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Bupropion for Overweight Women with Binge Eating Disorder: Randomized Double-blind Placebo-controlled Trial

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Abstract

Background—Binge eating disorder (BED) is defined by recurrent binge eating (eating unusually large quantities of food during which a subjective loss of control is experienced), marked distress about the binge eating, and the absence of inappropriate weight compensatory behaviors. BED is strongly associated with excess weight and many available psychological and pharmacological approaches fail to produce much weight loss. The objective of this study was to perform a randomized placebo-controlled trial to evaluate the short-term efficacy of bupropion for the treatment of BED in overweight and obese women.

Methods—Sixty-one overweight and obese (Mean BMI=35.8) women with BED were randomly assigned to receive bupropion (300 mg/d) or placebo for 8 weeks. Participants were enrolled from November 2006 to December 2010. No dietary or lifestyle intervention was given. Primary outcome measures were binge-eating frequency and percent BMI loss. Secondary outcome measures were dimensional measures of eating disorder psychopathology, food craving, and depression levels.

Results—Eighty-nine percent of randomized participants completed the trial without differential dropout between bupropion and placebo. Mixed effects analyses revealed significant time effects for all outcomes but that bupropion and placebo did not differ significantly on any outcome measure except for weight loss. Participants taking bupropion lost significantly more weight (1.8% BMI loss versus 0.6% BMI loss; F=10.57, p=002).

Conclusions—Bupropion was well tolerated and produced significantly greater – albeit quite modest – short-term weight loss in overweight and obese women with BED. Bupropion did not improve binge eating, food craving, or associated eating disorder features or depression relative to placebo. Our findings do not support bupropion as a stand-alone treatment for BED. The preliminary findings regarding short-term weight losses suggest the need for larger and longer-term trials to evaluate the potential utility of bupropion for enhancing outcomes of psychological interventions with demonstrated effectiveness for BED but which fail to produce weight loss.

Keywords

bupropion; binge eating disorder; obesity; weight loss; food craving; pharmacotherapy

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Binge-eating Disorder (BED), included in Appendix B of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition – Text Revision (DSM-IV-TR) as a research category [1], is proposed as a formal diagnosis in the DSM-5. BED is defined by recurrent binge eating (eating unusually large quantities of food during which a subjective loss of control is experienced), marked distress about the binge eating, and the absence of inappropriate weight compensatory behaviors. BED is a prevalent problem and is associated with obesity and heightened levels of medical and psychiatric comorbidity [2]. BED is distinct from the other eating disorders and obesity [3–5], and is more prevalent than the other eating disorders (anorexia and bulimia nervosa) [2].

Critical review and meta-analysis of the treatment literature for BED concluded that several different medications – through varied mechanisms – have short-term efficacy relative to placebo for reducing binge eating and producing modest weight loss [6]. Randomized clinical trials of antidepressant SSRIs have reported mixed results for the remission of binge eating (e.g., [7–10]) and little or no weight losses. Studies of fluoxetine, fluvoxemine, sertraline, and citalopram have reported weight loss differences of approximately 0–3 kg compared to placebo, depending on the duration of the trial (see [6] for summary and effect sizes across studies). Placebo-controlled trials of the currently available anti-obesity medication orlistat [11, 12] (sibutramine has been recently withdrawn from the market) have reported significant but modest effects for producing weight loss but not for reducing binge eating. Placebo-controlled trials of anticonvulsants topiramate and zonisamide [13–15] have reported significant effects for reducing both binge eating and weight (with a mean improvement in weight loss of approximately 3–4 kg compared to placebo) but have also reported high rates of dropout and adverse events. Psychological treatments, such as cognitive behavioral therapy, are effective for reducing binge eating but do not reduce weight [8, 16].

The association between BED and obesity [2] and the possible heightened risk for developing future metabolic problems [17] highlight the need to find methods to effectively reduce weight – in addition to eliminating binge-eating – in persons with BED [18]. Bupropion is an antidepressant which has been shown to be an efficacious treatment for smoking cessation [19–22]. Bupropion, a selective re-uptake inhibitor of dopamine and noradrenalin, reduces cravings for nicotine [21, 23] and food [24] potentially by increasing extracellular dopamine [25]. Bupropion has shown some promise for treating obesity in two placebo-controlled trials [24, 26]. Anderson et al. [26] reported that both 300mg/d and 400 mg/d bupropion dosing produced significantly greater weight loss than placebo when paired with a calorie deficit of 600 kcal/day. Jain and colleagues [24], in a study with obese patients with subclinical levels of depression, reported that 300 mg/d of bupropion resulted in significantly greater weight losses than placebo when added to a 500 kcal per day deficit diet [24]. Since food cravings and negative mood are thought to contribute to binge eating [27–29], and because both the noradrenaline [30] and dopamine [31] systems have been implicated in binge eating, bupropion may be a promising psychopharmacological agent for treating overweight persons with BED.

The current study was a randomized double-blind trial designed to test the efficacy of bupropion in the treatment of overweight and obese women with BED. Patients were randomized to receive 300 mg bupropion or placebo for eight weeks. No dietary or lifestyle intervention was given. It was hypothesized that compared to placebo, bupropion would result in significantly greater decreases in the frequency of binge eating episodes and body weight among women diagnosed with BED. Secondary hypotheses were that compared to placebo, bupropion would produce greater reductions in negative mood, food cravings, and eating disorder psychopathology.

Method

Participants

Participants were 61 overweight or obese (BMI ≥ 25) women with BED recruited via advertisements for overweight women seeking treatment for binge eating and weight loss. Entrance criteria required that participants meet full DSM-IV-TR research criteria for BED, have a BMI 25–50, and be aged 18–65 years. Exclusion criteria were: diabetes; seizure disorders; uncontrolled hypertension; hypothyroidism; current pregnancy or breastfeeding; history of severe renal, hepatic, neurological, chronic pulmonary disease, or other unstable medical disorder; gallbladder disease; current medications or herbal supplements with psychoactive properties; current treatment for eating/weight; serious psychiatric disorder that warrant a higher level of treatment (e.g., bipolar disorder, current substance use disorder); homicidal or suicidal ideation. A history of anorexia nervosa or bulimia nervosa was an exclusion due to previous research showing elevated risk of grand mal seizure among bulimic patients taking bupropion [32]. The study was powered *a priori* to detect a difference of 1.7 binge episodes per week between conditions with 80% power using a total sample size of 56 and alpha level of 0.05.

The 61 randomized female participants had a mean age of 44.1 (*SD*=12.5) years and mean BMI of 35.8 (*SD*=6.8). Eighty-eight percent (*N*=54) attended/finished college, and 84% (*N*=51) were Caucasian, 8% (*N*=5) were African-American, 5% (*N*=3) were Hispanic, and 3% (*N*=2) were “other” ethnicity.

Procedure

Treatment assignment was performed independently from the investigators by a research-pharmacist at a separate Yale facility. Participants were randomly assigned with stratification by obesity grade (i.e., BMI 25 to 29.9=overweight, 30 to 34.9=Grade 1 obesity, 35 to 39.9=Grade 2 obesity, ≥ 40=Grade 3 obesity) and by smoking history (current and former versus never) to bupropion or placebo. We stratified by smoking status since it is possible that smoking history/status could moderate treatment outcomes [33]. Following the operational definition of smoking used in Healthy People 2010 [34], participants were classified as smokers if they reported smoking over 100 cigarettes in their lifetime. Never smokers were those who denied smoking over 100 cigarettes in their lifetime.

This randomized double-blind treatment trial was designed to test the efficacy of bupropion-only without any additional dietary or lifestyle intervention. Participants were instructed to

continue eating in their typical pattern for the duration of the 8-week trial. To ensure concealment of the randomization, medication (bupropion, placebo) was prepared in identical-appearing capsules. The Bupropion-SR 300 mg/day schedule consisted of Bupropion-SR 150 mg tablets taken once daily for the first 3 days, then taken twice daily for study days 4–56. The placebo administration followed the same schedule. Assessment appointments occurred every 2 weeks, during which participants were weighed and evaluated for adverse events, and self-monitoring records (described below) were collected.

Assessments

The assessments allowed for determination of diagnoses and eligibility, for characterization of baseline functioning and measurement of clinical changes, and for ongoing assessment of safety and compliance with treatment. Participants were screened and evaluated using clinical and diagnostic interviews conducted by doctoral-level research-clinicians trained in eating and weight disorders.

The Structured Clinical Interview for DSM-IV (SCID-I/P) [35] was used to determine BED diagnosis and Axis I psychiatric lifetime and current comorbidity. A questionnaire with interview follow-up assessed smoking status and history. The Eating Disorder Examination Interview (EDE) [36], a semi-structured, investigator-based interview, was administered to assess eating disorder psychopathology and to confirm the BED diagnosis. The EDE focuses on the previous 28 days except for diagnostic items, which are rated for *DSM-IV-TR* duration stipulations. The EDE assesses the frequency of *objective bulimic episodes* (*OBEs*; i.e., binge-eating defined as unusually large quantities of food with a subjective sense of loss of control), which corresponds to the *DSM-IV-TR* definition of binge-eating. The EDE also assesses *subjective bulimic episodes* (SBEs), which are marked by a subjective sense of loss of control over eating smaller amounts of food. The EDE comprises four subscales (*dietary restraint, eating concern, weight concern,* and *shape concern*) and a total global score. Items are rated on 7-point forced-choice scales (range 0–6), with higher scores reflecting greater severity/frequency. The EDE has well-established inter-rater and test-retest reliability [37] and validity [38]. In the present study, inter-rater reliability, determined using N=21 clinician pairs, was excellent, with reliability coefficients of 0.84 for binge episode days and ranging 0.72–0.91 for subscales.

Self-report measures—The Food Craving Inventory (FCI) [39, 40] was administered at baseline and at all assessment visits. The FCI is a brief measure of specific food cravings and has been validated for use with obese patients with BED [40]. The FCI assesses the frequency of cravings over the past month, and generates 4 subscales (high fats, sweets, carbohydrates/starches, and fast food fats) and a total score. The Beck Depression Inventory (BDI) [41] 21-item version is a well-established self-report [42] measure of symptoms of depression. The BDI was administered at baseline, and at all assessment visits.

Self-monitoring—Participants were instructed in daily self-monitoring of binge eating episodes (Self-Monitoring; [38, 43]). Self-monitoring was taught based on EDE definitions of different types of overeating episodes involving the loss of control (i.e., OBEs and SBEs). Each daily record specifically asked whether participants had any OBEs and SBEs and, if

so, how many episodes. Patients self-monitored on a daily basis throughout treatment and records were reviewed at each assessment visit for completeness. This prospective method of obtaining binge eating data overcomes a number of pitfalls of retrospective methods [38, 43]. At the first clinic appointment, prior to administration of the medication, all participants retrospectively self-reported the frequency of binge episodes occurring over the previous 7 days using EDE definitions. This frequency was used as the baseline measure of binge episodes.

Assessment visits occurred at Weeks 2, 4, 6, and 8 (post-treatment). At each assessment visit, participants were weighed and self-monitoring forms were collected. At Weeks 0, 2, 4, 6, and 8 participants completed the FCI and BDI, and were evaluated for side effects/ adverse events. Participants were paid $100 following completion of the 8-week assessment.

Analytic Plan

Data were analyzed using SPSS v19. Baseline analyses (t-tests and χ^2) tested for group differences on demographic variables. Rate of change in binge frequency and weight change (percent BMI loss) between the bupropion and placebo groups were tested using mixed effects regression for continuous outcomes [44, 45]. Mixed effects models allow for different numbers of observations per subject, use all available data on each subject, and are unaffected by randomly missing data. Mixed effects models also have the capacity to test and account for individual difference contributions to the treatment outcome [46–48]. Mixed effects regression also provides flexibility in modeling the correlation structure of the data. For these analyses, time, medication group, and their interaction were tested, as well as random subject effects. Several different error structures were considered (e.g., AR1, independence), and the best fitting structure was selected based on information criteria. Data on subjects who discontinued the study protocol but have subsequent measurements were used in the primary analyses as randomized. A series of complementary binary logistic regression analyses tested the effects of bupropion vs. placebo on the categorical outcome of remission from binge eating. Remission was defined as 28 days of continuous abstinence from binge eating.

Results

Overall, 93 participants were evaluated for eligibility and 61 were randomized to bupropion (n=31) or placebo (n=30). The 32 participants who were not randomized to treatment were excluded due to non-interest or for failure to meet eligibility criteria. Overall, 54 (89%) of the 61 randomized participants completed the trial and all participants who remained in the study at 8 weeks completed the post-treatment assessment. The two treatment conditions (bupropion vs. placebo) did not differ significantly in completion rates (87% bupropion vs. 90% placebo; χ^2=0.13, p=.72). Three participants voluntarily withdrew from the placebo condition (no reason given), three withdrew from the bupropion condition (no reason given), and one was withdrawn from the bupropion condition due to a medical event. No medication-related adverse events were reported. No seizures were reported. The two treatments did not differ significantly on any demographic feature (Table 1).

Table 2 summarizes BMI and the clinical measures at baseline and post-treatment (Week 8). At baseline, the bupropion and placebo groups did not differ significantly on BMI or on any of the clinical measures (ANOVAs not reported, p-values range .09–.94).

Table 3 summarizes results of the mixed effects models testing change in clinical outcomes. Significant effects for time were found for all variables, indicating all clinical outcomes improved significantly over the course of the study. Mixed effects models revealed that bupropion and placebo differed significantly for percent BMI loss but not for any other outcome variable. Bupropion and placebo groups did not differ on binge eating frequency, any measures of eating psychopathology, food craving, or depressed mood at post-treatment. Figure 1 shows the pattern of weight loss at each time point throughout the study. Participants in the bupropion condition lost an average of 1.8% (sd=2.6) of their body weight, and participants in the placebo condition lost a mean percent body weight of 0.6% (sd=2.1). Expressed in terms of absolute weight loss, participants in the bupropion condition lost 1.68 kg (sd=2.59) after 8 weeks on the study medication, compared to 0.43 kg (sd=2.12) for participants taking placebo. Figure 2 shows the weekly binge eating frequency and remission rates by treatment group. The test for medication versus placebo on rates of change in binge eating (Table 3) was not statistically significant when measured continuously (p=.16) nor when evaluated categorically in terms of remission from binge episodes (defined as no binge episodes during the past four weeks): (42% (n=13) versus 27% (n=8); $\chi^2(1, n=61)=1.58$, phi coefficient=0.16, p=.21).

Discussion

This randomized double-blind controlled trial tested the short-term efficacy of bupropion in the treatment of overweight and obese women with BED. Overall, the medication was well-tolerated and no medication-related adverse events were experienced. The bupropion and placebo groups did not differ in rates of dropout from the study, which was low overall with 89% of the participants completing treatment. After 8 weeks of treatment, significant improvements were observed for eating-specific and general psychopathology, although these improvements did not differ significantly between bupropion and placebo. Significant overall improvements were observed in terms of reduced frequency of binge eating and binge eating remission (defined as zero OBEs for the last 28 days of treatment) although the bupropion and placebo groups did not differ significantly in remission rates (42% vs. 27%, respectively).

However, 300 mg/d of bupropion resulted in significantly greater weight loss (1.8% or 1.68 kg) compared to placebo (0.6% or 0.43 kg). Collectively, our findings do not support bupropion as a stand-alone treatment for BED. The findings regarding short-term weight losses –significant albeit very modest during this brief 8-week trial – suggest the need for larger and longer-term trials to evaluate the potential utility of bupropion for enhancing outcomes of psychological interventions with demonstrated efficacy for BED but which fail to produce weight loss.

The remission rates and percent reductions in binge eating frequency observed in this pharmacotherapy-only trial (42% vs 27% for bupropion and placebo, respectively) are

comparable in magnitude to those observed generally in pharmacotherapy-only trials for BED [6]. For example, Wilfley et al. [49] reported remission rates (defined as zero OBEs in the last *two weeks* of treatment) of 44% for sibutramine and 30% for placebo. The magnitude of differences between bupropion and placebo for binge eating outcomes, however, was not statistically significant and this adds to the mixed literature for pharmacotherapy-only [e.g., [8] [50]; see [6] for review]. Such findings may perhaps reflect partly the relatively limited sample size and insufficient power to detect small effect sizes. However, it is unlikely that the brief length of the trial obscured potential effects on binge-eating given that response to antidepressant treatments to BED are generally quite rapid and observed by four weeks [51]. However, given its unique mechanism of action, bupropion cannot be directly compared to other classes of pharmacotherapy (e.g., anticonvulsants, weight loss medications) that have shown some efficacy in reducing binge eating [6].

Weight losses at 8 weeks were comparable to previous reports with several different medications tested for obese patients with BED, except for the reports of greater weight losses with topiramate [6], but were less than those reported in two previous RCTs of bupropion for the treatment of obesity without co-morbid BED [24, 26]. Importantly, the present study tested medication-only whereas the previous obesity trials tested bupropion and placebo administered concurrently with reduced calorie diets and for longer durations [24, 26]. Additionally, the dosing in the current study (300 mg/day) was less than that administered in previous reports which administered in doses of 400 mg/day [26] and 300 mg/day, increasing to 400 mg/day in the event of modest initial weight loss [24]. Future studies should test bupropion in longer trials, at higher dosing, and administered concurrently with either cognitive behavioral therapy (CBT) or behavioral weight loss treatment to determine whether there is an additive effect. Previous research employing these designs with other specific pharmacological agents have found limited benefit of medication over and above that provided by CBT or behavioral weight loss treatments in terms of binge eating, although they have found an advantage for certain medication in terms weight loss. For example, Grilo et al. [12] found no differences in binge eating remission or percent reduction in binge eating between orlistat and placebo when administered alone or in combination with CBT. However, the CBT+orlistat group lost significantly more weight than the group taking placebo. Similarly, Claudino et al. [15] reported that reductions in binge eating frequency did not differ for topiramate and placebo administered concurrently with CBT, although the topiramate group lost significantly more weight after 21 weeks. A slightly longer trial comparing orlistat to placebo when administered concurrently with a calorie-reduced diet found greater weight loss at 24 weeks for orlistat, but no differences in terms of binge eating frequency at post-treatment [11].

This study has several strengths and limitations that should be noted as context for interpreting its findings. The study completion rate was quite high, with 89% of participants completing the trial and providing post-treatment data. It should be noted, however, that subject payment ($100 for completing the post-treatment evaluation) may have contributed partly to our high retention rates. The study also enrolled overweight (i.e., BMI ≥25 and <30) as well as obese (BMI≥30) women into the study, which increases its generalizability. Finally, because of the possibility that smoking history/status could moderate treatment

outcomes [33], participants were stratified by smoking history/status to ensure equivalence across cells. Limitations include the short study duration and sample size; it is possible, for example, that longer treatment might have resulted in greater weight losses or a larger sample size with greater power might have allowed statistical detection of smaller differences between active and placebo conditions. The lack of follow up after medication discontinuation is also a limitation; unfortunately this is the case for all published RCTs of medication-only treatments for BED to date [6], except for one recent report [52]. With this context, we cautiously conclude that our findings do not support bupropion as a stand-alone treatment for BED although the findings regarding short-term weight losses suggest the need for longer-term trials to evaluate further the potential utility of bupropion for enhancing outcomes of other interventions with demonstrated efficacy for BED but which fail to produce weight loss.

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Clinical Points

1. Binge eating disorder is strongly associated with excess weight and many available psychological and pharmacological approaches fail to produce much weight loss.
2. In this 8-week RCT, Bupropion was well tolerated and produced significantly greater – albeit quite modest – short-term weight loss in overweight and obese women with BED.
3. In this 8-week RCT, Bupropion did not improve binge eating, food craving, or associated eating disorder features or depression relative to placebo.

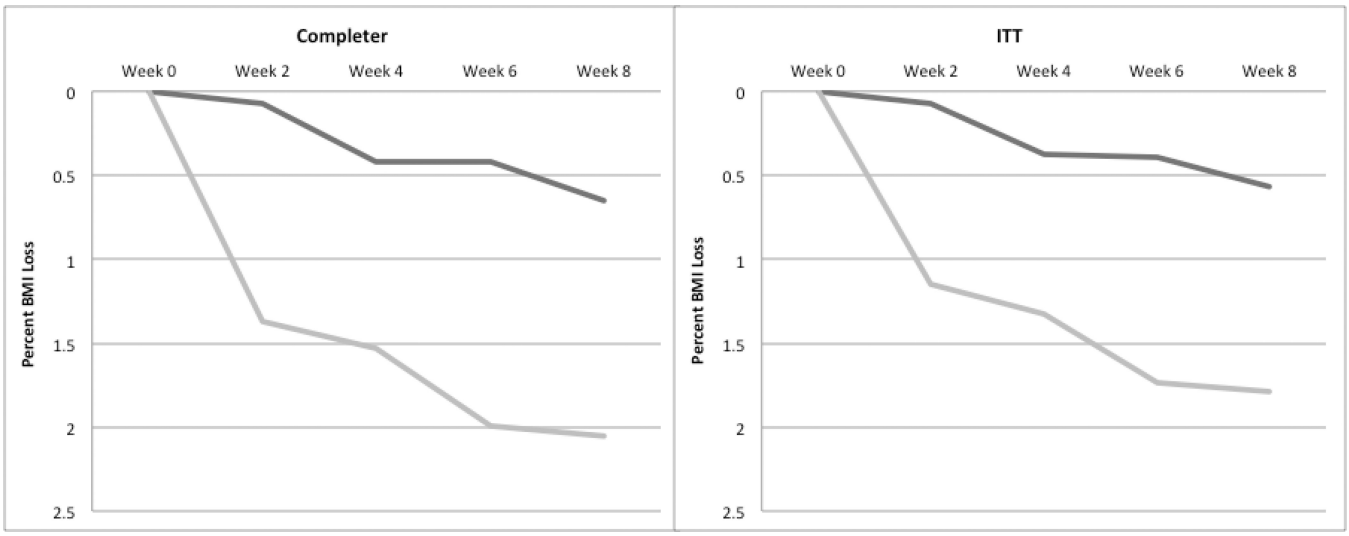

Figure 1.

Mean Percent BMI loss for Completer data (LEFT) and ITT (missing values replaced with 0% BMI loss; RIGHT).

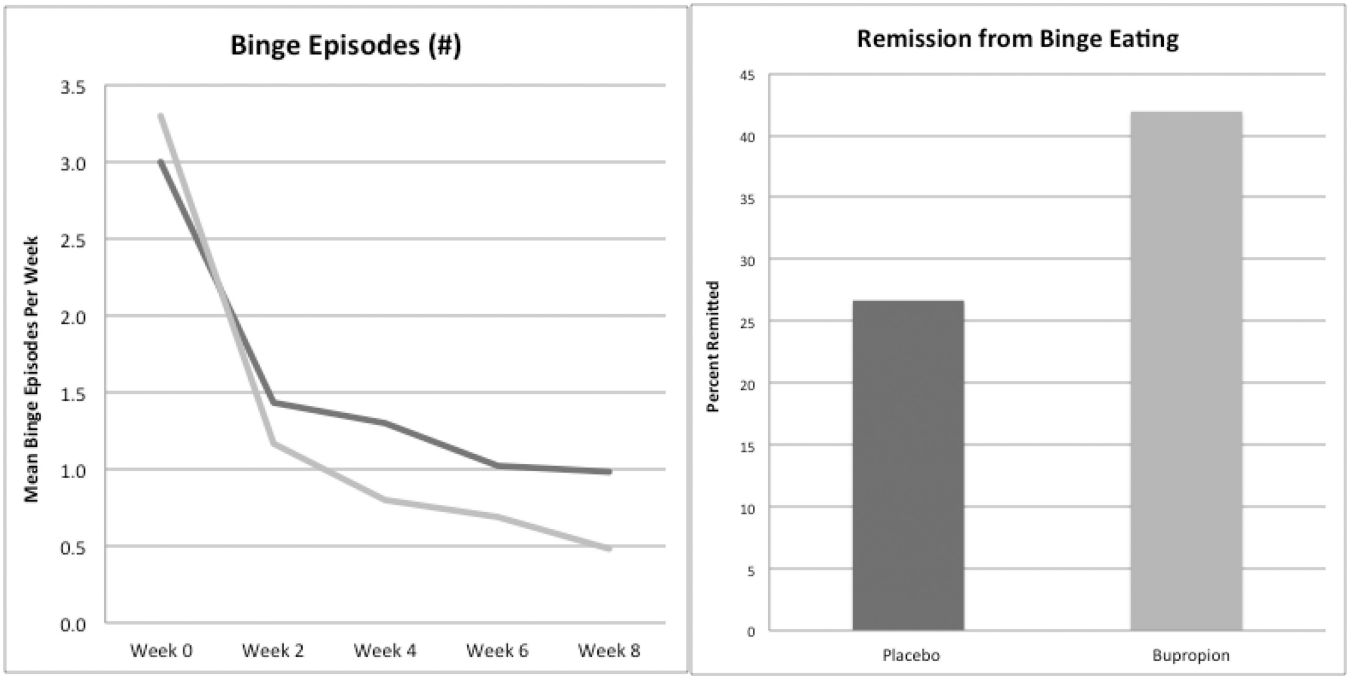

Figure 2.
Improvement in Binge Eating during the 8-week study phase

Table 1

Demographic and Psychological Characteristics of Participants

	Placebo (n=30)		Bupropion (n=31)		Total		Test statistic	
	M	sd	M	sd	M	sd	F	p-value
Age (years)	43.1	13.0	45.2	12.1	44.15	12.5	0.412	.523
	%	n	%	n	%	n	χ^2	
Race: % Non-white	10.0	(n=3)	22.6	(n=7)	16.4	(n=10)	1.761	.185
Education: % College	63.3	(n=19)	61.3	(n=19)	62.3	(n=38)	0.027	.869
Axis I comorbidity (Lifetime)	80.0	(n=24)	67.7	(n=21)	73.8	(n=45)	1.184	.277
Mood disorder (lifetime)	53.3	(n=16)	51.6	(n=16)	52.5	(n=32)	0.018	.893
Anxiety disorder (lifetime)	43.4	(n=13)	32.3	(n=10)	37.7	(n=23)	0.796	.372
Substance Use Disorder (lifetime)	33.3	(n=10)	16.1	(n=5)	24.6	(n=15)	2.434	.119
Smoking (lifetime)	56.7	(n=17)	45.2	(n=14)	50.8	(n=31)	0.807	.369

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Table 2

Clinical Measures at Baseline and Post-treatment[a]

	Placebo (n=30)				Bupropion (n=31)			
	Week 0		Week 8		Week 0		Week 8	
	M	sd	M	sd	M	sd	M	sd
BMI[b]	35.4	(7.1)	35.2	(7.4)	36.2	(6.6)	35.7	(6.6)
EDE Restraint[c]	1.8	(1.2)	1.6	(0.8)	1.6	(1.2)	1.4	(1.0)
EDE Eating Concern[c]	2.0	(1.4)	1.1	(1.3)	1.8	(1.2)	1.0	(1.2)
EDE Shape Concern[c]	3.7	(1.1)	2.9	(1.5)	3.5	(1.4)	2.4	(1.3)
EDE Weight Concern[c]	3.3	(1.0)	2.6	(1.0)	3.2	(1.2)	2.6	(1.0)
EDE Global[c]	2.7	(0.8)	2.0	(0.9)	2.5	(1.1)	1.8	(0.9)
OBE (EDE; monthly)[b]	13.6	(6.5)	6.3	(8.0)	17.8	(11.9)	5.0	(9.4)
OBE (SR; per week)[b]	3.0	(2.6)	1.0	(1.5)	3.3	(3.3)	0.8	(1.2)
SBE (EDE; monthly)[b]	10.3	(14.2)	7.5	(8.4)	13.5	(11.2)	9.3	(21.4)
SBE (SR; per week)[b]	2.7	(3.4)	2.3	(2.4)	3.6	(2.7)	2.2	(4.2)
BDI[b]	10.8	(6.1)	8.7	(7.2)	13.4	(9.8)	8.0	(8.3)
FCI-Total[b]	2.4	(0.7)	2.0	(0.6)	2.6	(0.6)	2.0	(0.6)

[a] Missing values at Week 8 (n=7) replaced with baseline values.

[b] Administered at all biweekly assessment visits.

[c] Administered at baseline and post-treatment.

Abbreviations: EDE=Eating Disorder Examination. OBE=Objective binge episodes. SBE=Subjective binge episodes. SR = Self-report via daily monitoring. BDI=Beck Depression Inventory. FCI=Food Craving Inventory.

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Table 3

Mixed Effects models

	Post tx value different from zero		Time		Medication	
	F	p	F	p	F	p
Percent BMI[a] loss	4.14	.05	5.65	.02	10.57	.00
EDE Restraint[b]	116.47	.00	4.08	.05	1.39	.24
EDE Eating Concern[b]	101.81	.00	85.13	.00	0.84	.36
EDE Shape Concern[b]	303.49	.00	65.82	.00	1.71	.20
EDE Weight Concern[b]	315.71	.00	28.34	.00	0.05	.82
EDE Global[b]	335.94	.00	122.08	.00	2.06	.15
OBE (EDE)[b]	121.44	.00	55.35	.00	0.08	.77
OBE (SR)[a]	17.95	.00	7.78	.01	2.01	.16
SBE (EDE)[b]	22.54	.00	2.89	.09	0.96	.33
SBE (SR)[a]	10.53	.00	6.32	.02	0.47	.50
BDI[a]	28.27	.00	22.65	.00	0.04	.84
FCI-Total[a]	319.41	.00	63.07	.00	0.10	.76

[a] Administered at all biweekly assessment visits.

[b] Administered at baseline and post-treatment.

Abbreviations: EDE=Eating Disorder Examination. OBE=Objective binge episodes. SBE=Subjective binge episodes. SR = Self-report via daily monitoring. BDI=Beck Depression Inventory. FCI=Food Craving Inventory.