

Comparison of Nortriptyline and Bupropion as Smoking Cessation Aids: Implications for Patients with Severe Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Smoking cessation is the single most effective way of preventing progression of chronic obstructive pulmonary disease (COPD), and it is imperative that patients with this disease quit smoking. However, there is only limited information on the role of non-nicotine replacement therapy for achieving smoking cessation in these patients.

Objective: To review the efficacy and toxicity of the 2 most commonly employed forms of non-nicotine replacement therapy and to determine the implications of this information as it pertains to patients with advanced COPD.

Methods: A MEDLINE search was performed for the period 1996–2002 to identify randomized placebo-controlled trials examining the use of bupropion or nortriptyline for smoking cessation. The search terms were “smoking cessation”, “abstinence”, “bupropion”, and “nortriptyline”. Trials with less than 6 months’ follow-up, those examining smoking cessation in patients with primary mental illness, and those dealing with relapse or having a primary objective of identifying predictors of response were excluded from review.

Results: Bupropion and nortriptyline were comparable to each other and both were superior to placebo in terms of smoking cessation. Nuisance side effects occurred more often with nortriptyline.

Conclusions: Bupropion and nortriptyline are both effective therapies for smoking cessation. In patients with advanced COPD, nortriptyline may offer some advantages over bupropion.

Key words: smoking, bupropion, nortriptyline, chronic obstructive pulmonary disease

RÉSUMÉ

Historique : La désaccoutumance au tabac est le moyen le plus efficace de prévenir l'évolution de la maladie pulmonaire obstructive chronique (MPOC), et il est impératif que les patients atteints de MPOC cessent de fumer. Cependant, on ne dispose que de peu de données sur le rôle de la thérapie de remplacement non nicotinique (TRNN) dans la désaccoutumance au tabac chez ces patients.

Objectif : Examiner l'efficacité et la toxicité des deux formes de TRNN les plus utilisées et déterminer la portée des résultats pour les patients atteints de MPOC avancée.

Méthodes : Une recherche sur MEDLINE a été effectuée pour la période allant de 1996 à 2002, afin de repérer les essais cliniques aléatoires comparatifs contre placebo évaluant l'emploi du bupropion ou de la nortriptyline dans la désaccoutumance au tabac. Les termes utilisés pour la recherche étaient «smoking cessation», «abstinence», «bupropion» et «nortriptyline». Les essais comportant une période de suivi inférieure à six mois, ceux évaluant la désaccoutumance au tabac chez les patients atteints d'un trouble mental primaire ainsi que ceux traitent les rechutes ou visent premièrement à déterminer les indicateurs prévisionnels de la réponse ont été exclus.

Résultats : Le bupropion et la nortriptyline étaient comparables et tous deux supérieurs au placebo pour la désaccoutumance au tabac. Les effets indésirables incommodes étaient plus fréquents avec l'emploi de la nortriptyline.

Conclusions : Le bupropion et la nortriptyline sont tous deux des traitements antitabagiques efficaces. Chez les patients atteints d'une MPOC avancée, la nortriptyline pourrait offrir certains avantages sur le bupropion.

Mots clés : tabagisme, bupropion, nortriptyline, maladie pulmonaire obstructive chronique

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INTRODUCTION

Bupropion is one of the most common therapies employed to aid in smoking cessation.¹ In 1999 in Canada, there were approximately 1.1 million visits to a physician for smoking cessation advice. Eighty-five percent of these visits resulted in a drug recommendation, 90% of which were for bupropion.¹ This agent, however, may not be the ideal drug for all patients, as it has been associated with serious allergic, cardiovascular, and central nervous system side effects.²

The adverse effect profile of bupropion may be an even greater problem for patients with advanced chronic obstructive pulmonary disease (COPD). In this population, smoking cessation is desirable, as it may favourably alter the progression of the disease. These patients often have disabling dyspnea, disruptions in the normal sleep cycle, and anxiety secondary to advanced lung disease and malnutrition.³ Bupropion, which is chemically related to the anorectant diethylpropion,⁴ may inhibit the ability of patients with COPD to maintain or gain body weight, which is a desired endpoint to help deal with the chronic respiratory insufficiency. In addition, central nervous system toxicity associated with bupropion may aggravate underlying anxiety and insomnia in this population.

In addition to bupropion, several oral non-nicotine replacement therapies have been studied for smoking cessation, including fluoxetine, sertraline, citalopram, and nortriptyline. The first 3 of these drugs have not been particularly useful, but nortriptyline has found use for this indication.⁵ Given the very limited data (one published paper) for the population of interest (patients with COPD), how should the practitioner make decisions about the most appropriate drug for promotion of smoking cessation? The purpose of this review was to compare published trials of bupropion and nortriptyline with a view to providing guidance for practitioners treating nicotine-dependent patients with COPD.

METHODS

A MEDLINE literature search was performed (for the period 1966–2002) to identify randomized, placebo-controlled trials and meta-analyses examining the use of the antidepressants bupropion and nortriptyline for smoking cessation. The search terms were “smoking cessation”, “abstinence”, “bupropion”, and “nortriptyline.” Only studies with a follow-up duration of at least 6 months were included. Studies that described smoking cessation in patients with primary mental illness were excluded. Trials were also excluded if they dealt with

relapse or if the primary objective was to identify predictors of response to oral therapy. In addition, a recent Cochrane review of antidepressants was examined.⁵

RESULTS

Four trials of nortriptyline^{6,9} and 5 trials of bupropion^{9,13} were identified. A number of other studies involving bupropion were excluded for the following reasons: published in abstract form only,^{14,15} included patients with psychiatric diseases,^{16,17} dealt specifically with relapse,^{18,21} had inadequate duration of follow-up,²²⁻²⁴ was not placebo-controlled,²⁵ or evaluated predictors of success or other aspects of smoking cessation.²⁶⁻²⁹ Only one trial specifically included patients with COPD,¹² and that study population had much less severe disease than the population intended as the focus of the current review. One paper compared nortriptyline and bupropion.⁹

Nortriptyline versus Placebo

Prochazka and others⁶ conducted a double-blind, randomized, controlled trial of nortriptyline in 214 veteran subjects who were already enrolled in a behavioural smoking cessation program. Subjects in the treatment group received nortriptyline, titrated to a target dose of 75 mg/day over 1 week, with target blood concentrations of 50–150 ng/mL, based on concentrations established for the treatment of depression. The primary endpoint was self-reported sustained smoking abstinence within 1 week, confirmed by an expired carbon monoxide concentration of 9 ppm or less and verified by urine cotinine concentration of less than 50 ng/mL at 6 months. The point prevalence abstinence rate was significantly higher at 6 months in the nortriptyline group (14%) than in the placebo group (3%), an absolute difference of 11%. The number needed to treat to achieve abstinence in one patient was 9 (95% confidence interval [CI] 6–25). The incidence of adverse effects was significantly higher in the nortriptyline group than the placebo group: dry mouth (59% v. 22%), dysgeusia (19% v. 8%), gastrointestinal upset (38% v. 23%), and drowsiness (22% v. 8%).

Nortriptyline was also evaluated as a smoking cessation aid by Hall and others.⁷ This randomized, double-blind, placebo-controlled trial enrolled 199 participants and employed a 2 x 2 x 2 factorial design, in which the efficacy of nortriptyline was assessed, along with that of cognitive behavioural therapy and health education. The duration of follow-up was 64 weeks. Patients were further classified with respect to the presence or absence of major depressive disorder. A

history of major depressive disorder was present in 65 (33%) of the patients. Nortriptyline was associated with a better smoking cessation rate after 12 weeks of treatment (as assessed by carbon monoxide concentrations less than 10 ppm and urine cotinine concentrations less than 341 nmol/L) than placebo (odds ratio [OR] 2.4, 95% CI 1.8–3.4, $p < 0.04$). The absolute risk reduction for this endpoint was 17%, and the number needed to treat was 6. In the nortriptyline group, 24% of the subjects achieved continuous abstinence over the 64-week trial, compared with 12% in the placebo group (OR 2.3, 95% CI 1.1–5.0), which translates to a number needed to treat of 8. The incidences of dry mouth (78% v. 33%), lightheadedness (49% v. 22%), shaky hands (23% v. 11%), and blurred vision (16% v. 6%) were significantly higher in the nortriptyline group than in the placebo group. The authors concluded that there is evidence to support use of nortriptyline for smoking cessation in patients with or without a major depressive disorder.

A third study⁸ evaluated the efficacy of nortriptyline relative to that of placebo in 144 patients enrolled in a 5-week antismoking program. The primary endpoint of this randomized, double-blind study was smoking cessation for at least 1 week at the end of the 5-week behavioural program. Secondary endpoints included 3- and 6-month abstinence rates, adherence, and side effects. The investigators also performed a univariate analysis of prognostic factors influencing cessation rates.

The 6-week cessation rate was significantly higher among patients receiving nortriptyline than those receiving placebo (44% v. 19%, $p < 0.001$). The absolute risk reduction was 25%, resulting in a number needed to treat of 4. Abstinence rates at 6 months were 21% for the nortriptyline group and 5% for the placebo group (number needed to treat 6). The most common side effects cited were dry mouth and constipation; however, the incidence of adverse effects in the 2 groups was not significantly different. In this study,⁸ the Fagerstrom questionnaire was used to determine the degree of nicotine dependence. Patients scoring at least 7 points were considered highly nicotine-dependent. In the univariate analysis of prognostic factors influencing smoking cessation, the Fagerstrom test score ($p = 0.005$) and use of nortriptyline ($p < 0.001$) were the only significant prognostic factors. In the subset of patients with Fagerstrom scores of at least 7, nortriptyline was highly effective for smoking cessation ($p < 0.001$), but in patients scoring less than 7 points, there was no difference in cessation rates between nortriptyline and placebo ($n = 20$ in both groups, $p = 0.1$). Although the subgroup analysis was underpowered, these findings suggest, but do not

prove, that nortriptyline may be effective only for patients with a strong ~~physiological~~ dependence on nicotine. In the study by Prochazka and others,⁶ Fagerstrom test score did not significantly influence cessation rates, but the average score in that study was 5.8, which is under the 7-point cut-off used by da Costa and others.⁸

Bupropion versus Placebo

A double-blind, randomized, placebo-controlled trial of bupropion for smoking cessation was conducted by Jorenby and others.¹⁰ Subjects were randomly assigned to receive placebo, nicotine patch (21 mg during weeks 2 to 7, 14 mg during week 8, and 7 mg during week 9), bupropion (150 mg every morning for 3 days, then 150 mg twice a day for a total of 9 weeks), or bupropion plus nicotine patch (with the previously described dosage schedules). The primary endpoints were point prevalence rates of abstinence at 6 and 12 months of follow-up. Secondary endpoints included withdrawal symptoms, body weight, and Beck Depression Inventory score. At 6 months, point prevalence rates were lower in the bupropion group than the placebo group (35% v. 19%, absolute risk reduction of 16%, number needed to treat 6). Similar results were reported for 12-month abstinence rates (bupropion 30%, placebo 16%, absolute risk reduction 14%, number needed to treat 7). The incidence of weight gain was significantly higher in the placebo group than among bupropion-treated patients. The authors concluded that bupropion alone or in combination with the nicotine patch is effective for promoting long-term smoking cessation.

Hurt and others¹¹ conducted a randomized, double-blind, placebo-controlled dose-response study that compared the efficacy of sustained-release bupropion 100 mg, 150 mg, or 300 mg in 615 volunteers. The target quit date was set at 1 week after treatment initiation, and self-reported abstinence was confirmed by carbon monoxide concentration in expired air of 10 ppm or less at 7 weeks. At 6 months, point prevalent abstinence rates were 28% in the bupropion 150 mg group and 16% in the placebo group ($p < 0.05$). At 12 months, abstinence rates were 23% in patients treated with bupropion 150 mg and 12% in the placebo group ($p < 0.05$). These data translate to absolute risk reductions of 12% and 11% at 6 and 12 months, respectively, with numbers needed to treat of 8 and 9. Abstinence rates for patients receiving the 300-mg dose were also significantly higher than those in placebo-treated patients at 6 and 12 months. However, there were no significant differences in 6- or 12-month abstinence rates for patients receiving bupropion 100 mg and those receiving placebo. Common side effects



included insomnia (in 21% of the placebo group, 29% of the bupropion 150 mg group, and 33% of the bupropion 300 mg group; $p = 0.008$ for comparison of 300-mg dose with placebo) and dry mouth (in 5% of the placebo group, 13% of the bupropion 150 mg group, and 13% of the bupropion 300 mg group; $p = 0.01$ for comparison of 150-mg and 300-mg doses with placebo). The 300-mg dose was more effective initially, but the 300-mg and 150-mg doses were equally effective at 1 year. The authors recommended the 300-mg dose (150 mg twice daily) on the basis of higher initial cessation rate and a similar side effect profile.

Tashkin and others¹² conducted a randomized, double-blind, placebo-controlled study of bupropion (150 mg daily for 3 days, then 150 mg twice daily for 80 days) for smoking cessation in subjects with (primarily) mild COPD. A total of 411 subjects underwent randomization, 404 received at least one dose of medication, and 278 completed the 6-month follow up. The primary efficacy measure was self-reported continuous abstinence for 4 weeks (weeks 4 through 7 of the trial), which was confirmed by exhaled carbon monoxide concentration of less than 10 ppm. The continuous 4-week abstinence rate was significantly higher in the bupropion group than the placebo group (28% v. 16%, $p = 0.003$), which translated into an absolute difference of 12% and a number needed to treat of 8. Five percent of the patients in each group were withdrawn from the study. The most common causes of withdrawal were anxiety (5 patients) and insomnia (4 patients) in the bupropion group and headache (3 patients) in the placebo group. Adverse events that were frequently reported in the bupropion and placebo groups included insomnia (24% v. 12%), headache (6% v. 6%), and dry mouth (6% v. 5%).

Ahluwalia and others¹³ conducted a randomized, placebo-controlled trial of bupropion 300 mg daily for 7 weeks in 600 African-American subjects. Slightly fewer than 30% of the subjects were characterized as having possible clinical depression. According to an intention-to-treat analysis, the abstinence rates were 36% in the bupropion group and 19% in the placebo group. At 26 weeks, the abstinence rates were 21% and 14%, respectively. Patients with continuous abstinence had lower withdrawal scores and were more likely to gain weight (although the degree of weight gain was not reported). Patients who received bupropion had lower body weight over time. Fewer symptoms of depression were reported by patients receiving bupropion during the first 7 weeks. Although the effect on smoking cessation diminished with time, abstinence rates remained higher

in the bupropion group at 26 weeks. Differences in degree of weight gain and depressive symptoms were no longer significant at 26 weeks. Insomnia was reported more frequently in the bupropion group (29%) than the placebo group (21%).

Nortriptyline versus Bupropion

Only one trial has compared the efficacy of nortriptyline with that of bupropion.⁹ This randomized, controlled trial of 220 smokers employed a 2 x 3 design: medical management versus psychological intervention, and bupropion versus nortriptyline versus placebo. Exclusion criteria were current major depressive disease or use of any psychiatric medication, prior use of nortriptyline or bupropion, or any admission to hospital for psychiatric reasons within the previous year. Medical management included advice to stop smoking, written information about smoking cessation, and monitoring of adverse effects. Time was set aside over the first 11 weeks (approximately 35 minutes in total) to discuss the patient's progress with smoking cessation. The psychological intervention consisted of medical management plus 5 group sessions. At 24 weeks, both drugs were superior to placebo, with abstinence rates of 24%, 22%, and 16% associated with bupropion, nortriptyline, and placebo, respectively. Psychological intervention was found to be more effective than medical management, with quit rates of 26% and 16%, respectively. The incidence of withdrawal due to adverse effects was 8%, 4%, and 4% in the bupropion, nortriptyline, and placebo groups, respectively, and withdrawal from the study for any reason occurred in 15%, 10%, and 26% of the patients in these 3 groups. At 52 weeks, the abstinence rate for participants without a history of major depressive disease (approximately two-thirds of the study population) was 27% in the nortriptyline group and 24% in bupropion group; among patients who had a history of major depressive disease, the abstinence rates were 16% in the nortriptyline group and 38% in the bupropion group.

DISCUSSION

Both nortriptyline and bupropion have been associated with improvements in smoking cessation rates, and both drugs have been cited as effective in a Cochrane review⁵ and by the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines.³

Placebo-controlled trials have documented the effectiveness of bupropion and nortriptyline for smoking cessation. The one trial in which the effectiveness of these



drugs was compared directly suggested that bupropion and nortriptyline are equally effective. However, a larger proportion of patients who were being treated with bupropion withdrew from the study than was the case in the nortriptyline group. Subgroup analysis suggested that bupropion may be more effective than nortriptyline in patients with major depressive disease but that the drugs are equally effective in patients with no history of major depressive disease.

According to these data, in patients with advanced COPD who do not have major depressive disease, appropriate smoking cessation therapy should be selected primarily on the basis of adverse effects. In the study directly comparing the effectiveness of bupropion and nortriptyline for smoking cessation,⁹ nuisance side effects such as dry mouth and constipation occurred more commonly in nortriptyline-treated patients, but the incidence of withdrawal from the study because of adverse effects was higher in the bupropion group. Furthermore, Health Canada has issued an advisory regarding severe reactions associated with bupropion.²

For patients with COPD, smoking cessation is the only intervention that attenuates the abrupt progressive decline in pulmonary function.³⁰ Patients with more advanced pulmonary disease may also experience weight loss because of the increased oxygen demands associated with the disease. Weight loss has been identified as a prognostic factor for death, and therefore weight gain is desirable and improves survival in this population.³¹ In view of comparable efficacy and a lower incidence of adverse effects necessitating drug discontinuation, nortriptyline appears to offer advantages over bupropion for smoking cessation in patients with COPD.

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