A controlled trial of nortriptyline, sustained-release bupropion and placebo for smoking cessation: preliminary results

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Abstract

Purpose and methods: Cognitive behavior therapy (CBT) constitutes the basis of smoking cessation programs. Quitting rates are usually increased by the concomitant use of CBT and pharmacotherapy. There are studies showing the efficacy of bupropion and nortriptyline compared to placebo, but there is just one published comparison between these drugs, unfortunately with low power to detect significant differences. This study was designed to compare the efficacy of bupropion, nortriptyline and placebo in a group of smokers who also received intensive counseling therapy. We conducted a double blind, double-dummy, placebo-controlled trial for smoking cessation that lasted 9 weeks. Patients were randomized to receive nortriptyline 75 mg/day (52 subjects), bupropion 300 mg/day (53 subjects) or placebo (51 subjects). All smokers also received the same intensive cognitive behavior therapy. The target day for quitting smoking was usually day 10. Intensive counseling was provided at baseline, weekly during treatment, and at 10, 13, 16, 20 and 26 weeks. Abstinence was defined as continuous when the subject was not smoking since the target-quitting day (self-report) and had an expired carbon monoxide concentration of 10 ppm or less.

Results: 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.

Conclusions: Treatment with CBT+bupropion resulted in a better 6-month rate of smoking cessation compared to CBT+nortriptyline or CBT+placebo. Abstinence rate in the nortriptyline group was not statistically different from patients in the bupropion or placebo group.

Keywords: Smoking; Cessation; Counseling; Bupropion; Nortriptyline

One-third of the world adult population uses tobacco products [1]. Cigarette smoking remains the most important cause of preventable morbidity and mortality in developed countries. With the decline in tobacco use in many industrialized countries, the geography of smoking is shifting to the developing world [2].

In Brazil, every year 200,000 people die of tobacco-related illnesses [3]. The prevalence of smoking in Brazil in the 1990s was approximately 31% of the population, with rates varying among the different regions of the country. New data, collected in 2001–2002, show a drop in prevalence to around 20% [4,5].

The relationship between depressed mood and smoking behavior suggested that antidepressant drugs could have a role in smoking cessation. Results of clinical trials of antidepressant therapy for smoking cessation, especially using sustained-release bupropion and nortriptyline, have shown that these drugs are more effective than placebo, and their action is independent of their antidepressant properties. Hurt and colleagues [6] demonstrated that bupropion is an effective smoking cessation aid, with 6-month abstinence rate of 27% compared to 16% for subjects receiving placebo. Hall and colleagues [7] demonstrated that nortriptyline could also be effective in smoking cessation therapy, with a 6-month abstinence rate of 37% compared to
21% for subjects receiving the placebo. However, there are no studies directly comparing the efficacy of these two drugs, nortriptyline and bupropion, for smoking cessation.

Recently, we have shown that in ‘real-life’ conditions, Brazilian smokers do not need special treatment for quit, since the obtained results were similar to the registered in the international literature. In that study, one of the major problems related by the patients was the price of the drugs [8]. The prescription of a drug with more accessible price as nortriptyline probably would permit a greater number of smokers to try to stop smoking in population of low income.

This study was designed to determine the effectiveness of different treatment regimens to quit smoking, comparing bupropion, nortriptyline and placebo in a group of smokers who also received intensive cognitive behavior therapy.

1. Methods

1.1. Subjects, screening and randomization

This randomized, double blind, double-dummy, placebo-controlled study was conducted at São Lucas Hospital of the Pontifical Catholic University (PUCRS), in Porto Alegre, Brazil. The first subject was enrolled in April 2002 and follow-up was completed in March 2003. To be eligible for the study, subjects should to be cigarette smoker of at least 10 pack years of at least 18 years of age, being motivated to quit smoking, and having a Fagerström score of at least 4. Subjects were excluded for the following reasons: serious or unstable clinical or psychiatric disorders (including history of severe depression); pregnancy or lactation; alcohol or any other drug abuse. Exclusion criteria also included current use of other smoking cessation treatments, regular use of other drug abuse. Exclusion criteria also included current use of other smoking cessation treatments, regular use of any other tobacco product and contraindications to either of the drugs used, as history of seizures, recent myocardial infarct or use of monoamineoxidase inhibitors.

Subjects were screened in a pretreatment session by completing a standardized questionnaire, which included topics about his/her smoking history. Of 200 persons screened, 156 were enrolled. The subjects were randomly assigned to one of three treatments: 51 subjects were assigned to the placebo group, 52 subjects to nortriptyline group, and 53 subjects to bupropion group. All of them also received the same cognitive behavior therapy (CBT) based on international guidelines [9]. Therapy included motivation, identification of smoking triggers, coping responses, weight management, and skills to the use of medications. Subjects also received a supportive phone call from one of the authors on the target-quitting date. They also received a pamphlet about smoking-related diseases and smoking cessation tips.

1.3. Follow-up period

Follow-up assessments and relapse prevention counseling were conducted during clinic visits at 10, 13 and 26 weeks. In addition, subjects received phone calls during this period in months 4 and 5. All follow-up counseling sessions lasted at least 15-min.

1.4. Medication

Subjects in the nortriptyline group received an initial dose of 25 mg/day for 5 days, followed by 25 mg nortriptyline capsules in the morning and 50 mg nortriptyline capsules in the evening on days 6–60. In the bupropion group, smokers received an initial dose of 150 mg each morning for 5 days followed by one 150 mg bupropion tablet in the morning and another in the evening on days 6–60. All subjects in the nortriptyline and bupropion groups received in addition placebo tablets or placebo capsules, respectively, in the morning and evening on days 1–60. In the placebo group, patients received one placebo capsule and one placebo tablet in the morning and evening on days 1–60. Placebo capsules were manufactured by Hospital São Lucas Pharmacy and nortriptyline were encapsulated to be identical to placebo. Placebo tablets were manufactured by Almapal Technology, Inc. (São Paulo, Brazil) and were identical to bupropion. Thus, both investigators and patients were blind to the treatment.

1.5. Assessments

At baseline, after an initial interview that included information on smoking history and after a physical examination, vital signs and exhaled carbon monoxide (PiCO Smokerlizer, Bedfont, UK) were recorded, and the Beck Depression Inventory (BDI) and the Fagerström Test Dependence Nicotine (FTDN) were administered. For the BDI, scores higher than 20 indicated moderate-to-severe depression. For the FTDN, scores ranged from 0 to 10, with higher scores indicating more severe dependence. During the follow-up periods, each visit vital signs were recorded, carbon monoxide content of expired air was measured, and self-reported smoking status and adverse events were assessed.

During the treatment and follow-up periods, in each visit...
1.6. **Outcome measures**

For the analyses of the primary outcome, the rate of continuous abstinence at 3 and 6 months of follow-up, 156 patients were included. Subjects were considered abstinent if they reported not smoking since the target-quitting day and had an expired carbon monoxide concentration of 10 ppm or less. Participants to be considered abstinent at 6 months, should also be abstinent at 3 months. All subjects who discontinued treatment early or whose follow-up was lost were classified as smokers.

Secondary outcome measures included withdrawal symptoms and adverse events. The symptoms analyzed were anxiety, craving, irritation, tachycardia, lack of attention and nervousness. A composite symptom score was used to analyze withdrawal; each symptom received a score depending on severity (from zero=no symptom to 3=severe symptoms).

1.7. **Statistical analysis**

Chi-square and analysis of variance (ANOVA) were used to test for baseline differences in demographic and smoking-history variables. All statistical tests were two-sided and had an alpha level of 0.05. Sample size was calculated presuming that abstinence rates for active drug therapy groups (nortriptyline and bupropion) would be twice the placebo abstinence rate.

2. **Results**

2.1. **Baseline characteristics**

The baseline characteristics of the study subjects are shown in Table 1. There were no significant differences among the patients of the three groups.

2.2. **Abstinence rates**

The rates of continuous abstinence were not significantly different among the groups at 3 months of follow up (56.5, 44.2 and 39.2%, \( p > 0.05 \) for the bupropion group, nortriptyline group and placebo group, respectively). At 6 months, only subjects of the bupropion group had a significantly higher rate of abstinence (41.5%) than the placebo group (21.6%, \( p = 0.05 \)). The abstinence rate for the nortriptyline group (30.8%) was not statistically different from the placebo group (\( p = 0.40 \)) and from the bupropion group (\( p = 0.35 \)). Analyses of the rates of continuous abstinence showed that the rates were higher with bupropion than nortriptyline, but this difference was not statistically significant (OR 1.60; 95% CI 0.66–3.86; \( p = 0.35 \)), as shown in Table 2.

### Table 1

**Baseline characteristics of the subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo( ^a )</td>
</tr>
<tr>
<td></td>
<td>( n = 51 )</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>41.5 ± 10.4</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>70.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.2 ± 14.2</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
</tr>
<tr>
<td>Elementary-school or less</td>
<td>25.5</td>
</tr>
<tr>
<td>High-school</td>
<td>49.0</td>
</tr>
<tr>
<td>College graduate or more</td>
<td>25.5</td>
</tr>
<tr>
<td>Pack years</td>
<td>29.1 ± 17.7</td>
</tr>
<tr>
<td>Expired carbon monoxide (ppm)</td>
<td>23.9 ± 9.9</td>
</tr>
<tr>
<td>Fagerstrom score</td>
<td>5.9 ± 1.8</td>
</tr>
<tr>
<td>Beck depression inventory score</td>
<td>12.2 ± 8.0</td>
</tr>
</tbody>
</table>

\( ^a \) Therapeutic regimes included intensive counseling.

### Table 2

**Primary efficacy outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo( ^a )</td>
</tr>
<tr>
<td></td>
<td>( n = 51 )</td>
</tr>
<tr>
<td>Abstinence at 6 mo-no (%)</td>
<td>11 (12.6)</td>
</tr>
<tr>
<td>Odds ration (95%CI)</td>
<td>1.0</td>
</tr>
<tr>
<td>Compared to placebo</td>
<td>(0.61–4.33)</td>
</tr>
<tr>
<td>Compared to nortriptyline</td>
<td>–</td>
</tr>
<tr>
<td>( p )-value</td>
<td>–</td>
</tr>
<tr>
<td>Compared to placebo</td>
<td>–</td>
</tr>
</tbody>
</table>

\( ^a \) Therapeutic regimes included intensive counseling.

2.3. **Withdrawal symptoms**

Patients of all three groups reported similar withdrawal symptoms during the first 2 weeks of treatment, with composite symptom scores of 7.3 ± 5.4, 6.0 ± 3.7 and 5.5 ± 4.6; \( p = 0.31 \) for bupropion group, nortriptyline group and placebo group, respectively.

2.4. **Safety**

Table 3 shows the most common side effects reported by subjects in any of the groups. Dry mouth and drowsiness were the most commonly reported adverse events in the nortriptyline group (67.3 and 19.2%, respectively). In the bupropion group, the most commonly reported adverse events were dry mouth (50.9%), insomnia (50.9%), abdominal cramps (20.8%) and diarrhea (11.3%). There were no severe adverse events during this trial.
In the present study, 30.8% of subjects in the nortriptyline group were abstinent at 6 months, in the same range of rates reported before. However, the abstinence rates of treatment with nortriptyline were not significantly better than placebo in our trial.

The cognitive behavior therapy used in this trial was very intense. This approach may explain the high abstinence rates detected in the placebo group (21.6%). In addition, subjects in our study were all volunteers highly motivated to stop smoking. These factors may have enhanced cessation rates in this group and it is probably the reason why we were not able to show, with this sample size, statistically significant differences between nortriptyline and placebo groups.

The adverse events reported here were similar with literature. The most common adverse events in the bupropion group were insomnia (50.9%) and dry mouth (50.9%), while in the nortriptyline group were dry mouth (67.3%) and drowsiness (19.2%). These symptoms, although frequent, were tolerated, and none of the patients needed to stop the medication due to adverse effects. This finding is similar to other studies with these medications [6, 7,21–23]. Abdominal cramps and diarrhea were related in the bupropion group and in placebo group. Probably, these complain were symptoms of abstinence, sometimes difficult to differentiate from adverse events.

We report here a comparison of the efficacy of nortriptyline and bupropion for smoking cessation, showing that bupropion is a better form of therapy compared to nortriptyline and placebo. Nortriptyline seems to be a well-tolerated drug, but with success rates between those using bupropion and those using placebo.

It is, however, necessary to include a larger number of patients to better evaluate the role of this drug for smoking cessation, specially comparing its efficacy to bupropion and nicotine replacement therapy. So, we are still including more smokers and studying the pharmacogenetic of such drugs in a subset of patients [24,25].

3. Discussion

In this study, we found no significant difference among the three treatments, although bupropion regimen had a higher abstinence rate when compared to placebo. To our knowledge, there is only one another study with this design, comparing smoking abstinence rates in a three-arm design including nortriptyline, bupropion and placebo. All smokers received the same intensive cognitive behavior therapy. In that study, Hall and colleagues [10] found no difference between nortriptyline, bupropion or placebo in a previous study with 1 year of follow-up.

Treatment with bupropion resulted in significantly higher 6-month abstinence rate than the placebo group, similar to previous findings in the literature [6,8,11–16]. Hurt and colleagues [6] and Jorenby and colleagues [13] observed a 6-month abstinence rate of 27 and 35%, respectively. Recently, Tonstad and colleagues [16] demonstrated a 6-month abstinence rate of 45%, a result close to ours 41.5% reported here.

On the other hand, nortriptyline has also been shown to be effective for smoking cessation, albeit in just a few studies. Hall and colleagues [7] in a controlled trial of found 6-month abstinence rate of 37 and 21% for nortriptyline and placebo, respectively. Costa and colleagues [17] in another controlled trial of nortriptyline versus placebo observed an abstinence rate of 20.6% in the nortriptyline group and 5.3% in the placebo group, results comparable to a study by Prochazka et al. [18]. Recently, Prochazka et al. [19] published a study about the role of this drug when added to nicotine replacement therapy.

A recent systematic review shows that the antidepressants bupropion and nortriptyline aid long-term smoking cessation (OR 2.06 and 2.79, respectively). The fact that only some forms of antidepressants increase cessation rates and that they do so regardless of depressive symptoms strongly suggest that their mode of action is independent of their antidepressant effect [20].


