Sustained-Release Bupropion for Pharmacologic Relapse Prevention after Smoking Cessation

A Randomized, Controlled Trial

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Background: Smoking relapse is common after successful pharmacologic treatment for smoking cessation. No previous studies have examined long-term drug therapy used expressly for prevention of smoking relapse.

Objective: To evaluate the efficacy of bupropion to prevent smoking relapse.

Design: Randomized, placebo-controlled trial.

Participants: 784 healthy community volunteers who were motivated to quit smoking and who smoked at least 15 cigarettes per day.

Intervention: The participants received open-label, sustained-release bupropion, 300 mg/d, for 7 weeks. Participants who were abstinent throughout week 7 of open-label treatment were randomly assigned to receive bupropion, 300 mg/d, or placebo for 45 weeks and were subsequently followed for an additional year after the conclusion of the medication phase. Participants were briefly counseled at all follow-up visits. At the end of open-label bupropion treatment, 461 of 784 participants (58.8%) were abstinent from smoking.

Measurement: Self-reported abstinence was confirmed by an expired air carbon monoxide concentration of 10 parts per million or less.

Results: The point prevalence of smoking abstinence was significantly higher in the bupropion group than in the placebo group at the end (week 52) of drug therapy (55.1% vs. 42.3%, respectively; P = 0.008) and at week 78 (47.7% vs. 37.7%; P = 0.034) but did not differ at the final (week 104) follow-up visit (41.6% vs. 40.0%). The median time to relapse was significantly greater for bupropion recipients than for placebo recipients (156 days vs. 65 days; P = 0.021). The continuous abstinence rate was higher in the bupropion group than in the placebo group at study week 24 (17 weeks after randomization) (52.3% vs. 42.3%; P = 0.037) but did not differ between groups after week 24. Weight gain was significantly less in the bupropion group than in the placebo group at study weeks 52 (3.8 kg vs. 5.6 kg; P = 0.002) and 104 (4.1 kg vs. 5.4 kg; P = 0.016).

Conclusions: In persons who stopped smoking with 7 weeks of bupropion treatment, sustained-release bupropion for 12 months delayed smoking relapse and resulted in less weight gain.

Many effective behavioral and pharmacologic therapies are now available for treatment of smoking. The most effective strategy for treatment is combined behavioral intervention and pharmacologic therapy (1). Effective pharmacologic interventions for smoking cessation include several types of nicotine replacement and use of the non-nicotine medication bupropion (2, 3). Despite treatment advances, smoking relapse after successful intervention for smoking cessation occurs in 70% to 80% of patients within 6 to 12 months (4).

Studies of relapse prevention strategies suggest that teaching coping skills may reduce the risk for relapse, but other behavioral therapies have shown little benefit (5, 6). Because pharmacologic therapy for smoking cessation has been proven effective and behavioral relapse prevention strategies alone have shown no great benefit, pharmacologic therapy for relapse prevention should be evaluated.

Bupropion has been proven an effective intervention for smoking cessation, both as a single therapy and in combination with nicotine-patch therapy (2, 3). Because bupropion is effective for initiating abstinence from smoking and is safe for long-term therapy, we hypothesized that prolonged bupropion treatment in recently abstinent smokers would decrease the relapse rate. We compared sustained-release bupropion treatment with placebo for 1 year in participants who achieved initial abstinence after 7 weeks of therapy with open-label, sustained-release bupropion.

METHODS

Participants

This randomized, double-blind, placebo-controlled study of relapse prevention was performed at five sites (Mayo Clinic, Rochester, Minnesota; the Palo Alto Cen-

ter for Pulmonary Disease Prevention, Palo Alto, California; Brown University, Providence, Rhode Island; Oregon Health Sciences University, Portland, Oregon; and Massachusetts General Hospital, Boston, Massachusetts) and was approved by the institutional review board at each site. We recruited participants through advertisements and press releases. After passing an initial screening interview by telephone, participants attended an informational meeting. At this meeting, the study was explained and the participants completed questionnaires and gave written, informed consent. The volunteers were eligible for study inclusion if they were 18 years of age or older, had smoked an average of at least 15 cigarettes or more per day for the past year, were motivated to stop smoking, and were in generally good health. Only one smoker per household was allowed in the study. Exclusion criteria included a personal or family history of a seizure disorder; history of severe head trauma; predisposition to seizures (such as history of brain tumor or stroke); history or current diagnosis of anorexia nervosa or bulimia; presence of an unstable medical or psychiatric condition; pregnancy; lactation; dependence on alcohol or other nonnicotine substance in the past year; current use of psychotropic medications; previous use of bupropion; current use of tobacco products other than cigarettes; or current use of any therapy for smoking cessation (such as nicotine replacement therapy; fluoxetine, clonidine, buspirone, or doxepin therapy; or behavioral therapy). Persons with current major depression were also excluded. Potential participants were deemed to have current major depression if: 1) they met the criteria for this condition on the basis of their responses in a structured clinical interview (conducted by a trained study assistant), or 2) they were judged to have major depression by the physician performing the entrance history and physical examination (7).

Treatment

Beginning at the baseline visit and continuing through study week 7, all participants received open-label, sustained-release bupropion (bupropion SR), 300 mg/d (150 mg/d for 3 days, followed by 150 mg twice daily). At the baseline visit, participants were instructed to set a target quitting date after 1 week of medication use (usually day 8 of therapy). Each participant attended weekly follow-up visits during the 7-week open-label

phase. Participants were eligible for random assignment to receive bupropion or placebo in the double-blind phase if they 1) reported not smoking (not even a puff) during week 7 of the open-label phase and 2) had their self-report confirmed by an expired carbon monoxide level of 10 parts per million (ppm) or less. The randomly assigned participants returned for 14 visits during the double-blind phase (at weeks 8, 9, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52) and 5 visits during the follow-up year (at weeks 53, 56, 64, 78, and 104). Participants also received a telephone follow-up at 21 months after study enrollment. At the baseline physical examination, each participant received a brief personalized message from the examining physician to stop smoking, set a target quitting date, and received self-help material that was based on a smoking cessation program designed by the U.S. National Cancer Institute (8). At each visit during the open-label and double-blind study phases, study assistants counseled participants for approximately 10 to 15 minutes. Randomization to the placebo or bupropion groups was computer generated at a central location; the investigators did not know the patient assignments. All bupropion and placebo pills were identical in shape, size, and color.

Assessments

At baseline, participants had a physical examination; underwent chest radiography, laboratory testing, and electrocardiography; and completed a Fagerström Tolerance Questionnaire and a Beck Depression Inventory. The Fagerström Tolerance Questionnaire is a widely used measure of nicotine dependence with scores that range from 0 to 11; scores of 6 or greater indicate higher levels of dependence (9, 10). At each visit through week 53, study assistants recorded adverse experiences, as well as use of study and concomitant medications. Participants maintained a daily diary of withdrawal symptoms (11) and daily cigarette use that was reviewed at each visit through week 12. The Beck Depression Inventory (administered at baseline and weeks 7, 8, 12, 52, 53, 56, 78, and 104) is a 21-item, self-administered questionnaire that assesses severity of depressive symptoms (12). Smoking status was self-reported at each visit; reports of abstinence were considered validated with a measurement of carbon monoxide level in expired air of no higher than 10 ppm.

Outcome Measures

The main outcomes of interest were 1) weekly point-prevalence abstinence during medication treatment, 2) continuous abstinence during medication treatment, and 3) time to first relapse. Secondary outcomes included weight change over time and point prevalence and continuous-abstinence rates after completion of drug therapy. The weekly point-prevalence smoking status was defined as 1) self-report of not smoking during the previous 7 days that was confirmed by an expired air carbon monoxide level of 10 ppm or lower and 2) two or fewer consecutive missed visits. Smoking relapse was defined as a self report of smoking or an expired air carbon monoxide level greater than 10 ppm. Participants were also considered to have smoking relapse if they missed more than two consecutive visits. All participants meeting the abstinence criteria at every visit were considered continuously abstinent. Self-report determined the date of smoking relapse. For participants who self-reported not smoking but who were classified as smoking because of an elevated carbon monoxide level or because of consecutive missed visits, the date of relapse was defined as the day after the most recent previous study visit at which smoking abstinence was biochemically confirmed.

Statistical Analysis

We determined that we needed a sample size of 170 participants in each randomly assigned treatment group to detect a significant between-group difference in end-of-treatment abstinence rates of 0.15 at a significance level of 0.05 and a power of 0.80. Assuming an abstinence rate of 35% for week 7 of the open-label phase, we determined that up to 1000 enrollees were needed to ensure a minimum sample of 340 nonsmoking participants (170 per group) for randomization. The 1-week point prevalence for smoking status during week 7 of the open-label bupropion phase was used to determine eligibility for random assignment to receive placebo or active sustained-release bupropion, 300 mg/d. To compare the baseline characteristics of the bupropion and placebo recipients, we used the two-sample t-test and the chi-square test for analysis of continuous and categorical variables, respectively. The efficacy of bupropion for preventing smoking relapse during the double-blind

medication phase and follow-up phase was assessed by analyzing time to first smoking relapse.

We used Kaplan–Meier survival estimates and a proportional hazards regression model (13, 14) to analyze time to first smoking relapse. For this analysis, time to first relapse was defined as the date of first relapse minus the date of randomization. For participants without relapse, time to first relapse was censored by using the date of their final (week 104) study visit. For the proportional hazards regression analysis, the response variable was time to first smoking relapse, and the independent variable was treatment. Randomization was stratified according to study site to ensure that similar numbers of participants were assigned to the treatment groups at each site. We verified that the treatment effect was not dependent on study site by performing an initial analysis that included the interaction of treatment by study site. Subsequently, we used a proportional hazards regression analysis with study site as a stratification factor to assess differences between treatment groups.

Rates of point prevalence and continuous smoking abstinence were compared between treatment groups by using a logistic regression analysis with smoking status as the dependent variable and treatment group and study site as independent variables. Again, the treatment by study site interaction term was included to assess whether the effect of treatment depended on study site. After verifying that the effect of treatment was not dependent on study site, we performed a logistic regression analysis to assess differences in rates of abstinence (point prevalence or continuous abstinence) between treatment groups with study site as a covariate. In addition, we calculated exact 95% CIs for continuous abstinence and point-prevalence rates.

Body weight was analyzed among 1) all participants, regardless of smoking status; 2) participants who had not relapsed to smoking by the end of the medication phase; and 3) participants with no relapse throughout the study. Weight change was calculated for each visit. Analysis of covariance models were used to compare the mean weight change from baseline between the placebo and bupropion groups. In these models, weight change from baseline was the dependent variable, treatment group was the independent factor, and the baseline weight and week-7 weight change from baseline were included as covariates. New adverse events reported during the 45-week double-blind medication phase were

compared between the placebo and bupropion groups by using the Fisher exact test.

For all comparisons, intention-to-treat analyses were performed; we considered two-sided P values of 0.05 or less to indicate significant findings not attributable to chance. P values were not adjusted for multiple comparisons. All analyses were performed by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

This study was supported by research grants from Glaxo Wellcome, Inc., Research Triangle Park, North Carolina. Investigators independently managed and administered the study protocol at each site, and data were analyzed by one of the authors at Mayo Clinic, Rochester, Minnesota. Decisions about data presentation and publication were made jointly by all authors on the basis of the scientific merits of the study.

RESULTS

Open-Label Bupropion Phase

Of 1006 total volunteers interested in stopping smoking, 784 met the study criteria and were enrolled in the open-label bupropion phase of the study (Figure 1). The mean ($\pm$SD) age of all enrolled participants was 45.4 $\pm$ 9.8 years; 54% were women, and 96.8% were white. The baseline smoking rate was 27.3 $\pm$ 10.1 cigarettes per day, the average age at which regular smoking first began was 17.1 $\pm$ 3.6 years, and the mean score on the Fagerström Tolerance Questionnaire was 7.3 $\pm$ 1.6.

Among the 784 participants enrolled in the study, 461 (58.8% [95% CI, 55.3% to 62.3%]) were biochemically confirmed to be abstinent from smoking during the final week of the 7-week open-label bupropion phase. Of these 461 participants, 429 were randomly assigned to receive placebo or bupropion for the 45-week double-blind medication phase. The 32 abstinent individuals not randomly assigned were withdrawn from the study because of scheduling difficulty ($n = 20$), an adverse event ($n = 10$), or protocol deviation ($n = 2$).

Baseline Characteristics and Adherence Rates

Table 1 presents the baseline characteristics of the 429 randomly assigned participants. With the exception of the mean Beck Depression Inventory score, which was higher in the bupropion group than in the placebo

group (4.3 $\pm$ 4.6 vs. 3.2 $\pm$ 3.6; $P = 0.005$), baseline characteristics did not differ significantly between the two treatment groups. A total of 347 participants (80.9%; 175 in the placebo group and 172 in the bupropion group) remained in the study through the 45-week double-blind medication phase, and 317 participants (73.9%; 158 in the placebo group and 159 in the bupropion group) completed the entire study. Of the 347 participants completing the scheduled study visits through week 52, 90 participants (49 placebo recipients and 41 bupropion recipients) prematurely discontinued medication use. The primary reasons for discontinuing medication use included withdrawn consent ($n = 50$ [27 placebo recipients and 23 bupropion recipients]) and adverse events ($n = 31$ [15 placebo recipients and 16 bupropion recipients]). The 257 participants who continued use of medication (placebo or bupropion) throughout the double-blind phase reported taking 95% of the prescribed dosages (median, 97% [range, 61% to 100%]). Of the 112 participants who did not complete the 2-year study, 82 (40 placebo recipients and 42 bupropion recipients) withdrew during the double-blind medication phase (primarily because of withdrawn consent [$n = 71$; 38 placebo recipients and 33 bupropion recipients]), and 30 (17 placebo recipients and 13 bupropion recipients) withdrew in the follow-up year.

Point-Prevalence Abstinence

Table 2 shows the point-prevalence abstinence rates and 95% CIs at selected time points according to treatment group. At the end of the double-blind medication phase, the point-prevalence abstinence rate was significantly higher in the bupropion group than in the placebo group (55.1% vs. 42.3%, respectively; $P = 0.008$); this represents a 30.3% improvement in the bupropion group compared with the placebo group. The point-prevalence abstinence rates remained significantly higher in the bupropion group compared with the placebo group through week 78 (6 months after the end of medication treatment). At the end of the study, the point-prevalence abstinence rates were similar between groups (41.6% for the bupropion group and 40.0% for the placebo group).

Relapse and Continuous Abstinence

The median time to smoking relapse from randomization was 65 days for the placebo group and 156 days
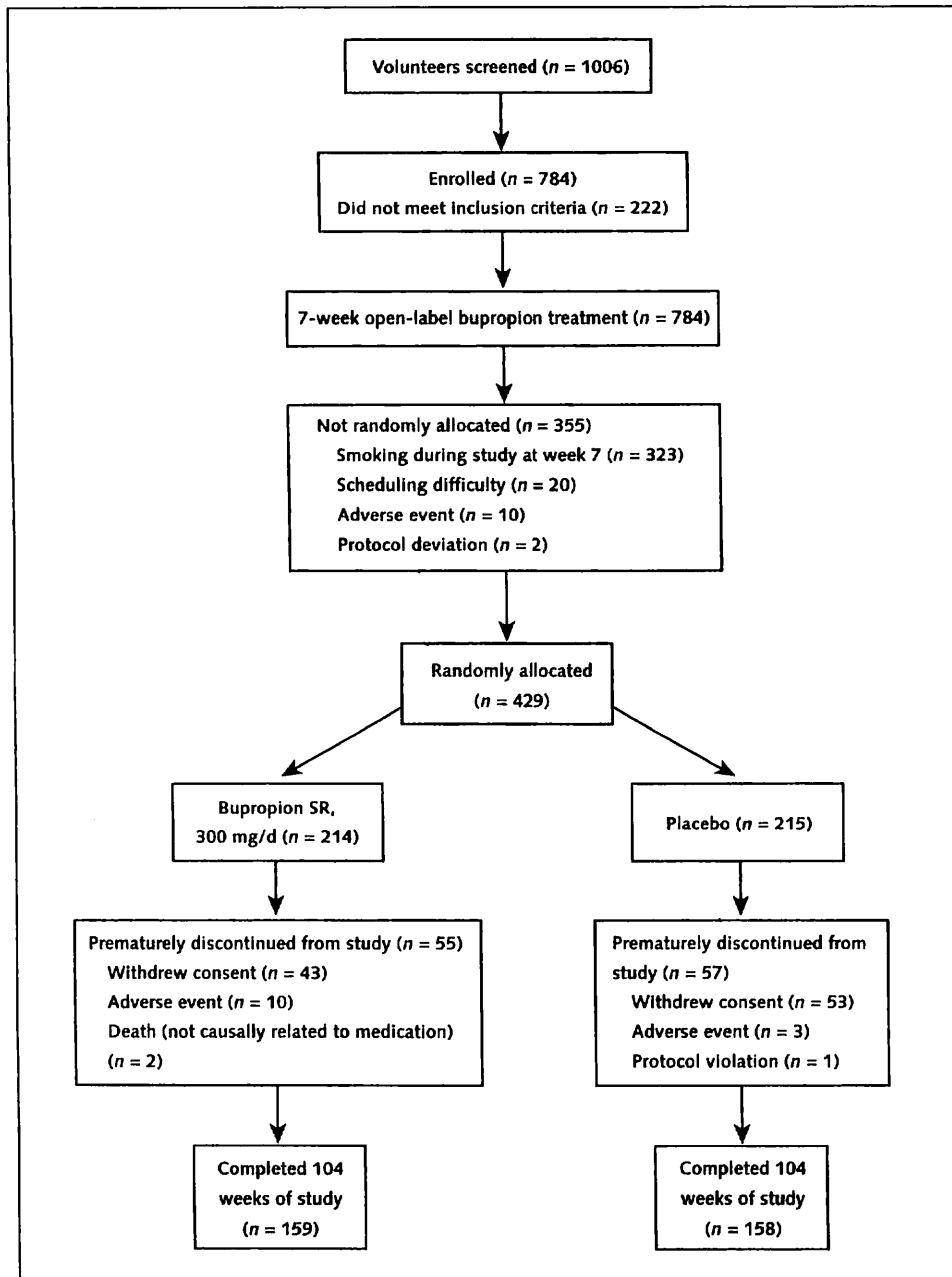
SR = sustained release.

for the bupropion group ($P = 0.021$, rank-sum test). Figure 2 shows the Kaplan–Meier estimates of smoking relapse for each treatment group. Overall, relapse curves across time did not significantly differ between treatment groups ($P = 0.100$, proportional hazards regression stratified by study site). The percentage of participants with continuous abstinence was significantly

higher in the bupropion group at 5 weeks than in the placebo group (study week 12) (68.7% [CI, 62.0% to 74.8%] vs. 58.1% [CI, 51.2% to 64.8%]; $P = 0.023$) and at 17 weeks after randomization (study week 24) (52.3% [CI, 45.4% to 59.2%] vs. 42.3% [CI, 35.6% to 49.2%]; $P = 0.037$). No significant difference was seen between the bupropion and placebo groups for the con-

Table 1. Baseline Characteristics of the Randomly Assigned Participants, according to Treatment Group*

Characteristic	Placebo Group (n = 215)	Bupropion Group (n = 214)
Mean age ± SD (range), y	45.4 ± 9.2 (20.2–71.9)	47.0 ± 9.7 (20.3–72.7)
Women, %	47.9	54.7
White participants, %	97.7	96.3
Marital status, %		
Married	59.1	64.5
Divorced or separated	23.7	18.2
Never married	8.4	11.7
Widowed	2.3	1.4
Other	6.5	4.2
Level of education, %		
Less than high school graduation	3.7	4.2
High school graduation	23.7	21.0
Some post–high school education	48.4	49.1
College graduation or higher	24.2	25.7
Mean cigarettes smoked per day ± SD (range), n	26.2 ± 9.6 (15–70)	27.4 ± 10.6 (15–70)
Mean age ± SD at start of smoking regularly (range), y	16.9 ± 3.2 (9–31)	17.5 ± 3.8 (11–37)
Fagerström Tolerance Questionnaire†		
Mean score ± SD	7.1 ± 1.6	7.3 ± 1.5
Score < 6, %	15.9	13.1
Score ≥ 6, %	84.1	86.9
Number of previous attempts to stop smoking, %		
0	4.2	4.7
1 or 2	40.9	46.7
3 or 4	36.3	29.0
≥5	18.6	19.6
Longest previous period of smoking cessation, %		
Never abstinent	4.2	4.2
<1 day	2.8	1.4
1 day to <1 week	19.5	14.0
1 week to <1 month	17.2	12.6
1 month to <6 months	31.6	36.5
6 months to 1 year	7.9	13.6
>1 year	16.7	17.8
Previously used nicotine patch, %	48.4	47.7
Previously used nicotine gum, %	29.3	33.2
Other smoker in household, %	27.0	28.5
History of major depression, %	16.7	20.6
Beck Depression Inventory‡		
Mean score ± SD	3.2 ± 3.6	4.3 ± 4.6
Score ≤ 9, %	94.3	88.3
Score 10 to 18, %	5.2	9.9
Score 19 to 29, %	0.5	1.9
Score ≥ 30, %	0.0	0.0
Study site, %		
Portland, OR	17.8	18.7
Rochester, MN	34.4	34.6
Providence, RI	14.4	13.6
Boston, MA	15.4	14.0
Palo Alto, CA	18.1	19.2

* Because of rounding, not all percentages total 100.
† The range of possible scores on the Fagerström Tolerance Questionnaire is 0 to 11; a score ≥ 6 indicates higher levels of nicotine dependence (9, 10). Data were missing for one participant in the placebo group.
‡ Beck Depression Inventory scores can range from 0 to 63. A score ≤ 9 is considered normal; 10 to 18 indicates mild-to-moderate depression; 19 to 29 indicates moderate-to-severe depression, and ≥30 indicates severe depression (12). Data were missing for 4 placebo recipients and for 1 bupropion recipient. P = 0.005 by comparing mean depression score between placebo and bupropion recipients.

tinuous abstinence rates through the end (study week 52) of drug treatment (35.5% [CI, 29.1% to 42.3%] vs. 32.1% [CI, 25.9% to 38.8%]) or for completion of follow-up (study week 104) (29.0% [CI, 23.0% to 35.6%] vs. 26.0% [CI, 20.3% to 32.5%]).

Weight Change

Figure 3 shows the mean weight change from the start of the open-label medication phase for all 429 participants who were randomly assigned. By study week 8, weight gain was greater in the placebo group than in the

Table 2. **Point-Prevalence Abstinence Rates***

Time since Randomization†	Participants Not Smoking (95% CI), %		P Value‡
	Placebo Group (*n* = 215)	Bupropion Group (*n* = 214)	
5 wk (12 wk)	69.3 (62.7–75.4)	81.8 (75.9–86.7)	0.003
17 wk (24 wk)	54.0 (47.0–60.8)	67.8 (61.1–74.0)	0.003
29 wk (36 wk)	47.0 (40.2–53.9)	57.0 (50.1–63.7)	0.036
45 wk (52 wk)§	42.3 (35.6–49.2)	55.1 (48.2–61.9)	0.008
49 wk (56 wk)	40.5 (33.8–47.4)	52.3 (45.4–59.2)	0.013
71 wk (78 wk)	37.7 (31.2–44.5)	47.7 (40.8–54.6)	0.034
97 wk (104 wk)	40.0 (33.4–46.9)	41.6 (34.9–48.5)	>0.05

* Self-reports of smoking abstinence for the past 7 days that were confirmed by an expired air carbon monoxide level ≤ 10 parts per million.
† Participants who abstained from smoking during week 7 of receiving open-label bupropion were randomly assigned. Time in parentheses denotes time since the open-label phase began.
‡ *P* values are for comparison of placebo recipients with bupropion recipients by using a logistic regression analysis with smoking status as the dependent variable, treatment group as the independent variable, and study site as a covariate.
§ The final week of study medication.

bupropion group, and this trend continued throughout the study. At the end of the 52 weeks of medication, the placebo group had gained an average of 5.6 kg compared with 3.8 kg in the bupropion group (*P* = 0.002). At the end of the study (at 24 months), the mean weight gain in the placebo group was 5.4 kg compared with 4.1 kg in the bupropion group (*P* = 0.016). Among 145 total participants without a smoking relapse during the 45-week double-blind phase, the mean weight gain at the end of medication treatment was 7.9 kg for the placebo group (*n* = 69) compared with 4.7 kg for the bupropion group (*n* = 76) (*P* < 0.001). Of 118 total participants without smoking relapse during the entire 2-year study, the mean weight gain at the end of the study was 8.6 kg for the placebo group (*n* = 56) compared with 6.9 kg for the bupropion group (*n* = 62) (*P* = 0.012).

Safety

Table 3 shows all adverse events reported at least once by at least 10% of participants during the 7-week open-label bupropion phase or in either treatment group during the 45-week double-blind medication phase. The adverse events reported during the double-blind medication phase refer to the onset of new adverse episodes. Adverse events that began during the open-label phase and had not resolved until the double-blind phase were included with the open-label phase data only. During the open-label bupropion phase, 81 of the 724 participants experiencing at least one adverse event prematurely stopped bupropion treatment. Five serious adverse events were reported during the open-label phase,

but none of these serious events are believed to have been caused by bupropion.

Of the 429 randomly assigned participants, 366 (177 placebo recipients and 189 bupropion recipients) reported having developed at least one new adverse

Figure 2. **Observed cumulative smoking relapse, according to treatment group.**
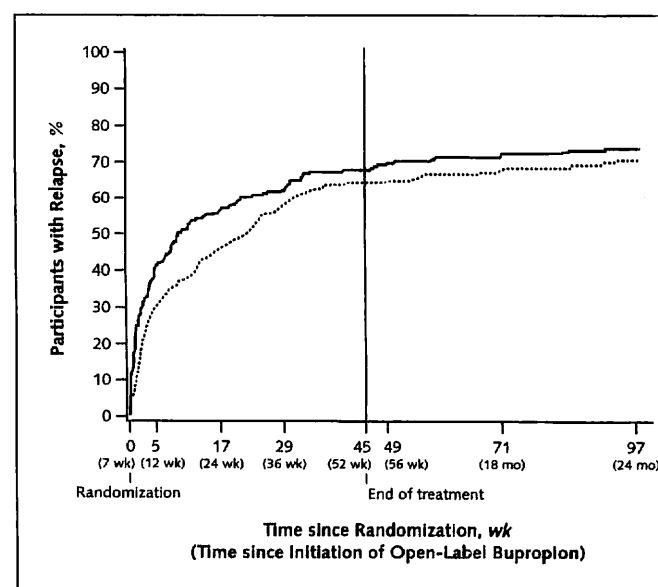
The median time since randomization to smoking relapse was 65 days for the placebo group (*solid line*) and 156 days for the bupropion group (*dotted line*) (*P* = 0.021, rank-sum test). Bupropion use had a significant effect compared with placebo at weeks 5 and 17 since randomization (study weeks 12 and 24, respectively). Compared with placebo, bupropion use had no significant effect on preventing smoking relapse across time for the entire study duration after randomization (*P* = 0.100 by proportional hazards regression).

Figure 3. Mean change in weight from baseline.
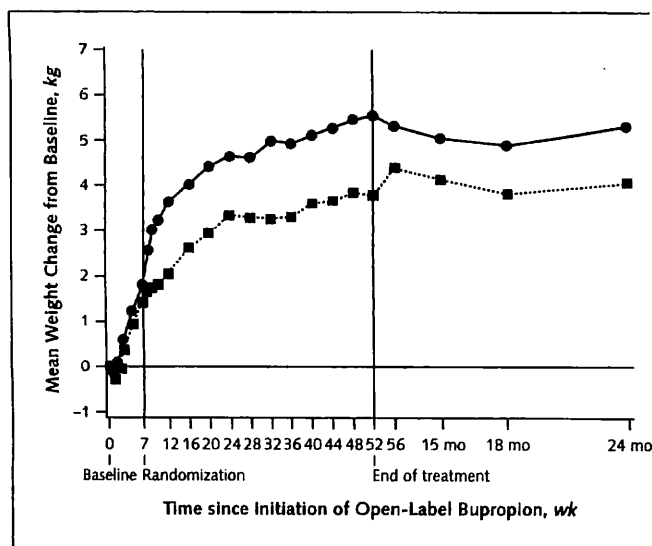
The mean change in weight from baseline was significantly greater than zero ($P < 0.001$ by the one-sample t-test) at week 3 and at each subsequent visit for both the placebo (*solid line*) and bupropion (*dotted line*) groups. The mean weight changes significantly differed between the placebo and bupropion groups ($P < 0.05$ with adjustment for baseline weight and week-7 weight change from baseline) at each visit after randomization except at weeks 10, 12, and 24. Data were available for 215, 213, 156, and 152 participants in the placebo group and 214, 213, 162, and 150 participants in the bupropion group at baseline and weeks 7, 52, and 104, respectively. During the first 7 weeks of treatment, both groups received active bupropion.

event during or immediately after (within 1 week) the 45-week double-blind medication phase. No significant differences were seen between groups in the frequency of experiencing any adverse event, including events not

listed in **Table 3.** Forty-one participants (17 placebo recipients and 24 bupropion recipients) prematurely discontinued the double-blind medication treatment because of an adverse event. The most common reasons for early discontinuation of medication use were depression or depressed mood (8 placebo recipients and 5 bupropion recipients), increased irritability (0 placebo recipients and 3 bupropion recipients), and elevated liver function test results (1 placebo recipient and 2 bupropion recipients). Participants reported a total of 20 serious adverse events during or immediately after the double-blind phase. Two patients, both in the bupropion group, died during the study; one died accidentally during the double-blind phase, and the other died of pancreatic cancer at approximately 9 months into the postmedication follow-up phase. None of these serious adverse events were attributed to the study medication.

DISCUSSION

This evaluation of long-term pharmacologic therapy was designed expressly for prevention of relapse to smoking. We found that use of sustained-release bupropion delayed relapse after initial smoking cessation, but this effect was not maintained throughout the 2-year study. The bupropion group had significantly higher point prevalence of abstinence than did the placebo group for the entire medication treatment period (12 months). This significant difference was sustained through the first 6 months of follow-up (during which time recipients received no treatment); however, abstinence rates did not differ between groups at the conclusion of

Table 3. **Adverse Events***

Adverse Event	All Participants during 7-Week Open-Label Bupropion Phase (n = 784)	During 45-Week Double-Blind Medication Phaset	
		Placebo Recipients (n = 215)	Bupropion Recipients (n = 214)
		%	
Insomnia	49.5	7.4	10.3
Headache	33.3	17.2	24.3
Dry mouth	15.3	0.0	0.9
Nausea	12.9	2.8	3.7
Restlessness	12.0	5.1	4.2
Rhinitis	8.5	23.3	17.8
Influenza	4.6	17.2	16.4
Upper respiratory tract infection	4.3	23.7	17.3
Accidental injury	2.6	12.6	14.5

* Adverse events experienced at least once by at least 10% of the participants during the open-label phase or in either group during or immediately after the double-blind phase. Adverse events are listed in decreasing order according to the overall frequency during the open-label phase.
† Onset of new episodes of adverse events after randomization. For all adverse events, including those not summarized in the table, the frequency of reports did not differ significantly between the placebo and bupropion groups.

the 2-year study. The median time to smoking relapse was also more than doubled in the group receiving sustained-release bupropion compared with participants receiving placebo. In addition, the rates of continuous abstinence were significantly higher in the bupropion group than in the placebo group for approximately 6 months from the start of medication treatment. However, we found that after study week 24, no significant differences in continuous abstinence rates and overall survival (relapse) curves did not differ between groups (Figure 2). These results are mixed, in part reflecting the differences between point-prevalence end points (which included brief smoking lapses) and continuous abstinence end points (in which no lapses were allowed). In addition, according to the point-prevalence criterion, there appeared to be treatment benefit for participants receiving bupropion treatment for 18 months (6 months off medication); however, after 2 years of follow-up, (1 year off medication) no between-group differences were detected.

Research on relapse prevention has almost exclusively examined the effect of behavioral therapy for preventing relapse after smoking cessation (15). Behavioral treatment for relapse prevention results in relapse rates of approximately 70% within 1 year (16). Viewing our results conservatively by including for analysis participants who were smoking at the end of open-label treatment (355 participants divided equally between the placebo and bupropion conditions) results in a 1-year abstinence rate of 30.2% (118/[214 + 177]). This compares favorably with results with behavioral treatments that often are time intensive and require special expertise to deliver.

A second significant finding in our study was the attenuation in postcessation weight gain among participants treated with sustained-release bupropion compared with those receiving placebo. The effects of bupropion on weight gain were evident by week 8, and bupropion treatment showed a sustained and significant effect compared with placebo throughout the medication treatment phase and for 1 year of follow-up, after medication treatment was discontinued. The most marked effects on weight gain were seen in the participants who remained abstinent through week 52 (at the end of medication treatment). Among these participants, the group receiving sustained-release bupropion gained an average of 3.2 kg less than the placebo group

after 1 year in the study. Among participants with sustained abstinence, the group receiving bupropion continued to have significantly less weight gain than the placebo group at the 2-year follow-up.

Our results differ from the findings of other investigations of pharmacologic therapy for smoking cessation that have evaluated postcessation weight gain. Both nicotine gum and nicotine nasal spray have been shown to attenuate weight gain after smoking cessation, although weight gain in these studies rebounded after medication treatment was stopped (17–19). Nicotine patch therapy has generally not been demonstrated to reduce postcessation weight gain (20, 21) but delay of weight gain by more thorough nicotine replacement was demonstrated in one study (22). In two other studies of sustained-release bupropion (2, 3), one showed a significant effect on attenuating weight gain with bupropion, 300 mg/d, during the 7-week medication treatment while the other showed an effect early (during first 4 weeks of treatment). Although weight gain after smoking cessation is not typically a relapse risk, concerns about weight gain may impede attempts to stop smoking (23, 24). Because bupropion use attenuates weight gain after smoking cessation, this treatment may prove particularly useful among patients who are concerned about weight gain and view this effect as a disincentive to quitting smoking (25).

Bupropion treatment was well tolerated in our sample; the most commonly reported side effects were insomnia and headache. However, the rates of any adverse events did not differ between the placebo and bupropion groups. Bupropion was not considered to cause any serious adverse event experienced by study participants. We did not note any seizures among the adverse events, although seizures have been reported in association with bupropion treatment (26). Our study excluded persons with a significant risk for seizure.

The strengths of our study include its large sample size and multiple study centers in a randomized, placebo-controlled trial. Our study also has limitations. As in all clinical trials, persons who are recruited and enroll in a research study may not be representative of the general population. In addition, our participants received brief individual counseling on a regular basis, along with follow-up for up to 2 years. This degree of behavioral intervention may not be easily duplicated in most clinical settings and was probably important in maintaining

abstinence in both treatment groups. Moreover, approximately 19% of the randomly assigned participants dropped out of the study before the end of drug treatment, and a total of 26% dropped out by the end of the study (week 104). Participants who dropped out were considered to have relapsed to smoking, but information on other important factors, such as weight gain, was not collected and therefore could not be included in the analysis. Finally, we provided long-term treatment to all participants meeting the abstinence criterion at week 7 of open-label treatment regardless of any perceived individual need. In clinical practice, the decision to treat patients with long-term bupropion therapy would depend on the need for long-term treatment as perceived by the patient or physician. An approach such as this may improve the efficacy of relapse prevention therapy. Our results suggest that persons who have stopped smoking may benefit from extended treatment with sustained-release bupropion.

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