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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

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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 any other tobacco product and contraindications to either of the drugs used, as history of seizures, recent myocardial infarct or use of monoaminooxidase 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].

The Ethics Committee of the University approved the study protocol. All participants provided a written informed consent.

1.2. Treatment period

The treatment period lasted 9 weeks. Target-quitting date was set for the second week, usually day 10. Participants attended six 15-min individual counseling sessions, weekly during the first month and biweekly during the second month. All sessions were conducted by the same physician (co-author FMH) and provided cognitive behavioral therapy 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 treatment and follow-up periods, in each visit vital signs were recorded, carbon monoxide content of expired air was measured, and self-reported smoking status and adverse events were assessed.