

Bupropion SR Enhances Weight Loss: A 48-Week Double-Blind, Placebo- Controlled Trial

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Abstract

ANDERSON, JAMES W., FRANK L. GREENWAY, KEN FUJIOKA, KISHORE M. GADDE, JAMES MCKENNEY, AND PATRICK M. O'NEIL. Bupropion SR enhances weight loss: a 48-week double-blind, placebo-controlled trial. *Obes Res.* 2002;10:633–641.

Objective: To critically examine the efficacy of bupropion SR for weight loss.

Research Methods and Procedures: This 24-week multi-center, double-blind, placebo-controlled study randomized obese adults to placebo, bupropion SR 300, or 400 mg/d. Subjects were counseled on energy-restricted diets, meal replacements, and exercise. During a 24-week extension, placebo subjects were randomized to bupropion SR 300 or 400 mg/d in a double-blinded manner.

Results: Of 327 subjects enrolled, 227 completed 24 weeks; 192 completed 48 weeks. Percentage losses of initial body weight for subjects completing 24 weeks were 5.0%, 7.2%, and 10.1% for placebo, bupropion SR 300, and 400 mg/d, respectively. Compared with placebo, net weight losses were 2.2% ($p = 0.0468$) and 5.1% ($p < 0.0001$) for bupropion SR 300 and 400 mg/d, respectively. The percentages of subjects who lost $\geq 5\%$ of initial body weight were 46%, 59%, and 83% (p vs. placebo < 0.0001) for placebo, bupropion SR 300, and 400 mg/d, respectively; weight losses of $\geq 10\%$ were 20%, 33%, and 46% (p vs. placebo =

0.0008) for placebo, bupropion SR 300, and 400 mg/d, respectively. Withdrawals, changes in pulse and blood pressure did not differ significantly from placebo at 24 weeks. Subjects who completed 48 weeks maintained mean losses of initial body weight of 7.5% and 8.6% for bupropion SR 300 and 400 mg/d, respectively.

Discussion: Bupropion SR 300 and 400 mg/d were well-tolerated by obese adults and were associated with a 24-week weight loss of 7.2% and 10.1% and sustained weight losses at 48 weeks.

Key words: weight loss, pharmacotherapy, bupropion SR, lifestyle, pedometer, meal replacements

Introduction

Obesity is a major global health problem (1,2) that contributes significantly to risk for developing coronary artery disease, diabetes, hypertension, as well as premature disability and death (3,4). Current therapies are limited and maintenance of weight loss may be suboptimal (5). Although there is a growing consensus that pharmacotherapy is appropriate for many individuals who are unable to lose weight through less intensive measures, effective pharmacotherapy is not available for many patients. Only two agents—sibutramine and orlistat—are Food and Drug Administration (FDA)-approved for long-term pharmacotherapy of obesity in the United States. New therapeutics are needed because medical contraindications or intolerable side effects may prevent use of one or both of these agents for some individuals (6–9). Additional pharmacotherapeutic agents would serve to address this problem.

Sustained-release bupropion (bupropion SR) is an FDA-approved agent for treatment of major depression and for smoking cessation. Bupropion SR seems to have a weight-neutral effect for most depressed individuals of normal weight. However, controlled trials with depressed individuals suggest that bupropion SR may be associated with

Submitted for publication December 17, 2001.

Accepted for publication in final form February 12, 2002.

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weight loss in overweight or obese subjects (10,11). In addition, weight gain after treatment for smoking cessation was less in bupropion SR-treated subjects than in placebo-treated subjects (12). A small randomized, controlled study suggested that bupropion SR may enhance weight loss for nondepressed, obese subjects prescribed an energy-restricted diet (13).

This randomized, placebo-controlled trial was designed to study the efficacy, safety, and tolerability of bupropion SR for weight loss in nondepressed obese adults as part of a basic lifestyle-intervention program that included dietetic and lifestyle counseling, daily meal replacements, an exercise prescription, and self-monitoring of food intake and exercise. The primary objective was to assess weight loss during the 24-week placebo-controlled period and the secondary objective was to study weight changes over the next 24 weeks of continued treatment.

Research Methods and Procedures

Subjects

Six medical centers in the United States recruited obese individuals from their practices and the community. Eligible subjects were women and men 18 to 65 years old with a body mass index (BMI) of 30 to 44 kg/m². Women were either infertile or used appropriate contraceptive measures. Subjects were excluded if they had predisposition to seizures; history of bulimia or anorexia nervosa; significant cardiovascular disease; current depression; uncontrolled hypertension; diabetes; untreated hypothyroidism; addiction to nicotine (current smoker) or recent cessation of smoking; use of weight loss agents in the past 3 months; history of significant hepatic, renal, gastrointestinal, or psychiatric disease; history of alcohol or substance abuse; or history of bupropion SR use in the past 12 months.

The institutional review board for human studies at each institution approved the study and all subjects signed informed consent forms.

Protocol

This was a 24-week multicenter, randomized, double-blind, placebo-controlled, parallel-group study. After 24 weeks, the placebo group was randomized to active drug treatment with maintenance of double-blinding and all subjects participated in the 24-week extension. The allocation of placebo-treated subjects to active treatment during the second half of the study was done to facilitate subject recruitment and to enhance retention of placebo-treated subjects for the duration of the study. After meeting screening criteria, subjects were weighed, measured, and presented for venipuncture after a 14-hour fast. Subjects participated in a 2-week run-in period to assess their ability to keep records and use a pedometer. Subjects were then randomized to placebo, bupropion SR (Wellbutrin SR or

Zyban) 300 mg/d, or 400 mg/d for the initial 24-week treatment period and began a lifestyle-intervention program of mild to moderate intensity. At randomization a dietitian instructed subjects in energy-restricted diets with a deficit of 600 kcal/d based on recommendations of the World Health Organization (14). The recommended menu plan included mandatory use of two servings daily of canned, liquid meal replacements (220 kcal/serving) in the form of Slim-Fast for the first 24 weeks and one serving daily for the last 24 weeks. We encouraged subjects to use meal replacements for breakfast and lunch and to consume an energy-restricted evening meal. Also, at randomization, subjects were prescribed exercise goals of 1000 kcal increase/wk of expended energy by walking or equivalent activity compared with pedometer readings. Subjects maintained daily records of food intake and physical activity assessed by pedometer. Specific weight loss goals were established for each subject encouraging loss of initial body weight as follows: 2% at 4 weeks, 3.5% at 8 weeks, and 5% at 12 weeks. These lifestyle goals were reinforced at 12 subsequent visits throughout the 48-week study.

Subjects visited the clinic at randomization (0), 2, 4, 8, 12, 16, 20, 24, 26, 30, 36, 42, and 48 weeks. After medical histories and review of inclusion criteria, study physicians performed physical examinations and evaluated the Beck Depression Index (BDI) (15), electrocardiograms, and laboratory studies. Baseline measurements were made at randomization. Concurrent medications, adverse events, drug accountability, weight, and blood pressure measurements were done at each visit. Waist circumference, chemistry panel, complete blood count, urinalysis, lipid profile, serum glucose measurements, and serum pregnancy test were performed at 0, 24, and 48 weeks. At each visit a dietitian provided brief individual lifestyle counseling that included a review of self-monitoring (meal replacement use, dietary intake, pedometer readings, and other physical activity) and reiteration of diet and physical activity goals for the next session.

At 24 weeks, subjects on bupropion SR continued their assigned treatment without interruption. Subjects on placebo were randomly assigned to bupropion SR 300 mg/d or 400 mg/d. The 26-week visit was used to reassess subjects, although double-blinded, after the placebo group had been started on active medication.

Assignment and Masking

Subjects were randomly assigned to placebo, bupropion SR 300 mg/d, and 400 mg/d in a 1:1:1 ratio for 24 weeks of treatment. To mask treatment assignments despite the different sizes of the 100-mg and 150-mg tablets, all subjects took six tablets of placebo or bupropion SR tablets daily. Subjects randomized to bupropion SR 300 mg/d received 150 mg/d for 3 days and then 300 mg/d; bupropion SR 400 mg/d subjects received 150 mg/d for 3 days, 300

mg/d for the next 11 days, and subsequently 400 mg/d. At 24 weeks when subjects taking placebos were randomized to active treatment, their dose was initiated and increased in the same manner.

Statistical Analysis

The primary endpoint was weight change—absolute (kilograms) and percentage—from baseline to week 24. Power calculations were performed for this endpoint. Sample-size determination was based on the authors' data and the scientific literature (5–9). The minimum sample size of 65 subjects per group was calculated to detect a difference in weight change between treatment groups of 2.5 kg, assuming SD of 5.1 kg. The significance level was set to be $\alpha = 0.05$ and power of 80%.

All continuous variables were analyzed as change from baseline. Three different types of analyses were performed: analysis of completers only; last-observation-carried-forward (LOCF) or intention-to-treat analysis; and multivariate analysis of actual observations using the mixed model approach. We consider the mixed model analysis to be the most accurate and appropriate for these data because compared with LOCF analysis we avoid artificial data imputation beyond the time-point of subject withdrawal (16). Williamson (17) also criticized the LOCF analysis for weight-loss studies. For completers' analyses, the response variable was change from baseline at 24 and 48 weeks and baseline values using analysis of covariance. To assess differences between treatment groups and differences over time, a mixed linear model was used with treatment as a fixed effect, site as a random effect, and the number of weeks as a repeated factor. Lipid variables were analyzed in the same manner except the triglyceride values were logarithmically transformed.

Results

Participant Flow

We screened 407 subjects and randomized 327 subjects (278 women and 49 men) with sites randomizing from 51 to 59 subjects. Participants included 245 whites, 71 blacks, and 11 with other ethnic/racial backgrounds; they were well-distributed across treatment groups. One hundred subjects (30.6%) withdrew over 24 weeks with this number per group: placebo, 32; bupropion SR 300 mg/d, 33; and 400 mg/d, 35. Withdrawals did not differ significantly across sites or treatment groups. An additional 35 subjects withdrew over the last 24 weeks with this number per group: bupropion SR 300 mg/d, 10; bupropion SR 400 mg/d, 13; placebo to bupropion SR 300 mg/d, 3; and placebo to bupropion SR 400 mg/d, 9. Withdrawals did not differ significantly among treatment groups.

Baseline Characteristics

The baseline characteristics of subjects randomized to treatment groups were similar and did not differ significantly

Table 1. Baseline characteristics of subjects

Variable	Bupropion		Bupropion
	Placebo	SR, 300 mg/d	SR, 400 mg/d
Number enrolled	112	110	105
Age (years)	42.7	43.9	43.6
SD	9.3	11.4	10.2
Sex			
Women	95	92	91
Men	17	18	14
Weight (kg)	100.3	100.6	99.8
SD	16.2	14.9	15.2
Body mass			
index (kg/m ²)	36.2	36.5	36.3
SD	3.7	4.1	4.3

Values are means (SD).

cantly among groups (Table 1). Subjects had an average BMI of 36.3 kg/m² and a baseline weight of 100.2 kg. There were no significant differences across treatment groups or gender for the following: fasting serum glucose, cholesterol, low-density lipoprotein-cholesterol, and triglycerides concentrations; pulse; blood pressure; or waist circumference. Women had significantly higher high-density lipoprotein-cholesterol concentrations than men. BDI scores did not differ significantly among groups and averaged 8.8 (95% confidence intervals [CI]: 8.0 to 9.6) for all subjects.

Weight Changes

Subjects in all groups lost weight steadily (Figure 1). Because weight losses in percentages and kilograms were almost identical, we have presented values as the percentage losses from initial body weights. Body weights differed significantly from baseline values at 2 through 48 weeks for all groups. Weight loss with bupropion SR 300 mg/d differed significantly from placebo at 20 weeks. Weight loss with bupropion SR 400 mg/d differed from 300-mg/d doses significantly at 24, 26, 30, 36, and 42 weeks and from placebo at 12, 16, 20, and 24 weeks.

Bupropion SR-treated subjects lost weight in a dose-dependent manner (Table 2). For subjects who completed the 24-week study (completers), weight losses were as follows: placebo, 5.0%; bupropion SR 300 mg/d, 7.2%; and bupropion SR 400 mg/d, 10.1%. The net weight losses (treatment – placebo) were 2.2% and 5.1% for bupropion SR 300 and 400 mg/d, respectively. Weight losses for LOCF, albeit smaller than those in the completers' analyses, nevertheless showed differences among groups with values

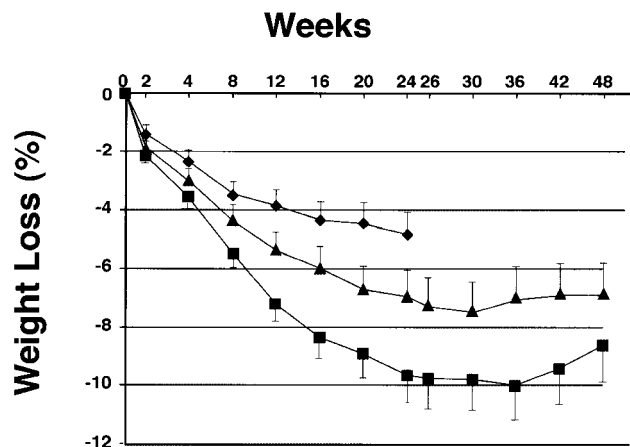


Figure 1: The percentage weight loss over 48 weeks. Values are mean ± SEM for the percentage weight loss from baseline. Subjects treated with bupropion SR 300 mg/d had significantly greater weight losses than subjects treated with placebo at 20 weeks ($p < 0.05$). Subjects treated with bupropion SR 400 mg/d had significantly greater weight loss than those treated with bupropion SR 300 mg/d at 24, 26, 30, 36, and 42 weeks ($p < 0.05$) and with placebo at 12, 16, 20, and 24 weeks ($p < 0.0001$). ♦, placebo; ▲, bupropion SR 300 mg/d; ■, bupropion SR 400 mg/d.

of 4.0%, 5.7%, and 7.7% for placebo, bupropion SR 300 mg/d and 400 mg/d, respectively. For completers, weight loss with bupropion SR 300 mg/d was significantly greater than with placebo and weight losses with bupropion SR 400 mg/d were greater than with placebo and with bupropion SR 300 mg/d.

After week 24, subjects on placebo were randomized to active treatment and subsequently lost additional weight; they had weights at 48 weeks, -6.4% and -7.2% of initial values, for bupropion SR 300 mg/d and 400 mg/d, respectively, with the completers' analyses. These values did not differ significantly from values for 48 weeks of treatment with bupropion SR 300 or 400 mg/d (Table 2). Weight loss in 48-week bupropion-treated subjects reached a nadir at 32 or 36 weeks and body weight increased nonsignificantly during subsequent weeks. Weight losses as the percentage of initial body weights at 48 weeks were 7.5% and 8.6% for bupropion SR 300 mg/d and 400 mg/d, respectively with the completers' analyses. Weight losses for the LOCF did not differ significantly.

Table 2. Weight changes for LOCF and completers' analyses

Group	LOCF				Completers			
	24 Weeks		48 Weeks		24 Weeks		48 Weeks	
	n	Weight loss (%)	n	Weight loss (%)	n	Weight loss (%)	n	Weight loss (%)
Placebo	112	4.0		NA	80	5.0	NA	NA
95% CI		5.4 to 2.6				6.8 to 3.3		
Placebo to Bupropion SR 300 mg/d		NA	58	5.2		NA	37	6.4
95% CI				7.1 to 3.4				9.0 to 3.7
Placebo to Bupropion SR 400 mg/d		NA	54	4.5		NA	31	7.2
95% CI				6.4 to 2.6				10.0 to 4.3
Bupropion SR 300 mg/d	110	5.7	110	5.4	77	7.2	67	7.5
95% CI		7.1 to 4.3		6.9 to 3.9		9.0 to 5.5		9.6 to 5.3
Difference Bupropion 300 – placebo		1.7*		NA		2.2†		NA
95% CI		3.2 to 0.1				4.0 to 0.4		
Bupropion SR 400 mg/d	105	7.7	105	6.9	70	10.1	57	8.6
95% CI		9.1 to 6.3		8.4 to 5.4		11.9 to 8.3		10.8 to 6.3
Difference Bupropion 400 – placebo		3.7‡		NA		5.1‡		NA
95% CI		5.2 to 2.2				6.9 to 3.2		
Bupropion Difference (400 mg – 300 mg)		2.0†		1.5		2.9§		2.0
95% CI		3.6 to 0.5		0.2 to -3.2		4.8 to 1.0		4.3 to -2.3

Significant differences are shown.

LOCF, last observed carried forward; CI, confidence interval; NA, not applicable.

* $p = 0.08$; † $p = 0.047$; ‡ $p < 0.0001$; § $p = 0.007$.

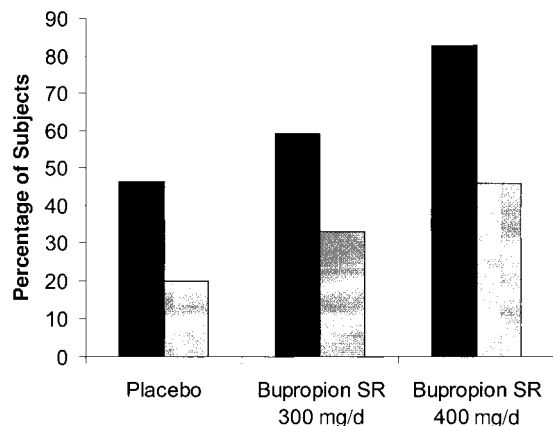


Figure 2: The percentage of subjects losing $\geq 5\%$ (dark bars) or $\geq 10\%$ (light bars) of initial body weight.

Five and Ten Percentage Weight Losses

Significantly greater numbers of subjects achieved weight losses of 5% and 10% with bupropion SR 400 mg/d than with placebo at 24 weeks (Figure 2). For completing subjects the percentages of subjects who lost $\geq 5\%$ of initial body weight were as follows: placebo, 46.3%; bupropion SR 300 mg/d, 59.2%; and bupropion SR 400 mg/d, 82.9% (p vs. placebo < 0.001). The percentages of subjects who lost $\geq 10\%$ of initial body weight were as follows: placebo, 20.0%; bupropion SR 300 mg/d, 32.9%; and bupropion SR 400 mg/d, 45.7% (p vs. placebo = 0.0008). At 48 weeks, the percentages of subjects in 5% and 10% weight-loss groups did not differ significantly across groups with these values: placebo to bupropion SR 300 mg/d, 51.4% and 21.6%; placebo to bupropion SR 400 mg/d, 58.1% and 35.5%; bupropion SR 300 mg/d, 58.2% and 25.9%; and bupropion SR 400 mg/d, 64.9% and 40.4%, for 5% and 10% weight loss, respectively.

Secondary Outcomes

Changes in fasting plasma values, pulse, blood pressure, and waist circumference at 24 weeks are summarized in Table 3. Fasting serum glucose concentrations decreased significantly from baseline with bupropion SR 400 mg/d. Changes in total serum cholesterol and low-density lipoprotein-cholesterol concentrations were similar across groups. High-density lipoprotein-cholesterol concentrations increased significantly with bupropion SR 300 mg/d and 400 mg/d. Fasting serum triglycerides concentrations decreased significantly with bupropion SR 300 mg/d and approached statistical significance with bupropion SR 400 mg/d.

Bupropion SR treatment was associated with an increase in pulse rate of 1.8 beats/min at 24 weeks but these changes were not significant. Between 4 and 20 weeks, pulse rates increased significantly from baseline by 2.4 to 5.2 beats/min with both doses of bupropion SR; these changes differed

significantly from placebo only for bupropion SR 300 mg/d at 16 weeks. The changes in pulse rates for bupropion SR 400 mg/d did not differ significantly at any visit from values for either bupropion SR 300 mg/d or placebo. Systolic and diastolic blood pressure decreased in all three groups and there were no significant differences between bupropion SR 300 mg/d and placebo or between bupropion SR 400 mg/d and either treatment group at any weekly visit. Waist circumference decreased significantly ($p < 0.001$) in all treatment groups with no significant differences among groups.

The BDI score decreased significantly in all groups with the following decreases: placebo, 1.5 (95% CI: 2.7 to 0.4); bupropion SR 300 mg/d, 3.9 (95% CI: 5.1 to 2.7); and 400 mg/d, 2.8 (95% CI: 4.1 to 1.5). With bupropion SR 300 mg/d, the decrease in the BDI score was significantly greater than with placebo ($p = 0.033$).

Adherence to Medication and Lifestyle Procedures

Adherence was assessed at 24 weeks; 92% of subjects took $\geq 80\%$ of their medication and this did not differ significantly across groups. At least 80% of recommended meal replacements (two daily) were consumed by 96% of all subjects over the 24 weeks; differences among groups were not significant. All groups of subjects significantly ($p < 0.0001$) increased their physical activity and approached or exceeded the recommended increase in physical activity (100%) as measured by pedometers with the following increases: placebo, 85%; bupropion SR 300 mg/d, 97%; and 400 mg/d, 135% (p vs. placebo < 0.031).

Withdrawals and Adverse Events

The numbers of adverse events (those exceeding 5% for any group) for each treatment group for 24 weeks of placebo-controlled treatment are summarized in Table 4. There were no significant differences in the occurrence of adverse events across groups. The 23 subjects who had early exits (withdrawals) related to adverse events were in these categories (major adverse events only listed in parenthesis): placebo, 6 subjects (decreased concentration, 1; dizziness, 1; palpitations, 1; and abnormal laboratory values, 1); bupropion SR 300 mg/d, 8 subjects (insomnia, 2; palpitations, 1; and anxiety, 1); and bupropion SR 400 mg/d, 9 subjects (anxiety, 4; hypertension, 1; and abnormal laboratory values, 1). The one subject who withdrew because of hypertension was concerned about slight increases in her blood pressure readings at home, but had stable normal values at clinic. Anxiety or insomnia led to withdrawal more often with bupropion SR treatment than with placebo but these differences were not statistically significant.

Discussion

In this study bupropion SR significantly facilitated weight loss in a dose-dependent manner when used with a

Table 3. Baseline values and changes from baseline at 24 weeks for fasting serum glucose and lipid values, blood pressure, pulse, and waist circumference*

Variable	Placebo (n = 112)		Bupropion SR 300 mg/d (n = 110)		Bupropion SR 400 mg/d (n = 105)	
	Baseline	Change	Baseline	Change	Baseline	Change
Glucose (mg/dL)	95.5	0.06	95.2	-1.82	95.4	-2.71†
	0.97	1.04	1.11	1.06	0.85	1.06
Cholesterol (mg/dL)	203.2	-3.4	202.3	-4.37	190.7	-2.55
	3.33	2.33	3.03	2.38	2.92	2.49
LDL-cholesterol (mg/dL)	123.9	-2.69	121.3	-2.43	113.9	-2.95
	2.38	2.01	2.78	2.02	2.43	2.13
HDL-cholesterol (mg/dL)	51.4	0.62	53.4	1.46‡	51	2.61§
	1.08	0.56	1.37	0.57	1.44	0.6
Triglycerides (mg/dL)	134.1	-2.87	141.6	-20.6¶	132	-11.3
	9.52	6.58	7.83	7.22	8.53	9.91
Pulse (beats/min)	70.1	-0.19	70.3	1.77	70.9	1.8
	0.67	0.82	0.77	0.85	0.74	0.87
Systolic BP (mm Hg)	120.3	-2.61	121.8	-1.55	120.2	-1.73
	1.03	1.25	1.06	1.27	1.11	1.29
Diastolic BP (mm Hg)	78.6	-0.46	78.6	-0.03	77.2	-0.88
	0.68	1.27	0.66	1.28	0.68	1.3
Waist circumference (cm)	105.6	-4.89**	105.8	-5.19**	105.2	-6.68**
	1.26	0.96	1.17	0.99	1.24	1

Values are means and SEM.

* *p* vs. baseline: † 0.0316; ‡ 0.0282; § 0.0014; ¶ 0.0178; || 0.0529; ** <0.001.

There were no significant differences between treatment groups.

LDL, low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure.

basic lifestyle intervention program. The lifestyle intervention program was designed to enable subjects to lose $\geq 5\%$ of their initial body weight over 24 weeks with placebo treatment; subjects, on average, exceeded this goal. Subjects who completed 24 weeks of treatment with bupropion SR 400 mg/d lost 10.1% of their initial body weight loss and had a net weight loss (compared with placebo) of 5.1%. These weight losses are consistent with the guidelines for approval of antiobesity agents by the U.S. FDA (18) and the European Agency (19). The weight losses we observed for the LOCF analysis with bupropion SR 400 mg/d are comparable to those reported with the two agents approved for long-term treatment of obesity (6–9). However, it is difficult to compare different agents across clinical trials because of differences in experimental design. Many previous studies (8,9,20) used a weight-loss run-in period that enhances total weight loss and may affect net weight loss.

The weight losses at 48 weeks did not differ significantly from those at 24 weeks. The weight changes—from +0.3% to -0.3% of initial body weight with bupropion SR 300

mg/d and from +0.8 to +1.5% with bupropion SR 400 mg/d—between 24 and 48 weeks are consistent with the weight change reported by a number of other clinical trials with dexfenfluramine (21), sibutramine (20), and orlistat (8,22). The failure to lose further weight during the last 24 weeks may relate to decreased intensity of the intervention—use of only one meal replacement daily and decreased frequency of visits—in our study. This loss of effect on weight or other outcome variables with nutrition interventions over time is commonly seen and may relate to diet fatigue and decreased adherence to the prescribed diet (23), to regression to the mean, or to other factors.

The precise mechanism for bupropion SR that is responsible for effects on weight loss is unknown. Bupropion has dual neurotransmitter properties as a norepinephrine and dopamine reuptake inhibitor (24). Bupropion has no clinically significant effect on serotonin neurotransmission and essentially no affinity for muscarinic, histaminergic or α -adrenergic receptors (25). These effects on norepinephrine and dopamine in the central nervous system may con-

Table 4. Number of adverse events reported by subjects in different treatment groups

Adverse events	<i>n</i>		
	Placebo	Bupropion SR 300 mg/d	Bupropion SR 400 mg/d
Number of subjects	112	110	105
Upper respiratory complaints	42	36	37
Flu-like symptoms	6	10	7
Other respiratory complaints	8	4	9
Headaches	26	21	29
Myalgias	11	7	8
Other musculoskeletal complaints	24	26	23
Dry mouth	10	20	18
Other oral complaints	12	6	10
Nausea or vomiting	12	11	11
Constipation	12	14	13
Diarrhea	7	6	12
Other gastrointestinal complaints	18	12	17
Insomnia	9	7	10
Dermatologic complaints	12	5	8

There were no significant differences between groups.

tribute to weight loss (26). Human studies suggest that dopamine D₂ receptor density is significantly lower in morbidly obese individuals (BMI > 40 kg/m²) than in lean control subjects (27). Agents having norepinephrine effects can affect blood pressure and pulse rates (26). The effects of bupropion SR on blood pressure and pulse were transient and do not seem clinically important in this study. Whereas modest increases in systolic and diastolic blood pressure are noted with sibutramine treatment (6,7), we observed no significant changes from baseline in blood pressure among any treatment group at 24 weeks. Although sibutramine 15 mg/d significantly increases the pulse rate by ~6 beats/min (6,7), bupropion SR did not significantly affect pulse rate at 24 weeks. Overall, the safety of bupropion SR at the doses we used seems comparable to the other two agents approved for long-term treatment of obesity. Although seizures were not observed in this study or by Gadde et al. (13), this agent is contraindicated for persons with history of seizures or bulimia (Wellbutrin SR package insert).

Physical activity has an important adjunctive role in facilitating weight loss for individuals on energy-restricted diets (28). Increments in physical activity that expend 1000 kcal/wk or walking one mile daily are commonly recommended (28), but increments that expend >2500 kcal/wk may be required to have a significant impact on the rate of weight loss (29,30). Use of pedometers by our subjects may

have contributed to compliance to physical activity recommendations. Racette et al. (31) and Pronk and Wing (32) suggest that exercise is the cornerstone for long-term maintenance of weight loss.

Meal replacements—shakes, bars, or entrées—can have a significant adjunctive role in weight loss and maintenance of weight loss (33,34). The recent reports of Rothacker (35) and Ashley et al. (36) highlight this growing interest. In controlled trials, meal replacement use is associated with significantly more weight loss than control diets (33,34,36). Use of two meal replacements daily in our trial probably contributed importantly to the effectiveness of our intervention. Hill (37) suggests that meal replacements may help individuals to make transitions from their usual diet to a health-promoting diet. Thus, meal replacements, like physical activity, may be an adjunct for making dietary changes and maintaining these changes over intermediate- or long-term periods (38).

In summary, bupropion SR in conjunction with a lifestyle intervention program was associated with a dose-related reduction in body weight at 24 weeks. Subjects who completed 24 weeks of treatment with bupropion SR 400 mg/d lost 10.1% of their initial body weight and had a net loss of 5.1% of their initial body weight compared with placebo. With LOCF analysis, weight loss was 7.7% with bupropion SR 400 mg/d and the net decrease was 3.7%. The initial weight losses at 24 weeks were generally sustained at 48

weeks. Bupropion SR was well-tolerated, and the early exits and adverse events did not differ significantly from those of placebo. The lifestyle intervention of increased physical activity, use of two meal replacements daily, and self-monitoring may have enhanced weight loss. Because of its effectiveness and safety, bupropion SR warrants consideration as an adjunct to lifestyle changes for enabling obese individuals to lose weight.

Acknowledgments

Supported by the Obesity Research Network and Glaxo-SmithKline.

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