The cost-effectiveness of antidepressants for smoking cessation in chronic obstructive pulmonary disease (COPD) patients

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ABSTRACT

Objectives  In healthy smokers, antidepressants can double the odds of cessation. Because of its four times lower costs and comparable efficacy in healthy smokers, nortriptyline appears to be favourable compared to bupropion. We assessed which of both drugs was most effective and cost-effective in stopping smoking after 1 year compared with placebo among smokers at risk or with existing chronic obstructive pulmonary disease (COPD).

Methods  A total of 255 participants, aged 30–70 years, received smoking cessation counselling and were assigned bupropion, nortriptyline or placebo randomly for 12 weeks. Prolonged abstinence from smoking was defined as a participant’s report of no cigarettes from week 4 to week 52, validated by urinary cotinine. Costs were calculated using a societal perspective and uncertainty was assessed using the bootstrap method.

Results  The prolonged abstinence rate was 20.9% with bupropion, 20.0% with nortriptyline and 13.5% with placebo. The differences between bupropion and placebo (relative risk (RR) = 1.6; 95% confidence interval (CI) 0.8–3.0) and between nortriptyline and placebo (RR = 1.5; 95% CI 0.8–2.9) were not significant. Severity of airway obstruction did not influence abstinence significantly. Societal costs were €1368 (2.5th–97.5th percentile 193–5260) with bupropion, €1906 (2.5th–97.5th 120–17761) with nortriptyline and €1212 (2.5th–97.5th 96–6602) with placebo. Were society willing to pay more than €2000 for a quitter, bupropion was most likely to be cost-effective.

Conclusions  Bupropion and nortriptyline seem to be equally effective, but bupropion appears to be more cost-effective when compared to placebo and nortriptyline. This impression holds using only health care costs. As the cost-effectiveness analyses concern some uncertainties, the results should be interpreted with care and future studies are needed to replicate the findings.

Keywords  Antidepressants, bupropion, COPD, cost-effectiveness, nortriptyline, smoking cessation.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality world-wide and is related causally to smoking [1]. Many patients with COPD continue to smoke [2]. Others who try to quit fail repeatedly. Patients with COPD who still smoke are expected to experience additional barriers. One barrier for a successful quit attempt could be the presence of psychological problems such as depression or anxiety [3,4]. Because nicotine may have an antidepressant effect [5], this provides a rationale for the use of antidepressant drugs for smoking cessation in these patients.

In healthy smokers, the antidepressants bupropion and nortriptyline can double the odds of cessation and increase the number of quitters by 10% after 6 months to 17–20% compared with placebo [6]. In the Netherlands, the costs of a 12-week treatment of nortriptyline are approximately €50 and for bupropion SR approximately €210. Because it costs four times less and has comparable...
efficacy, nortriptyline would seem to be the preferable choice for smoking cessation in otherwise healthy smokers.

We conducted a randomized, double-blind placebo-controlled trial to assess the efficacy of bupropion and nortriptyline compared to placebo in smokers with and at risk of COPD [7]. This trial showed that the prolonged abstinence rate from week 4 to the end of week 26 in participants using bupropion was 28%, with nortriptyline 25%, and with placebo 15% [7]. The estimated risk of relapse in participants with existing COPD was more than 30% higher compared to that in participants at risk for COPD. The primary objective of this paper was to assess the cost-effectiveness of the two drugs after 12 months compared to placebo using data from this trial. A secondary objective was to assess possible determinants of smoking cessation.

**METHODS**

**Participants**

We included participants between 30 and 70 years of age, at risk for or with mild to moderately severe COPD, who smoked at least 10 cigarettes per day and were motivated to quit [7]. At risk for COPD was defined as forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) from 0.7 to 1.0, combined with the presence of cough, sputum production or dyspnoea. Mild to moderately severe COPD was defined as FEV1/FVC < 0.7 and FEV1 between 30 and 80% [1]. After screening, eligible participants were assigned randomly bupropion SR (150 mg/day), nortriptyline (75 mg/day) or matching placebo for 12 weeks (Fig. 1). All patients received individual face-to-face smoking cessation counselling (3 × 20 minutes) and telephone calls (6 × 5 minutes).

![Flowchart](image-url)
Efficacy outcome

The efficacy outcomes for this study were prolonged abstinence from smoking, which was defined as a participant’s report of no cigarettes per day (not even a puff) from week 4 to week 52 after the target quit date, confirmed by urinary cotinine values (cut-off point 60 ng/ml). This was measured at 4, 12, 26 and 52 weeks. At baseline, we also measured the number of cigarettes smoked per day, the number of previous quit attempts, the Fagerström Test for Nicotine Dependence (FTND) score [8], the Beck Depression Inventory (BDI) score [9] and previous use of nicotine replacement therapy (NRT).

Cost estimates

The cost estimates included the direct medical and indirect non-medical costs related to COPD and the costs of the intervention offered according a societal perspective: [10]

1 Direct medical costs
- Prescription medication, which were calculated using the pharmacotherapy manual of the Health Care Insurance Board (http://www.cvzkompassen.nl). In this manual, the costs of the use of medication are presented, often per month. The price year of the manual used was 2004. For the years 2002 and 2003, prices were adjusted using the consumer price index.
- Medication without prescription, which were specified by the participants themselves.
- Visits to health care providers, which were based on fixed prices described in the Dutch guidelines for economic evaluation in health care [11].
- (Un)paid home care which was based on fixed prices [11].

2 Indirect non-medical costs
- Absenteeism from work, which was measured in lost working hours. The costs associated with being absent from paid work were calculated using the friction cost method, which assumes that organizations need a certain time, the friction period, to restore the initial production level when an employee is absent from work. The productivity costs per hour varied between €20 and €47, depending on age group and gender. The total productivity costs were multiplied by a correction factor of 0.8, which represents the elasticity regarding lost work time and productivity [11]. Absenteeism from unpaid work was valued at €8.30 per hour.

3 Intervention costs
- The use of bupropion and nortriptyline. The costs were calculated conservatively. If the amount of bupropion or nortriptyline used was unclear or more than 80%, then 100% of the total treatment costs were calculated, i.e. for bupropion SR €208.98 and for nortriptyline €50.82. If compliance was less than 80% but more than 50%, then 80% of the treatment costs were calculated. If less than 50% of the medication was used, then 50% of the treatment costs were calculated.
  - Counselling sessions, of which the costs of contacts with a pulmonary nurse were calculated and set at €23.00 per face-to-face counselling session and €5.75 per telephone session.
  - Travel costs were calculated per face-to-face counselling session and for visits to health care providers. Both were based on fixed prices [11].

The volume of health care resource use related to COPD was registered in cost diaries. The validity of the used cost diary to obtain data on health care consumption has been assessed previously [12]. Costs were calculated by multiplying the volumes with the estimated prices. In total, nine cost diaries were handed out to every participant, covering 4 weeks each. In order to provide an estimate of the total costs incurred during the 12 months, we interpolated the costs in the registered weeks to the weeks in which participants did not have to complete a cost diary. The costs were not discounted, as the time horizon of the trial was 1 year.

Analyses

The sample size was determined assuming a 26-week biochemically verified quit rate of 10% in the placebo and 25% in the treatment groups ($\alpha = 0.05$ two-tailed; $\beta = 0.80$). In order to detect a significant difference in abstinence rate after 26 weeks, 100 participants per group had to be included.

Intention-to-treat analyses were performed in which all dropouts were considered to be smokers.

We performed logistic regression analysis with prolonged abstinence from smoking from weeks 4 to 52 and also examined whether other variables were associated with prolonged abstinence. In these analyses, all multivariate logistic regression models were adjusted for treatment assignment. We used a backward stepwise elimination approach with prolonged abstinence from smoking from weeks 4 to 52 as dependent variable and the following independent variables: gender, BDI, severity of the pulmonary obstruction (at risk for COPD or stages I, II, III COPD), FTND, previous use of NRT, previous quit attempts and the number of cigarettes smoked per day. The importance of each possible covariate was verified by a comparison of the $-2$ log-likelihood for the model including that variable with the $-2$ log-likelihood from the model without that variable. A variable was dropped if the difference in $-2$ log-likelihood was statistically significant at the $P = 0.05$ level.
Incremental cost-effectiveness analyses

If up to three cost diaries per participant were missing, we imputed the data by carrying forward available data. If four or more cost diaries were missing or if a patient dropped out, the costs of the missing costs diaries were imputed by the mean costs of all participants who missed up to three diaries. This method was chosen to ensure that we were as conservative as possible with regard to a possible contrast in costs between the patient groups [13]. Using sensitivity analyses, we assessed whether the results were robust to changes in imputation method of the cost diaries.

The incremental cost-effectiveness ratio (ICER) is defined as the difference in mean costs between two groups divided by the mean difference in quitters, resulting in cost per additional quitter. The uncertainty of the ICERS was estimated using non-parametric bootstrapping [14], by which 1000 samples of the same sample size as the original data set were drawn with replacement. From the sampling distribution of the ICERs, acceptability curves were generated representing the probability that an intervention is most cost-effective over a range of cost-effectiveness thresholds.

RESULTS

Participants

Of the 611 assessed for eligibility, 255 participants were included in the study (Fig. 1). The baseline characteristics of these participants are described in Table 1.

Abstinence from smoking

After 12 months, 18 of the 86 participants (20.9%) in the bupropion group, 16 of the 80 participants (20.0%) in the nortriptyline group and 12 of the 89 participants (13.5%) in the placebo group achieved prolonged abstinence. Neither the abstinence rate of bupropion nor nortriptyline differed significantly from placebo. The relative risk (RR) and the crude odds ratio (OR) for bupropion versus placebo were RR 1.6 [95% confidence interval (CI) 0.8–3.0] and OR 1.7 (95% CI 0.8–3.8). For nortriptyline versus placebo, this was RR 1.5 (95% CI 0.8–2.9) and OR 1.6 (95% CI 0.7–3.6), respectively.

Multivariate logistic regression indicated that previous use of NRT and the FTND score were associated with prolonged abstinence from weeks 4 to 52 at \( P < 0.05 \), independent of treatment assignment. Participants who had used NRT previously were less likely to achieve prolonged abstinence (OR = 0.48; 95% CI 0.25–0.94), as were participants who were more dependent on nicotine (OR = 0.83: 95% CI 0.72–0.97). The OR for prolonged abstinence adjusted for the FTND score and previous use of NRT for bupropion versus placebo was 1.6 (95% CI 0.7–3.7) and 1.6 (95% CI 0.7–3.6) for nortriptyline.

Costs

The number of participants who completed all cost diaries was low. Only 53.7% of the participants returned at least six of the nine booklets they received. Eighteen per cent of the participants returned no booklet at all. Table 2 indicates that the costs in the nortriptyline group were higher than in the bupropion and placebo groups, in particular the costs for visits to health care providers and absenteeism from work. Table 2 also presents the mean costs and shows that the deviation (bootstrapped 2.5th percentile to 97.5th percentile) around the mean is large in the nortriptyline group.

In the nortriptyline group, four participants had costs higher than one standard deviation above the mean.

Table 1 Baseline characteristics of participants by treatment condition.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Bupropion SR (n = 86)</th>
<th>Nortriptyline (n = 80)</th>
<th>Placebo (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>Mean 51.1 SD 8.3</td>
<td>Mean 51.2 SD 9.1</td>
<td>Mean 51.3 SD 8.4</td>
</tr>
<tr>
<td>Number of cigarettes smoked/day</td>
<td>24.2 SD 9.4</td>
<td>22.2 SD 7.6</td>
<td>23.6 SD 8.8</td>
</tr>
<tr>
<td>Number of previous quit attempts</td>
<td>2.4 SD 1.8</td>
<td>2.6 SD 1.9</td>
<td>2.6 SD 1.7</td>
</tr>
<tr>
<td>FTND score</td>
<td>6.2 SD 2.1</td>
<td>6.0 SD 2.2</td>
<td>5.9 SD 2.1</td>
</tr>
<tr>
<td>Beck Depression Inventory score</td>
<td>10.6 SD 8.7</td>
<td>8.5 SD 5.2</td>
<td>9.4 SD 6.7</td>
</tr>
<tr>
<td>Post-bronchodilator FEV₁/ %predicted</td>
<td>86.3 SD 21.0</td>
<td>83.1 SD 21.7</td>
<td>87.4 SD 23.0</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>66.7 SD 13.4</td>
<td>65.5 SD 13.6</td>
<td>65.1 SD 15.3</td>
</tr>
<tr>
<td>Female</td>
<td>52 % 60.5</td>
<td>36 % 45.0</td>
<td>43 % 48.3</td>
</tr>
<tr>
<td>Previous use of NRT</td>
<td>38 SD 44.2</td>
<td>43 SD 53.8</td>
<td>56 SD 62.9</td>
</tr>
</tbody>
</table>

FTND: Fagerström Test for Nicotine Dependence; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; NRT: nicotine replacement therapy; SD: standard deviation.
Table 2  Mean reported volumes and mean costs per participant per week subtracted from the cost diaries and the mean intervention cost per participant for the total study duration (costs in €).

<table>
<thead>
<tr>
<th>Cost diaries</th>
<th>Bupropion</th>
<th></th>
<th>Nortriptiline</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean reported volume</td>
<td>Mean costs</td>
<td>Mean reported volume</td>
<td>Mean costs</td>
<td>Mean reported volume</td>
<td>Mean costs</td>
</tr>
<tr>
<td>Prescribed medication</td>
<td>0.16 prescriptions</td>
<td>2.13</td>
<td>0.18 prescriptions</td>
<td>2.18</td>
<td>0.28 prescriptions</td>
<td>3.39</td>
</tr>
<tr>
<td>Medication without prescription</td>
<td>0.07 medications</td>
<td>1.45</td>
<td>0.05 medications</td>
<td>0.69</td>
<td>0.04 medications</td>
<td>0.02</td>
</tr>
<tr>
<td>Health care providers</td>
<td>0.06 visits</td>
<td>1.63</td>
<td>0.20 visits</td>
<td>5.54</td>
<td>0.07 visits</td>
<td>2.04</td>
</tr>
<tr>
<td>Travel cost health care provider</td>
<td>0.06 visits</td>
<td>0.24</td>
<td>0.20 visits</td>
<td>1.16</td>
<td>0.07 visits</td>
<td>0.29</td>
</tr>
<tr>
<td>Home care</td>
<td>0.02 hours</td>
<td>0.23</td>
<td>0.24 hours</td>
<td>1.96</td>
<td>0.19 hours</td>
<td>1.53</td>
</tr>
<tr>
<td>Absenteeism</td>
<td>0.5 hours</td>
<td>10.95</td>
<td>1.7 hours</td>
<td>30.97</td>
<td>0.6 hours</td>
<td>11.22</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study medication</td>
<td>62% of pp used over 80% or unclear</td>
<td>173.50</td>
<td>55% of pp used over 80% or unclear</td>
<td>39.73</td>
<td>65% of pp used over 80% or unclear</td>
<td>0</td>
</tr>
<tr>
<td>Counselling</td>
<td>7.3 sessions</td>
<td>87.24</td>
<td>7.3 sessions</td>
<td>86.46</td>
<td>7.5 sessions</td>
<td>88.13</td>
</tr>
<tr>
<td>Travel cost counselling</td>
<td>2.7 sessions</td>
<td>6.00</td>
<td>2.7 sessions</td>
<td>5.93</td>
<td>2.7 sessions</td>
<td>6.00</td>
</tr>
<tr>
<td>Mean imputed costs of diaries</td>
<td>1102</td>
<td>0–4988</td>
<td>1774</td>
<td>0–17602</td>
<td>1118</td>
<td>0–6500</td>
</tr>
<tr>
<td>Mean intervention costs</td>
<td>267</td>
<td>150–316</td>
<td>132</td>
<td>56–159</td>
<td>94</td>
<td>33–109</td>
</tr>
<tr>
<td>Mean total costs</td>
<td>1368</td>
<td>193–5260</td>
<td>1906</td>
<td>120–17761</td>
<td>1212</td>
<td>96–6602</td>
</tr>
</tbody>
</table>

pp: patient population.
(cut-off point €6860). In the bupropion and placebo groups, there was also one participant with total costs higher than €6860. Sensitivity analyses showed that when varying from intention-to-treat analyses to analyses of participants who missed a maximum of three cost diaries, or to participants with costs lower than one standard deviation above the mean, the direction of the study conclusions remained the same, although the costs per quitter for each comparison were reduced, still indicating a necessary investment to gain one quitter.

Cost per quitter

Both bupropion and nortriptyline were more effective in increasing the abstinence rate than placebo, but the costs according to the societal perspective were lower in the placebo group. The ICER demonstrate that, if comparing bupropion with placebo, €2097 (2.5th–97.5th percentile to 25 662–27 403) has to be invested to gain one additional quitter. If using nortriptyline instead of placebo, then the additional costs per quitter were €10 640 (2.5th–97.5th to 79 047–94 844). To obtain a difference of one quitter using bupropion rather than nortriptyline, then €57 753 (2.5th–97.5th to 129 265–225 678) less needs be spent to gain one quitter. Figure 2 shows that the placebo intervention is most cost-effective, if society is willing to pay zero or less than €2000 for a quitter. In this situation, additional effectiveness is regarded to be worthless. Bupropion is most cost-effective if society is willing to pay more than €2000 per quitter (crossing lines placebo and bupropion).

DISCUSSION

The objective of this paper was to examine whether bupropion and nortriptyline in combination with a behavioural intervention were more effective and more cost-effective than placebo in improving prolonged abstinence in smoking patients at risk for COPD or with existing COPD. The effectiveness of bupropion and nortriptyline converged at a 20% success level. The severity of airway obstruction or depression score on the BDI did not influence the outcome. Participants who had used NRT previously and/or patients who were more dependent on nicotine were less likely to remain abstinent.

Because of the lower costs of nortriptyline itself and the almost equal effectiveness compared with bupropion, we expected nortriptyline to be the most cost-effective intervention. However, the costs in the placebo group (€1212) were lower than the costs in the bupropion group (€1368) and lower than in the nortriptyline group (€1906). In the nortriptyline group, high costs were registered in the cost diaries for visits to health care professionals and sick leave from work. Because of its higher efficacy than placebo, bupropion was most likely to be a cost-effective intervention if society is willing to pay more than €2000 for a quitter. In the case of a direct comparison between antidepressant drugs (without placebo), bupropion was always the most probable cost-effective intervention. If we adopt the perspective of the health care provider, which excludes costs for medication without prescription and absenteeism), the cost differences between the groups hold. For bupropion, nortriptyline and placebo, these costs in the diary change from a total average of 283.14, 174.62 and 112.62 into, respectively, 270.74, 142.96 and 101.38 (based on Table 2).

One caveat in this study is that a considerable number of cost diaries were not completed, leading to a certain degree of imputation. We decided to use a method leading to a conservative imputation for finding a cost difference between the groups. Other imputation strategies might have been used, leading to a larger cost contrast between the groups, indicating an even more favourable result for the bupropion strategy. A possible reason for the high costs in the nortriptyline group could be that participants using nortriptyline experienced more side effects of the treatment. Wagena et al. reported that, in the first 6 months of this study, significantly more participants using nortriptyline reported dry mouth, diarrhoea or constipation, and fatigue [7]. Side effects corresponded with higher costs in all three groups. Having stopped earlier with the study medication was associated with higher costs only in the nortriptyline group. One of the limitations of cost-effectiveness calculations is that cost data typically have a highly positively skewed distribution, as in reality only a few people are responsible for high health care costs. It is therefore not valid to exclude these participants from the analyses [15]. Further studies should investigate whether the use of nortriptyline is related to higher medical consumption, due possibly...
to side effects, and hence whether these findings can be replicated.

Only one other randomized trial has evaluated the efficacy of bupropion in patients with COPD, but did not report 12-month data or cost analyses [16]. In a study by Hall et al. [17] the effectiveness of bupropion, nortriptyline and placebo, in combination with psychological therapy, were compared in ‘healthy’ smokers (n = 220). The 52-week prolonged abstinence rate was 16% with bupropion, 10% with nortriptyline and 8% with placebo [17]. In the current study, the efficacy of the antidepressants and placebo was 5–10% higher. This is in contrast to our expectations, because we had expected that patients who have already developed COPD have more difficulty quitting than ‘healthy’ smokers.

Hall et al. also published cost-effectiveness data which demonstrated that, in otherwise healthy smokers, nortriptyline was more cost-effective than bupropion if only intervention costs were included [18]. This is not surprising, as in the current study the intervention costs for nortriptyline were also lower than for bupropion, and the efficacy in both groups was approximately the same. Unfortunately, Hall et al. did not present the costs of health services use, which was higher in the nortriptyline group in the current study and the main cause for the difference in cost-effectiveness.

One other study in healthy smokers receiving intensive counselling therapy compared the effects of nortriptyline and bupropion with placebo [19]. The sustained abstinence rates at 6 months were 21.6% in the placebo group, 30.8% in the nortriptyline group (P = 0.40) and 41.5% in the bupropion group (P = 0.05). The odds ratio was not statistically different for smokers using nortriptyline or bupropion (OR 1.60; 95% CI 0.66–3.86; P = 0.35). The most common adverse events were dry mouth and drowsiness in the nortriptyline group and dry mouth and insomnia in the bupropion group. Cost-effectiveness and medical consumption due to side effects were unfortunately not investigated.

CONCLUSIONS

After 1 year the efficacy of bupropion and nortriptyline are both approximately 20%. The effect in the placebo group was not significantly lower and resulted in a 14% abstinence rate. The severity of airway obstruction did not influence the outcome. If society is willing to pay more than €2000 for a quitter, bupropion in combination with a behavioural intervention seems to be the most cost-effective compared to nortriptyline and placebo in patients at risk for COPD or with existing COPD. However, as the analyses concern some uncertainties, these results should be interpreted with care.

Declarations of interest

Lundbeck BV provided nortriptyline free of charge. GSK was not involved financially. E. J. Wagena worked for Solvay Pharmaceuticals from March 2005 and has been employed by Astellas Pharma since January 2006. During the study, he was employed by Maastricht University and the Maastricht University Hospital. J. L. Severens is a member of the International (Health Outcome) Advisory Board of GlaxoSmithKline. This employment and membership had no influence on this study or the views expressed in this paper.

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