

A COMPARISON OF SUSTAINED-RELEASE BUPROPION AND PLACEBO FOR SMOKING CESSATION

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ABSTRACT

Background and Methods Trials of antidepressant medications for smoking cessation have had mixed results. We conducted a double-blind, placebo-controlled trial of a sustained-release form of bupropion for smoking cessation. We excluded smokers with current depression, but not those with a history of major depression. The 615 subjects were randomly assigned to receive placebo or bupropion at a dose of 100, 150, or 300 mg per day for seven weeks. The target quitting date (or "target quit date") was one week after the beginning of treatment. Brief counseling was provided at base line, weekly during treatment, and at 8, 12, 26, and 52 weeks. Self-reported abstinence was confirmed by a carbon monoxide concentration in expired air of 10 ppm or less.

Results At the end of seven weeks of treatment, the rates of smoking cessation as confirmed by carbon monoxide measurements were 19.0 percent in the placebo group, 28.8 percent in the 100-mg group, 38.6 percent in the 150-mg group, and 44.2 percent in the 300-mg group ($P < 0.001$). At one year the respective rates were 12.4 percent, 19.6 percent, 22.9 percent, and 23.1 percent. The rates for the 150-mg group ($P = 0.02$) and the 300-mg group ($P = 0.01$) — but not the 100-mg group ($P = 0.09$) — were significantly better than those for the placebo group. Among the subjects who were continuously abstinent through the end of treatment, the mean absolute weight gain was inversely associated with the dose (a gain of 2.9 kg in the placebo group, 2.3 kg in 100-mg and 150-mg groups, and 1.5 kg in the 300-mg group; $P = 0.02$). No effects of treatment were observed on depression scores as measured serially by the Beck Depression Inventory. Thirty-seven subjects stopped treatment prematurely because of adverse events; the frequency was similar among all groups.

Conclusions A sustained-release form of bupropion was effective for smoking cessation and was accompanied by reduced weight gain and minimal side effects. Many participants in all groups were smoking at one year. (N Engl J Med 1997;337:1195-202.)

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nicotine may act as an antidepressant in some smokers.^{3,4} The development of a depressed affect or depression after smoking cessation may lead to relapse.⁵⁻⁷

Results of clinical trials of antidepressant therapy for smoking cessation have been mixed. The initial experience with doxepin was promising; however, no large trials have been reported.⁸ The results of trials of fluoxetine have not been published. A serotonin-uptake inhibitor had no effect on smoking rates in heavy smokers.⁹ An immediate-release form of bupropion (300 mg per day for 12 weeks) showed efficacy in two double-blind, placebo-controlled trials, one with 42 male smokers and the other with 190 smokers.¹⁰ On the basis of these results, we evaluated the efficacy and safety of a sustained-release form of bupropion (Zyban, Glaxo Wellcome) as an aid to smoking cessation. This form of bupropion was recently approved by the Food and Drug Administration as a prescription drug for the indication of smoking cessation.

METHODS

Subjects

This randomized, double-blind, placebo-controlled, dose-response study was performed at three sites (Mayo Clinic, Rochester, Minn.; the Palo Alto Center for Pulmonary Disease Prevention, Palo Alto, Calif.; and West Virginia University, Morgantown) and approved by each center's institutional review board. Recruitment was conducted through advertisements and press releases. A total of 742 volunteers who were interested in stopping smoking were evaluated, of whom 615 met the study criteria and underwent randomization. After an initial screening interview conducted by telephone, subjects attended an informational meeting at which the study was explained, questionnaires completed, and written informed consent provided.

The subjects were eligible for inclusion if they were at least 18 years of age, had smoked an average of 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 the presence or a

PHARMACOLOGIC treatments such as nicotine-replacement therapy have been shown to help smokers stop smoking. Using a medication that does not contain nicotine, such as an antidepressant, has intrigued investigators for several reasons. Smokers are more likely to have a history of major depression than nonsmokers,^{1,2} and

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family history of a seizure disorder, a history of severe head trauma, predisposition to seizures (such as a history of brain tumor or stroke), a history or current diagnosis of anorexia nervosa or bulimia, the presence of an unstable medical or psychiatric condition, pregnancy, lactation, a history of dependence on alcohol or a non-nicotine substance within the past year, current use of psychotropic medications, previous use of bupropion, current use of tobacco products other than cigarettes, and current use of any nicotine-replacement therapy, fluoxetine, clonidine, buspirone, or doxepin. Subjects with current depression as assessed by the physician were also excluded. Those with a history of major depression as assessed by a structured clinical interview were not excluded.¹¹

At the base-line visit subjects were randomly assigned to receive either a sustained-release form of bupropion at a dose of 100 mg per day (50 mg twice a day), 150 mg per day (150 mg each morning and placebo each evening), or 300 mg per day (150 mg per day for three days, followed by 150 mg twice a day) or placebo (twice a day). All the tablets were identical in appearance. Subjects set a target quitting date (or "target quit date") after one week of medication (usually the eighth day). They returned weekly during the 7-week treatment phase, then at 8, 12, 26, and 52 weeks for follow-up. The subjects were telephoned 3 days after the target quitting date and at 4, 5, 7, 8, 9, 10, and 11 months. At the base-line physical examination, each subject received a brief, personalized message to stop smoking from the physician and self-help material based on the National Cancer Institute program.¹² In this program, which has been validated as an effective intervention for smoking cessation, the physician asks each patient whether he or she smokes, advises all smokers to stop smoking, helps the patient set a quitting date, and arranges a follow-up visit.

Subjects underwent chest roentgenography, laboratory testing, electrocardiography, and physical examination. We obtained data on smoking history, asked subjects to keep a daily diary to record smoking rates and symptoms of nicotine withdrawal,¹³ and administered several questionnaires.¹⁴⁻¹⁶ The eight-item Fagerström Tolerance Questionnaire is a widely used measure of nicotine dependence with a score ranging from 0 to 11; a score of 6 or greater indicates higher levels of dependence.¹⁷ The Beck Depression Inventory is a 21-item questionnaire completed by the subject that assesses the severity of depressive symptoms.¹⁵ Total scores range from 0 to 63, with scores of 9 or below considered to be within the normal range. Scores of 10 to 18 indicate mild-to-moderate depression, scores of 19 to 29 indicate moderate-to-severe depression, and scores of 30 or higher indicate severe depression. Each week we collected the subjects' daily diaries and recorded concomitant medication use, adverse events, vital signs, and the carbon monoxide content of expired air. Self-reported abstinence was considered validated by a carbon monoxide level in expired air of 10 ppm or below. Brief individual counseling (approximately 10 to 15 minutes) was provided by a study assistant at each visit.

Statistical Analysis

The sample size was based on the ability to detect a difference between active treatment and placebo at the end of treatment, given a projected abstinence rate of 40 percent in the bupropion groups and 24 percent in the placebo group. Approximately 130 subjects were needed for each treatment group, in order to have a two-sided alpha level of 0.05 and a power of 0.80 to detect such a difference. To ensure an adequate sample, 150 subjects were enrolled in each treatment group.

The base-line characteristics of the four groups of subjects were compared by analysis of variance for continuous variables and chi-square analysis for categorical variables. The efficacy of smoking cessation was evaluated with the use of weekly point-prevalence abstinence rates and rates of continuous abstinence. For the point-prevalence rates, subjects were classified as abstinent if they reported not smoking during the previous seven days and this report was confirmed by an expired carbon monoxide value of 10

ppm or less. To be classified as continuously abstinent, the subjects had to be confirmed as not smoking on the basis of carbon monoxide measurement at each visit. In all cases, an intention-to-treat analysis was performed. Subjects who missed a follow-up visit were considered to be smoking. Randomization of subjects was stratified according to site to ensure that similar numbers of subjects were assigned to each group at each site. However, to verify the assumption that the effect of treatment was not dependent on the study site, the efficacy of smoking cessation was first evaluated with logistic-regression modeling. In these models, the dependent variable was smoking status, as confirmed by carbon monoxide measurement, and the independent variables were dose (placebo vs. 100 mg vs. 150 mg vs. 300 mg of bupropion) and study site (California vs. Minnesota vs. West Virginia). We included an interaction term to assess whether the effect of dose was dependent on the study site. After verifying that the effect of treatment was not dependent on the study site, we performed a logistic-regression analysis to assess differences between groups including site as a covariate. The comparisons of placebo with 100 mg of bupropion, placebo with 150 mg of bupropion, and placebo with 300 mg of bupropion were identified a priori to be of specific interest.

Body weight was analyzed among subjects who were continuously abstinent during the treatment phase. The absolute change in weight from base line was calculated weekly from the start of medication through the end of treatment. The effect of dose was evaluated with a two-factor repeated-measures analysis of variance model, with dose as an independent continuous cross-classification factor and time as the repeated factor. We included an interaction term to assess whether the effect of dose was consistent over time. Linear regression and pairwise dose comparisons were used to supplement these analyses.

Withdrawal symptoms were assessed daily with a composite withdrawal score computed as the mean of the nine items included in the daily diary. Symptoms of nicotine withdrawal included craving for a cigarette; depressed mood; difficulty falling asleep; awakening at night; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; and increased appetite. The severity of each symptom was scored by the subject on a five-point scale as absent (0), slight (1), mild (2), moderate (3), or severe (4). For each subject a base-line withdrawal score was calculated with data from all diaries completed before the start of medication, during which time the subjects were instructed to continue smoking their usual number of cigarettes. Withdrawal-symptom scores obtained after the target quitting date were analyzed as the change from base line. The data were summarized daily for the first week after the target quitting date and as weekly means for each of the next five weeks. For each group, the mean change in the withdrawal score was compared with zero by the one-sample t-test. The effect of treatment was evaluated with a two-factor repeated-measures analysis of variance model in which change in the withdrawal score was the dependent variable, treatment group was an independent cross-classification factor, and time was the repeated factor. Separate analyses were performed for the daily summary of week 1 and the weekly summary of the entire treatment phase. In addition to the overall model, separate pairwise analyses were performed that compared each active-treatment group with placebo.

Symptoms of depression were assessed with the Beck Depression Inventory¹⁵ at base line and at weeks 2 and 6 after the target quitting date. Depression scores were analyzed in terms of the change from base line. For each group, the mean change in the depression score was compared with zero by the one-sample t-test. The effect of treatment was evaluated with a two-factor repeated-measures analysis of variance model in which change in the depression score was the dependent variable, treatment group was an independent cross-classification factor, and time was the repeated factor. Fisher's exact test was used to compare the rates of adverse events for each active-treatment group with those in the placebo group.

RESULTS

The base-line characteristics of the subjects are presented in Table 1. There were no significant differences among the groups. A total of 219 subjects (148 during the treatment phase and 71 subsequently) did not complete the 12-month study. Of these subjects, 196 (89 percent) withdrew their consent for various reasons (e.g., scheduling difficulties or perceived lack of benefit); 15 stopped participating because of an adverse event, 6 because of protocol deviations, and 1 for administrative reasons; 1 subject died. The rate of completion of the study increased with the dose and was 57 percent, 65 percent, 64 percent, and 71 percent for the placebo, 100-mg, 150-mg, and 300-mg groups, respectively ($P=0.01$ by logistic-regression analysis in which dose was treated as a continuous variable).

The biochemically confirmed point-prevalence smoking-cessation rates according to treatment are

shown in Table 2. At the end of the treatment phase (week 6 after the target quitting date), the cessation rate for each of the three active-treatment groups was significantly better than for the placebo group. Subjects who received 300 mg of bupropion per day had a significantly better ($P=0.005$) cessation rate than those who received 100 mg per day. The respective point-prevalence smoking-cessation rates at six weeks and one year were 19.0 percent and 12.4 percent in the placebo group and 44.2 percent and 23.1 percent in the group that received 300 mg of bupropion. At one year, the smoking-cessation rates for the 150-mg and 300-mg groups — but not the 100-mg group — were significantly better than that for the placebo group. When dose was treated as a continuous variable, a significant dose effect was detected at all periods ($P<0.001$ at week 6, $P=0.003$ at 3 months, $P=0.03$ at 6 months, and $P=0.02$ at 12 months).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE SUBJECTS.*

CHARACTERISTIC	PLACEBO (N = 153)	100 mg OF BUPROPION (N = 153)	150 mg OF BUPROPION (N = 153)	300 mg OF BUPROPION (N = 156)
Age (yr)	43.0±10.7	44.1±10.5	42.3±11.3	45.0±11.8
Female sex (%)	59.5	58.2	50.3	50.6
White race (%)	96.7	96.7	96.7	94.2
No. of cigarettes smoked/day in past year	26.5±9.0	26.2±8.5	27.5±9.6	27.2±10.8
Fagerström score†	7.3±1.7	7.3±1.6	7.3±1.6	7.1±1.7
No. of previous serious attempts to quit‡	3.7±5.0	3.5±3.4	4.2±6.5	4.3±5.4
Previous use of nicotine patch (%)	40.5	42.5	39.2	48.7
Previous use of nicotine gum (%)	37.9	36.0	34.0	35.3
Other smokers in the household (%)	39.2	26.8	34.0	33.6
History of major depression (%)	20.3	22.9	17.0	14.1
Beck Depression Inventory score§	4.7±5.0	4.2±3.7	4.1±4.2	4.2±4.2
Marital status (%)				
Married	58.2	66.0	51.6	62.2
Divorced or separated	26.8	18.3	25.5	21.8
Never married	10.5	11.8	17.7	10.3
Widowed	2.0	2.0	3.9	5.1
Other	2.6	2.0	1.3	0.6
Level of education (%)				
Less than high-school graduate	4.6	2.0	3.9	3.2
High-school graduate	17.7	23.5	18.3	19.9
Some education after high school	48.4	40.5	45.1	46.2
College graduate	29.4	34.0	32.7	30.8
Study site (%)				
Palo Alto, Calif.	34.0	33.3	34.0	34.0
Rochester, Minn.	33.3	33.3	33.3	33.3
Morgantown, W.V.	32.7	33.3	32.7	32.7

*Plus-minus values are means ±SD. Because of rounding, not all percentages total 100.

†The range for the Fagerström score is 0 to 11; a score of 6 or greater indicates higher levels of nicotine dependence.^{14,17} Data were missing for two subjects in the 100-mg group and one subject in the 300-mg group.

‡Data were missing for two subjects in the 300-mg group.

§The scores on the Beck Depression Inventory can range from 0 to 63, with scores of 9 or below considered to be within the normal range. Scores of 10 to 18 indicate mild-to-moderate depression, scores of 19 to 29 moderate-to-severe depression, and scores of 30 or higher severe depression.¹⁵ Data were missing for four subjects each in the placebo and 300-mg groups and two subjects each in the 100-mg and 150-mg groups.

TABLE 2. POINT-PREVALENCE SMOKING-CESSATION RATES CONFIRMED BY CARBON MONOXIDE MEASUREMENT.*

TIME AFTER TARGET QUITTING DATE	PERCENTAGE OF SUBJECTS NOT SMOKING				P VALUE†			
	PLACEBO (N=153)	100 mg OF BUPROPION (N=153)	150 mg OF BUPROPION (N=153)	300 mg OF BUPROPION (N=156)	OVERALL	PLACEBO VS. 100-mg DOSE	PLACEBO VS. 150-mg DOSE	PLACEBO VS. 300-mg DOSE
	6 wk‡	19.0	28.8	38.6	44.2	<0.001	0.04	<0.001
3 mo	14.4	24.2	26.1	29.5	0.01	0.03	0.01	<0.001
6 mo	15.7	24.2	27.5	26.9	0.06	0.06	0.01	0.02
12 mo	12.4	19.6	22.9	23.1	0.06	0.09	0.02	0.01

*Point prevalence was estimated weekly.

†The P values given are from analyses that did not include site as a covariate; therefore, they can be obtained directly from the given cessation rates. In logistic-regression analyses that included site as a covariate the same differences were found to be statistically significant. The overall P value is for the simultaneous comparison of all four groups treated categorically. When dose was treated as a continuous variable, a significant dose effect was detected at all times (P<0.001 at week 6, P=0.003 at 3 months, P=0.03 at 6 months, and P=0.02 at 12 months). The pairwise dose comparisons presented were identified a priori, and the corresponding P values are unadjusted.

‡Week 6 was the final week of study medication.

Figure 1 shows the rates of continuous abstinence from the target quitting date through the end of treatment (10.5 percent in the placebo group, 13.7 percent in the 100-mg group, 18.3 percent in the 150-mg group, and 24.4 percent in the 300-mg group). The rate of continuous abstinence was significantly better in the group that received 300 mg of bupropion than in the placebo group (P=0.001) and in the group that received 100 mg of bupropion (P=0.02).

Weight Change

The mean change in weight from the start of medication (base line) for the 103 subjects who were continuously abstinent during the treatment

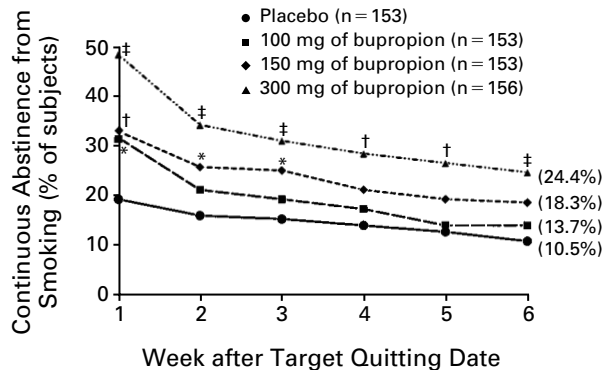


Figure 1. Rates of Confirmed Continuous Abstinence from the Target Quitting Date through the End of Treatment.

Self-reported abstinence was confirmed by a finding of an expired carbon monoxide concentration of 10 ppm or less. The asterisks (0.01<P≤0.05), daggers (0.001<P≤0.01), and double daggers (P≤0.001) indicate significant differences from placebo. All subjects are included at all time points.

phase is shown in Figure 2. At the end of treatment, the subjects had gained a mean of 2.9 kg in the placebo group (16 subjects), 2.3 kg in the 100-mg group (21 subjects) and the 150-mg group (28 subjects), and 1.5 kg in the 300-mg group (38 subjects). Weight change was negatively associated with the dose (P=0.003, by repeated-measures analysis of variance), with evidence of an interaction between dose and time (P=0.04) that indicated a larger disparity between doses at later periods. For each of the first six weeks after the target quitting date, weight change was negatively associated with dose, with less weight gain found with higher doses of bupropion. Of the 59 subjects who were continuously abstinent from the target quitting date to the six-month follow-up visit, the mean weight gain was not significantly associated with dose: 5.5 kg in the placebo group (9 subjects), 6.6 kg in the 100-mg group (10 subjects), 4.4 kg in the 150-mg group (21 subjects), and 4.5 kg in the 300-mg group (19 subjects).

Symptoms of Depression and Withdrawal

During the medication phase, there was no evidence of a difference in change among treatment groups in the mean scores on the Beck Depression Inventory. In addition, the change in scores from base line was not significantly different from zero for any group either two weeks after the target quitting date (mean ±SD change, -0.3±4.7 in the placebo group [121 subjects], +0.4±4.1 in the 100-mg group [124 subjects], +0.6±4.9 in the 150-mg group [123 subjects], and +0.3±5.0 in the 300-mg group [128 subjects]) or at the end of treatment (-0.8±4.7 [103 subjects]; +0.5±5.5 [115 subjects]; -0.4±5.7 [110 subjects], and +0.8±5.2 [128 subjects], respectively).

The mean changes from base line in the compos-

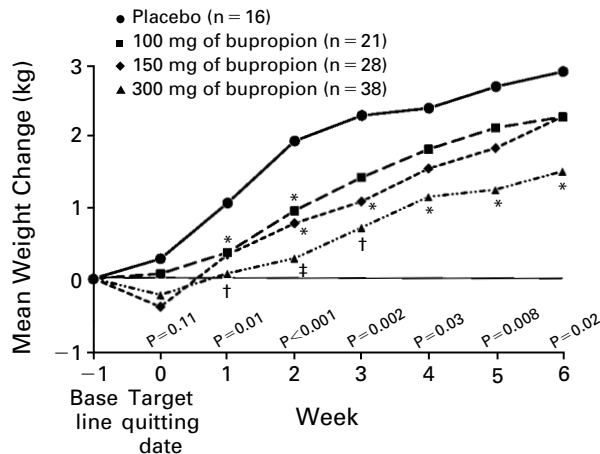


Figure 2. Mean Change in Weight from Base Line through the End of Treatment among 103 Subjects Who Were Continuously Abstinent.

Weight was analyzed at the end of each week. The mean weight change was significantly greater than zero ($P < 0.05$ by the one-sample t-test) at weeks 1 through 6 in the placebo group, at weeks 2 through 6 in the 100-mg and 150-mg groups, and at weeks 3 through 6 in the 300-mg group. The P values shown are for the effect of dose assessed with a linear regression model in which absolute change in weight was the dependent variable and dose was the independent variable. Asterisks ($0.01 < P \leq 0.05$), daggers ($0.001 < P \leq 0.01$), and the double dagger ($P \leq 0.001$) indicate a significant difference (by the two-sample t-test) from placebo. The number of subjects with data available is the same for all periods except week 5, for which data were missing for one subject in the 150-mg group. Treatment was started at base line.

ite withdrawal scores are shown in Figure 3. For each group, the mean change from base line was significantly greater than zero (i.e., withdrawal symptoms increased) at all periods. For the first week after the target quitting date, the change in the withdrawal scores was not significantly different among the four treatment groups. In the analysis of the weekly means, a significant treatment effect was detected ($P < 0.001$). From the pairwise comparisons of the active-treatment groups with the placebo group, only the 100-mg group had significantly more withdrawal symptoms ($P = 0.008$) than the placebo group. There were no significant interactions between time and treatment.

Despite explicit instructions to the contrary, seven subjects used nicotine-replacement products during the study, only one of whom stopped smoking at any point. That subject chewed one piece of nicotine gum on day 17 before remembering he was not to do so.

Safety

All adverse events reported one or more times by at least 10 percent of subjects in any given treatment group are shown in Table 3. A total of 37 subjects

stopped treatment prematurely because of adverse events (8 in the placebo group [5 percent], 9 in the 100-mg group [6 percent], 7 in the 150-mg group [5 percent], and 13 in the 300-mg group [8 percent]). Tremor, headaches, rash, and urticaria were the most common reasons for stopping treatment.

Three serious adverse events were reported during or immediately after the medication phase. A 23-year-old man assigned to receive 300 mg of bupropion per day reported extreme irritability, restlessness, anger, anxiety, and cravings soon after he stopped smoking. The study medication was stopped, and he began treatment with a nicotine patch. Two days later he was doing well. A 66-year-old woman assigned to the 300-mg group had an allergic reaction manifested by a pruritic rash, angioedema, dyspnea, and petechiae. She had received bupropion for 24 days, but had begun taking amoxicillin-clavulanate for the treatment of bronchitis 8 days before the onset of the reaction. The bupropion and amoxicillin-clavulanate were stopped, and the reaction resolved after treatment with antihistamines, epinephrine, and corticosteroids. The reaction was judged to be most likely related to amoxicillin-clavulanate. A 63-year-old woman with preexisting cardiomyopathy and hypertension had cardiac and pulmonary arrest four days after completing the treatment phase (300-mg group) and died nine days later.

DISCUSSION

We found that the sustained-release form of bupropion was an effective treatment for smoking cessation, although many participants in all groups were smoking at one year. There was a significant dose response at all periods. Furthermore, the rates of abstinence at one year were significantly better in the 150-mg group ($P = 0.02$) and the 300-mg group ($P = 0.01$) than in the placebo group. Although the 300-mg dose was the most effective initially, its effects were not significantly different from those of the 150-mg dose at the end of treatment or at one year. Nonetheless, the 300-mg dose was the only one to show a difference in the rates of continuous abstinence from the target quitting date through the end of treatment. Thus, we would recommend using the 300-mg dose (150 mg twice a day) as the target dose for most patients, given the favorable side-effect profile and the fact that there was less weight gain during the medication phase with this dose. Because steady-state plasma levels of bupropion are usually reached within eight days, we started the medication at least seven days before the target quitting date in order to ensure that these levels were attained.¹⁸ We used bupropion for seven weeks on the basis of pilot studies and experience with nicotine-patch therapy, which showed that extending treatment beyond eight weeks does not appear to increase efficacy.¹⁹ Although this duration of

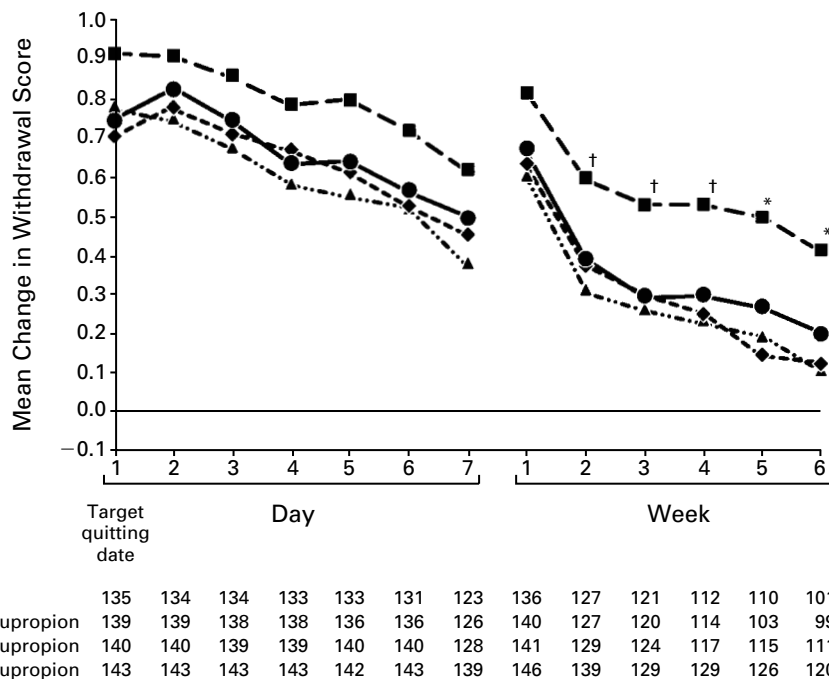


Figure 3. Mean Change from Base Line in the Withdrawal Score.

For each group, the mean change from base line was significantly greater than zero ($P < 0.05$ by the one-sample t-test) in all periods. Asterisks ($0.01 < P \leq 0.05$) and daggers ($0.001 < P \leq 0.01$) indicate a significant difference from placebo (by the two-sample t-test). The numbers of subjects for whom data were available are listed below the figure.

TABLE 3. ADVERSE EVENTS AMONG SUBJECTS.*

ADVERSE EVENT	PLACEBO (N=153)	100 mg OF BUPROPION (N=153)	150 mg OF BUPROPION (N=153)	300 mg OF BUPROPION (N=156)	percent			
Headache	29.4	30.7	31.4	32.7				
Insomnia	20.9	30.1	29.4	34.6†				
Rhinitis	17.0	10.5	12.4	10.3				
Dry mouth	4.6	7.2	13.1‡	12.8‡				
Anxiety	11.1	6.5	5.9	5.1				

*Adverse events that were experienced one or more times by at least 10 percent of subjects in any group are listed in decreasing order according to overall frequency. No significant differences were found between any bupropion groups and placebo for adverse events reported by less than 10 percent of subjects in all groups with the exception of bronchitis and vasodilatation, which each occurred in six subjects in the 100-mg group and no subjects in the placebo group ($P = 0.03$).

† $P = 0.008$ for the comparison with placebo by Fisher's exact test.

‡ $P = 0.01$ for the comparison with placebo by Fisher's exact test.

therapy may be adequate, a longer duration may be appropriate if relapse is a concern. Antidepressants are commonly used for several months to treat depression or chronic pain and have little potential for abuse. We did not, however, study a longer duration of treatment.

Another important finding was the significantly

smaller weight gain in subjects who continuously abstained from smoking and who were receiving higher doses of bupropion. The typical weight gain associated with successful smoking cessation is 3 to 4 kg,²⁰ and it is a concern that inhibits many smokers (especially women) from attempting to stop.²¹ Nicotine-replacement therapy has had mixed results in con-

trolling weight gain after smoking cessation,²²⁻²⁷ with nicotine gum and nicotine nasal spray showing the greatest benefit. A medication effective for smoking cessation that is also capable of minimizing the associated weight gain would offer a major advantage.²⁸ Bupropion seems to have that potential, even though the differences observed were moderate, and the effect seems to be limited to the time the drug is used. The effect of a longer treatment period on weight gain has not been determined.

Nicotine activates central nervous system pathways to release norepinephrine, dopamine, and other neurotransmitters^{29,30} and elevates dopamine levels in areas of the brain associated with the reinforcement of the effects of amphetamines, cocaine, and opiates.³¹⁻³³ Bupropion is a weak inhibitor of the neuronal uptake of norepinephrine and dopamine but has no effect on serotonin.³⁴ Its dopaminergic and noradrenergic activities could be responsible for its efficacy in smoking cessation, with the dopaminergic activity affecting areas of the brain having to do with the reinforcement properties of addictive drugs and the noradrenergic activity affecting nicotine withdrawal.³⁴ We observed no treatment effects on depression scores as measured serially by the Beck Depression Inventory; thus, the mechanism for bupropion's efficacy is unlikely to be through its antidepressant effects. However, subjects with current depression were excluded from this study. Further study is needed for a full understanding of the responsible mechanisms.

Bupropion was well tolerated, with the most frequent adverse effects being headache, insomnia, and dry mouth. Antidepressants are associated with a small risk of seizure.³⁵ For sustained-release bupropion used for the treatment of depression, this risk is 0.1 percent for doses of up to 300 mg per day (i.e., one seizure per 1000 subjects receiving bupropion for varying periods of time — from a few weeks to more than a year).³⁶ Our study lacked adequate power to evaluate seizures at these low rates. None of the 462 subjects in this study who received bupropion had a seizure. However, we excluded potential subjects who had a personal or family history of seizures, a history of severe head trauma, eating disorders, or active alcoholism. In clinical practice, patients should be screened for the possibility of seizure before they start treatment with bupropion.

Even though relief of nicotine-withdrawal symptoms is not a prerequisite for smoking cessation, we were puzzled by the finding that subjects who received 100 mg of bupropion a day had a higher mean score for withdrawal symptoms. A possible explanation is that a dose of 50 mg twice a day was sufficient to produce side effects that could be interpreted as similar to withdrawal symptoms, but was not sufficient to reduce the severity of true withdrawal symptoms.

The strengths of our study are the sample size, the use of multiple centers, the dose response, and the efficacy demonstrated by point-prevalence rates and rates of continuous abstinence. However, subjects who enroll in clinical trials are motivated to stop smoking and may not be representative of the general population of smokers. Much remains to be learned, such as the optimal duration of treatment, the potential role of combination therapy with nicotine-replacement products, and the use of bupropion for smoking cessation in smokers with depression.

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