ONLINE FIRST

Bupropion for Smoking Cessation in Patients With Acute Coronary Syndrome

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Background: Smokers hospitalized with acute coronary syndrome (ACS) are at high risk for subsequent ischemic events. Nevertheless, over two-thirds of patients continue to smoke after an acute myocardial infarction. Bupropion hydrochloride has proven efficacy as a smoking cessation aid, but data regarding its safety and efficacy in ACS patients are limited.

Methods: In a double-blind, randomized controlled trial, we compared the safety and efficacy of 8 weeks of treatment with bupropion slow-release (SR) or placebo for smokers hospitalized with ACS as an adjunct to nurse-led hospital- and telephone-based support. Primary efficacy outcome was smoking abstinence at 1 year. Primary safety outcome was clinical events at 1 year.

Results: A total of 151 patients were enrolled; all but 2 completed follow-up. Abstinence rates at 3 months were 45% and 44% in the bupropion SR and placebo groups, respectively ($P=.99$); 37% vs 42% ($P=.61$) at 6 months; and 31% vs 33% ($P=.86$) at 1 year. On multivariate analysis, an invasive procedure performed during index hospitalization was an independent predictor for smoking abstinence at 1 year (odds ratio [OR], 4.2; 95% confidence interval [CI], 1.22-14.19). Presence of adverse effects attributed to treatment was a negative predictor for smoking cessation (OR, 0.23; 95% CI, 0.07-0.78). Treatment with bupropion SR was not associated with an increase in clinical events or change in blood pressure or body mass index, but dizziness was more common compared with placebo (14% vs 1.4%; $P=.005$).

Conclusion: In hospitalized patients with ACS who received continuous, intensive nurse counseling about smoking cessation, bupropion did not increase the rates of smoking abstinence.

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CIGARETTE SMOKERS ARE 3 times more likely to experience a myocardial infarction (MI) than nonsmokers. Persistent smoking following an acute MI carries a 50% higher chance of death in the first 2 years.[1,2] Smoking cessation is considered a highly cost-effective intervention in these patients, with 1 death prevented for every 11 patients who stopped smoking.[1] Physicians inform patients about the overwhelming evidence demonstrating the cardiovascular hazards of tobacco use and the health benefits from smoking cessation, but more than two-thirds of patients will continue to smoke after an MI, even after a brief hospital-based smoking cessation intervention.[3] This has led the Joint Commission on the Accreditation of Health Care Organization to include smoking cessation professional assistance after acute MI as a quality-of-care measure for US hospitals with 90% availability in 2006.[4]

Bupropion hydrochloride slow release (SR) is an antidepressant with the most established evidence as a smoking cessation aid. Treatment with bupropion doubles the odds of long-term smoking cessation.[5,6] Bupropion was shown to be more effective than nicotine replacement therapy for ambulatory smoking cessation in the general population,[7,8] as well as effective and safe in patients with stable cardiovascular disease.[9,10]

In a recent systematic review, the most effective method for smoking cessation support in hospitalized patients was found to be nurse-led motivational support with continued telephone counseling after discharge. Adding nicotine replacement therapy resulted in a nonsignificant trend toward efficacy over counseling alone.[11,12] Pharmaceutical cessation aids may double smoking cessation and reduction rates, but only 1 trial has examined the safety and efficacy of bupropion in hospitalized patients with acute coronary syndrome

(ACS).[13] In this study, bupropion was reported to be safe for use in patients with ACS and increased short-term quitting rate at 3 months but was not superior to placebo after 1 year of follow-up.

In light of the proven efficacy and safety of bupropion in patients with stable cardiovascular disease, and the need for further studies in patients with ACS, the aim of the current study was to evaluate the long-term efficacy and safety of adding bupropion SR to in-hospital and postdischarge counseling and to determine the predictors of smoking abstinence at 1 year in these high-risk patients.

METHODS

We performed a randomized, double-blind, placebo-controlled trial in the 2 separate campuses of the Hadassah Medical Center in Jerusalem, Israel. We evaluated the efficacy and safety of bupropion SR in hospitalized patients with ACS. Nurses and physicians participating in the trial were hospital staff with some experience in smoking cessation who received additional coaching from a smoking cessation specialist (I.L.). The training included 5 sessions in which the smoking cessation specialist explained the significance and evidence for in-hospital and outpatient counseling and options for medical therapy for smoking cessation. In addition, practical training was given to the staff. The study was approved by the institutional ethics committee, and all participants gave informed consent.

PARTICIPANTS

Inclusion criteria for this trial included adults hospitalized for ACS (including unstable angina and MI), weighing more than 45 kg and smoking more than 10 cigarettes/d. Patients were required to exhibit intention to quit smoking. Patients were excluded from participating if they had prior use of bupropion in the past year or nicotine replacement therapy in the past 6 months; had a known sensitivity to bupropion; had epilepsy or prior major head trauma and/or surgery; had clinical depression or was prescribed antidepressants; had been diagnosed as having anorexia nervosa and/or bulimia; exhibited liver or kidney dysfunction; or were receiving treatment with monoamine oxidase inhibitors. Pregnant or lactating women were also excluded.

RECRUITMENT

Smokers hospitalized with ACS were approached on their second day of hospitalization by a research nurse (M.C.), who introduced the patient to the importance of smoking cessation and the trial's protocol and randomization process. The inclusion and exclusion criteria were evaluated, and the patient's medical and laboratory data were obtained, including demographics and the Fagerström tobacco addiction questionnaire.[14]

INTERVENTION

Participants were randomized to bupropion SR (hereinafter, bupropion group) or identical placebo. Numbered study bottles were supplied by the study coordinator and remained concealed from the patients and medical staff. All participants were forcedly abstinent from smoking during the hospitalization. Participants began to take the study medication during the index hospitalization.

The participants were instructed to take the study pill, bupropion SR, 150 mg, or identical placebo, once a day for 3 days, and then twice a day for 2 months. Participants were told to take medication regardless of smoking status. Counseling consisting of at least 15 minutes of motivational support was given to all participants during hospitalization and continued after discharge.

FOLLOW-UP

After 1 month of treatment, patients were invited for a hospital-based assessment of health status, support counseling, and a clinical follow-up. Compliance with medications (by counting the remaining pills) and with smoking abstinence was evaluated by the interviewer. During this visit, the patient received the second bottle of medication or placebo. At least 2 planned face-to-face encounters with a study physician and a research nurse were performed after hospital discharge (at 1 and 2 months) and by telephone-based follow-up thereafter.

Planned weekly telephone-call follow-up was accomplished by the research nurse during the first and second months, and during the rest of the year with a monthly telephone call. Telephone calls included motivational support and a semistructured interview exploring adherence to research protocol, possible adverse effects of the medication, and changes in health and smoking status. Specifically, the participants were asked whether they remained completely abstinent from smoking, and if not, when they returned to smoking and how many cigarettes they smoked per day. Any patient who returned to smoking was given at least 10 minutes of motivational support to attempt quitting again; the drug regimen was not changed. The total planned time of face-to-face and telephone-call interviews was at least 100 minutes during the first 2 months, and at least 100 minutes during the following 10 months.

The research physicians were consulted as to whether patients should be withdrawn from the study for any change in health status or adverse effects mentioned during the telephone-call–based interviews. All patients were given a 24-hour telephone hotline option, allowing them to directly contact one of the research physicians.

OUTCOME MEASURES

Primary efficacy outcome measure was self-reported continuous abstinence from smoking 1 year after the index hospitalization. Clinical and safety outcomes were all-cause mortality and any hospitalization at 1 year. Secondary outcomes included continuous smoking abstinence at 3 and 6 months. Secondary safety outcomes included the event of an ACS or any chest pain during follow-up, adverse effects attributed to study medication, and change in blood pressure or body mass index (BMI).

STATISTICAL ANALYSIS

The sample size was based on the ability to detect a difference in the primary efficacy end point between active treatment and placebo at 1 year. We assumed an abstinence rate of 30% in the bupropion group and 15% in the placebo group. Approximately 250 participants were needed in order to have a 2-sided α level of .05 and a power of 0.80 to detect such a difference. Interim analysis was performed after recruitment of 150 patients.

Primary efficacy and safety analyses were performed on an intent-to-treat basis. Pearson χ^2 test or Fisher exact test were used to compare categorical variables between groups, and t test was used to compare continuous variables. Paired t test was used to evaluate change in BMI and blood pressure. We fitted unconditional logistic regression models to estimate the predictors of quitting at 1 year for all participants included in the study. The odds ratios (ORs) and 95% confidence intervals (CIs) were adjusted by including terms for age, sex, the presence of cardiovascular risk factors, group allocation, invasive procedure (cardiac cath-

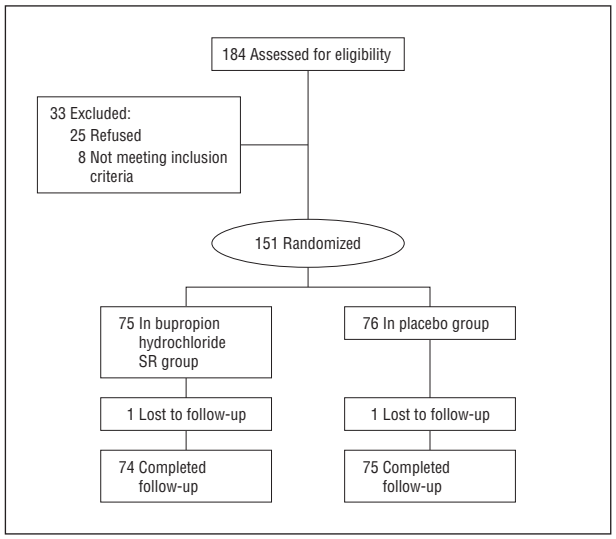

Figure 1. Study flowchart. SR indicates slow release.

eterization, percutaneous coronary intervention [PCI], or coronary artery bypass graft [CABG]) performed during the index hospitalization, cigarettes smoked per day, Fagerström test of nicotine dependence, and the presence of any adverse effect. We assessed heterogeneity by comparing regression models with and without interaction terms, based on the likelihood ratio test.

All reported *P* values are 2-sided. $P<.05$ was considered statistically significant. Statistical analysis was performed with SAS statistical software (version 9.1; SAS Institute Inc, Cary, North Carolina).

RESULTS

PARTICIPANTS

The study was stopped after an interim analysis was performed and revealed no advantage of bupropion SR over placebo in smoking abstinence rates at 12 months. From December 2003 through May 2005, 184 patients were approached; 25 patients refused to participate in the trial, and 8 were excluded because of they had liver failure, were prescribed antidepressants, had experienced past head trauma, or were undergoing hemodialysis. Altogether, 151 patients were randomized to receive either bupropion SR (75 patients) or placebo (76 patients) (**Figure 1**). One patient from each group was lost to follow-up. Baseline demographics and clinical characteristics are presented in **Table 1**. All patients recruited to the study were given in-hospital counseling that included at least one 15-minute contact and postdischarge support.

EFFICACY

Compliance with study medication was 85.3% in the bupropion group and 78.9% in the placebo group (*P*=.39). The overall continuous smoking abstinence rate at 1 year was 32%: 31% in the bupropion group and 33% in the placebo group (*P*=.86). At 3 and 6 months there was also no difference between the groups: 45% in the bupropion group vs 44% in the placebo group (*P*=.99) at 3 months; and 37% vs 42% (*P*=.61) at 6 months (**Figure 2**).

Table 1. Baseline Characteristics of Study Participants

Characteristic	Study Group[a] Bupropion Hydrochloride SR (n=74)	Placebo (n=75)	*P* Value
Age, mean (SD), y	52.4 (11)	51.5 (9)	.56
Males	57 (76)	62 (83)	.26
Diabetes mellitus	19 (26)	19 (25)	.99
Hypertension	33 (45)	29 (39)	.43
Hyperlipidemia	37 (50)	47 (63)	.08
Cigarettes/d, mean (SD)	32.3 (16)	30.1 (15)	.38
Pack-years, mean (SD)	56 (39)	48 (28)	.15
Fagerström test, mean (SD)	7.3 (2)	7.3 (2)	.92
Smoking in family	47 (63)	44 (59)	.22
Abnormal ECG findings on admission	41 (55)	41 (55)	.99
Systolic BP, mean (SD), mm Hg	123 (17)	123 (20)	.95
Diastolic BP, mean (SD), mm Hg	76 (11)	72 (13)	.07
BMI, mean (SD)	27.7 (5)	27.9 (6)	.85
Invasive procedure	55 (75)	59 (79)	.35
Diagnosis at discharge			
Myocardial infarction	31 (43)	29 (39)	.74
Unstable angina pectoris	17 (24)	20 (27)	.70
Stable angina pectoris	10 (14)	12 (15)	.82
Chest pain	14 (19)	14 (19)	.99

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; ECG, electrocardiogram; SR, slow release.

[a] Data are presented as number (percentage) except where noted.

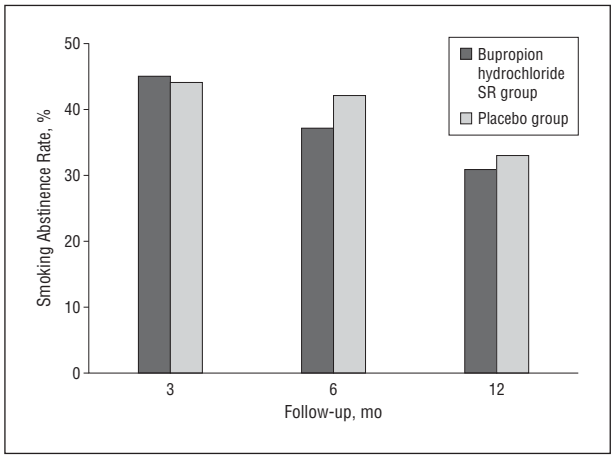

Figure 2. Efficacy of bupropion hydrochloride compared with placebo. SR indicates slow release.

PREDICTORS OF CONTINUOUS ABSTINENCE AT 1 YEAR

On multivariate logistic regression analysis, the only independent predictor of smoking abstinence at 1 year was an invasive procedure performed during hospitalization (OR, 4.2; 95% CI, 1.22-14.19) . The presence of any adverse effect attributed to study medication decreased the chances of abstinence (OR, 0.23; 95% CI, 0.07-0.78). Group allocation was not found to be an independent predictor for quitting (**Table 2**).

Table 2. Multivariate Model of Smoking Abstinence at 1 Year

Variable Category	OR (95% CI)	*P* Value
Age, y		
<45	1 [Reference]	
45-59	0.65 (0.23-1.87)	.81
>59	0.35 (0.08-1.46)	.17
Sex		
Male	1 [Reference]	
Female	0.98 (0.85-1.12)	.91
Treatment group		
Placebo	1 [Reference]	
Bupropion hydrochloride SR	0.90 (0.39-2.09)	.81
Invasive procedure		
None	1 [Reference]	
Any	4.20 (1.22-14.19)	.02
Risk factors		
None	1 [Reference]	
Any	0.41 (0.16-1.10)	.08
Adverse effects		
None	1 [Reference]	
Any	0.23 (0.07-0.78)	.02
Fagerström test of nicotine dependence		
≤7.5 (median)	1 [Reference]	
>7.5	1.00 (0.43-2.50)	.94
Cigarettes/d		
≤20	1 [Reference]	
>20	0.74 (0.30-1.80)	.50

Abbreviations: CI, confidence interval; OR, odds ratio; SR, slow release.

Table 3. Clinical Adverse Events During 1 Year of Follow-up

	Study Group, No. (%)		
Adverse Event	Bupropion Hydrochloride SR	Placebo	*P* Value
Death	0	0	.99
Any hospitalization	26 (36)	29 (39)	.70
Suicide attempt	0	0	.99
MI	2 (3)	1 (1)	.62
ACS	2 (3)	5 (7)	.44
Chest pain	11 (15)	14 (19)	.66

Abbreviations: ACS, acute coronary syndrome; MI, myocardial infarction; SR, slow release.

SAFETY

Bupropion was found to be safe when compared with placebo as an aid for smoking cessation in the acute care of patients hospitalized for ACS. There were no mortality and no suicide attempts in the entire group, including the 2 patients lost to follow-up. During the 12-month follow-up period, 36% of patients in the bupropion group and 39% in the placebo group were rehospitalized (*P*=.70). The rate of MI and any ACS was relatively low, and there was no difference between the groups (**Table 3**). During follow-up no change was found in systolic or diastolic blood pressure, nor in the BMI, in either group (**Table 4**). Similar rates of adverse effects were reported for the bupropion and placebo groups (**Table 5**), except for an increased rate of dizziness among bupropion users (14% vs 1.4%; *P*=.005).

COMMENT

In this double-blind, placebo-controlled trial of smokers who were hospitalized with ACS, bupropion SR was found to be safe but not more effective than placebo as a smoking cessation aid when added to intensive nurse-led hospital- and telephone-based support during 12 months of follow-up. Although we did not detect any significant adverse effect in the bupropion group, there was a significant increase in the rate of dizziness among the active drug users. Predictors of smoking abstinence at 1 year in the entire group were an invasive procedure performed during the index hospitalization and the absence of adverse effects attributed to study medication.

The importance of smoking cessation assistance has been widely studied and proved to be highly cost-effective.[15] It has also been recognized that the hospitalization period is an important opportunity to intervene in this high-risk population.[16,17] However, even in recently published studies, patients with unstable angina and MI were excluded from smoking cessation trials due to unproven safety of bupropion in these patients.[18] The importance of the current study was therefore to provide more evidence for the safety of bupropion in this acute setting.

The overall rate of continuous smoking abstinence at 1 year was 32%, which is higher than rates reported in other studies.[7,9] Most studies reported a continuous smoking abstinence rate of 10% to 20% in the control group at 1 year. Explanation for this difference might be the efficacy of the intensive smoking cessation counseling given to all recruited patients, both during hospitalization and later by telephone. A recently published meta-analysis[11] concluded that intensive smoking cessation counseling alone in hospitalized patients increased the chance of quitting by 65%, and the total abstinence rate can be as high as 27% in the most intensive approach. It is possible, therefore, that the added value of bupropion over intensive counseling is small. Our findings are in agreement with those of the only other study performed in hospitalized patients with ACS, which did not find any added effect of bupropion over intensive counseling in patients with ACS.[13] Another explanation that cannot be ruled out is that our outcome measurement, self-reported cigarette smoking, was not validated by an objective method, such as exhaled carbon monoxide levels. Participants might be eager to satisfy the medical staff, and the rate of self-reported abstinence might be an overestimation, although this effect is expected to be equal in both treatment groups.

To understand the predictors of smoking cessation in this population, we performed a multivariate analysis. Interestingly, the only significant independent predictors we found for total smoking abstinence at 1 year were an invasive procedure (coronary angiography, PCI, or CABG) performed during the index hospitalization (OR, 4.2; *P*=.02) and the presence of any adverse effect attributed to study medication decreased the chances of quitting (OR, 0.23; *P*=.02) . Since we could not find a plausible biologic explanation for the association between invasive pro-

Table 4. Mean Change in Baseline Parameters

Parameter	Bupropion Hydrochloride SR Group	*P* Value	Placebo Group	*P* Value
Systolic BP, mm Hg	−0.4 (20.0)	.90	0.2 (24.6)	.97
Diastolic BP, mm Hg	0.9 (2.3)	.70	−4.3 (15.4)	.12
BMI	−0.3 (1.6)	.24	−0.4 (1.8)	.25

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; SR, slow release.

cedure and smoking cessation, we hypothesize that the dreaded psychological effect of hospitalization with an acute cardiac problem, which is intensified by the experience of undergoing an invasive procedure, has a significant, long-term effect on the motivation to quit smoking. As others have pointed out, the seriousness of the illness as reflected by the treatment strategy increases the chances of quitting. In addition, these high-risk patients are probably more frequently urged by their cardiologists to stop smoking.[19] We believe that intensive counseling in this setting further enhances the chances of quitting, and although not tested directly in the current study, is responsible for the high long-term quitting rate in the entire group, which may have masked the effect of bupropion.

It seems that bupropion is safe to use in smokers hospitalized with ACS. During the 2 months of treatment and 1 year of follow-up, no serious adverse events were attributed to bupropion. Postmarketing surveillance has raised new questions about the safety of smoking cessation medications. In 2008 the US Food and Drug Administration published a health advisory note reporting a possible association between varenicline and bupropion and an increased risk of suicidal ideation and behavior.[20] Although no such events were recorded in the current study, the sample size is too small for these rare events. In the current study, there was no increase in clinical events in bupropion users compared with placebo. In our study, in which the findings are in agreement with those of others, no notable change in blood pressure was documented.[21] Weight gain, which is a common bothersome problem during tobacco withdrawal,[22] was not documented in this study in either group. In a recently published review, bupropion was found to limit postcessation weight gain at the end of treatment but had no long-term effect.[23]

The current study provides important data in this high-risk patient population. Our findings emphasize the unique opportunity to approach heavy smokers during hospitalization with ACS, in a forced nonsmoking environment, utilizing the effect of a life-threatening condition and particularly the effect of an invasive procedure, which is indicated today in most patients with ACS, in order to achieve long-term high-abstinence rates. The lack of clinically significant adverse events in bupropion users in this setting expands the armamentarium that can be used by the caregivers.

Several studies and 1 meta-analysis have demonstrated that varenicline, a selective $\alpha_4\beta_2$ nicotinic receptor partial agonist, is more effective than placebo and bupropion SR in short- and long-term smoking abstinence.[24-27] However, this drug should be evaluated in hospitalized patients with ACS in order to determine its safety in this population.

Table 5. Adverse Effects

Adverse Effect	Study Group, No. (%)		*P* Value
	Bupropion Hydrochloride SR	Placebo	
Sleep disturbance	16 (22)	14 (19)	.69
Headache	19 (26)	19 (26)	.99
Mouth dryness	21 (29)	18 (24)	.58
Nausea	4 (5)	6 (8)	.74
Anxiety	4 (5)	4 (5)	.99
Dizziness	10 (14)	1 (1)	.005
Constipation	1 (1)	5 (7)	.21
Rash	3 (4)	1 (1)	.37

Abbreviation: SR, slow release.

Our study has several limitations. First, because recruitment to the study was stopped early after the interim analysis was performed, the sample size might be too small to detect a rare significant adverse event.

Second, the primary efficacy outcome was self-reported abstinence from smoking at 12 months. As mentioned, we had an unexpectedly high rate of reported quitting in the placebo arm. Because reported quitting status was not confirmed by an objective method, such as a carbon monoxide concentration in exhaled air, we could not exclude false reporting of abstinence, which might have masked the effect of bupropion.

Third, patients who agree to participate in clinical trials of smoking cessation might not be representative of the general population of patients hospitalized with ACS. However, in the current study, over 80% of the patients approached finally participated and completed follow-up.

In summary, our results suggest that although bupropion SR is safe in patients hospitalized with ACS, it had no added value over placebo in this population when combined with intensive smoking cessation counseling. Given the high long-term complete abstinence rate observed, we feel that approaching this population at this time point is crucial, and special efforts should be made to apply the multidisciplinary approach. Adding bupropion to intensive counseling may be considered in selected patients such as patients with post-MI depression.

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Author Contributions: The principal investigators, Drs Planer, Lev, and Lotan, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Planer, Lev, Elitzur, Ouzan, Pugatsch, Rom, and Lotan. *Acquisition of data:* Planer, Lev, Elitzur, Ouzan, Pugatsch, Chasid, Rom, and Lotan. *Analysis and interpretation of data:* Planer, Lev, Sharon, and Lotan. *Drafting of the manuscript:* Planer, Lev, Sharon, and Ouzan. *Critical revision of the manuscript for important intellectual content:* Lev, Elitzur, Pugatsch, Chasid, Rom, and Lotan. *Statistical analysis:* Planer and Sharon. *Obtained funding:* Rom. *Administrative, technical, and material support:* Pugatsch, Rom, and Lotan. *Study supervision:* Ouzan, Chasid, Rom, and Lotan.

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