Pilot Study

Naltrexone + Bupropion Combination for the Treatment of Binge-eating Disorder with Obesity: A Randomized, Controlled Pilot Study

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ABSTRACT

Purpose: Binge-eating disorder (BED), the most prevalent eating disorder, is associated strongly with obesity and functional impairments. Few evidence-based treatments for BED exist; a pharmacotherapy effective in reducing both binge eating and weight needs to be identified. This placebo-controlled double-blind pilot RCT evaluated the acute effects of naltrexone + bupropion (NB) on BED with obesity and examined the longer-term effects through 6-month follow-up after the discontinuation of medication.

Methods: Twenty-two adult patients with BED were randomized to receive 12 weeks of double-blind treatment with fixed-dose NB (naltrexone + bupropion XL 50/300 mg) or placebo. Independent (blinded) researcher–clinicians evaluated patients at major outcome time points (baseline, posttreatment, and 6-month follow-up after the treatment period); patients were also evaluated for the tracking of course/tolerability throughout treatments and at 3-month follow-up. Primary outcomes were changes from baseline in binge-eating frequency and percentage weight. Secondary outcomes were changes in eating-disorder psychopathology and depression.

Findings: A total of 22 patients were enrolled (86.4% women; mean age, 50.4 years), with 77.3% of patients completing treatments; completion rates (NB, 83.3%; placebo, 70.0%) and adverse events did not differ significantly between NB and placebo. Analyses revealed significant reductions from baseline in binge-eating, eating-disorder psychopathology, depression, and weight during treatment, but these changes with NB did not differ significantly from those with placebo. The percentage of patients who attained 3% weight loss was significantly greater with NB than with placebo (45.5% vs 0%); weight-loss and binge-eating reductions were significantly correlated in the group that received NB. At 6-month follow-up, outcomes remained improved relative to baseline, with no significant differences between NB and placebo.

Implications: The findings from this pilot RCT suggest that NB was well-tolerated in these patients with BED and comorbid obesity. Most outcomes were not statistically different between NB and placebo. A larger-scale, adequately powered RCT is needed for determining the efficacy of NB in the treatment of BED. ClinicalTrials.gov identifier: NCT02317744. (*Clin Ther*. 2021;43:112–122) © 2020 Elsevier Inc.

Key words: binge-eating disorder, bupropion, eating disorders, naltrexone, obesity, pharmacotherapy.

INTRODUCTION

Binge-eating disorder (BED) is characterized by recurrent binge eating (ie, eating unusually large quantities of food, accompanied by a feeling of loss

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of control), marked distress, and the absence of inappropriate weight-compensatory behaviors.[1] BED, the most prevalent formal eating-disorder diagnosis,[2] has been significantly associated with medical and psychiatric comorbidities,[3] and functional impairments.[2] BED has been associated strongly with obesity[2] and with a heightened risk for obesity-related metabolic problems.[4]

Although controlled treatment research has provided empiric support for certain pharmacologic approaches,[5] many patients do not cease binge eating or lose weight.[6] Producing weight loss in patients with BED comorbid with obesity has been particularly challenging. The majority of treatment studies have reported little weight loss,[7] and the weight losses reported in studies of treatments for BED are less than those in obesity without BED.[8] Of the medications for BED tested to date and available on the market, only 2 have been found to significantly reduce both binge eating and weight. The use of topiramate, an antiseizure agent, has been associated with significantly reduced binge eating and weight relative to placebo[9] and with significantly enhanced outcomes compared to placebo, when added to cognitive–behavioral therapy.[10] The use of topiramate, however, has been associated with concerning adverse events and limited tolerability, leading to very high discontinuation rates.[11]

Lisdexamfetamine dimesylate, a prodrug stimulant and the sole medication that the US Food and Drug Administration (FDA) has approved for use in the treatment of BED, in addition to being associated with a significant reduction in binge eating relative to placebo, has been reported to reduce weight.[12] Importantly, weight loss was examined as a safety measure rather than as a clinical outcome, and the FDA approval of lisdexamfetamine dimesylate includes a Limitation of Use specifying that it is not indicated or recommended for weight loss and noting that its safety and efficacy in the treatment of obesity have not been demonstrated. Thus, effective pharmacologic approaches to reducing both binge eating and weight in BED remains a pressing need. Such research should include follow-up assessments of longer-term outcomes after discontinuation of medications, which are sorely needed for informing clinicians about the durability of the outcomes and the risk for relapse.[13] To date, follow-up assessments in randomized, controlled trials (RCTs) of pharmacotherapy-only for BED have been reported in only 2 studies, and both suggested high and rapid relapse rates.[14,15]

Although several FDA-approved weight-loss medications are currently available, to date none has been tested as a monotherapy for BED.[13] The use of 1 specific agent, the combination of naltrexone + bupropion (NB), seems logical given the putative mechanisms of action relevant for reducing both binge eating and weight, per hypothesized effects on the brain regions involved in the regulation of food intake and weight, based, in turn, on the findings from research on the mechanisms of action of leptin.[16] The anorectic effects of leptin result from its excitatory effects on pro-opiomelanocorin (POMC) neurons in the melanocortin system of the hypothalamus.[17] Stimulated POMC signaling decreases food intake and increases energy expenditure, but is then inhibited by endogenous feedback.[17] The combination of naltrexone + bupropion is thought to stimulate POMC neurons (bupropion) plus block endogenous feedback that inhibits POMC activity (naltrexone).[16,18] Several double-blind RCTs have reported that NB was effective in promoting weight loss in patients with obesity.[18–22] Naltrexone and bupropion have been marketed for many years and are now available as generic products. Fixed-dose combination extended-release tablets became available in 2014 as a branded product with FDA approval for use as an adjunct to a reduced-calorie diet and increased physical activity in long-term weight management in adults with obesity (or with a body mass index [BMI] of 27 or greater in the presence of weight-related comorbidity). The present double-blind pilot RCT evaluated the acute effects of NB delivered for 12 weeks and examined the longer-term effects through 6-month follow-up after the discontinuation of medication in patients with BED with obesity.

METHODS

Participants

Participants were 22 consecutively assessed patients who met the criteria for BED and obesity. Respondents to media advertisements for the treatment study at a medical school program and who passed initial screening were assessed for eligibility during in-person evaluations. Eligibility criteria included an age of 18–65 years, full *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*

(DSM-5)[1]—defined criteria for BED, and a BMI of 30—50 kg/m^2. Exclusion criteria in this pilot RCT were minimal and were: the receipt of any concurrent treatment for eating/weight concerns, the presence of any medical condition that might have influenced eating/weight (eg, uncontrolled diabetes or hypothyroidism) or contraindications for using NB (eg, seizure disorder, the presence of uncontrolled/elevated blood pressure of >160/>95 mm Hg), the use of any medication contraindicated for use with NB (eg, selective serotonin reuptake inhibitors, opioid medications), the presence of any severe mental illness that would have interfered with clinical assessment or dictated alternative treatments (eg, psychosis or bipolar disorder), and/or pregnancy/breastfeeding.

The study protocol was approved by the institutional review board at Yale University (New Haven, Connecticut). Participants provided written informed consent.

Measures

Assessments were performed by trained and monitored doctoral-level research clinicians following specific protocols. The Mini-International Neuropsychiatric Interview version 7.0[23] was used for establishing *DSM-5*—based BED diagnosis and for determining psychiatric exclusions. The Eating Disorder Examination (EDE),[24] a semi-structured, investigator-based interview, was used for confirming BED diagnosis, for assessing binge-eating frequency and eating-disorder psychopathology levels at baseline, and for assessing those primary (binge eating) and secondary (eating-disorder psychopathology) outcomes at predefined assessment time points posttreatment (ie, end of treatment) and at 6-month follow-up (ie, 6 months after the completion or discontinuation of treatments and 9 months following randomization).

The Eating Disorder Examination—Questionnaire (EDE-Q),[25] the self-report version of the EDE interview, was administered at baseline, monthly throughout treatment, at posttreatment, and at follow-ups; the EDE-Q was used throughout treatment for the assessment of time-course changes with less burden than the EDE interview (given only at baseline, posttreatment, and 6-month follow-up) and for providing data complementary to those obtained from the EDE interview. Both the EDE and EDE-Q assess the frequency of binge-eating episodes during the previous 28 days and generate a global eating-disorder psychopathology severity score. Both the EDE and EDE-Q have good test—retest reliability in patients with BED[26,27] and converge adequately.[28,29] The Beck Depression Inventory (BDI)[30] is a well-established measure of depression level.[31] The BDI was administered at baseline, monthly, at posttreatment, and at follow-up.

Percentage weight loss was calculated as the difference between weight at a given time point and the baseline weight, divided by the baseline weight; negative values indicated weight loss. Weight was measured at baseline, monthly, at posttreatment, and at follow-up.

Randomization, Blinding, and Independent Assessments

A biostatistician created the randomization schedule (unrestricted in blocks of 12 with a 1:1 ratio), which was implemented independent of the investigators by the Investigational Drug Service, Yale Investigational Drug Service. Investigators, assessors, and patients were all blinded to the medication conditions (double-blind) throughout the study until after the 6-month follow-up assessment was completed in all patients. NB and placebo, prepared by the Investigational Drug Service, as identical-appearing capsules and matched in frequency (including up-titration, full dose, and down-titration), are described below.

Medication

Active medication was a combination of naltrexone 50 mg + bupropion XL 300 mg. Previous RCTs of this combination (eg, Greenway et al[19]) performed by the manufacturer used 16 mg of sustained-release naltrexone and 180 mg of sustained-release bupropion dosed twice daily (totals, 32 mg of naltrexone and 360 mg of bupropion); however, the present study used generically available naltrexone 50 mg and bupropion XL 300 mg taken together once daily. This dosing using generic products, which are available at a cost substantially lower than that of the branded NB product, has some potential advantages. One advantage is the use of the extended-release formulation of bupropion, which allows for once-daily dosing. Importantly, using standard-release naltrexone rather than the sustained-release formulation available only in the branded

combination medication is not a pharmacokinetic disadvantage. Despite a short initial serum half-life, the pharmacologic activity of naltrexone is long lived, with an effective half-life of over 3 days, consistent with the terminal phase of plasma clearance.[32]

The up-titration schedule for the study medications was as follows: study day 1, placebo lead-in (both groups); study days 2 and 3, 150 mg of bupropion (active-treatment group) or placebo capsules (placebo group); study days 4 and 5, 300 mg of bupropion (active-treatment group) or placebo capsules (placebo group); study days 6 through 84 (end), 50 mg of naltrexone and 300 mg of bupropion (active-treatment group) or placebo capsules (placebo group). At the end of 12 weeks, participants followed a down-titration protocol of 7 days of 150 mg of bupropion (active-treatment group) or placebo capsule (placebo group).

Statistical Analysis

Analyses comparing treatment groups were intent to treat, performed in all randomized patients, using all available data without imputation except for complementary analyses, described below.

Mixed-models analyses were performed without imputation for the primary outcomes (binge-eating frequency, percentage weight loss) and for secondary outcomes (global eating-disorder psychopathology, depression scores) with fixed effects of medication group (1 vs 0), time (months 1, 2, and posttreatment), and the interaction of group and time. Distributions of data were examined; binge eating had some positive skewness, and square-root transformation was applied to achieve normality. In each model, different variance–covariance structures were evaluated and the best-fitting structure was selected based on the Bayesian-Schwarz criterion. Least-squares means were estimated from all models and compared as necessary to explain significant effects in the models. In the complementary analyses for comparing reductions in primary outcomes variables (reduction from baseline in binge-eating, as determined by EDE interview; percentage weight loss; and the percentage of patents who attained 3% weight loss), by group at the primary posttreatment and 6-month assessment time points, the *t* test was employed for the continuous variables and the Fisher exact test for the dichotomous variable. In this 12-week RCT, a 3% loss in weight, rather than the more common 5% cutoff point used in previous RCTs of NB, was analyzed for the treatment of obesity, which had 24- to 56-week durations.[18–22]

RESULTS

Randomization, Patients' Characteristics, and Completion/Follow-up Rates

Figure 1 summarizes the flow of patients throughout the study. Of the 268 screened individuals, 40 were evaluated in person, and 22 met eligibility and were randomized to treatment. The mean (SD) age of the participants was 50.4 (8.8) years; BMI, 37.1 (5.9); 86.4% (n = 19) were women; 72.7% (n = 16) self-identified as white; and 86.4% (n = 19) attended or finished college. The 2 treatment groups did not differ significantly with regard to demographic variables (age, sex, race/ethnicity, education) or baseline clinical characteristics (Table I), except for BMI, which was higher in the placebo than in the NB group ($P < 0.05$). Of the 22 patients randomized, 17 (77.3%) completed treatment. As analyses were intent to treat, all patients were followed up even if they stopped taking the study medication. Two patients who were withdrawn during the course of treatment did not complete the posttreatment assessment. One patient (placebo group) was withdrawn from the study because of an emergent medical condition considered as unrelated to the RCT and that required treatment. Sixteen patients (72.7%) completed follow-up assessments performed 6 months after the treatment period ended and after medications were discontinued.

Treatment completion rates were 83.3% with NB and 70.0% with placebo (77.8% if excluding the patient withdrawn); this difference was not significant ($P = 1.00$ [Fisher exact test]). Assessment rates at posttreatment (91.6% vs 90.0%) and at 6-month follow-up (66.7% vs 80%) were not significantly different between NB and placebo.

Treatment Outcomes

Table II summarizes the clinical variables in the NB and placebo treatment conditions at the major time points (baseline, posttreatment, and 6-month follow-up).

The mean (SD) reductions in EDE-based binge-eating episodes at posttreatment were not significantly different between the NB and placebo conditions (–8.27 [24.88] vs –5.50 [9.91]; *t*

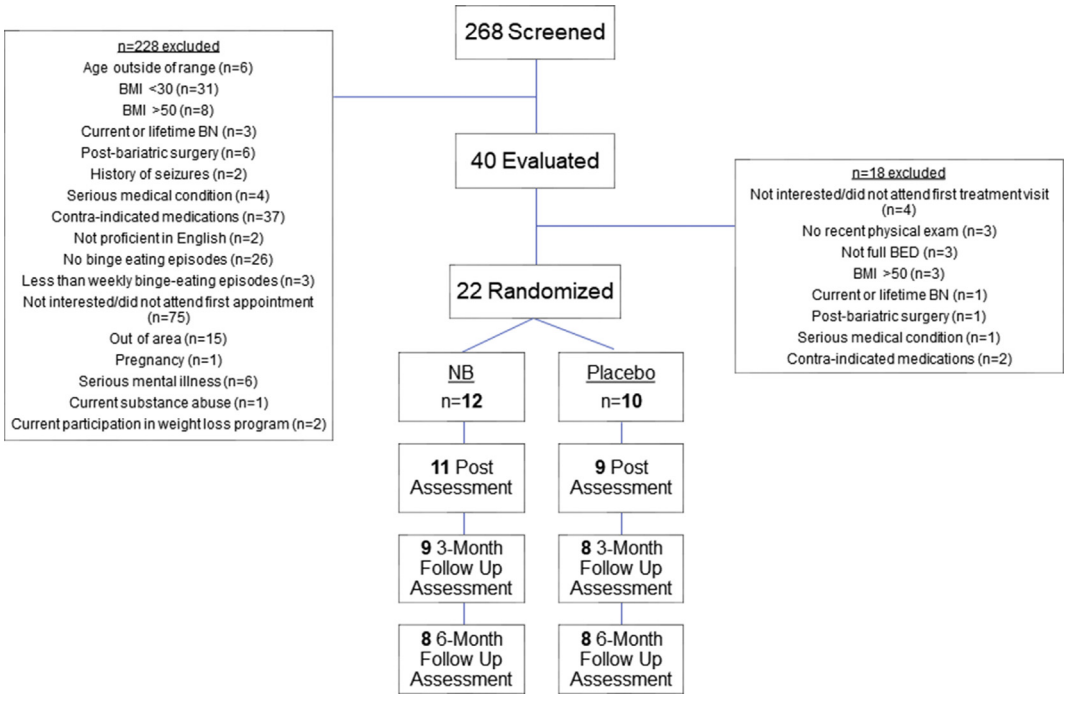

Figure 1. CONSORT diagram of patient flow through eligibility determination, study treatment, and follow-up assessment phases. BED = binge-eating disorder; BMI = body mass index; BN = bulimia nervosa; NB = naltrexone/bupropion.

[17] = 0.30; $P = 0.77$) (Figure 2A). On complementary ITT mixed-models analysis of the course of binge-eating throughout treatment (assessed using the EDE-Q), overall, the frequency of binge-eating episodes was decreased throughout the course of treatment (F [3,31.8] = 11.92; $P < 0.0001$). However, the frequencies of binge eating were not significantly different between the 2 treatment groups (F [1,24.7] = 2.21; $P = 0.15$), nor did the rates of reduction differ between groups, as reflected by the nonsignificant time-by-group interaction (F [3,31.8] = 0.94; $P = 0.43$).

On analysis of percentage weight loss (ie, reduction in weight proportional to baseline weight), the difference between NB and placebo at posttreatment was not significant (–2.20% [3.51%] vs –1.10% [1.05%]; t (10.9) = 0.95; $P = 0.37$). On examination of weight loss categorically, a significantly greater percentage of patients who received NB achieved at least 3% weight loss at posttreatment (45.5%; n = 5) compared with the patients who received placebo ($P = 0.045$ [Fisher exact test]; $\phi = 0.510$); intent-to-treat analysis in which failure was imputed for missing data also revealed that patients who received NB were significantly more likely to attain 3% weight loss ($P = 0.045$ [Fisher exact test]).

In terms of the course of the weight changes, mixed models of percentage weight loss revealed a statistically nonsignificant trend for treatment-by-time interaction (F [2,16.9] = 2.85; $P = 0.09$) (Figure 2B), although the differences were not significantly different between groups overall (F [1,19.5] = 2.40; $P = 0.14$), nor was the time effect significant across all patients (F [2,16.9] = 0.19; $P = 0.83$). The NB group had a significantly greater percentage weight loss than did the placebo group at month 2 (F [1,19.8] = 4.42; $P = 0.048$), but not at the other time points (month 1, F [1,18.3] = 0.38 [$P = 0.543$]; post, F [1,18.5] = 2.17 [$P = 0.16$]).

Global eating-disorder psychopathology was decreased significantly over the course of treatment (F [3,49.3] = 7.86; $P < 0.001$), but NB and placebo did

Table 1. Demographic features and clinical characteristics of the study patients.

Characteristic	NB (n = 12)	Placebo (n = 10)	Test Statistic*	*P*	Effect Size
Age, mean (SD),y	51.17 (7.95)	49.40 (10.13)	0.21	0.65	0.010
Female sex, no. (%)†	11 (92)	8 (80)		0.57	0.169
Race/ethnicity, no. (%)			6.12	0.11	0.527
White	9 (75)	7 (70)			
Black	3 (25)	0			
Hispanic	0	2 (20)			
Asian	0	1 (10)			
Education, no. (%)			4.47	0.11	0.451
High school	1 (8)	2 (20)			
Some college	9 (75)	3 (30)			
College or more	2 (17)	5 (50)			

NB = naltrexone/bupropion.
* χ^2 was used for categorical variables (effect size ϕ); *F* was used for continuous variables (effect size η_p^2).
† Fisher exact test (no test statistic or effect size) was used for comparing men and women; no other sex identity was reported.

not differ significantly overall in global eating-disorder psychopathology (F [1,19.4] = 0.76; P = 0.39) or in the rate of change (F [3,49.3] = 0.80; P = 0.50).

Depression (BDI) scores were reduced significantly over the course of treatment overall (F [3,49.9] = 7.13; $P < 0.001$). The difference between the NB and placebo groups, however, was not significantly different overall (F [1,20.3] < 0.01; P = 0.97), nor were the rates of reduction between the 2 treatment conditions (F [3,49.9] = 0.66; P = 0.58).

The percentage weight loss and the reduction in binge-eating frequency (from baseline to post) were significantly correlated in the NB group (r = 0.80; P = 0.005), but there was no correlation in the placebo group (r = –0.04; P = 0.92); the difference in correlations between groups was significant (based on the Fisher r to z comparison: Z = 1.97; P = 0.049).

Follow-up Outcomes

Six months after the cessation of treatment, the group that received NB had a statistically nonsignificantly greater mean (SD) reduction from baseline in binge-eating frequency than did the group that received placebo (–13.25 [13.01] vs –6.25 [5.82]; t [9.70] = 1.39; P = 0.20). The percentage weight loss (calculated as change from baseline) at follow-up was statistically nonsignificantly greater in the NB than in the placebo condition (–0.72% [3.66%] vs –0.28% [4.59%]; t [13] = 0.20; P = 0.84).

Categorically, 2 patients (25%) in the NB group and 2 patients (25%) in the placebo group exceeded 3% weight loss (P = 1.00 [Fisher exact test]). Decreases between baseline and follow-up in global eating-disorder psychopathology on the EDE were not significantly different between the NB and placebo groups (t [14] = 0.04; P = 0.97). Depression scores also showed decreases from baseline to follow-up that were not significantly different between NB and placebo (t [14] = –0.46; P = 0.65).

Percentage weight loss and reductions in binge eating from baseline to 6-month follow-up were not significantly correlated in either the NB group (r = –0.47; P = 0.16) or the placebo group (r = 0.16; P = 0.70), and correlation magnitudes did not differ from each other (Z = –1.01; P = 0.31).

Tolerability

The Supplemental Table (see the online version at https://doi.org/10.1016/j.clinthera.2020.10.010) summarizes adverse events over the course of treatment

Table II. Effects of naltrexone/bupropion (NB) on outcomes measures across major time points. Data are given as mean (SD).

Parameter	NB (n = 12)	Placebo (n = 10)	Test Statistic	*P*	Effect Size
Binge-eating frequency (past month)*			3.09	0.09	0.134
Baseline	20.08 (13.81)	11.30 (8.35)			
Posttreatment	12.00 (30.86)	4.00 (7.65)			
Δ vs baseline	−8.27 (24.88)	−5.50 (9.91)			
6-month follow-up	5.38 (8.58)	3.25 (4.8)			
Δ vs baseline	−13.25 (13.01)	−6.25 (5.82)			
Global eating-disorder psychopathology*			2.18	0.16	0.098
Baseline	3.01 (1.41)	2.22 (1.03)			
Posttreatment	1.97 (1.33)	1.56 (0.87)			
6-month follow-up	2.42 (1.55)	1.76 (1.69)			
Depression (BDI) scores			0.03	0.87	0.001
Baseline	13.92 (7.88)	14.50 (8.02)			
Posttreatment	10.73 (10.08)	8.38 (10.38)			
6-month follow-up	11.13 (9.01)	8.63 (10.2)			
Body mass index					
Baseline	34.85 (6.13)	39.84 (4.54)	4.54	0.046	0.185
Posttreatment	34.52 (6.64)	40.07 (4.79)			
6-month follow-up	35.91 (7.39)	40.28 (3.97)			
Percentage weight change from baseline			—	—	—
Posttreatment	−2.20 (3.51)	−1.10 (1.05)			
6-month follow-up	−0.72 (3.66)	−0.28 (4.59)			

BDI = Beck Depression Inventory.
* Binge eating and global eating-disorder psychopathology were assessed using the Eating Disorder Examination.

with NB and placebo. χ^2 Analyses revealed no significant differences in the percentages of patients in the two groups who reported any of the specific events. Considered cumulatively, *F* tests revealed that the number of reported adverse events during the 1st and 3rd months of treatment did not differ significantly between the NB and placebo groups; during the 2 nd month of treatment, the mean number of adverse events per patient reported was significantly higher in the group that received NB than in the group that received placebo (2.00 [1.73] vs 0.33 [0.82]; F [1,13] = 4.76; P = 0.048; η_p^2 = 0.268) (see Supplemental Table in the online version at https://doi.org/10.1016/j.clinthera.2020.10.010).

DISCUSSION

This study was the first to evaluate the potential effectiveness of NB, a generic formulation of an FDA-approved weight-loss medication, in the treatment of BED in persons with obesity. The findings from this small-sample double-blind pilot RCT suggest that NB was well tolerated in these patients with BED and comorbid obesity. The NB and placebo groups did not statistically differ with regard to most outcomes. Patients receiving NB were significantly more likely than were those receiving placebo to attain 3% weight loss in this 12-week trial; weight loss and binge-eating reductions were significantly correlated in the NB group but not in the placebo group.

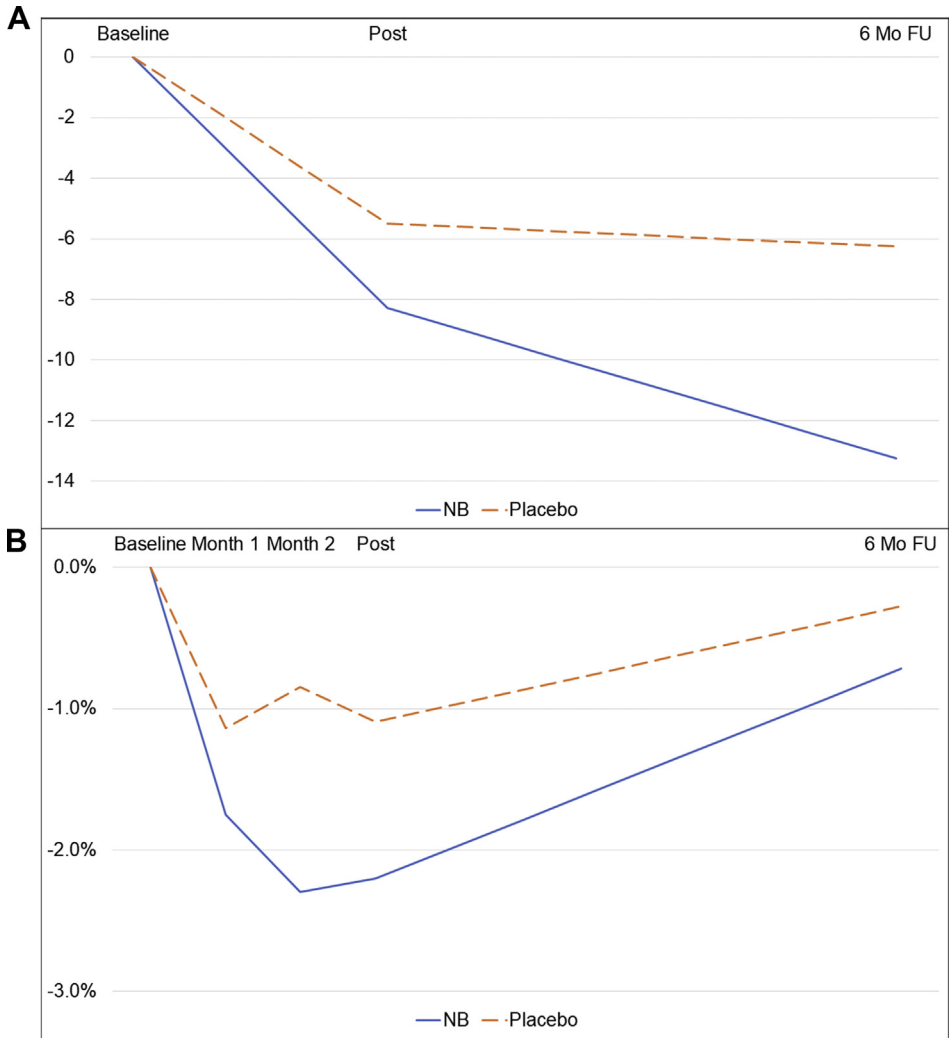

Figure 2. A. Effects of naltrexone/bupropion (NB) treatment on binge-eating frequency (A) and percentage weight loss (B) at posttreatment and 6-month follow-up (FU) (after treatment cessation). Binge-eating frequency was measured by the Eating Disorder Examination; differences were not statistically significant. Percentage weight loss was calculated as the difference between time point weight and baseline weight, divided by baseline weight. Negative values reflect weight loss. Weight loss was significantly greater with NB than with placebo at month 2 but not at other time points. Group and time did not have main effects, although the group-by time-interaction showed a nonsignificant trend ($P = 0.085$).

While the sample size was too small to permit generalizability, the study population was relatively diverse in terms of sex, race, and education and had very few exclusionary criteria (mostly safety considerations). The completion rates, tolerability profile, and overall improvements with time—which were mostly not statistically significantly different between NB and placebo—observed in this pilot study point to the need for a larger-scale and adequately powered RCT to evaluate the efficacy of NB in the treatment of BED in persons with obesity.

Several points can be offered as additional context for the findings from this pilot RCT. A previous *post hoc* analysis of data from an open-label trial of NB in 25 patients with major depressive disorder and overweight/obesity reported some improvements in binge-eating features in addition to reductions in depressive symptoms[33]; importantly, 12 of the 25 patients were discontinued from treatment, with 10 of those attributable to adverse events. Reviews and meta-analyses of data from RCTs of FDA-approved weight-loss agents in the treatment of obesity have noted that with the branded formulation of NB, the effect sizes were generally in the intermediate range, and that the rates of discontinuation due to adverse events were toward the upper range of among those from available medications.[34,35] In the present pilot RCT, 83.3% of patients who received NB completed the 12-week treatment, and the prevalences of reported adverse events did not differ from those in the placebo group. Importantly, in contrast to studies which tested the branded version of medication, NB was delivered without guidance regarding a reduced-calorie diet, increased physical activity, or a behavioral/lifestyle platform for long-term weight management.[22] Finally, in the present study, NB was composed of the generic products, which are available at a substantially lower cost than are the branded products, and which have the potential advantage of once-daily dosing by using the extended-release formulation of bupropion.

The use of NB in the treatment of BED is currently being evaluated in 2 larger-scale RCTs, one testing NB versus placebo (ClinicalTrials.gov identifier: NCT03539900) and the second testing NB and behavioral weight-loss therapy, alone and in combination (ClinicalTrials.gov identifier: NCT03045341). Both studies include follow-up designs that are important for determining the durability of the effects of NB as well as for identifying the periods of risk for relapse, including whether (or in whom) it is reasonable to discontinue medications. Presently, there exists only 1 medication that has been approved by the FDA for use in the treatment of BED (lisdexamfetamine dimesylate); this medication is contraindicated in persons with a history of substance misuse, and its tolerability and efficacy in obesity and weight loss have not been established. Thus, the identification of additional potential pharmacologic treatments for BED, particularly in patients with excess weight, represents an important research need.[36]

CONCLUSIONS

The findings from this pilot RCT suggest that NB was well tolerated in these patients with BED and comorbid obesity. NB and placebo did not statistically differ with regard to most outcomes. A larger, adequately powered RCT is needed for determining the efficacy of NB in the treatment of BED.

AUTHOR CONTRIBUTIONS

C.M. Grilo provided conceptualization, methodology; validation; investigation; writing, editing, and final review of the manuscript; and visualization. J.A. Lydecker provided methodology; project administration; validation; formal analysis; investigation; writing, review, editing, and final review of the manuscript; and visualization. P.T. Morgan provided methodology; investigation; and writing, review, editing, and final review of the manuscript. R. Gueorguieva provided formal analysis and writing, review, editing, and final review of the manuscript.

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DISCLOSURES

C.M. Grilo has received consultant's fees from Sunovion and Weight Watchers; honoraria for lectures, Continuing Medical Education activities, and presentations at scientific conferences; and royalties from Guilford Press and Taylor & Francis. R. Gueorguieva has received royalties from CRC Press, and consultant's fees from Cohen Veterans Bioscience. The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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APPENDIX A

Supplementary Table. Side effects over the course of treatment by medication condition.

	Month 1				Fisher's	Month 2				Fisher's	Month 3				Fisher's
	NB		Placebo			NB		Placebo			NB		Placebo		
	n	%	n	%		n	%	n	%		n	%	n	%	
Nausea	5	46%	2	25%	0.633	3	33%	0	0%	0.23	2	20%	1	14%	1.00
Constipation	2	18%	1	13%	1.00	2	22%	0	0%	0.49	1	11%	1	14%	1.00
Headache	3	27%	4	50%	0.38	3	33%	1	17%	0.60	2	22%	1	14%	1.00
Vomiting	3	27%	0	0%	0.23	2	22%	0	0%	0.49	1	10%	0	0%	1.00
Dizziness	5	46%	1	13%	0.18	3	33%	0	0%	0.23	1	10%	0	0%	1.00
Insomnia	5	46%	1	13%	0.18	1	11%	0	0%	1.00	0	0%	1	14%	0.47
Dry mouth	2	18%	2	25%	1.00	3	33%	1	17%	0.60	3	30%	2	29%	1.00
Diarrhea	2	18%	2	25%	1.00	1	11%	0	0%	1.00	2	20%	0	0%	0.49

Note. NB = naltrexone/bupropion combination, n = number. Fisher's exact test compared each side effect at each time point; none was significant. The 2-sided p-values for Fisher's exact test is presented in the table. Considered cumulatively, F tests revealed that NB and placebo conditions did not differ significantly in the number of reported adverse events during the first month ($M = 2.45$, $SD = 1.57$ versus $M = 1.63$, $SD = 2.13$; $F(1,17) = 0.96$, $p = 0.34$, $\eta_p^2 = 0.053$). During the second month, patients receiving NB reported a significantly higher frequency of events than those receiving placebo ($M = 2.00$, $SD = 1.73$ versus $M = 0.33$, $SD = 0.82$; $F(1,13) = 4.76$, $p = 0.048$, $\eta_p^2 = 0.268$). During the third month, NB and placebo conditions did not differ significantly in the number of reported adverse events ($M = 1.20$, $SD = 1.55$ versus $M = 0.86$, $SD = 1.21$; $F(1,15) = 0.24$, $p = 0.63$, $\eta_p^2 = 0.016$).