Bupropion for Weight Loss: An Investigation of Efficacy and Tolerability in Overweight and Obese Women

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Abstract

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Objective: On the basis of the clinical observations that bupropion facilitated weight loss, we investigated the efficacy and tolerability of this drug in overweight and obese adult women.

Research Methods and Procedures: A total of 50 overweight and obese (body mass index: 28.0 to 52.6 kg/m^2) women were included. The core component of the study was a randomized, double-blind, placebo-controlled comparison for 8 weeks. Bupropion or placebo was started at 100 mg/d with gradual dose increase to a maximum of 200 mg twice daily. All subjects were prescribed a 1600 kcal/d balanced diet and compliance was monitored with food diaries. Responders continued the same treatment in a double-blind manner for an additional 16 weeks to a total of 24 weeks. There was additional single-blind follow-up treatment for a total of 2 years.

Results: Subjects receiving bupropion achieved greater mean weight loss (last-observation-carried-forward analysis) over the first 8 weeks of the study ($p = 0.0001$): 4.9% ± 3.4% ($n = 25$) for bupropion treatment compared with 1.3% ± 2.4% ($n = 25$) for placebo treatment. For those who completed the 8 weeks, the comparison was 6.2% ± 3.1% ($n = 18$) vs. 1.6% ± 2.9% ($n = 13$), respectively ($p = 0.0002$), with 12 of 18 of the bupropion subjects (67%) losing over 5% of baseline body weight compared with 2 of 13 in the placebo group (15%; $p = 0.0094$). In the continuation phase, 14 bupropion responders who completed 24 weeks achieved weight loss of 12.9% ± 5.6% with fat accounting for 73.5% ± 3.7% of the weight lost and no change in bone mineral density as assessed by DXA. Bupropion was generally well-tolerated in this sample.

Discussion: Bupropion was more effective than placebo in achieving weight loss at 8 weeks in overweight and obese adult women in this preliminary study. Initial responders to bupropion benefited further in the continuation phase.

Key words: bupropion, antidepressants, anorexigens, weight loss, body fat, body composition, bone density

Introduction

In the United States, ~97 million adults are estimated to be overweight or obese, with a substantial increase in prevalence in the recent years (1,2). Such individuals are at greater risk for numerous comorbid illnesses that include type 2 diabetes, coronary heart disease, hypertension, gallbladder disease, and osteoarthritis, with an overall increased risk of mortality from all causes (3–5). Significant reduction of obesity-associated illnesses and risk factors can be achieved with a modest (<10%) weight reduction (6). Although diet, exercise, behavior therapy, and pharmacotherapy can be effective, many obese patients fail to achieve significant benefit from any given treatment modality and the long-term outcome with most nonsurgical treatments is often unsatisfactory (7).

Bupropion, in various forms, is currently marketed in some countries for treatment of depression and to aid smokers to quit their habit. In 8-week premarketing trials of sustained-release bupropion in depression, mild weight loss was noted in a small percentage of subjects (8). However,

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the hypothesis that this drug might help obese patients to lose weight was developed from a series of clinical observations (by Dr. Gadde), revealing that obese patients attending a medical center weight management program had enhanced success in losing weight when treated with bupropion. In search of additional strategies for weight management in the clinically overweight and obese, we conducted this preliminary investigation of the efficacy and tolerability of bupropion. The current investigation is the first randomized, placebo-controlled study of bupropion in obesity.

Research Methods and Procedures

Subjects, Screening, and Randomization

The study was conducted at Duke University Medical Center with the institutional review board approval. All subjects gave written informed consent. A total of 50 women were selected from those referred by clinicians and from individuals responding to advertisement fliers posted in the area.

Subjects between 24 and 55 years of age and body mass indices of >27 kg/m^2 were included. Subjects were excluded for the following reasons: obesity of a known endocrine origin, such as hypothyroidism and Cushing's syndrome; history of seizure or head injury; history of bulimia or anorexia nervosa; serious/unstable medical or psychiatric illness; current alcohol or other substance abuse; history of alcohol dependence; and current use of monoamine oxidase inhibitors or medications that could interfere with interpretation of study results.

Computer-based randomization was carried out by the medical center research pharmacy, which also dispensed the study medication under blinded conditions.

Study Design

The initial phase of the study was an 8-week, double-blind, parallel-group comparison of bupropion and placebo. At week 8, response was defined as a weight loss of at least 4 kg or 5% of initial body weight. Thereafter, nonresponders in both groups participated in an 8-week crossover study in which they received the other study medication. Responders in the initial 8-week study and the crossover 8-week study continued the same treatment in a double-blind manner for an additional 16 weeks to a total of 24 weeks. The flow of subjects through the study is described in Figure 1.

Diet

Throughout the study, all subjects were instructed to follow a 1600 kcal/d diet. They were also instructed to record their energy intake in food diaries, which were provided to them. The diet emphasized a balance of all food groups and daily intake of eight glasses of water. Food diaries were reviewed at each visit and appropriate counseling was provided to the subjects. The diet program was relatively loosely structured to create realistic eating patterns, which could be sustainable after exiting the study.

Medication

Each tablet of the study medication contained sustained release bupropion (100 mg) or placebo. During the first week, the subjects received one tablet each morning (100 mg/d bupropion or placebo) for 3 days, followed by one tablet twice daily (200 mg/d bupropion or placebo) for the next 4 days. At the end of 1 week, an assessment was made by the study physician regarding tolerability, and if appropriate, the dose was increased to three tablets per day (two in the morning and one at supper, corresponding to a total daily dose of 300 mg bupropion or placebo). On day 11, the dose was further increased to four tablets per day (two tablets twice per day, corresponding to a total daily dose of bupropion 400 mg or placebo). The dosing was flexible and could be reduced at any time if adverse effects emerged. Medication compliance was monitored by a log sheet given to the subjects and a review of the number of tablets dispensed and returned.

Responders who entered the continuation phase remained on the same study treatment and continued to receive the same dose. For nonresponders, the study medication was discontinued over the next 4 days, and after a 3-day washout, they were switched to the crossover study medication. The dosing in the crossover study was identical to the one used in the first 8 weeks.

Visits and Measurements

In the first 8 weeks as well as in the 8-week crossover study, the subjects were seen at weeks 1, 4, and 8. In the 16-week continuation phase, the subjects were seen at 4-week intervals. At each visit, assessments were made as follows: weight; heart rate, and blood pressure; Beck Depression Inventory (BDI) (9); diet compliance; medication tolerability and adverse effects; and The Medical Outcomes Study Short-Form 36 (SF-36; except at the week-1 visit) (10). Adverse effects were based on spontaneous reporting by subjects as well as open-ended inquiry by the clinicians. An adverse event was defined as any new event that emerged during treatment or an event with an increase in severity compared with baseline. Body weight was measured to the nearest 0.1 kg by a calibrated electronic scale. The subjects were weighed in an examination gown $\sim$3 to 5 hours after their last meal. A scale was developed (by Dr. Gadde, copyright 1999; not validated) to assess diet compliance. The best compliance was given a score of 5 on a scale of 0 to 5. The diet compliance rating scale is provided in Table 1. This scale was administered in the first 8 weeks only.

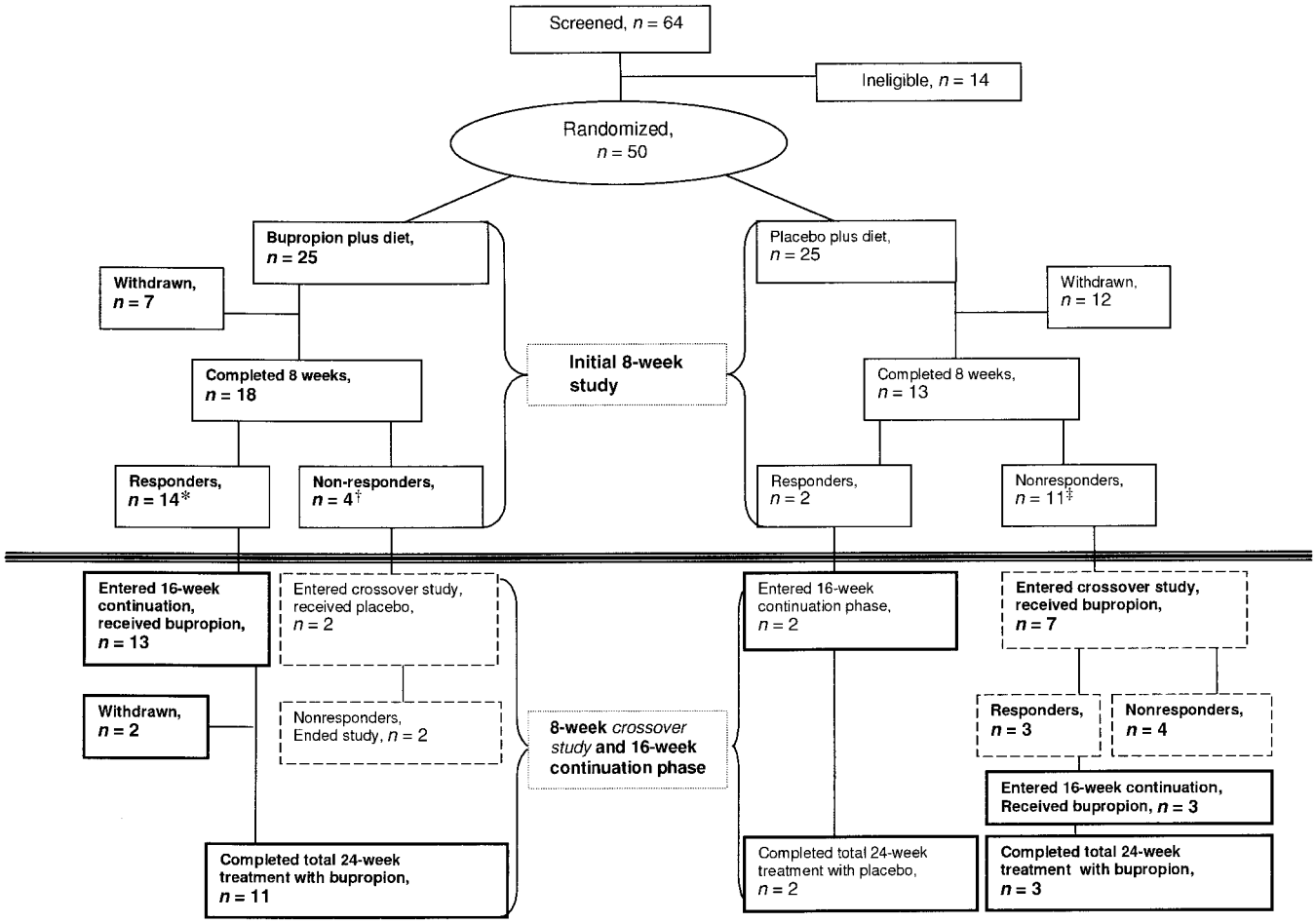


Figure 1: The top half of this schematic diagram shows the flow and disposition of subjects in the initial 8-week study. Nonresponders at the end of the initial 8-week study participated in an 8-week crossover study. The subjects who responded at the end of the initial 8-week study and the subjects who responded at the end of the 8-week crossover study entered a 16-week continuation phase. The bottom half of the diagram shows the flow and disposition of subjects in the 8-week crossover study and the 16-week continuation phase. Bold font is used to identify subjects receiving bupropion. The dashed line boxes represent the 8-week crossover study. The solid bold line boxes represent the 16-week continuation phase. *One bupropion responder opted not to enter the continuation phase. †Two bupropion nonresponders and ‡four placebo nonresponders opted not to enter the crossover study.

A total body scan to determine fat and lean masses and bone mineral density (BMD) was obtained by DXA (Hologic 2000, Waltham, MA) at the beginning of the study and at week 24 for responders who completed the continuation phase. All measurements were obtained using the same equipment and technique. The reliability of the scanner was ensured by monitoring repeat measurements, 15 minutes apart, on a sample of subjects.

Endpoints and Measures of Outcome

All 50 subjects were included in analyses of the primary outcome measures: change in weight compared with initial weight, percentage of subjects who achieved weight loss of 5% or more, and frequency of adverse events. Secondary outcome measures included diet compliance, BDI, heart rate, blood pressure, SF-36, body composition, and BMD.

Statistical Analysis

Descriptive statistics were generated using SAS software (SAS, Cary, NC). Differences in sample means between the two groups (bupropion vs. placebo) were tested with the two-sample *t* test. Although not reported, Mann–Whitney *U* statistics were computed to assess differences between the groups in location without distributional assumptions; results were consistent with the *t* tests. Proportions were compared using Fisher's exact test. The Wilcoxon signed-rank test was used to compare the weight change in the initial 8-week study to the weight change in the 8-week crossover study for the initial nonresponders due to the limited sample size. Changes in BMD were evaluated using a paired *t* test. Hypothesis tests were two-sided and statistical significance was defined as

Table 1. Diet compliance scale*

Score	Description
0	No diary returned; or, if returned, no entries or unscorable.
1	Poor diet compliance by verbal report. Less than 25% of required entries.
2	More than 20% in excess of prescribed caloric intake on most days. Poorly balanced diet on most days. Less than 50% of required diary entries.
3	In excess of prescribed caloric intake (10% to 20%) on most days. Balanced diet at least one-half of the time. At least 50% of required diary entries.
4	Good diet compliance on most days. Diet is generally balanced, but not always. Always returned diary, but some missing data.
5	Exceptional compliance with recommended caloric intake. Well-balanced diet. Diary always returned and well-recorded.

* Copyright 1999 by Kishore M. Gadde. Scale is not validated.

Table 2. Baseline characteristics of the subjects by treatment

Characteristic	Bupropion ($n = 25$)	Placebo ($n = 25$)	p Value
Age (years)	40.0 ± 1.5	40.4 ± 1.5	NS
Race			
Black	11 (44%)	12 (48%)	NS
White	13 (52%)	13 (52%)	
Hispanic	1 (4%)	0 (0%)	
Weight (kg)	101.3 ± 4.6	100.5 ± 3.1	NS
BMI (kg/m^2)	38.1 ± 1.5	36.9 ± 1.0	NS
Body fat (%)	42.5 ± 0.8	42.6 ± 0.9	NS
Duration of obesity (years)	16.7 ± 1.5	12.7 ± 1.0	0.033
Family history of obesity*	19 (76%)	22 (88%)	NS
BDI total score	6.2 ± 0.8	5.3 ± 0.8	NS

NS = not significant at $p > 0.10$; BMI = body mass index.
* Number of subjects and percentage in each group.

$p < 0.05$. The tabulated results are means ± SE and counts (percentages).

Linear mixed models with normal error structure were used to support conclusions of the initial 8-week study, accommodating the repeated measurements (weeks 1, 4, and 8) and missing data. Each outcome—percent weight loss and actual weight loss—was modeled with fixed effects due to baseline weight, treatment, week, and treatment by week. Time was treated categorically and the covariance of the repeated measurements was modeled as autoregressive (11).

Mixed model linear regression was used to model time-related changes in various outcome measures of the SF-36.

Results

Enrollment, Follow-Up, Premature Withdrawals, and Subject Characteristics

A total of 64 women were screened to obtain the 50 eligible subjects enrolled in the trial. These subjects were randomly assigned to one of two treatments using a 1:1 ratio—25 were assigned to receive bupropion and 25 to receive placebo.

The baseline characteristics of the subjects are shown in Table 2. There were no significant differences between the groups in age, race, family history of obesity, weight, body mass index, percentage of body fat, and depressive symptoms as measured by the BDI. Mean duration of obesity was longer in the bupropion group compared with the placebo group.

A total of 12 subjects in the placebo group and 7 subjects in the bupropion group did not complete the initial 8-week study. The reasons for premature withdrawal are shown in Table 3. Of the nine subjects who withdrew because of dissatisfaction with treatment, eight subjects were in the placebo group. In the continuation phase, two bupropion subjects withdrew before week 24.

Dose

The mean dose of bupropion was 352 ± 19 mg/d. A total of 18 of 25 subjects in the bupropion group received the maximum dose of 400 mg/d; 16 of 18 completers received the 400 mg/d dose.

Weight Change

Initial 8-Week Study. The subjects on bupropion therapy achieved greater weight loss than did those on placebo therapy over the first 8 weeks of the study. Using the last available measurement of each subject randomized to the study, bupropion subjects lost an average of 4.9% ± 0.7% ($n = 25$) body weight over the first 8 weeks compared with 1.3% ± 0.5% ($n = 25$) in the placebo group ($p = 0.0001$) with 12 of 25 (48%) vs. 2 of 25 (8%), respectively ($p = 0.0036$) losing ≥5% (Figure 2). In absolute terms, the

Table 3. Reasons for discontinuation during the initial 8 weeks by treatment

Reason	Bupropion ($n = 25$)	Placebo ($n = 25$)	p Value
Dissatisfied	1 (4%)	8 (32%)	0.023
Intercurrent*	1 (4%)	1 (4%)	NS
Protocol violation	2 (8%)	2 (8%)	NS
Side effects	2 (8%)	0 (0%)	NS
Lost to follow-up	1 (4%)	1 (4%)	NS
Total	7 (28%)	12 (48%)	NS

NS = not significant at $p > 0.10$.
* Job change required two subjects—one in each group—to move out of the area.

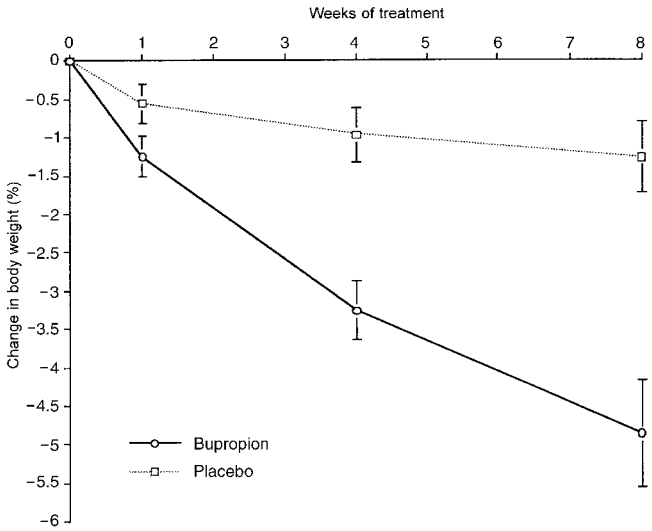


Figure 2: Lines connect treatment means ± SE over time. All 50 subjects are included with the last observation carried forward. The sample size for each group was 25 at every time-point in the graph.

average weight loss was 5.0 ± 0.7 kg vs. 1.2 ± 0.5 kg ($p = 0.0001$). The difference between the two groups in weight loss at 8 weeks was estimated as 3.6% ± 0.6% ($p = 0.0001$) or 4.4 ± 0.7 kg ($p = 0.0001$) from the linear repeated measurement models with adjustment for baseline weight.

For the subjects who completed the first 8 weeks, the comparison was 6.2% ± 0.7% ($n = 18$) vs. 1.6% ± 0.8% ($n = 13$), respectively ($p = 0.0002$), with 12 of 18 of the bupropion subjects (67%) losing at least 5% of their initial body weight compared with 2 of 13 in the placebo group (15%; $p = 0.0094$). The subjects completing the first 8 weeks lost an average of 6.4 ± 0.7 kg vs. 1.5 ± 0.8 kg, respectively ($p = 0.0001$).

8-Week Crossover Study. In the crossover phase, 3 of 7 initial placebo nonresponders and 0 of 2 initial bupropion nonresponders were judged as responders. The seven subjects who initially received placebo and had a median weight gain of 0.3% went on to have a median weight loss of 2.4% (Wilcoxon signed-rank test; $p = 0.03$) during the subsequent 8-week treatment with bupropion.

Continuation Phase. A total of 18 subjects (16 receiving bupropion and 2 receiving placebo) who had met the responder criterion qualified and entered the double-blind, 16-week continuation phase. Fourteen of the 16 subjects receiving bupropion and both subjects receiving placebo completed a total of 24 weeks. Of the two subjects who prematurely withdrew from the bupropion group, one cited dissatisfaction with achieved weight loss (3.6%) at week 12, and another withdrew at week 16 citing a family crisis, after achieving an 11.1% weight loss.

Week-24 completers in the bupropion group ($n = 14$) had a mean weight loss of 12.9% ± 1.5%. In absolute terms, the mean weight loss for week-24 completers was 12.5 ± 1.5 kg. When the last observations of the two prematurely withdrawn subjects were carried forward, the percent and absolute weight losses for the bupropion group were 12.2% ± 1.4% and 11.9 ± 1.4 kg, respectively. The two placebo subjects who completed 24 weeks achieved weight loss of 10.7% and 10.4%, respectively.

Body Composition and BMD. Four of the 16 bupropion subjects did not have two DXA measures for comparison because of the following reasons: two subjects weighed more than the scanner's maximum limit and two subjects withdrew early.

The combined change in fat and lean masses obtained with DXA matched 94.3% ± 5.0% of the weight change on the scale. Therefore, we were able to predict ratios of loss of fat and lean masses from the total weight lost.

For week-24 completers who received bupropion, the total weight lost represented loss of 73.5% ± 3.7% of fat mass and 26.5% ± 3.7% of lean mass. Of the total decrease in fat mass at week 24, nearly one-half (49.2% ± 1.5%) represented decrease in the trunk region.

BMD of lumbar vertebrae was used in the analysis because it is a sensitive measure of bone loss. Comparison of pre- and post-treatment BMD measures did not show significant change after 24-week treatment with bupropion (1.167 ± 0.029 to 1.144 ± 0.033 g/cm^2).

Health Survey

Week-24 completers receiving bupropion reported improvement over time in health as measured by the SF-36 subscales for General Health ($p = 0.021$) and Health Transitioning ($p = 0.001$). The score for the subscale Physical Functioning also increased with time, although the association was only marginally significant ($p = 0.070$). No other subscales approached significance.

Table 4. Adverse events during the initial 8 weeks by treatment

Adverse event	Bupropion ($n = 25$)	Placebo ($n = 25$)	p Value
Insomnia	5 (20%)	1 (4%)	NS
Headache	1 (4%)	3 (12%)	NS
Dry mouth	13 (52%)	5 (20%)	0.038
Rash	2 (8%)	0 (0%)	NS
Nervousness	4 (16%)	1 (4%)	NS
Constipation	0 (0%)	2 (8%)	NS
Diarrhea	0 (0%)	1 (4%)	NS
Other	1 (4%)	2 (8%)	NS

NS = not significant at $p > 0.10$.

Diet Compliance

In the first 8 weeks, the subjects receiving bupropion showed a better compliance with diet and diary entries than those receiving placebo (84% vs. 32%; $p = 0.0004$).

Vital Signs

In the initial 8-week study, small decreases in heart rate and blood pressure—both systolic and diastolic—were seen with both treatments. The decreases were not statistically different between the treatment groups.

At week 24, decreases in heart rate (74.6 ± 2.1 to 70.1 ± 1.0; $p = 0.0003$) and blood pressure—both systolic (129.0 ± 5.0 mm Hg to 115.4 ± 2.2 mm Hg; $p = 0.0001$) and diastolic (83.2 ± 2.1 mm Hg to 78.6 ± 2.1 mm Hg; $p = 0.003$)—were noted in the bupropion group.

Adverse Effects

In the initial 8-week comparison (Table 4), dry mouth was the only treatment-emergent adverse effect that was significantly more common in the bupropion group than in the placebo group (13 of 25 = 52% vs. 5 of 25 = 20%; $p = 0.04$). Two of the 25 subjects in the bupropion group experienced a skin rash and discontinued treatment. For one of these subjects, the rash was severe enough to require an emergency room visit and treatment with a glucocorticoid.

The most frequent adverse effects in the bupropion group ($n = 16$) in the continuation phase were dry mouth (12 of 16) and insomnia (4 of 16).

Follow-Up

Fourteen bupropion subjects and one placebo subject completed 1-year, single-blind follow-up. The 14 bupropion subjects achieved a mean weight loss of 14.2% ± 2.2% at 1 year.

One bupropion subject who had regained most of the initial weight loss and completed the first year with a net loss of 2.8% chose not to participate in the second-year, single-blind extension, citing dissatisfaction with treatment. Of the 13 bupropion subjects that entered the second year, one subject discontinued the study because of geographic relocation. The 12 bupropion subjects who completed 2 years achieved a mean weight loss of 13.6% ± 2.1%.

One placebo subject who completed 24 weeks chose not to continue further. The one placebo subject who continued beyond 24 weeks achieved a weight loss of 9.7% at 1 year and 3.3% at 2 years.

Discussion

The present study is the first randomized, placebo-controlled trial evaluating the efficacy of bupropion as a weight management therapy.

The key findings of this study are that bupropion therapy led to more weight loss compared with placebo treatment in the first 8 weeks and that the weight loss efficacy of bupropion was sustained during the continuation phase.

This study was designed to capture the weight loss efficacy of bupropion in the setting of an office-based clinical practice rather than an intensely structured weight loss program. Because men and women have different energy requirements, it was necessary, given the limited sample size, to eliminate gender as a confounding variable in the analysis. Ancillary interventions, such as diet and behavior therapy, were minimal. Failure of 19 of the 50 enrolled subjects to complete the first 8 weeks and the minimal response in the placebo group may be a reflection of the chosen design. Nevertheless, bias introduced as a result of early terminations should be considered while interpreting the results of this study. The greater success achieved by the bupropion group in the first 8 weeks might have been influenced by a greater number of early terminations and poorer compliance with diet in the placebo group. We do not know the precise reasons for better diet compliance in the bupropion group, but we speculate that the drug may have exerted beneficial effects on one or more of the following: appetite regulation, food cravings, and motivation.

Results of the crossover study, albeit a small sample, showed a trend for bupropion therapy to be more effective than placebo. When the subjects who failed to respond to placebo were switched to bupropion, some of them responded to the drug.

Although the bupropion subjects who completed 24 weeks achieved a weight loss of 12.9% ± 1.5%, it must be interpreted with the understanding that only those subjects who had achieved at least 4 kg or 5% weight loss in the first 8 weeks were eligible to enter the continuation phase.

There was no change in BMD associated with weight loss achieved at week 24 with bupropion treatment. Previous studies using DXA technology have reported loss of bone

density with weight loss (12,13), whereas one recent study (abstract) that used in vivo neutron activation technique reported no change in bone density with weight loss (14).

Although bupropion was generally well-tolerated in this study, the safety and tolerability data from this study must be interpreted with caution because of the small size of this cohort. Clinicians should be aware of the seizure risk associated with bupropion. The incidence of seizure with the sustained release form of bupropion at the maximum dose of 400 mg/d used in the present study is estimated to be ~4 in 1000 (8). Bupropion is contraindicated for patients with histories of bulimia, anorexia, or seizure because such individuals may carry a greater seizure risk with use of this drug. In this study, considerable time and effort was spent in identifying and excluding such high-risk subjects. Because such an extensive assessment may not occur in primary care and other general clinical settings, the seizure potential discussed above remains the primary safety concern with the potential use of this drug in weight management. Given the high prevalence of binge-eating pattern in obese patients, it is imperative to rule out associated purging behavior and laxative abuse if bupropion is considered as a tool in the management of obesity.

Bupropion is an aminoketone. The precise mechanism of the drug that is responsible for its effects on weight in obese patients is unknown. The neuropharmacological effects of bupropion include a weak inhibition of norepinephrine and dopamine uptake and decreased expression of tyrosine hydroxylase in the locus ceruleus of the rat (15–17). Dopamine plays a significant role in regulating food intake. An increase in extracellular dopamine concentration is seen in the nucleus accumbens after feeding (18). Drugs that increase brain dopamine concentration can suppress hunger (19), whereas drugs such as antipsychotics that block dopamine D_1 and D_2 receptors are known to induce weight gain (20). Further evidence for the role of dopamine in weight regulation comes from a recent report (21) of decreased striatal D_2 receptor availability in obese individuals. The weight loss efficacy of bupropion may be related to its effects on catecholamine neurotransmitters. Nevertheless, drugs that are known to block uptake of monoamine neurotransmitters more potently have not been associated with significant effects on human body weight. Hence, one could speculate that there might be a yet unknown mechanism of bupropion primarily responsible for its effect on weight.

In summary, the findings of this study provide the preliminary evidence that bupropion facilitates weight loss in overweight and obese subjects. Additional studies with larger sample sizes including both genders are needed to confirm these preliminary observations. The small sample size of this study does not permit us to draw conclusions regarding the safety of bupropion use in overweight and obese patients. Although bupropion therapy resulted in significant weight loss, the associated seizure risk complicates its use in obesity. Alternative norepinephrine and dopamine uptake inhibitor drugs should be investigated as adjunctive therapies in weight management.

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