Effectiveness of Sustained-Release Bupropion in the Treatment of Smoker Patients with Cardiovascular Disease

Jaqueline Scholz Issa, Glória Heloise Perez, Jayme Diament, Angela Giuliana Zavattieri, Kátia Ulrich de Oliveira
Instituto do Coração do Hospital das Clínicas – FMUSP – São Paulo, SP - Brazil

Summary

Objectives: To evaluate the effectiveness of and tolerability to sustained-release bupropion, in smokers with cardiovascular diseases treated in a smoking cessation service, as well as to investigate variables predictive of success or failure in smoking cessation.

Methods: Sustained-release bupropion was prescribed to 100 current smokers with cardiovascular disease for 12 weeks. Patients were followed for 52 week. The variables studied were gender, age, number of cigarettes, exhaled carbon monoxide, nicotine dependence (Fagerstrom Tolerance Questionnaire), depression (Beck Depression Inventory), anxiety (State-Trait Anxiety Inventory), alcohol consumption (Alcohol Use Disorders Identification Test), number of diagnoses other than smoking, adverse events, and use of medications concomitantly with sustained-release bupropion.

Results: Abstinence rate was 50% at week 12 and 25% at week 52. The logistic regression analysis showed that ageing was positively associated with success, whereas the worsening of the condition, as verified by the presence of a higher number of other health conditions associated with smoking, was negatively associated with success.

Conclusion: We conclude that the prescription of bupropion for smokers with cardiovascular diseases proved to be safe and effective, especially during the treatment period (week 12).

Key words: Bupropion; smoking/treatment; cardiovascular diseases.

Introduction

Smoking cessation in patients with atherosclerotic cardiovascular disease is indeed a great challenge. Although the morbidity and mortality rates from cardiovascular diseases decline by 50% after smoking cessation[1], part of this population finds it difficult to quit smoking. Finding effective methods for helping smokers with heart disease quit smoking has become a strategic need in the treatment of cardiovascular diseases.

Because sustained-release bupropion is effective when compared to nicotine replacement therapy (NRT)[2] and placebo[3], it has been used as first-line treatment for smoking cessation since 2001[4].

Objective

The primary objective of this study was to evaluate the effectiveness of sustained-release bupropion in smoking cessation in smokers with cardiovascular diseases followed up on an outpatient basis for smoking treatment. The secondary objective was to observe drug tolerability, taking into account the routine use of several chronic medications by the study population. Additionally, this study aimed at investigating variables that could predict success or failure in smoking cessation.

Mailing address: Jaqueline Scholz Issa •
R. Dr. Estevam de Almeida, 74/64 – 05014-010 – São Paulo, SP
E-mail: jissa@cardiol.br
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Methods

Sustained-release bupropion was prescribed as a single drug in the treatment of smoking in 100 smokers with cardiovascular diseases followed up on an outpatient basis. Their age ranged from 24 to 75 years; 40 were females and 60 were males.

Exclusion criteria were history of convulsion; anorexia; bulimia; sequelae of stroke; previous neurosurgery; head trauma; alcohol abuse; uncontrolled diabetes mellitus; hepatic failure; use of monoamine oxidase inhibitors; bupropion use; or any other smoking cessation treatment.

Clinical study - After signing the consent form, the patients were clinically assessed, and the exhaled carbon monoxide (CO) concentration was measured with the Smokerlyser Bedfont instrument. The smoking cessation treatment was based on the prescription of sustained-release bupropion for 12 weeks and medical follow-up. Patients were instructed to take one 150-mg tablet for 3 days, and, after the fourth day; an additional 150-mg tablet was to be taken 8 hours after the first tablet. This dose was maintained up to week 12. Patients were told to stop smoking on the eighth day after the first day of medication and not to drink alcoholic beverages during treatment.

The Fagerström Tolerance Questionnaire[5] was used to assess nicotine dependence. The total score ranges from 0 to 10, with scores ≥6 indicating nicotine dependence. Depression was evaluated with the Beck Depression Inventory (BDI) [6,7].This

scale is comprised of 21 items, with response scores ranging from 0 to 63, assessing the presence and severity of depressive symptoms. The cut-off point criterion used was that proposed by the Center for Cognitive Therapy, with scores ≥10 indicating depressive mood. The State and Trait Anxiety Inventory (STAI)[8,9] was used to assess anxiety. Two scales with 20 items each comprise this inventory. One of them evaluates the anxiety state, which is characterized by the subjective perception of feelings of tension and apprehension followed by reactions of the autonomic nervous system at a particular moment. Trait anxiety, analyzed with the other scale, refers to a relatively stable tendency to perceive situations as threatening and to react to them with anxiety. Alcohol consumption was evaluated with the AUDIT – Alcohol Use Disorders Identification Test[10], with Portuguese version by Figlie[11], which is a 10-item questionnaire that assesses alcohol consumption, abuse, and dependence. Scores range from 0 (no use) to 40, with scores ≥8 indicating alcohol abuse or dependence.

All questionnaires were applied during the baseline visit.

Subsequent evaluations were conducted at weeks 3, 8, 12, 24, and 52. The smoking status reported by the patient was confirmed by exhaled carbon monoxide measurements. The presence of adverse events reported during the use of sustained-release bupropion as well as the clinical course throughout the 52-week patient follow-up were analyzed.

Statistical analysis - Patients were divided, according to the main outcome of smoking cessation, into 2 groups: Success Group (SG) and Failure Group (FG). They were assessed at two moments: at weeks 12 and 52. The latter was focused on finding variables related to smoking relapse, excluding patients who had already failed to quit smoking with sustained-release bupropion at week 12.

The variables studied were gender; age; number of cigarettes per day; exhaled carbon monoxide concentration; nicotine-dependence score; alcohol consumption; use of chronic medications; number of diagnoses other than smoking (comorbidities); adverse events related to the use of bupropion; depression, anxiety trait, and anxiety state.

The chi-square test or Fisher's exact test were used in the univariate analysis for categorical variables, and the Student *t* test or Mann-Whitney test were used for continuous variables with normal or non-normal distribution, respectively. A multivariate analysis was performed using the logistic regression model. The forward method was used to select explanatory variables; p values < 0.05 were considered significant.

SPSS for Windows version 10.0 was used for the statistical analysis.

Results

The most frequent clinical diagnoses were coronary artery disease, arterial hypertension, and dyslipidemia (Figure 1).

Success rate for smoking cessation was of 50% at week 12 and 25% at week 52 (Figure 2).

With regard to the number of medical comorbidities and adverse events (Table 1), the univariate analysis at week 12 revealed significant differences among patients in the success and failure groups (Table 1).

A significant difference was verified when comparing success rates among men and women (Figure 3), thus raising interest in comparisons between genders. Significant differences were also observed between men and women relative to age, comorbidities, use of medications, occurrence of adverse events, depression and anxiety scores, and alcohol consumption. Compared with men, women were younger, more depressive and anxious, had fewer medical comorbidities, used fewer medications, and consumed less alcohol. Additionally, women referred a greater number of adverse events than men (Table 2).

Logistic regression analysis included gender, age, alcohol consumption, side effects, comorbidities, BDI, and anxiety trait and state score variables. Age was positively correlated whereas comorbidities were negatively correlated with success (Table 3). That is, older and healthier patients were more likely to achieve success at week 12 when compared with younger, sicker individuals. The other variables, including gender, were not statistically significant in the multivariate analysis.

At week 52 of follow-up, success rate was 25%, that is, 50% of the patients of both genders relapsed. A total of 13 women (32.5%) and 12 men (20%) were abstinent. No significant difference was observed between genders.

Univariate analysis and logistic regression analysis performed in the late phase of the study (week 52) did not demonstrate

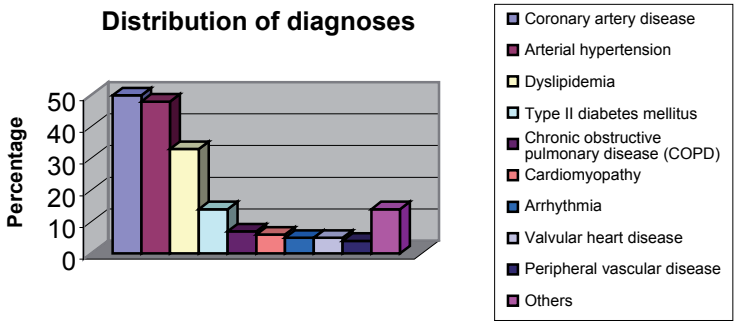

Fig. 1 - *Frequency of distribution of diagnoses in studied population.*

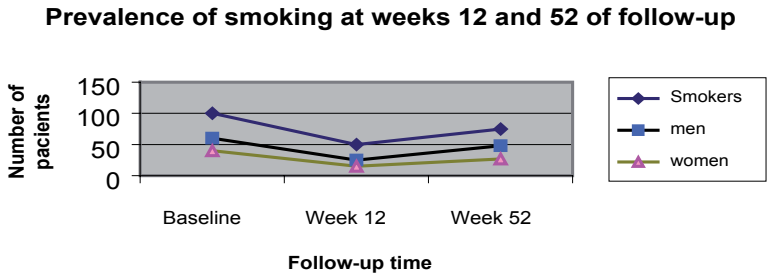

Fig. 2 - *Smoking prevalence at weeks 12 and 52 of the follow-up.*

Table 1 - Comparison of success and failure rates at week 12 of treatment with sustained-release bupropion using the univariate analysis

Variable	Success group (n= 50)	Failure group (n= 50)	p-Value
Age (years)	52.6 ± 10.5	50.6 ± 9.9	0.31
Carbon Monoxide (ppm)	14.3 ± 7.4	16.5 ± 8.5	0.19
Number of cigarettes	20.4 ± 6.61	23,9 ± 13.1	0.09
Comorbidities	1.6 ± 0.8	2.3 ± 1.1	0.001*
Number of medications	2.8 ± 1.7	3.4 ± 2	0.137
Dependence score	6.9 ± 0.68	6.8 ± 1.2	0.61
Adverse events	2.1 ± 1.1	1.5 ± 1.2	0.02 *
Alcohol consumption	1.1 ± 4.7	1.7 ± 4.2	0.53
Anxiety trait	46 ± 12	44 ± 11.7	0.45
Anxiety state	43.5 ± 11.4	44.9 ± 13	0.62
Depression Inventory	12 ± 8.7	12 ± 9	0.99

** = p>0.05. Note: Variables expressed as mean and standard deviation.*

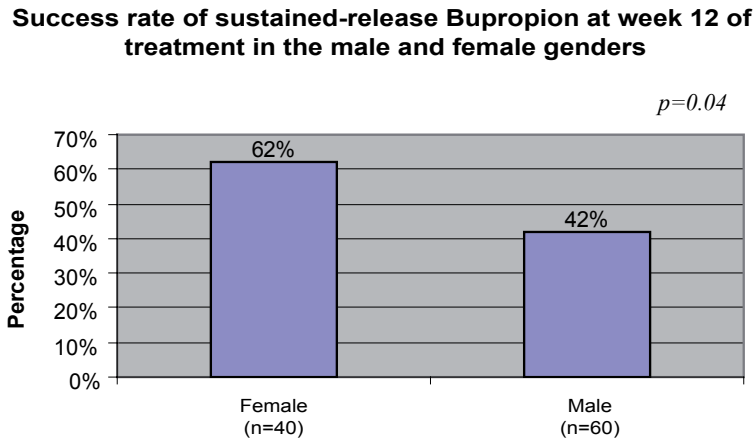

Fig. 3 - *Success rate of sustained-release bupropion at week 12 by gender.*

Table 2 - Comparison between genders

Variable	Female (n=40)	Male (n=60)	p-Value
Age (years)	48 ± 9.1	53.9 ± 10.2	0.004 *
Number of cigarettes	23.6 ± 10.1	21.2 ± 10.8	0.24
Carbon monoxide (ppm)	15.1 ± 7.6	16.5 ± 8.6	0.48
Comorbidities	1.4 ± 0.8	2.3 ± 1.1	<0.001*
Dependence score	6.9 ± 0.9	6.7 ± 1.1	0.41
Adverse events	2.2 ± 1.3	1.5 ± 1	0.008 *
Number of medications	2.5 ± 1.7	3.7 ± 1.9	0.004*
Depression Inventory	14.6 ± 8.1	10.1 ± 8.8	0.02*
Trait anxiety	50.2 ± 11.1	41.9 ± 11.1	0.001*
Anxiety state	48.2 ± 11.3	42.0 ± 10.8	0.014*
Alcohol consumption	0.31 ± 1.11	2.23 ± 5.78	0.03 *
Consumo de álcool	0,31 + 1,11	2,23 + 5,78	0,03*

** p<0.05. Note: Variables expressed as mean and standard deviation.*

Table 3 – Variables predictive of success at week 12 of treatment with sustained-release bupropion as determined by the logistic regression model

Variable	p value	Odds ratio (95% confidence interval)
Age	0.026	1.07 (1.007-1.125)
Comorbidities	< 0.001	0.33 (0.182-0.607)

variables correlated with success and/or failure (Table 4).

Tolerability - Medication was discontinued in 9% of the patients due to angioedema (1%), severe anxiety attack (4%), skin rash (1%), dizziness (1%), nausea (1%), and headache (1%). The most frequent adverse events were: dry mouth (44%), insomnia (interrupted sleep – 30%), and constipation (14%). In the majority of cases, insomnia resolved between weeks 3 and 4 of treatment (Figure 4). No increased blood pressure levels were reported among hypertensive patients taking the medication. Also, no drug interaction was observed between sustained-release bupropion and the medications routinely taken by the patients. The frequency distribution of medications is shown in Figure 5.

Clinical course - During the observation period, 3 deaths (stroke, lung cancer, and ischemic cardiomyopathy) and 3 nonfatal cardiovascular events (2 myocardial infarctions and 1 stroke) occurred. Patients were not using sustained-release bupropion when these events occurred, and all were in the failure group.

Table 4 – Comparison between success and failure groups at week 52 of follow-up using the univariate analysis

Variable	Success group (n = 25)	Failure group (n = 25)	Valor de p
Age (years)	53 + 7.9	52.2 + 12.7	0.78
Carbon monoxide concentration (ppm)	12.9 + 5.5	15.8 + 9	0.19
Number of cigarettes	21.6 + 6.7	19 + 7.2	0.18
Comorbidities	1.7 + 0.8	1.6 + 0.9	0.75
Number of medications	2.8 + 1.6	2.9 + 1.7	0.74
Dependence score	7.04 + 0.6	6.7 + 0.7	0.14
Adverse events	2.2 + 1	1.9 + 1.2	0.31
Depression inventory	11.6 + 9.5	12.3 + 8.1	0.62
Anxiety trait	48.1 + 13.6	44.1 + 10	0.35
Anxiety state	44.5 + 14.1	42.6 + 8.4	0.58
Alcohol consumption	0.5 + 1.3	1.7 + 6.5	0.98

*n = number of patients. * p < 0.05. Note: Variables expressed as mean and standard deviation.*

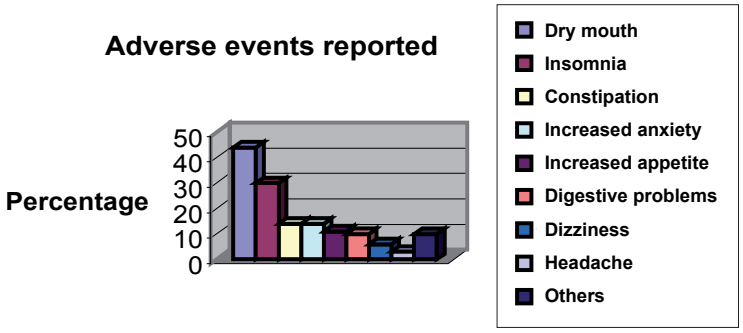

Fig. 4 - *Frequency of adverse events reported with sustained-release bupropion.*

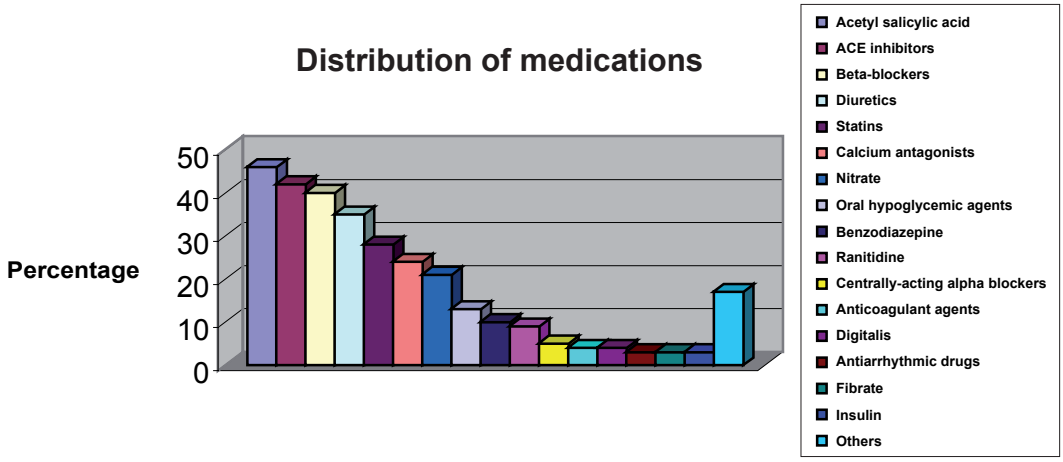

Fig. 5 - *Frequency of distribution of routinely taken medications in studied population.*

Discussion

The smoking cessation rate during use of sustained-release bupropion (week 12) was 50%, which is similar to those obtained in treatment protocols of smokers without medical comorbidities[3].

The differences in success rates observed between men and women at week 12 (62.5% women vs. 41.7% men) using the univariate analysis may have been influenced by the presence of confounding variables (Table 2). In the logistic regression, gender was not a predictor of success. Anyway, other differences between genders may have influenced the higher success rates observed among women. Higher consumption of alcoholic beverages among men may have interfered in the result, considering that all patients were instructed to completely interrupt alcohol consumption while using sustained-release bupropion, thus suggesting the possibility of a lower compliance to treatment among male patients. Another important fact was the significant difference in the frequency of adverse events reported among women. Studies on bupropion associate higher frequencies of adverse events with the presence of therapeutic serum levels[12]. These facts suggest that there was higher compliance to treatment among women, and this may consequently have influenced the higher success rate at week 12 of the study. However, the higher compliance among women should be considered as a hypothesis, since serum sustained-release bupropion levels were not determined during the study. Additionally, depression and anxiety scores were significantly higher among women when compared with those among men (Table 2), and the use of bupropion is known to be associated with a reduction in anxiety and depression levels[13], which could also have contributed to the higher compliance to the treatment among women.

The Beck Depression Inventory used to assess depressive symptoms in the present study was not significantly different in the success group in relation to the failure group both during the phase of bupropion use (12 weeks) and during the 52-week follow-up, although the mean score had been higher than 10 in both groups, thus suggesting the presence of depressive symptoms.

Data suggest that depressive smokers had 40% less chance to succeed in smoking cessation[14] than non-depressed smokers before the introduction of bupropion. Considering that

bupropion has an antidepressive effect through a mechanism involving increase in dopamine and norepinephrine levels, a higher efficacy in depressive smokers is possible, and this would explain why different results were not obtained between the success and failure groups.

Ageing and the presence of a higher number of comorbidities were predictive of success. Paradoxically, sicker patients were those who most frequently failed to quit smoking. Possibly, the deterioration of the clinical status causes patients to disbelieve in the benefits of smoking cessation. Ageing increases the likelihood of success, and this has already been observed in other studies on smoking treatment[15].

Detection of variables predictive of relapse was not possible in this study, and relapse rates were 50% for both genders at week 52.

Studies[16] suggest that relapse rates may be reduced with the use of bupropion for a period longer than 12 weeks and this may actually be a way to maintain the success rates obtained at week 12 of treatment.

Smokers not willing to restrict alcohol consumption during smoking cessation treatment should be prescribed nicotine replacement therapy instead of bupropion to prevent treatment discontinuation, as was observed among the male patients.

Reporting of improvement of clinical status in 88% of the patients who quit smoking is a very significant fact. The prospect of improvement in the clinical status should be used to encourage and motivate patients with cardiovascular diseases to quit smoking.

Patients with worsened clinical status should be emphatically instructed on the benefits that smoking cessation will bring to their health conditions. Additionally, we understand that the most appropriate moment for a smoker with cardiovascular diseases to participate in a smoking cessation program is the period immediately following the cardiovascular event that resulted in hospitalization, because data suggest that 50% of the smokers quit smoking after such an event. This rate is attributed to smoking restriction in the hospital environment and to the fact that the patients are highly motivated. However, 50% of the smokers who quit smoking after hospitalization due to cardiovascular disease relapse within 6 months of the cardiovascular event that resulted in smoking cessation[17].

Approaching smokers during hospitalization could reduce relapse rates[18], thus preventing them from resuming smoking and, more importantly, it would prevent a later reduction in the probability of success due to deterioration of the clinical condition, in a less favorable psychomotivational stage, as was observed in this study. The greater number of medical comorbidities, indicating a poorer clinical condition, was an important predictor of failure in our case series (Table 3).

Conclusion

In conclusion, sustained-release bupropion is safe and effective in the treatment of smokers with cardiovascular diseases, and factors like age and the presence of comorbidities interfere with the success rates obtained.

The retrospective comparison of the high success rates observed among women in this study with the results of studies with nicotine replacement therapy[19] allows us to consider that sustained-release bupropion is the treatment of choice for smoker women with cardiovascular diseases.

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