A CONTROLLED TRIAL OF SUSTAINED-RELEASE BUPROPION, A NICOTINE PATCH, OR BOTH FOR SMOKING CESSATION

DOUGLAS E. JORENBY, PH.D., SCOTT J. LEISCHOW, PH.D., MITCHELL A. NIDES, PH.D., STEPHEN I. RENNARD, M.D., J. ANDREW JOHNSTON, PHARM.D., ARLENE R. HUGHES, PH.D., STEVENS S. SMITH, PH.D., MYRA L. MURAMOTO, M.D., DAVID M. DAUGHTON, M.S., KIMBERLI DOAN, B.S., MICHAEL C. FIORE, M.D., M.P.H., AND TIMOTHY B. BAKER, PH.D.

ABSTRACT

Background and Methods Use of nicotine-replacement therapies and the antidepressant bupropion helps people stop smoking. We conducted a double-blind, placebo-controlled comparison of sustained-release bupropion (244 subjects), a nicotine patch (244 subjects), bupropion and a nicotine patch (245 subjects), and placebo (160 subjects) for smoking cessation. Smokers with clinical depression were excluded. Treatment consisted of nine weeks of bupropion (150 mg a day for the first three days, and then 150 mg twice daily) or placebo, as well as eight weeks of nicotine-patch therapy (21 mg per day during weeks 2 through 7, 14 mg per day during week 8, and 7 mg per day during week 9) or placebo. The target day for quitting smoking was usually day 8.

Results The abstinence rates at 12 months were 15.6 percent in the placebo group, as compared with 16.4 percent in the nicotine-patch group, 30.3 percent in the bupropion group ($P<0.001$), and 35.5 percent in the group given bupropion and the nicotine patch ($P<0.001$). By week 7, subjects in the placebo group had gained an average of 2.1 kg, as compared with a gain of 1.6 kg in the nicotine-patch group, a gain of 1.7 kg in the bupropion group, and a gain of 1.1 kg in the combined-treatment group ($P<0.05$). Weight gain at seven weeks was significantly less in the combined-treatment group than in the bupropion group and the placebo group ($P<0.05$ for both comparisons). A total of 311 subjects (34.8 percent) discontinued one or both medications. Seventy-nine subjects stopped treatment because of adverse events: 6 in the placebo group (3.8 percent), 16 in the nicotine-patch group (6.6 percent), 29 in the bupropion group (11.9 percent), and 28 in the combined-treatment group (11.4 percent). The most common adverse events were insomnia and headache.

Conclusions Treatment with sustained-release bupropion alone or in combination with a nicotine patch resulted in significantly higher long-term rates of smoking cessation than use of either the nicotine patch alone or placebo. Abstinence rates were higher with combination therapy than with bupropion alone, but the difference was not statistically significant. (N Engl J Med 1999;340:685-91.)

EACH year, approximately 20 million of the 50 million smokers in the United States try to quit smoking, but only about 6 percent of those who try succeed in quitting in the long term.[1] Nicotine-replacement therapies, such as the nicotine patch and nicotine gum, boost the rates of smoking cessation by a factor of 1.4 to 2.6 in comparison with placebo treatments,[2] but 70 to 80 percent of smokers who use these therapies still start to smoke again.

Affect or mood appears to exert potent effects on the motivation to use nicotine.[3-5] For instance, among smokers, symptoms of nicotine dependence are correlated with the magnitude of affective symptoms of depression.[6] In population-based studies, smokers are more likely than nonsmokers to have symptoms of affective disorders.[6] Persons with a negative affect are more likely to start smoking and less likely to be able to quit[7-9] — effects that may be related to changes in dopaminergic activity in the brain.[10] Antidepressants or anxiolytics may therefore be efficacious cessation aids.[3,11] Hurt and colleagues[12] demonstrated that bupropion is an effective smoking-cessation aid: at 12 months, the abstinence rates were 23 percent among subjects assigned to receive 300 mg of bupropion per day for 7 weeks and 12 percent among subjects assigned to receive placebo. We compared bupropion, placebo, a nicotine patch,[2] and a combination of bupropion and the nicotine patch with regard to efficacy.[13] We also examined whether treatment with bupropion ameliorates nicotine-withdrawal symptoms such as negative mood.

METHODS

Subjects, Screening, and Randomization

Subjects were recruited at four study sites by advertisements in the media. The first subject was enrolled in August 1995, and follow-up was completed in March 1997. Of a total of 1182 persons who were screened, 893 met the screening criteria and were enrolled: 218 in Arizona, 227 in California, 220 in Nebraska, and 228 in Wisconsin. The subjects were randomly assigned to one

From the Center for Tobacco Research and Intervention, University of Wisconsin Medical School, Madison (D.E.J., S.S.S., M.C.F., T.B.B.); the Arizona Program for Nicotine and Tobacco Research, University of Arizona, Tucson (S.J.L., M.L.M.); Los Angeles Clinical Trials, Los Angeles (M.A.N., K.D.); the Pulmonary and Critical Care Medicine Section, University of Nebraska Medical Center, Omaha (S.I.R., D.M.D.); and Glaxo Wellcome, Research Triangle Park, N.C. (J.A.J., A.R.H.). Address reprint requests to Dr. Jorenby at 1300 University Ave., Rm. 7278 MSC, Madison, WI 53706.

of four treatments with use of an unequal-cell design: 160 subjects were assigned to receive placebo, 244 to receive the nicotine patch, 244 to receive bupropion, and 245 to receive bupropion and the nicotine patch. Randomization was not balanced within sites.

The subjects were screened by means of a telephone interview and a pretreatment session that included a physical examination, electrocardiography, and chest roentgenography. The study protocol was approved by the institutional review board at each site. All participants provided written informed consent.

To be eligible for the study, subjects had to be at least 18 years of age, to smoke at least 15 cigarettes per day, to weigh at least 45.4 kg (100 lb), to be motivated to quit smoking, and to speak English. Only one smoker per household was allowed to enroll in the study. Subjects were excluded for the following reasons: serious or unstable cardiac, renal, hypertensive, pulmonary, endocrine, or neurologic disorders, as assessed by the study-site physician; ulcers; seizure or dermatologic disorders; a current diagnosis of major depressive episode or a history of panic disorder, psychosis, bipolar disorder, or eating disorders; use of a nicotine-replacement therapy within six months before study enrollment; pregnancy or lactation; abuse of alcohol or a non–nicotine-containing drug within the preceding year; use of a psychoactive drug within the week before enrollment; use of an investigational drug within the month before enrollment; prior use of bupropion; current use of other smoking-cessation treatments; and regular use of any noncigarette tobacco product.

Treatment Period

The treatment period was nine weeks. Target quitting dates were set for the second week, usually day 8. Participants were assessed weekly and attended a brief (15 minutes or less) individual counseling session for smoking cessation each week. Counseling topics included motivation, identification of smoking triggers, coping responses, weight management, and use of the medications. The counselors used a standardized treatment developed by Hurt and colleagues.[12] The subjects also received a supportive telephone call from a counselor approximately three days after the target quitting date.

Follow-up Period

Follow-up assessments and relapse-prevention counseling occurred during clinic visits 10, 12, 26, and 52 weeks after the start of the study. In addition to clinic visits, subjects received eight telephone calls from a counselor during this period, one per month in months 3, 4, and 5 and 7 to 11. All follow-up counseling was less than 10 minutes in duration per call.

Medications

Subjects in the two bupropion groups received 150-mg tablets of sustained-release bupropion (Zyban, Glaxo Wellcome), and all other subjects received identical-appearing tablets. In the bupropion groups, subjects received 150 mg of bupropion in the morning and a placebo tablet in the evening on days 1, 2, and 3 of treatment; and one bupropion tablet in the morning and one in the evening on days 4 to 63. All other subjects took placebo tablets twice daily from days 1 to 63. Subjects in the nicotine-patch groups used one patch (Habitrol, Novartis Consumer Health) per day for eight weeks beginning on the quitting day (day 8). All other subjects applied a placebo patch each day for eight weeks. The patches used from weeks 2 to 7 each contained 21 mg of nicotine; those used during week 8 each contained 14 mg, and those used during week 9 each contained 7 mg.

Assessments

At base line, serum cotinine, vital signs, and exhaled carbon monoxide were determined; data on smoking history were obtained; and three questionnaires were administered. The portion of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV), concerning mood disorders was used to assess whether subjects had mood disorders. The Beck Depression Inventory[14] assesses the severity of depression. Scores of 0 to 9 are considered to be normal, scores of 10 to 18 indicate mild-to-moderate depression, scores of 19 to 29 indicate moderate-to-severe depression, and scores of 30 to 63 indicate severe depression. The Fagerström Tolerance Questionnaire[15] measures nicotine dependence. Scores can range from 0 to 11, with higher scores indicating more severe dependence.

During the treatment period, vital signs were assessed and the carbon monoxide content of expired air was measured. All subjects were asked to keep a daily diary for the first 12 weeks of the study that included information on smoking status, craving, and withdrawal symptoms. During the follow-up period, the Beck Depression Inventory was given, vital signs and the carbon monoxide content of expired air were measured, and self-reported smoking status was assessed.

Measures of Outcome

All 893 subjects were included in analyses of the primary outcome. The primary outcome variable was the point-prevalence rate of abstinence at 6 and 12 months of follow-up. Subjects were considered to be abstinent if they reported not smoking since the preceding clinic visit and had an expired carbon monoxide concentration of 10 ppm or less. Subjects were considered to be continuously abstinent if they had not smoked after the quitting day, as confirmed by a carbon monoxide concentration of 10 ppm or less at all clinic visits during the 12-month study. Secondary outcome measures included withdrawal symptoms, body weight, and Beck Depression Inventory scores.

Statistical Analysis

Chi-square and analysis of variance were used to test for baseline differences in demographic and smoking-history variables.[16] All statistical tests were two-sided and had an alpha level of 0.05. Sample sizes were based on the results of a previous study of bupropion in which the abstinence rates at four weeks were 40 percent in the bupropion group and 24 percent in the placebo group.[12] We estimated that 130 subjects were needed in the placebo group and 230 subjects were needed in the treatment groups for the study to have a power of 0.80 to detect such a difference at an alpha level of 0.05. All subjects who discontinued treatment early or who were lost to follow-up were classified as smokers.

Logistic-regression analysis[17] was used to determine pairwise differences among groups in the abstinence rates. The Kaplan–Meier method was used to analyze differences in rates of continuous abstinence; homogeneity among treatments and pairwise differences were tested with the log-rank test.[16]

Withdrawal symptoms were assessed daily with a composite score calculated as the mean of eight items in the daily diary: craving for cigarettes; restlessness; increased appetite; depressed mood; anxiety; difficulty concentrating; irritability, frustration, or anger; and difficulty sleeping (DSM-IV symptoms plus craving).[18,19] The severity of each symptom was rated on a five-point scale, as absent (0), slight (1), mild (2), moderate (3), or severe (4). Repeated-measures analysis of variance was used to analyze the change in scores from base line (before smoking cessation) to after smoking cessation. Group coding was used that permitted tests of the independent and interactive effects of the two pharmacotherapies. In one analysis, the changes in scores during the first six days after the quitting date were analyzed; in a second analysis, the changes in scores during each week of the eight-week period after the quitting date were analyzed. To control experiment-wise error, Tukey's studentized range test[16] was used for pairwise group comparisons of changes in scores that were found to be significantly different; this same strategy was used to analyze body weight and Beck Depression Inventory scores. Adverse events that began or increased during the treatment phase were coded with COSTART

(Coding Symbols for Thesaurus of Adverse Reaction Terms),[20] and differences between groups were tested by Fisher's exact test.

RESULTS

Base-Line Characteristics and Rates of Discontinuation

The base-line characteristics of the study subjects are shown in Table 1. There were no significant differences among the groups. There were no significant interactions between site and treatment for the point-prevalence rates of abstinence at 6 and 12 months.

A total of 311 subjects (34.8 percent) discontinued treatment: 177 left the study and provided no additional information, whereas 134 stopped taking the medication but participated in follow-up assessments. Subjects in the placebo group had the highest rate of discontinued treatment (48.8 percent); the rates were 31.1 percent in the bupropion group, 35.7 percent in the nicotine-patch group, and 28.6 percent in the combined-treatment group.

Abstinence Rates

Figure 1A shows the point-prevalence rates of abstinence from smoking, as confirmed by biochemical tests. The point-prevalence rates of abstinence at four weeks were significantly higher in all three treatment groups (48.0, 60.2, and 66.5 percent for the nicotine-patch group, bupropion group, and combined-treatment group, respectively) than in the placebo group (33.8 percent; $P=0.005$, $P<0.001$, and $P<0.001$, respectively). Thereafter, only the bupropion group and the combined-treatment group had significantly higher point-prevalence rates of abstinence than the placebo group (Fig. 1A and Table 2).

Analyses of the rates of continuous abstinence (Fig. 1B) during the 12-month period showed that the rates were higher in all three active-treatment groups than in the placebo group ($P<0.001$), the rates were higher in the two bupropion groups than in the nicotine-patch group ($P<0.001$), and the rates in the two bupropion groups were not significantly different from one another ($P=0.61$). The mean (±SE) rates of continuous abstinence at 12 months were 5.6±0.02 percent in the placebo group, 9.8±0.02 percent in the nicotine-patch group, 18.4±0.03 percent in the bupropion group, and 22.5±0.03 percent in the combined-treatment group.

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

CHARACTERISTIC	PLACEBO (N=160)	NICOTINE PATCH (N=244)	BUPROPION (N=244)	NICOTINE PATCH AND BUPROPION (N=245)
Age (yr)	42.7±10.2	44.0±10.9	42.3±10.2	43.9±11.6
Female sex (%)	58.8	51.6	51.6	49.4
White race (%)	93.1	93.0	93.9	92.2
Weight (kg)	74.2±14.6	76.9±17.4	76.5±16.2	76.1±16.1
Education (%)				
High-school graduate or less	24.4	21.3	21.3	18.4
Some education after high school	48.1	51.2	46.3	48.6
College graduate or more	27.5	27.5	32.4	33.1
No. of cigarettes smoked daily	28.1±10.6	26.5±9.4	25.5±8.8	26.8±9.4
Years of smoking cigarettes	25.6±9.9	26.8±11.1	24.6±10.5	26.7±11.6
No. of previous attempts to quit	2.8±3.0	2.7±2.4	3.1±4.7	2.5±2.4
Expired carbon monoxide (ppm)	30.2±12.2	28.3±9.9	28.4±11.1	28.7±11.1
Serum cotinine (ng/ml)	358±157	373±204	357±170	362±165
Fagerström score†	7.5±1.8	7.4±1.7	7.4±1.6	7.3±1.8
Other smokers in household (%)	37.1	28.3	28.7	24.5
Previous use of nicotine patch (%)	36.5	38.1	36.9	34.7
Previous use of nicotine gum (%)	34.0	23.4	28.3	28.2
History of major depression (%)‡	15.6	18.0	20.9	17.6
Beck Depression Inventory score§	4.0±4.4	3.9±4.5	4.4±5.1	3.5±4.7

*Plus–minus values are means ±SD. Percentages do not all sum to 100, because of rounding.

†The range for the Fagerström Tolerance Questionnaire score is 0 to 11, with scores of 6 or greater indicating higher levels of nicotine dependence.

‡History of major depression was assessed by the Structured Clinical Interview for the DSM-IV. Persons meeting criteria for a current diagnosis of major depression were excluded from the study.

§The scores on the Beck Depression Inventory can range from 0 to 63, with scores of 0 to 9 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.

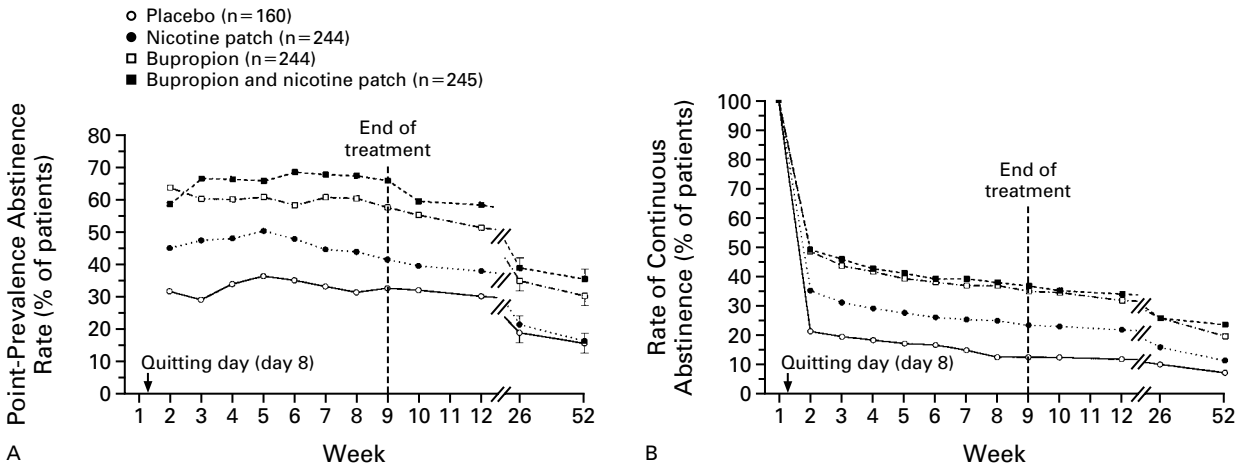


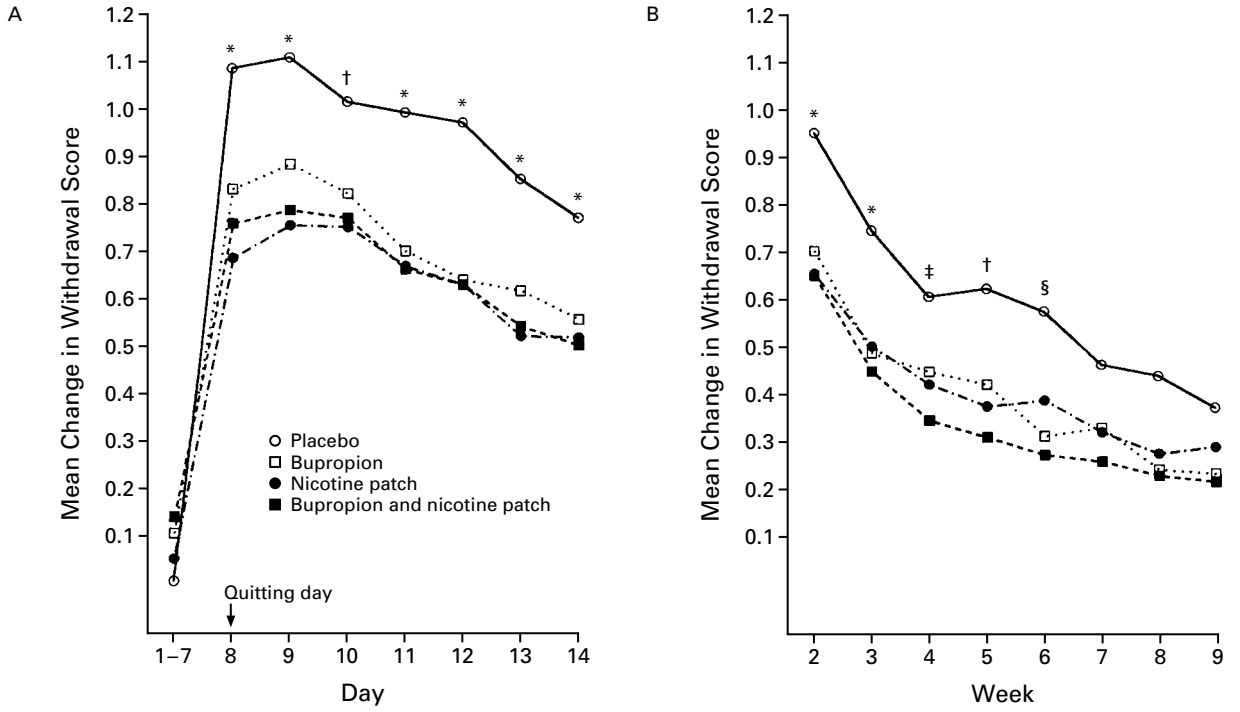
Figure 1. Point-Prevalence Rates of Abstinence (Panel A) and Rates of Continuous Abstinence (Panel B) during Treatment (Weeks 1–9) and Follow-up (Weeks 10–52).

The point-prevalence rates of abstinence at four weeks were significantly higher in all three treatment groups than in the placebo group ($P=0.005$ for the comparison with the nicotine-patch group, $P<0.001$ for the comparison with the bupropion group, and $P<0.001$ for the comparison with the group given the nicotine patch and bupropion). For continuous abstinence, all three active treatments were superior to placebo ($P<0.001$), bupropion alone and in combination with the nicotine patch was superior to the nicotine patch alone ($P<0.001$), and there was no significant difference between bupropion alone and bupropion in combination with the nicotine patch ($P=0.61$). I bars indicate standard errors.

TABLE 2. PRIMARY EFFICACY OUTCOMES.*

OUTCOME	PLACEBO (N=160)	NICOTINE PATCH (N=244)	BUPROPION (N=244)	BUPROPION AND NICOTINE PATCH (N=245)
No. evaluated at 6 mo	86	159	178	195
Abstinence at 6 mo — % (no.)	18.8 (30)	21.3 (52)	34.8 (85)	38.8 (95)
Odds ratio (95% CI)	—	1.2 (0.7–1.9)	2.3 (1.4–3.7)	2.7 (1.7–4.4)
P value				
For the comparison with placebo	—	0.53	<0.001	<0.001
For the comparison with patch	—	—	0.001	<0.001
For the comparison with bupropion alone	—	—	—	0.37
No. evaluated at 12 mo	82	152	169	181
Abstinence at 12 mo — % (no.)	15.6 (25)	16.4 (40)	30.3 (74)	35.5 (87)
Odds ratio (95% CI)	—	1.1 (0.6–1.8)	2.3 (1.4–3.9)	3.0 (1.8–4.9)
P value				
For the comparison with placebo	—	0.84	<0.001	<0.001
For the comparison with patch	—	—	<0.001	<0.001
For the comparison with bupropion alone	—	—	—	0.22

*Point-prevalence rates of abstinence were based on biochemically confirmed (by an expired carbon monoxide concentration of ≤10 ppm) self-report of abstinence during the seven days preceding assessment of smoking status at a given time. The treatment period was nine weeks. Odds ratios were computed by logistic-regression analysis, which was used to determine pairwise differences in abstinence rates. Subjects who discontinued treatment or were lost to follow-up before a visit were classified as smokers for that visit. CI denotes confidence interval.



No. at Risk								
Placebo	153	146	145	144	144	144	136	130
Bupropion	238	220	220	219	216	219	216	211
Nicotine patch	241	229	229	227	224	226	220	215
Bupropion and nicotine patch	237	225	226	225	224	224	219	212

No. at Risk								
Placebo	147	128	117	110	101	94	92	89
Bupropion	223	215	208	202	195	192	190	186
Nicotine patch	230	221	212	199	190	181	172	170
Bupropion and nicotine patch	226	220	211	209	204	199	196	196

Figure 2. Mean Change from Base Line in Composite Withdrawal Scores.

The changes in scores were analyzed daily during the first six days after the quitting date (Panel A) and then weekly until the end of treatment (Panel B). The mean changes in scores could range from −4 to +4. Tukey's studentized range test was used to assess differences among the groups. Asterisks indicate $P<0.05$ for the comparison with all three active-treatment groups. Daggers indicate $P<0.05$ for the comparison with the nicotine-patch group and the combined-treatment group. Double dagger indicates $P<0.05$ for the comparison with the combined-treatment group. Section mark indicates $P<0.05$ for the comparison with the bupropion group and the combined-treatment group.

Symptoms of Withdrawal and Depression

Figure 2 shows the mean changes in withdrawal symptoms from base line for all subjects (regardless of whether or not they were smoking). The changes were analyzed daily during the first six days after the quitting date and then weekly until the end of treatment. All four groups had significant increases in withdrawal symptoms during the first week of treatment ($P<0.001$). However, the changes were smaller in the three active-treatment groups than in the placebo group during the first six days after the quitting date and during the following weeks.

The Beck Depression Inventory scores were within the range of normal at base line (Table 1). Treatment had no effect on the scores. Analyses did not show any interaction between repeated measures and treatment during treatment and follow-up.

Weight Change

At the beginning of treatment, there were no significant differences in mean body weight among the four groups (Table 1). By week 7 (after which the nicotine-patch dose was decreased from 21 to 14 mg per day), subjects in the placebo group had gained an average of 2.1 kg, as compared with a gain of 1.6 kg in the nicotine-patch group, 1.7 kg in the bupropion group, and 1.1 kg in the combined-treatment group. Pairwise group comparisons by Tukey's studentized range test at week 7 indicated that the subjects in the combined-therapy group had gained significantly less weight than those in the placebo group ($P<0.05$) or the bupropion group ($P<0.05$). There were no significant differences between groups in mean weight changes after week 7.

Safety

Table 3 shows the adverse events reported by 10 percent or more of the subjects in any of the groups. Insomnia was the most commonly reported adverse event, occurring among 47.5 percent of the subjects in the combined-treatment group, 42.4 percent of those in the bupropion group, 30.0 percent of those in the nicotine-patch group, and 19.5 percent of those in the placebo group. Reactions at the application site and dream abnormalities were most common among the subjects who used the nicotine patch.

A total of 79 subjects (8.8 percent) discontinued medication because of adverse events: 6 in the placebo group (3.8 percent), 16 in the nicotine-patch group (6.6 percent), 29 in the bupropion group (11.9 percent), and 28 in the combined-treatment group (11.4 percent). The rates of discontinuation of treatment were higher among those receiving bupropion ($P=0.004$) and those receiving combined treatment ($P=0.007$) than among those receiving placebo. There was a nonsignificant trend ($P=0.24$) toward a greater incidence of new or worsening hypertension during the treatment period among those receiving combined therapy than among those receiving placebo (6.1 percent vs. 3.1 percent). No seizures were reported in any group.

Five serious adverse events were reported during treatment. Three were dermatologic or allergic reactions in subjects who were taking bupropion, one of whom was also using a nicotine patch. All three had rash and pruritus, and one also had shortness of breath and chest tightness. The symptoms began 14 to 20 days after the start of therapy. Treatment was stopped, and the three subjects received glucocorticoids and antihistamines. All had full resolution of symptoms. These reactions were attributed to bupropion.

The two other serious adverse events consisted of viral spinal meningitis in a 38-year-old woman 60 days after the initiation of nicotine-patch therapy and chest pain in a 46-year-old man who was hospitalized 4 days after beginning bupropion therapy. He was discharged one day later with a diagnosis of gastric reflux, and the symptoms resolved after treatment with omeprazole. The meningitis and gastric reflux were not attributed to the study medications.

TABLE 3. ADVERSE EVENTS.*

ADVERSE EVENT	PLACEBO (N=159)	NICOTINE PATCH (N=243)	BUPROPION (N=243)	BUPROPION AND NICOTINE PATCH (N=244)
	percent			
Anxiety	6.3	6.6	8.6	10.3
Dizziness	6.3	3.3	10.7	8.2
Dream abnormalities	2.5	18.1†	4.5	13.5†
Dry mouth	4.4	4.1	10.7†	9.0
Influenza-like syndrome	10.7	7.4	8.6	7.8
Headache	32.7	28.4	25.9	26.6
Infection	15.7	14.8	14.8	15.2
Insomnia	19.5	30.0†	42.4†	47.5†
Nausea	5.0	7.8	9.5	11.5†
Rhinitis	12.0	12.4	13.6	10.7
Application-site reaction	6.9	18.5†	11.9	15.2†

*Adverse events were reports of symptoms that began after or were exacerbated by treatment. Symptoms were coded with COSTART.[20] Only adverse reactions that were reported by at least 10 percent of the subjects in any of the groups are listed. The incidence of four additional adverse events, which were reported by fewer than 10 percent of subjects, was significantly different among the groups. Pharyngitis was more common in the three active-treatment groups than in the placebo group, and anorexia, constipation, and pruritus were more common in the group given bupropion and the nicotine patch than in the placebo group ($P<0.05$ for all comparisons).

†$P<0.05$ for the comparison with placebo.

DISCUSSION

We found that treatment with bupropion alone or in combination with a nicotine patch resulted in higher long-term abstinence rates than did the use of placebo or a nicotine patch alone. Treatment with both bupropion and the nicotine patch was not significantly better than treatment with bupropion alone either at the end of the treatment period or during follow-up. As compared with the use of placebo, treatment with the nicotine patch, the nicotine patch and bupropion, and bupropion alone all resulted in less severe withdrawal symptoms and less weight gain after smoking cessation. Previous research has also shown that bupropion and nicotine-replacement therapies can reduce weight gain after smoking cessation.[12,21-23] Although weight gain was lowest in the combined-treatment group, there were no significant differences in weight gain among the groups after week 7 of treatment.

The subjects in our study were all volunteers and thus may not be representative of the majority of smokers.[24] Moreover, all subjects underwent weekly biochemical tests to determine whether they were still smoking. Both these factors could have enhanced cessation rates. The fact that 19.8 percent of the subjects dropped out of the study must also be considered. Those who dropped out of the study were assumed to have resumed smoking, but data on factors such as weight, depression, and severity of withdrawal had to be treated as missing for these subjects, so the potential contribution of these factors remains unknown.

Analyses of data on continuous abstinence showed that relative to placebo, use of the nicotine patch was associated with higher abstinence rates during the 12-month follow-up period. The odds ratio for the comparison between the nicotine patch and placebo

at one year was 1.1, similar to values reported in previous work.[2] However, analyses of point-prevalence data showed no significant differences between these two groups during follow-up. It is unclear why the nicotine patch produced weak effects according to the point-prevalence analysis. One study suggested that the use of two placebos in a control group may produce higher smoking-cessation rates than the use of a single placebo.[25] This might account for the smaller difference in the long-term rates of smoking cessation between the placebo group and the nicotine-patch group in our study. The weak effects, however, seem unrelated to prior use of the nicotine patch. The rate of previous use of a nicotine patch was similar among the four groups. In the nicotine-patch group, there was no significant difference in the rates of continuous abstinence at 12 months between subjects who had previously used patches and those who had not (8.6 percent vs. 10.6 percent, $P=0.61$).

Supported by a grant from Glaxo Wellcome.

Dr. Jorenby has organized medical-education presentations sponsored by Glaxo Wellcome and SmithKline Beecham. Dr. Leischow has served as a consultant for McNeil Consumer Products, Pharmacia & Upjohn, and Glaxo Wellcome and has organized medical-education presentations sponsored by Glaxo Wellcome. Dr. Nides has served as a consultant for Glaxo Wellcome, Novartis, and SmithKline Beecham and has organized medical-education presentations sponsored by Glaxo Wellcome. Dr. Rennard has served as a consultant for Glaxo Wellcome, Novartis, and SmithKline Beecham and has organized medical-education presentations sponsored by Glaxo Wellcome. Dr. Muramoto has organized medical-education presentations sponsored by Glaxo Wellcome. Mr. Daughton has served as a consultant for SmithKline Beecham and Hoechst Marion Roussel and has organized medical-education presentations sponsored by Glaxo Wellcome and Hoechst Marion Roussel. Dr. Fiore has served as a consultant for Novartis, Glaxo Wellcome, SmithKline Beecham, and McNeil Consumer Products and has organized medical-education presentations sponsored by Novartis, Elan Pharma, Lederle Laboratories, Glaxo Wellcome, McNeil Consumer Products, and SmithKline Beecham. Dr. Baker has served as a consultant for SmithKline Beecham and has organized medical-education presentations sponsored by Elan Pharma and Glaxo Wellcome.

REFERENCES

1. Smoking cessation during previous year among adults — United States, 1990 and 1991. MMWR Morb Mortal Wkly Rep 1993;42:504-7.

2. Fiore MC, Bailey WC, Cohen SC, et al. Smoking cessation. Clinical practice guideline no. 18. Rockville, Md.: Agency for Health Care Policy and Research, April 1996. (AHCPR publication no. 96-0692.)

3. Baker TB, Morse E, Sherman JE. The motivation to use drugs: a psychobiological analysis of urges. In: Rivers C, ed. Nebraska symposium on motivation. Vol. 34. Alcohol use and abuse. Lincoln: University of Nebraska Press, 1987.

4. Brandon TH. Negative affect as motivation to smoke. Curr Dir Psychol Sci 1994;3:33-7.

5. Hall SM, Munoz RF, Reus VI, et al. Mood management and nicotine gum in smoking treatment: a therapeutic contact and placebo-controlled study. J Consult Clin Psychol 1996;64:1003-9.

6. Anda RF, Williamson DF, Escobedo LG, Mast EE, Giovino GA, Remington PL. Depression and the dynamics of smoking: a national perspective. JAMA 1990;264:1541-5.

7. Glassman AH, Covey LS. Smoking and affective disorder. Am J Health Behav 1996;20:279-85.

8. Kandel DB, Davies M. Adult sequelae of adolescent depressive symptoms. Arch Gen Psychiatry 1986;43:255-62.

9. Lipkus IM, Barefoot JC, Williams RB, Siegler IC. Personality measures as predictors of smoking initiation and cessation in the UNC Alumni Heart Study. Health Psychol 1994;13:149-55.

10. Fowler JS, Volkow ND, Wang GJ, et al. Inhibition of monoamine oxidase B in the brains of smokers. Nature 1996;379:733-6.

11. Ferry LH, Burchette RJ. Efficacy of bupropion for smoking cessation in non-depressed smokers. J Addict Dis 1994;13:249.

12. Hurt RD, Sachs DPL, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 1997; 337:1195-202.

13. Ascher JA, Cole JO, Colin JN, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995;56:395-401.

14. Beck AT, Steer RA. Beck Depression Inventory. Philadelphia: Center for Cognitive Therapy, 1978.

15. Fagerström KO. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict Behav 1978;3:235-41.

16. SAS/STAT user's guide, version 6. 4th ed. Cary, N.C.: SAS Institute, 1990.

17. Hosmer DW Jr, Lemeshow S. Applied logistic regression. New York: John Wiley, 1989.

18. Diagnostic and statistical manual of mental disorders, 4th ed.: DSM-IV. Washington, D.C.: American Psychiatric Association, 1994.

19. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry 1986;43:289-94.

20. Department of Health and Human Services. COSTART: coding symbols for thesaurus of adverse reaction terms. 3rd ed. Rockville, Md.: Food and Drug Administration, 1989.

21. Jorenby DE, Hatsukami DK, Smith SS, et al. Characterization of tobacco withdrawal symptoms: transdermal nicotine reduces hunger and weight gain. Psychopharmacology (Berl) 1996;128:130-8.

22. Leischow SJ, Sachs DPL, Bostrom AG, Hansen MD. Effects of differing nicotine-replacement doses on weight gain after smoking cessation. Arch Fam Med 1992;1:233-7.

23. Nides M, Rand C, Dolce J, et al. Weight gain as a function of smoking cessation and 2-mg nicotine gum use among middle-aged smokers with mild lung impairment in the first 2 years of the Lung Health Study. Health Psychol 1994;13:354-61.

24. Hughes JR. Tobacco withdrawal in self-quitters. J Consult Clin Psychol 1992;60:689-97.

25. Fagerström KO. Combined use of nicotine replacement products. Health Values 1994;18:15-20.

CORRECTION

Smoking Cessation

To the Editor: In their trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation (March 4 issue),[1] Jorenby et al. reach three conclusions. Their first conclusion — that bupropion is an effective treatment for nicotine dependence — is warranted, since previous studies have also found bupropion to be effective.[2] Their second conclusion is that bupropion plus the nicotine patch produces higher rates of abstinence than the nicotine patch alone, and their third is that bupropion alone produces higher rates of abstinence than the nicotine patch alone. These conclusions are based on the one-year point-prevalence rates of abstinence (i.e., the percentage of subjects who were abstinent at the one-year follow-up assessment). My concern with the last two conclusions is that the one-year point-prevalence rates for the nicotine-patch group and the placebo group were essentially identical (odds ratio=1.1); in other words, although typically efficacious, the nicotine patch was not efficacious with the use of this particular measure in this particular study. Adding any type of therapy that was not efficacious to bupropion therapy would produce the pattern of results reported: treatment with bupropion plus the ineffective therapy would be more effective than bupropion alone, and bupropion alone would be better than the ineffective therapy alone.

Jorenby et al. state that the odds ratios for the comparison between the nicotine patch and placebo were ``similar to values reported in previous work´´ and cite the guidelines of the Agency for Health Care Policy and Research (AHCPR); however, Table 16 of these guidelines lists odds ratios of 2.1 to 2.8 for the nicotine patch.[3] In addition, meta-analyses of the use of the nicotine patch under conditions identical to those in the study by Jorenby et al. (minimal intervention or treatment as a part of a family practice) report odds ratios of 2.1[4] and 3.5.[5]

For some unknown reason, treatments known to be active often perform poorly when used as controls in studies of new treatments.[6] Unfortunately, the results of neither a study of new and old treatments combined nor a comparison of old and new treatments can be unambiguously interpreted when the old treatment is not efficacious in the study.[6]

In summary, I am not questioning the efficacy of bupropion, but I do believe that we should be cautious in accepting the conclusions of Jorenby et al. with respect to the superiority of combined treatment and the superiority of bupropion over the nicotine patch until replicate studies are conducted in which the nicotine patch is found to be efficacious.

John R. Hughes, M.D.
University of Vermont
Burlington, VT 05401-1419

Editor's note: Dr. Hughes has received consulting fees and grants from many pharmaceutical firms, including Glaxo Wellcome, McNeil, Pharmacia & Upjohn, and SmithKline Beecham.

References

1. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999;340:685-691.
2. Goldstein MG. Bupropion sustained release and smoking cessation. J Clin Psychiatry 1998;59:Suppl 4:66-72.
3. The Agency for Health Care Policy and Research Smoking Cessation Clinical Practice Guideline. JAMA 1996;275:1270-1280.
4. Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. Lancet 1994;343:139-142.
5. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. JAMA 1994;271:1940-1947.
6. Clark PI, Leaverton PE. Scientific and ethical issues in the use of placebo controls in clinical trials. Annu Rev Public Health 1994;15:19-38.

The authors reply:

To the Editor: Dr. Hughes argues that our study does not constitute a good test of the relative efficacy of bupropion and the nicotine patch because the patch produced disappointing results. He argues, in essence, that any interpretation of our results should be deferred because the patch produced atypical effects. Analyses of both the point-prevalence rate and the rate of continuous abstinence indicated the superiority of bupropion. The correct odds ratio for the comparison of the nicotine patch with placebo among subjects with continuous abstinence was 1.8, not 1.1 as reported on page 691 of our paper. According to the AHCPR smoking-cessation guidelines, the size of this effect is typical of that reported in other nicotine-patch studies.[1] Despite the fact that the patch had a fairly typical and significant beneficial effect on the rates of continuous abstinence, bupropion was associated with even better outcomes. The results with respect to point-prevalence outcomes paralleled this differential.

We agree with Dr. Hughes that replication of results is vital. However, we would support this principle just as strongly if the nicotine patch had had better outcomes in our study. Although it is highly tempting to interpret or weight studies according to whether treatments perform in an expected manner, surely this approach would bias science in undesirable ways. We prefer the strategy of accepting our results as they are — recognizing that in the context of this study, bupropion resulted in higher long-term abstinence rates than did placebo or the nicotine patch.

Douglas E. Jorenby, Ph.D.
Michael C. Fiore, M.D., M.P.H.
Timothy B. Baker, Ph.D.

University of Wisconsin Medical School
Madison, WI 53706

References

1. Fiore MC, Bailey WC, Cohen SC, et al. Smoking cessation. Clinical practice guideline no. 18. Rockville, Md.: Agency for Health Care Policy and Research, April 1996. (AHCPR publication no. 96-0692.)