and 67 (37%) used less than 50% of the study medication that they were supposed to take. Medication compliance did not significantly differ between the 3 study groups (P = .28), although more participants receiving nortriptyline used less than 50% of their study medication (48% vs 34% of the bupropion SR–treated group vs 28% of the placebo group).

ABSTINENCE FROM SMOKING

Prolonged abstinence rates from smoking from week 4 to the end of week 26 after the TQD were higher in the bupropion SR– and nortriptyline-treated groups compared with the placebo group, although only the difference between the bupropion SR–treated and placebo groups was statistically significant (Table 2). Twenty-four (28%) of 86 participants receiving bupropion SR remained abstinent, compared with 20 (25%) of 80 participants receiving nortriptyline and 13 (15%) of 89 participants receiving placebo. When we restricted the analysis to subjects who were assessed at the different time points, treating those lost to follow-up as missing, the results were comparable. As we expected, significant differences between bupropion SR– and nortriptyline-treated groups were not found.

In patients with COPD, bupropion SR treatment was more efficacious than placebo in achieving prolonged abstinence from week 4 to week 26 (difference, 18.9% [95% CI, 3.6%–34.2%]; P = .02) (Table 3). In the same patient population, nortriptyline treatment also resulted in higher prolonged abstinence rates compared with placebo, although this difference failed to reach statistical significance (difference, 12.9% [95% CI, −0.8% to 26.4%]; P = .07). We found similar differences in prolonged abstinence rates between groups when patients were stratified according to the definition of COPD provided by the Global Initiative for Chronic Obstructive Lung Disease compared with that provided by the European Respiratory Society. Among participants at risk for COPD, we found much smaller differences in prolonged abstinence rates. Among the study groups overall, prolonged abstinence rates in men did not differ from those in women (difference, 1.3% [95% CI, −10.3% to 13.0%]; P = .70),

Table 2. Prolonged Abstinence Rates and 7-Day Point Prevalence Abstinence Rates*

<table>
<thead>
<tr>
<th>No. of Weeks After Target Quit Date</th>
<th>Bupropion Hydrochloride SR (n = 86)</th>
<th>Nortriptyline Hydrochloride (n = 80)</th>
<th>Placebo (n = 89)</th>
<th>% Point Difference Between Bupropion SR and Placebo†</th>
<th>P Value</th>
<th>% Point Difference Between Nortriptyline and Placebo†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged abstinence†</td>
<td>31.4 (27/86)</td>
<td>28.8 (23/80)</td>
<td>19.1 (17/89)</td>
<td>12.3 (−0.5 to 25.1)</td>
<td>.06</td>
<td>9.6 (−3.2 to 22.5)</td>
<td>.14</td>
</tr>
<tr>
<td>12</td>
<td>27.9 (24/86)</td>
<td>25.0 (20/80)</td>
<td>14.6 (13/89)</td>
<td>13.1 (1.2 to 25.1)</td>
<td>.03</td>
<td>10.2 (−1.7 to 22.2)</td>
<td>.09</td>
</tr>
<tr>
<td>Point prevalence abstinence</td>
<td>39.5 (34/86)</td>
<td>37.5 (30/80)</td>
<td>30.3 (27/89)</td>
<td>9.2 (−4.9 to 23.3)</td>
<td>.20</td>
<td>7.2 (−7.1 to 21.4)</td>
<td>.33</td>
</tr>
<tr>
<td>4</td>
<td>33.7 (29/86)</td>
<td>32.5 (26/80)</td>
<td>20.2 (18/89)</td>
<td>13.5 (0.5 to 26.5)</td>
<td>.04</td>
<td>12.3 (−1.0 to 25.5)</td>
<td>.07</td>
</tr>
<tr>
<td>12</td>
<td>30.2 (26/86)</td>
<td>28.8 (23/80)</td>
<td>19.1 (17/89)</td>
<td>11.1 (−1.6 to 23.8)</td>
<td>.09</td>
<td>9.6 (−3.2 to 22.5)</td>
<td>.15</td>
</tr>
</tbody>
</table>

Table 3. Prolonged Abstinence Rates From Week 4 to Week 26 Stratified for Chronic Obstructive Pulmonary Disease (COPD) and Depression*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bupropion Hydrochloride SR (n = 86)</th>
<th>Nortriptyline Hydrochloride (n = 80)</th>
<th>Placebo (n = 89)</th>
<th>% Point Difference Between Bupropion SR and Placebo†</th>
<th>P Value</th>
<th>% Point Difference Between Nortriptyline and Placebo†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>28.6 (12/42)</td>
<td>32.1 (9/28)</td>
<td>22.0 (9/41)</td>
<td>6.6 (−12.0 to 25.3)</td>
<td>.49</td>
<td>10.2 (−11.3 to 31.6)</td>
<td>.34</td>
</tr>
<tr>
<td>I, II, and III</td>
<td>27.3 (12/44)</td>
<td>21.2 (11/52)</td>
<td>8.3 (4/48)</td>
<td>18.9 (3.6 to 34.2)</td>
<td>.02</td>
<td>12.9 (−0.8 to 26.4)</td>
<td>.07</td>
</tr>
<tr>
<td>Depressed‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34.8 (8/23)</td>
<td>10.0 (1/10)</td>
<td>10.5 (2/19)</td>
<td>24.3 (0.4 to 48.1)</td>
<td>.08‡</td>
<td>−0.5 (−23.7 to 22.6)</td>
<td>&gt; .99†</td>
</tr>
<tr>
<td>No</td>
<td>25.4 (16/63)</td>
<td>27.1 (19/70)</td>
<td>15.7 (11/70)</td>
<td>9.7 (−4.0 to 23.4)</td>
<td>.17</td>
<td>11.4 (−2.0 to 24.9)</td>
<td>.10</td>
</tr>
</tbody>
</table>

Abbreviation: SR, sustained release.

*Data are given as percentage (numerator/denominator) or as percentage difference (95% confidence interval) unless otherwise indicated.
†Fisher exact test results were used if 1 or more expected cell values were less than 5. This can result in P > .05 while the 95% confidence interval does not include 0.
‡We used a cutoff score for the Beck Depression Inventory (BDI) of 15 to separate the participants with no or mild depression (BDI, <15) from the participants with moderate to severe depression (BDI, ≥15).
and participants who had previously used nicotine gum were less likely to achieve 26 weeks of prolonged abstinence from smoking (difference, 12.7% [95% CI, 2.8%-22.6%]; \( P = .02 \)).

We performed ancillary analyses to explore the efficacy of bupropion SR and nortriptyline treatments in smokers classified as depressed. Among these (20% [52/235] of the study population), rates of prolonged abstinence from smoking from week 4 to week 26 were significantly higher in participants who received bupropion SR compared with participants who received placebo (Table 3) (difference, 24.3% [95% CI, 0.4%-48.1%]; \( P = .08 \)).

Cox proportional hazards regression analysis, with treatment group, depression, sex, previous use of nicotine gum, and previous use of nicotine patch entered as covariates, showed that the estimated risk of relapse in participants with COPD was more than 30% higher compared with that in participants at risk for COPD (hazard ratio, 1.3 [95% CI, 1.0-1.7]; \( P = .03 \)).

### ADVERSE EVENTS

Forty participants (16%) discontinued medication because of adverse events: 8 (9% [8/89]) in the placebo group, 13 (15% [13/86]) in the bupropion SR–treated group, and 19 (24% [19/80]) in the nortriptyline-treated group. The rate of discontinuation of treatment was statistically significantly higher among the participants receiving nortriptyline (\( P < .01 \)) compared with the participants receiving placebo. Insomnia, dry mouth, and diarrhea or constipation were the most commonly reported adverse events by participants in the bupropion SR– and nortriptyline-treated groups (Table 4). Participants who received nortriptyline were significantly more likely to report dry mouth, diarrhea or constipation, and fatigue. No significant differences were found between the bupropion SR–treated and placebo groups. No seizures were reported in any group. One participant (taking placebo) was hospitalized during the treatment phase because of dermatologic reactions. She died 2 months later.

The most striking finding of this blinded, placebo-controlled, double-dummy randomized trial was that bupropion SR–treatment was significantly more efficacious in achieving prolonged abstinence compared with placebo, especially among participants with COPD. Although nortriptyline treatment also resulted in higher prolonged abstinence rates compared with placebo, this difference was not statistically significant. The finding that the nortriptyline-treated group consisted of fewer participants at risk for COPD might have affected the study results. The differences in prolonged abstinence rates between bupropion SR and nortriptyline treatments vs placebo were small and not statistically significant among the participants at risk for COPD.

Because smokers with COPD seem to be at increased risk of depression\(^ {11,12,22} \) and because nicotine addiction is often accompanied by comorbid depression or depressive symptoms,\(^ {23,24} \) we performed ancillary analyses to explore the efficacy of bupropion SR and nortriptyline treatment in smokers classified as depressed. Results indicated that bupropion SR treatment was efficacious in helping smokers who were classified as depressed in achieving prolonged abstinence from smoking throughout the 26-week period. The number of depressed participants from the nortriptyline-treated group was considered too low to study this relationship.

Only one randomized trial, to our knowledge, has evaluated the efficacy of an antidepressant for smoking cessation in patients with COPD. Tashkin et al\(^ {25} \) studied the effects of bupropion SR treatment in patients with COPD. The authors included 343 smokers with mild to moderate COPD (forced expiratory volume in 1 second between 50% and 80% of the predicted value according

### Table 4. Participants Reporting Adverse Events at Any Time Point

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Bupropion Hydrochloride SR (n = 86)</th>
<th>Nortriptyline Hydrochloride (n = 80)</th>
<th>Placebo (n = 89)</th>
<th>P Values†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>29 (33.7)</td>
<td>23 (28.8)</td>
<td>21 (23.6)</td>
<td>.14 and .45</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>24 (27.9)</td>
<td>49 (61.3)</td>
<td>18 (20.2)</td>
<td>.22 and &lt;.001</td>
</tr>
<tr>
<td>Blurry vision</td>
<td>6 (7.0)</td>
<td>8 (10.0)</td>
<td>2 (2.2)</td>
<td>.16 and .05</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (14.0)</td>
<td>4 (5.0)</td>
<td>7 (7.9)</td>
<td>.20 and .45</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13 (15.1)</td>
<td>16 (20.0)</td>
<td>15 (16.9)</td>
<td>.75 and .60</td>
</tr>
<tr>
<td>Nervousness</td>
<td>13 (15.1)</td>
<td>9 (11.3)</td>
<td>7 (7.9)</td>
<td>.13 and .45</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>11 (12.8)</td>
<td>6 (7.5)</td>
<td>7 (7.9)</td>
<td>.28 and .93</td>
</tr>
<tr>
<td>Diarrhea or constipation</td>
<td>29 (33.7)</td>
<td>38 (47.5)</td>
<td>23 (25.8)</td>
<td>.25 and .003</td>
</tr>
<tr>
<td>Mouth ulcer</td>
<td>10 (11.6)</td>
<td>11 (13.8)</td>
<td>6 (6.7)</td>
<td>.26 and .13</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>11 (12.8)</td>
<td>6 (7.5)</td>
<td>5 (5.6)</td>
<td>.10 and .62</td>
</tr>
<tr>
<td>Sweating</td>
<td>12 (14.0)</td>
<td>7 (8.8)</td>
<td>8 (9.0)</td>
<td>.30 and .96</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (8.1)</td>
<td>16 (20.0)</td>
<td>8 (9.0)</td>
<td>.24 and .04</td>
</tr>
</tbody>
</table>

Abbreviation: SR, sustained release.

*Data are given as number (percentage) unless otherwise indicated. Adverse events were symptoms that began after or were exacerbated by treatment. Only adverse reactions that were reported by at least 10% of the participants in any of the groups are listed.

†The first value refers to the comparison between bupropion SR and placebo, and the second refers to the comparison between nortriptyline and placebo.
to COPD-staging guidelines from the American Thoracic Society) and 61 smokers with severe COPD (forced expiratory volume in 1 second between 35% and 50% of the predicted value). They found a significant effect of bupropion SR treatment vs placebo (week 4 to week 26 prolonged abstinence rates, 16% vs 9%), although the effect was smaller than the difference that we found (13%). Both studies used the same recruitment methods, assigned participants to bupropion SR treatment or placebo for 12 weeks, and included participants who were comparable for age, number of cigarettes smoked per day, and Fagerstrom Test for Nicotine Dependence score. Hall et al26 conducted a clinical trial in which they studied the effects of bupropion SR and nortriptyline treatments for smoking cessation. Comparison of their results with ours is problematic not only because they did not specify eligibility criteria based on spirometric results but also because their results were based on 52 weeks of treatment (prolonged abstinence rates, 18% for bupropion SR, 10% for nortriptyline, and 8% for placebo).

There are some limitations to our findings. First, blinding of participants may not have been completely successful. A panel of 3 judges correctly distinguished bupropion SR and nortriptyline from the placebo formulation, indicating that participants receiving active drug were more likely to guess that they had received active drug. Although tests of blinding among participants might actually be tests of hunches regarding adverse events or efficacy,27-29 our finding that the active preparations and placebo were identical in appearance but different in taste or texture might have introduced bias. Because this is a common problem in medication trials, we were surprised that, to our knowledge, none of the earlier studies on bupropion SR or nortriptyline used an independent panel of judges to test the study medications. Furthermore, the blinding of participants was evaluated in only 4 of the earlier trials (prolonged abstinence rates, 18% for bupropion SR, 10% for nortriptyline, and 8% for placebo).

Second, although medication compliance did not significantly differ between the 3 study groups in our trial, compliance in general was poor, with approximately 55% of participants using 80% or fewer of the pills that they were asked to take. Poor compliance may have resulted in lower overall abstinence rates in our study population. Whether the differences in adverse events among the bupropion SR–treated, nortriptyline–treated, and placebo groups resulted in differences in prolonged abstinence rates could not be assessed. Some of the other studies on bupropion SR or nortriptyline reported the number of participants who completed the treatment (eg, Hall et al26,33 and Jorenby et al29), but we could not find any other study in which medication compliance was presented. Third, smokers in cessation clinical trials are a self-selected group who are motivated to quit, which limits the generalization of our findings. On the other hand, it represents the group of smokers for whom pharmacotherapy might be most appropriate. Because of the few participants with COPD, we could not evaluate whether the efficacy of bupropion SR and nortriptyline treatments differs among disease groups with mild, moderate, or severe COPD.

There are several strengths of the study. This clinical trial extends the existing knowledge on the efficacy of bupropion SR and nortriptyline treatments for smoking cessation among participants at risk for and with COPD. Furthermore, we were successful in following up study participants. Fewer than 5% of the participants who enrolled in the study were lost to follow-up at 26 weeks. Of the earlier articles on bupropion SR or nortriptyline treatment, only 4 succeeded in following up more than 80% of participants.26,32,33,35 In the study by Tashkin et al20 (in which the efficacy of bupropion SR treatment for smoking cessation in patients with COPD was studied), more than 20% were lost to follow up.

**Bupropion SR and nortriptyline treatments seem effective in helping smokers with COPD to quit. We found a small but nonsignificant difference between the effects of bupropion SR and nortriptyline. Nortriptyline might therefore be a useful alternative to bupropion SR for smokers with COPD. Future research should replicate our findings, assess the efficacy of bupropion SR and nortriptyline treatments in smokers at different stages of COPD (as well as in smokers with COPD who are depressed), and evaluate how medication compliance is related to study outcome.**

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**Additional Information:** Dr Wagena had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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