NCT03539900

Efficacy and Mechanisms of Naltrexone+Bupropion for Binge Eating Disorder

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HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2016-1)

Protocol Title: Efficacy and Mechanisms of Naltrexone+Bupropion for Obesity and Binge Eating

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(*If applicable*) **Clinicaltrials.gov Registration #:** NCT03539900

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   PRIMARY AIM 1. To conduct a double-blind, placebo-controlled parallel group study to evaluate the efficacy of naltrexone HCl and bupropion HCl (NB) versus placebo in patients with binge-eating disorder (BED), stratified by obesity status (n=50 per cell, n=200 total).

   Hypothesis 1.1. We hypothesize that NB will be superior to placebo for reducing binge eating among patients with BED.
   Hypothesis 1.2. We hypothesize that NB will be superior to placebo for reducing weight among BED patients with obesity.
   Hypothesis 1.3. We will examine whether BED patients with and without obesity derive differential benefit of NB versus placebo on reducing binge eating (i.e., does obesity moderate outcomes).

   PRIMARY AIM 2. To evaluate correlates and possible mechanisms underlying the effect of NB on binge eating among all participants (n=50 per cell, N=200 total). To evaluate the effect of NB on hypothalamic melanocortin and brain reward systems, eating behavior will be assessed with an established human laboratory paradigm designed to evaluate the ability to resist eating preferred high-caloric food and subsequent over-eating. We will evaluate potential mechanisms including eating peptides (leptin, ghrelin) involved in both homeostatic and hedonic aspects of eating, as well as food craving, mood, hunger, and control over eating.

   Hypothesis 2.1. We hypothesize that potential medication-related changes in eating behavior, eating peptides and craving assessed in the laboratory will mediate clinical outcomes during the 12-week treatment period (i.e., rates of binge eating).

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Hypothesis 2.2. We hypothesize that NB versus placebo will increase the ability to resist eating preferred high-calorie food, and will reduce overall calorie consumption in patients with BED.

Hypothesis 2.3. We will examine whether BED patients with and without obesity derive differential benefit of NB versus placebo with regards to their ability to resist eating or calories consumed (i.e., does obesity moderate outcomes).

EXPLORATORY AIM 3. To assess eating and drinking behavior, food craving, and mood 'in the field' in a subset of participants (n=60).

2. Probable Duration of Project: State the expected duration of the project, including all follow-up and data analysis activities.

   September 2017 – September 2024

3. Background: Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   Binge-eating disorder (BED) is a prevalent, refractory, and serious health problem, with national estimates identifying that 2.6% of adults meet criteria for BED [1]. With the recent inclusion of BED as a formal DSM-5 diagnosis [2], there has been increased attention on identifying effective pharmacotherapies for this disorder. This application focuses on evaluating the therapeutic potential of naltrexone combined with bupropion for BED.

   Recognized as a serious problem by Stunkard [3], only recently has BED become a research focus and established as a formal diagnosis in the DSM-5 [2]. BED is defined by recurrent episodes of binge eating without compensatory weight control methods that characterize bulimia nervosa. Binge eating is defined as eating an unusually large amount of food given the context coupled with a subjective sense of loss of control and diagnosis requires binge eating to be associated with marked distress [4]. Epidemiologic studies have found that BED is more prevalent than the other two formal eating disorders [5]. Estimates of BED are higher in adults with obesity (8%) and are much higher in most clinical settings [6, 7]. Of adults with current BED diagnosis, 42% meet criteria for obesity (BMI > 30) whereas 58% do not meet criteria for obesity (BMI < 30) [8]. BED is strongly associated with obesity, with rates of BED disproportionately increasing with increasing BMI. Adults with BED are 4 to 10 times more likely to present with BMI's of 30 or 40 or more, respectively [8]. BED may be a contributor to the development of obesity [9] and associated metabolic problems [10] in vulnerable individuals.

   Compared to other eating disorders, BED is prevalent across gender and ethnic/racial groups [11]. The prevalence of BED in the National Co-morbidity Survey Replication [1] was 3.5% among women and 2.0% among men. BED has diagnostic validity [12], is a stable construct [13], differs from other eating disorders and obesity [14-16], is strongly associated with elevated risk for psychiatric, and psychosocial problems [5, 15, 17, 18]. BED is associated with substantially increased risk of several chronic health conditions including cardio-metabolic disorders, musculoskeletal disorders, pain, and ulcers [8, 19], even when adjusting for BMI [10].

   Overall, several medications have short-term efficacy relative to placebo [20] and certain psychological treatments have efficacy [21] with important advantages over medication (alone or in combination) [20].

   Pharmacotherapy for BED has received research attention, albeit nearly all RCTs have been of short duration and without follow-up period to establish durability [20, 22, 23]. Critical review and meta-analysis show that

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several drugs – working through varied mechanisms – have short-term efficacy relative to placebo for reducing binge eating and produce weight loss ranging from modest to none [20]. Placebo-controlled trials of anticonvulsants topiramate and zonisamide [24-26] have reported effects for reducing both binge-eating and weight (average weight loss of roughly 3-4 kg compared to placebo), but have also shown high dropout and frequent adverse events that become near-universal and troubling with longer use [27]. SSRI antidepressants, initially regarded as a potential treatment strategy [e.g., 28] are characterized by small effect sizes relative to placebo [20], produce no weight loss at all [29] and are inferior to CBT [29, 30].

Lisdexamfetamine dimesylate (LDX) for BED. An important development was the FDA approval in January 2015 of a CNS stimulant, LDX, for the treatment of moderate-to-severe BED. Approval was based on findings from an integrated series of studies funded by the manufacturer. The phase II RCT demonstrated that 50mg and 70mg were superior to placebo [31, 32] for reducing binge-eating days and reported binge-eating abstinence rates of LDX versus placebo (Study 1: 40% versus 14%; Study 2: 36% versus 13%) at the end of the 11-week treatments. Importantly, no longer-term follow-up are presently available.

We are not using LDX for several reasons. The binge remission outcomes for LDX at 11-weeks [31] are less robust than those reliably produced by BWL for BED, and BWL outcomes are durable through 12-months post-treatment [33]. Most importantly, although LDX was associated with weight loss (mean 4.9 kg) [32], weight loss was examined as a safety measure, not a clinical outcome. The FDA approval and manufacturer product labeling included a Limitation of Use highlighting that LDX is not indicated or recommended for weight loss. This is because other CNS-stimulant sympathomimetic medications for weight loss have been associated with severe cardiovascular problems and the safety and efficacy of LDX for obesity have not been demonstrated.

Pharmacotherapy for Obesity. Sibutramine, which was effective for reducing both binge eating and weight in BED [34, 35], was withdrawn from the market in 2010 due to cardiovascular concerns. This left orlistat as the sole FDA-approved anti-obesity medication for longer-term use [36], until 2012. Placebo-controlled trials of orlistat for BED [37, 38] reported significant yet very modest effects for weight loss, but not for reducing binge eating when added to BWL or CBT. A recent RCT testing orlistat combined with BWL reported a moderator effect of significantly greater weight loss for orlistat than placebo for obesity without BED, but not for obesity with BED [39].

The 2012 FDA approval of two new anti-obesity medications (phentermine/ topiramate and lorcaserin) [40, 41] came after heated debate given significant concerns about limited efficacy and safety profiles, and questions about serious medical complications with longer use [40, 41]. The low rates of achieving 5% weight loss (less than 30% in all three of the phase III RCTs) was inflated due to the use of completer analyses despite the observed high drop-out rates (e.g., 45% in the BLOOM Trial) [42]. The combination phentermine/ topiramate had the highest effect sizes for weight loss, but this needs to be considered against the unfavorable adverse event and tolerability profile.

Behavioral Treatment for Obesity. Behavioral Weight Loss (BWL) counseling has been evaluated among patients with comorbid BED and obesity. BWL, a widely available "generalist" intervention, achieves good binge-eating outcomes plus produces modest weight loss over the short-term in persons with BED who also have comorbid obesity [43, 44]. BWL for BED in persons with co-morbid obesity outcomes, however, are less durable over time [44] and the observed weight losses achieved with BWL for BED appear to be dampened relative to those generally reported for BWL for obesity without BED [45, 46]. These results highlight that behavioral treatments for patients with BED and comorbid obesity do not produce consistent effects on both binge eating and weight loss, identifying a need for further treatment development. Additionally, many

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people with BED do not have excess weight or obesity and BWL for "normal weight" persons with BED has not been tested.

A test of NB for patients with BED without obesity is needed and the mechanistic background for NB medication supports the rationale for use in BED. The current RCT will test pharmacological treatment (without any behavioral intervention) so that findings are more scalable and broadly translatable to generalist settings. The published RCT pharmacotherapy literature for BED consists mainly of med-only vs placebo-only trials ranging from 6 to 24 weeks (many are 12 weeks) [23].

We performed a pilot RCT (HIC# 1409014705) with N=22 patients with BED and obesity and delivered the NB pharmacotherapy without concurrent behavioral weight loss. We observed no problems in the conduct of the pilot RCT. The pilot RCT found that NB was well-tolerated, reduced the frequency of binge eating, and promoted weight loss in the obese patients with BED with moderate effect sizes. Finally, we have an on-going recently-funded RCT (HIC# 1506016065) that is examining intensive BWL and NB, alone and combined (i.e., balanced 2 x 2 factorial design; thus, some patients also receive NB without BWL) in patients specifically with BED with obesity.

NB Pharmacotherapy

In September 2014, the FDA approved the combination of naltrexone and bupropion to treat obesity consisting of the following empirical support from several RCTs performed with obesity (but not BED). The putative mechanisms of action are described in Section VI.

Obesity Outcomes. Several large RCTs have reported that NB was effective in promoting significant, clinically-meaningful weight loss in patients with obesity [47-49]. NB showed greater weight loss than placebo, -6.5 vs -1.2% [49]; -8.2% vs -2.1% [48], and the following percentages achieving 5% weight loss: 56% vs. 18% [48], 52% vs. 15% [49]. Apovian, Aronne [50], in a study of 1496 patients with obesity, reported greater weight losses relative to placebo (-6.5% vs -1.9% at week 28 and -6.4% vs -1.2% at week 56) and greater likelihood of achieving 5% weight loss (56% vs 18% at 28 weeks).

The putative mechanisms of action for the two medications are relevant for binge eating in addition to weight loss. Naltrexone, an opioid receptor antagonist, is approved for treatment of alcohol and opioid dependence (O'Malley, Sinha, Grilo, et al., 2007). Naltrexone produces weight loss in lab animals but only minimal weight losses in most human studies (Malcolm et al. 1985; Billes & Greenway, 2013). Bupropion is thought to operate through dopaminergic, noradrenergic, and nicotinic acetyl-cholinergic mechanisms [51-53], may target reward processes that drive eating behaviors, consistent with its FDA indication for treating nicotine dependence and reduced weight gain during smoking cessation [54, 55]. Bupropion has been found to promote weight loss in several obesity RCTs. Li and colleagues [56], in a meta-analysis of five trials of bupropion, reported a mean difference in weight loss of 2.77 kg (CI, 1.1 to 4.5) between bupropion and placebo groups at 6 months. White & Grilo (2013) first reported preliminary support for a possible (albeit modest) weight loss benefit specifically in obese BED patients (see C.1).

NB was developed to target alterations in the hypothalamic melancortin system and the brain reward system (Billes et al., 2014), although the neurobiological mechanisms underlying its efficacy for weight loss are not fully understood. Within the hypothalamus, bupropion stimulates hypothalamic pro-opiomelancortin (POMC) neurons whereas naltrexone blocks opioid receptor-mediated POMC autoinhibition, resulting in weight loss and reductions in energy expenditure as hypothesized downstream effects (Wang et al., 2014). Within the reward system, dopamine drives the 'wanting' for highly palatable food, whereas the opiate system

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modulates the 'liking' (Billes et al., 2014). Preclinical studies identify that bupropion and naltrexone work synergistically on the reward system to reduce food intake (Sinnayah et al., 2007).

Although NB targets systems highly relevant for those with BED (Simon et al., 2016) and obesity (Jastreboff et al., 2013), very little work has examined potential mechanisms of NB in humans. Wang et al., (2014) examined responses to food cues in obese women and documented blunted activation in hypothalamic reactivity and increased activation in the anterior cingulate, suggesting greater self-control. Within clinical trial investigations, NB was associated with self-reported ability to control food intake as this was associated with weight loss (Fujioka et al., 2013). There was also mixed evidence that NB reduced food craving, which was assessed monthly. The effect of NB on food craving has yet to be assessed in response to actual food cues.

Leptin and ghrelin are involved in both homeostatic and hedonic aspects of eating (Farooqi et al., 2007; Malik et al., 2008), and may serve as important biomarkers of NB's effects on these systems. Leptin mediates regulation of energy balance and suppresses food intake, whereas ghrelin is a faster-acting hormone involved in the initiation of eating. Generally, obesity is associated with increased and decreased levels of leptin and ghrelin, respectively (Klok et al., 2007). However, alterations that occur in the homeostatic and reward systems as a result of obesity, and potentially BED, may make these systems less sensitive to appetite regulating substances such as leptin and ghrelin. Both leptin and ghrelin have been associated with increased neural activation to high-calorie food, food craving, and food intake (Jastreboff et al., 2014; Kroemer et al., 2012; Skibicka et al., 2012).

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

   Overview of Study Design

   This single-site, proof-of-concept, clinical trial is a double-blind, placebo-controlled, parallel group study to test the effectiveness of naltrexone + bupropion (NB) pharmacotherapy in BED patients with and without obesity. BED patients with (BMI > 30 and <50) and without obesity (BMI >21.5 and <29.9), will be randomized to NB (32 mg/day naltrexone combined with 360 mg/day bupropion) or placebo (n=50 per cell, n=200 total).

   Following eligibility screening and randomization, participants will start a 12-week medication treatment period, a treatment period consistent with other BED medication trials (McElroy et al., 2016). Participants will have four weeks of up-titration: one tablet daily (Naltrexone 8mg/ Bupropion 90mg; 1 week), then two tablets daily (Naltrexone 16mg/ Bupropion 180mg; 1 week), then three tablets daily (Naltrexone 24mg/ Bupropion 270mg; 1 week), to reach the full dose of four tablets daily (Naltrexone 32mg/ Bupropion 360mg). The dosage will continue for the remainder of the 3 months. Medication will be discontinued at the end of 3 months, and patients will then be followed 12-months post-treatment to assess the durability of medication effects. The primary outcome measure is reduction in binge-eating frequency.

   To evaluate correlates and mechanisms of NB on eating behavior, assessments will occur in the laboratory and in the field to optimize internal and external validity. Participants will complete human laboratory sessions ("lab sessions") before the start of medication and then during the final week of the 12-week medication period to evaluate the ability to resist eating preferred high-caloric food and subsequent over-eating. During the laboratory sessions, we will evaluate potential mechanisms including eating peptides

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(leptin, ghrelin) involved in both homeostatic and hedonic aspects of eating, as well as food craving, mood, hunger, and control over eating. Participants who are unable to complete a baseline lab session prior to the start of treatment may complete the lab session 4-6 weeks after beginning treatment. We believe that this period of time is sufficient to capture medication effects on eating behavior.

Finally, we plan to monitor ambulatory dynamic changes in stress with a wearable biosensor and collect daily information regarding eating behavior with self-initiated, scheduled, and random prompts to a smartphone 'in the field' during the first 6 weeks of the 12-week treatment period in a subset of participants (n=15 per cell, n=60 total; "Biosensor"). Eating and drinking behaviors will be tracked using an Android smartphone that is synced with a smartwatch (Garmin Vivosmart 4) to passively track stress states. During real-time episodes of calorie consumption, participants will be prompted to answer questions delivered to their smartphone related to food craving, mood, and stress.

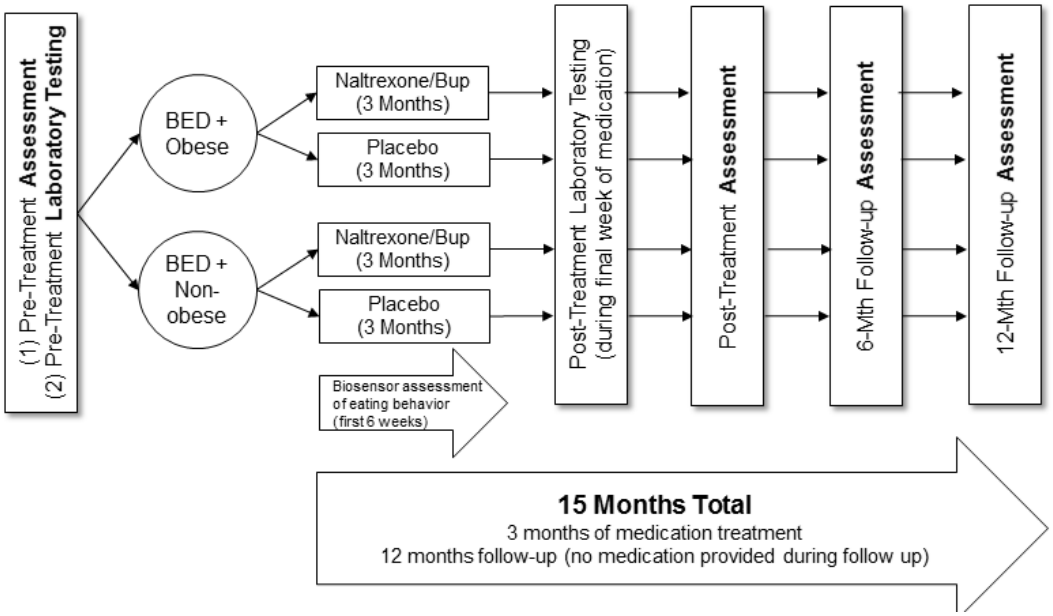

Figure 1. Overview of Study Design

Pre-Screening: Participants responding to recruitment efforts will be screened by telephone. If participants prefer to answer some of the pre-screening questions through the Yale Qualtrics system, participants will indicate their consent to the recruitment/pre-screening process in the online system. After the initial telephone screening, potentially eligible participants will be scheduled for an in-person assessment; participants will complete survey measures of eating behaviors and psychopathology and psychosocial functioning around the time of the in-person appointment. Potential participants will meet with a research assistant who will obtain informed consent and will screen the participant for inclusion and exclusion criteria. Participants who provide informed consent and are determined to be eligible will then participate in the study as depicted and described in the following paragraphs. See also Figure 1.

Baseline Assessment: Participants will complete a physical exam, vitals, and routine laboratory blood work (including lipid profile, Hb1Ac, and liver function tests) at which time the study physician will review the subject's medical status and medical eligibility criteria. Patients will also have a urine screen for opiates. As part of the determination of eligibility, participants will complete two interviews, the MINI International Neuropsychiatric Interview-Version 7.0 (MINI) and Eating Disorder Examination (EDE) to generate psychiatric

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diagnoses and detailed current eating disorder features and diagnoses. Other measures, for safety and establishment of baseline values, will also be obtained: BMI, vitals, eating behaviors, mood, and quality of life.

For a full description of instruments, see "Measures," which includes a grid depicting when each measure is administered. The baseline assessment will occur over 1-2 in-person meetings and is estimated to take a total of 2-3 hours in-person.

Randomization. Eligible participants who agree to participate and provide written informed consent will be randomized in equal proportions to one of the two treatments (using blocked randomization with random block sizes of 4 and 8 to obviate any secular trends). Gender will be balanced across cells (60% female). We will monitor randomization procedure and determine whether any systematic differences in demography (age, ethnicity/race) or clinical characteristics (psychiatric co-morbidity) become evident. We will consider adjustment to randomization if indicated (Kraemer & Fendt, 1990; Kraemer & Pruyn, 1990). The Biostatistician, Brian Pittman, will be responsible for developing the randomization schedule in conjunction with the Investigational Drug Pharmacy (IDS), at Yale-New Haven Hospital. The IDS will randomize participants to medication groups. Research study staff (clinicians *and* outcomes assessors) and participants will all remain blind to the medication condition.

Treatment Protocol for Naltrexone/Bupropion (NB) Pharmacotherapy. Medication will be prescribed at recommended doses per FDA-approval for obesity. NB medication will comprise naltrexone sustained-release (SR, 32 mg/day) combined with bupropion SR (360 mg/day) taken daily (8 mg naltrexone/90 mg bupropion in each tablet/capsule, two of which will be taken twice daily; both conditions will have the same frequency). Following regimens in previous RCTs, a dosing escalation approach will be used, beginning with a quarter of the full dose and increasing it weekly until the full dosing is achieved at week 4 (Greenway et al., 2010; Wadden et al., 2011). This dosing will continue for the remainder of the trial unless the patient develops intolerable side effects. If such occur, the physician may reduce the dosing to achieve tolerability. If the patient cannot tolerate the medication, has adverse effects, or is non-compliant with medication for > 7 consecutive days, s/he will be discontinued from the medication arm. For all participants taking medication for greater than 4 weeks, a 7-day taper will be provided. Physician/medication-management visits will be brief (10 minutes) and will focus on compliance with dosing and evaluating side effects. These visits will occur twice during first month and monthly thereafter unless clinical concerns require additional contacts. At the one-month treatment visit and at the end of treatment, patients will have their blood drawn to measure hepatic function for safety. Blood draws will occur either at Quest Diagnostics, at the Hospital Research Unit, or at the Church Street Research Unit. After the 12-month follow-up, patients will be informed (by research pharmacist) whether they were on NB or placebo. Medication double-blind will be maintained for the investigators and assessors until all participants have completed final 12-month follow-up assessments.

Monitoring and enhancing medication compliance. In addition to physician visits, several procedures will be used to monitor and enhance medication compliance including drug packaging, reminder calls, pill counts, and plasma trough medication levels. As we have done in prior studies, medication compliance will be assessed with pill counts. Medication will be dispensed in pill bottles; adverse events will be assessed at each appointment. Medication compliance will also be monitored through evaluation of a plasma level of naltrexone, 6-beta-naltrexol, and bupropion at weeks 4 and 12. Importantly, we plan to explore the relationship between compliance and study outcomes.

Withdrawal from Treatment and Other Treatments. Withdrawal/attrition from treatments will be examined. Use of other treatments during study will be assessed and considered in analyses. Patients will be asked about all forms of treatments during major assessments. We have considered criteria for removal of patients

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from the study, including worsening depression, suicidal ideation or binge eating, or failure to comply with medication. Previous experience suggests that worsening clinical status is rare; in such cases, Dr. Grilo and study physician would determine whether to remove the person from the study and provide referrals.

Procedures for Modeling Cue-Induced Eating Behavior.

Each participant will complete two laboratory sessions, the first scheduled prior to starting medication, and the second at the end of medication treatment (week 11-14). This pre-post evaluation by medication group will provide a powerful test of medication effects. Alternatively, if the pre-treatment laboratory session cannot be schedule prior to the beginning of treatment, participants may complete the session around one month of treatment (week 4-6). If we are unable to reschedule at the HRU/CSRU, the lab session will take place at 2 Church Street South in dedicated lab rooms in Dr. McKee's research space. Our previous eating study (HIC# 0909005678, McKee) took place in this setting and was very successful. There will be no blood collected throughout the lab session if it occurs at 2 Church St South, but baseline samples will be obtained on the 4th Floor YCCI unit. All other lab procedures will remain the same. Participants will not be excluded from the treatment study if they are not willing to do the lab sessions, or if they are not able to be scheduled for the lab sessions. Research procedures related to the treatment study (e.g., blood draws for liver function, lipids, and metabolic function) will still be drawn if lab sessions are not completed.

Laboratory sessions will be completed at the Hospital Research Unit (HRU) of the Yale Center for Clinical Investigation (YCCI) located at Yale-New Haven Hospital or the Church Street Research Unit (CSRU) at 2 Church Street South. Participants will be instructed not to eat past 10:00pm the night before the laboratory session. They will arrive at the HRU/CSRU at 7:30am. At the start of the lab session, participants will have an IV cannula inserted and complete the baseline assessments listed in Table 1. Participants will then receive breakfast to standardize time since last food consumption. Breakfast will be a breakfast bar that is approximately 150 calories provided by the Research Team. Participants will then be food deprived for the next 3 hours. Based on our prior work, this length of food deprivation is sufficient to increase food craving. After 3 hours of food deprivation, participants are presented with preferred high-caloric snacks. Participants will be asked to take their study medication prior to the second lab session. Scheduling is limited to HRU/CSRU and participant availability.

During a prior appointment, participants are presented with an extensive list of high-caloric salty (potato chips, peanuts) and sweet snack foods (cookies, chocolate), and are asked to select their top three salty and sweet options for a total of six options. During the lab session, participants will be presented with a standardized amount of each of their six preferred high-caloric foods. The snacks will be portioned to 750 calories of each (approximately 4-5 servings of each item). The weight of the food will be assessed at the start and end of each session, and calories consumed will be calculated from baseline evaluations of calories per gram. Each participant will receive the same presentation and amount of food across the two sessions.

Following the presentation of food, participants are then told that they can start eating at any time they wish over the next 3 hours. We model the ability to resist eating over a 3-hour period, to provide sufficient time to capture the effect of the high-caloric snack food triggering eating. Participants are informed that for each minute that they can resist eating, they will receive monetary compensation. The amount of money earned over the 3 hours starts at $0.35 per minute, and reduces by a penny every 5 minutes. By 180 minutes, the compensation has reduced to $0 per minute. Participants are provided this information in table format during the laboratory session. If a participant resists eating for the entire 3 hours, they will earn a total of $31.50. Participants will be videotaped and wear a smartwatch (wearable Biosensor) synced to a research

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smartphone during the eating session. The data will be coded and provide information about how fast participants eat and the order in which foods are selected.

When participants can no longer resist and decide to start eating, latency to eat will be recorded in seconds. Participants may eat as much as they wish until the end of the 3-hour ad-lib period. Measures of leptin, ghrelin, food craving, hunger, mood, and vitals will be assessed throughout the laboratory procedure (see Table 1). At the end of the period, participants will remain in the laboratory for an additional 1.5 hours to add a response cost if they chose not to consume any food during this period. In other words, they are not immediately able to leave the session to go eat.

Table 1: Procedures and assessments for laboratory sessions (also see Table 2).

PERIOD	TIMING	PROCEDURES
Baseline	7:30am	Urine pregnancy screen, breath alcohol level, CO level, height, weight, vitals, mood, food craving, hunger. IV inserted: Estradiol/progesterone (females only), liver function, lipids, glucose, insulin, and HbA1c, and overnight fasting levels of leptin, ghrelin. Lab 2 Only: Med level, liver function, Lipids, glucose, insulin, and HbA1c levels.
	8:00am	Standardized breakfast (no access to food until 11:00am = 3hours of food deprivation)
Deprivation	9:00am	Mood, food craving, hunger, vitals
	10:00am	Mood, food craving, hunger, vitals
Food Presentation	10:30am	Baseline 1: leptin, ghrelin
	10:45am	Baseline 2: leptin, ghrelin
	11:00am	Participant presented preferred high-caloric foods. Participant may initiate ad-lib eating session or earn money based on de-escalating schedule of reinforcement over next 180 minutes
	11:05am	Leptin, ghrelin, mood, food craving, hunger, vitals
	11:15am	Leptin, ghrelin, mood, food craving, hunger, vitals
Ad-lib Period	11:30am 12:00pm 12:30pm 1:00pm 1:30pm 2:00pm	Leptin, ghrelin, mood, food craving, hunger, vitals will be repeated every 30 minutes during the ad-lib period **from 11:05am to 2:00pm, whenever the participant decides to 'give in' and start eating, we will collect leptin, ghrelin, mood, food craving, hunger, vitals to capture the decision point to eat (before eating starts)
Wait Period & Discharge	2:45pm	Mood, food craving, hunger, vitals
	3:20pm	Mood, food craving, hunger, vitals
	3:30pm	Discharge

Procedures for Evaluating Naturalistic Eating Behavior and Stress with Wearable Biosensors.

Garmin Activity Tracker (Biosensor): We are collaborating with Dr. Deepak Ganesan (UMass) to evaluate ambulatory stress and eating behavior during the first 6-weeks of the treatment phase. We are currently using the same system to monitor stress and alcohol consumption (HIC#2000023970; PI, McKee) and it has been adapted to monitor stress and eating behavior. During the first 6-weeks of the treatment phase, we will assess ambulatory dynamic changes in stress with a wearable biosensor and collect daily information

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regarding eating behavior with self-initiated, scheduled, and random prompts to a smartphone. We will provide participants with the wearable biosensor (Garmin Vivosmart 4) and an Android cell phone to use that has the app installed where they will respond to daily prompts. If the equipment is not available when a participant is to start the treatment phase, they will not complete the Biosensor component.

Monitoring Stress Levels. To monitor ambulatory stress levels, we will use Garmin bands. These bands provide a 'stress score' (range 1-100) with a 3-minute granularity. The algorithm is proprietary, but Garmin acknowledges that one of the primary factors in the algorithm is heart rate variability (HRV). HRV is the beat-to-beat variation in heart rate, which has been shown to be associated with emotion regulation and likely contribute to binge eating[101]. We have shown that stress and substance use produce dynamic changes in HRV[102-104], and that HRV may be used as a stress indicator. With values provided every 3 minutes, we can model how dynamic changes in HRV are predictive of binge eating. We also plan to evaluate how location (e.g., GPS) affects stress levels and subsequent eating behavior. The Garmin band also provides daily metrics on steps, distance, heart rate, sleep duration, and sleep level classification. Access to this data is through a Garmin service to academic researchers https://developer.garmin.com/health-api/overview/. Data obtained from bands will be continuously transmitted to the mHealth Core Facility at UMass.

Monitoring Eating Behavior. During the 6-week monitoring period, we will monitor eating behavior in three ways through an app on the Android smartphone. 1) Participants will complete daily diaries every evening at 10PM or when participant initiates "End of Day" which assess eating throughout the day. Participants will answer questions about their daily eating pattern and stress. 2) Up to four times per day during waking hours, subjects will receive random prompts to assess whether they are currently eating or binge eating, as well as their stress. With these prompts, we will also be assessing GPS location, to determine medication response on these items when subjects are in various 'food-dense' environments (e.g., home, restaurant, neighborhood density of fast-food restaurants) 3) When subjects start to binge eat, they can initiate smartphone assessments assessing eating and stress. Additionally, they will complete an end-of-binge report that also assesses eating and stress.

The cell phone provided to participants will have the app already loaded and ready for use. The data that is input will be de-identified because it will be set up with a subject ID. This subject ID will be used to capture the data. UMass will not receive a "key" to identify the participants. This application does not qualify under the FDA definition as a medical device, and more specifically Software as a medical device ('FDA Software as a Medical Device (SAMD): Clinical Evaluation, Guidance for Industry and Food and Drug Administration Staff, issued on December 8, 2017'). Data collected from the app and the Garmin device will allow use to understand how stress affects your eating, and how the medication might affect this.

Data Management & Statistical Analysis: The mHealth Core Facility at the University of Massachusetts will assist with the collection of electronic data, transmitting and storage of the data, and providing collected and processed data to Yale. This data collection system (which integrates the Garmin Band data collection and the smartphone data collection) is being developed for the Yale-SCORE (HIC#2000023970; PI, McKee) and modified for this project. Statistical support for this project will be provided by biostatistician, Mr. Pittman.

The system involves a smartwatch that participants will wear on their non-dominant hand. The system is linked to a smartphone. Participants will be provided with a phone to use for the study duration. Participants will wear the system for the first six weeks of the 12-week medication period (3 weeks medication titration + 3 weeks at full dosing). We believe that this period of time is sufficient to capture medication effects on eating behavior. These "real-time" consumption behavior data, along with associated proximal data regarding behavior, mood, and stress variables – will be analyzed within subjects over time (to understand dynamic

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time-varying factors) and between subjects and these data will be linked to the available treatment outcome data including follow-ups.

Biosensor Arm:

We will have a separate Biosensor Arm to allow for a wider range of naturalistic eating behavior data collection. Participants in the "Biosensor Arm" will wear the Garmin band and interact with the app for a 6-week period. This 6-week monitoring period can occur at any time (see Biosensor Arm inclusion/exclusion). This will provide different insight into stress and eating behaviors and allow data to be collected on a wider range of participants. Participants will be provided with the Garmin band (Vivosmart 4), an Android phone with the app pre-loaded, and will follow the same procedures as described above (see Procedures for Evaluating Naturalistic Eating Behavior and Stress with Wearable Biosensors). The data management and statistical analysis will remain through the mHealth Core Facility at the University of Massachusetts as described above. The risks, data security & collection, and device information remain the same as the existing Biosensor piece.

The Biosensor Arm is identical to the Biosensor Portion of the main study. It is the same app. Participants do not have to be enrolled in the Main Study in order to participate in the Biosensor Arm.

Participants that did not complete the Biosensor as part of the main study while on medication, can now participate in the Biosensor Arm if interested. They will sign the Biosensor Consent Form in order to participate. Procedures will not be duplicated by any participant. The assessment table (Figure 2) lists the assessments completed in the Biosensor.

Assessments:

Participants will complete baseline assessments prior to starting the 6-week monitoring period. These assessments will help to identify possible eating disorder psychopathology and provide baseline information for stress and eating behaviors (i.e., EDE-Q/PSS). Participants will then complete the assessments at the end of the 6-week monitoring period.

Specific inclusion/exclusion criteria for the biosensor arm are listed in the inclusion/exclusion section of the protocol.

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Assessments.

Figure 2. Grid depicting when each assessment is obtained

			Pre		During Treatment					Follow-up		
Measure	Instrument and References	Type	Baseline	Lab #1	Week 2	Month 1	Month 2	Month 3	Lab #2	6 Month	12 Month	Biosensor
Screening Measures												
Axis I Disorders	MINI Psychiatric Interview	Interview	*									
Binge-Eating Disorder	EDE Interview	Interview	*					*		*	*	
BMI	Weight, height	RA Eval	*	*	*	*	*	*	*	*	*	
Metabolic Measures	Lipids, HbA1c	Blood		*					*	*	*	
	TSH (as needed)		*									
Safety Measures	Urine screen for pregnancy	Urine	*									
	Urine drug test for opiates		*									
Menstrual Cycle Data	Menstrual cycle calendar, hormone use, reproductive and gynecological status	Interview	*		*	*	*	*		*	*	
Medical History	Clinical data, incl. start of new treatments	Interview	*					*			*	
Eating Behavior & Food Craving												
Eating Disorders	EDE-Q	Self-Report	*		*	*	*	*		*	*	*
	ELOCS		*					*			*	
Eating Behavior	TFEQ	Self-Report	*			*	*	*		*	*	
	YFAS		*					*			*	
Food Craving	Brief Questionnaire of Food Craving	Self-Report		*					*			
	FCI-II		*			*	*	*		*	*	
Drive for Palatable Food	PFS	Self-Report	*			*	*	*		*	*	
	Control of Eating Questionnaire			*					*			
Hunger	Hunger Ratings	Self-Report		*					*			
	Health and Behaviors											
Depression	Beck Depression Inventory-II	Self-Report	*		*	*	*	*		*	*	
Affect	Circumplex Scale	Self-Report		*					*			
	Perceived Stress Scale	Self-Report										*
Quality of Life	SF-12	Self-Report	*					*			*	
Alcohol Use	Audit-2	Self-Report	*					*			*	
Physical Activity	Godin Leisure Time Exercise Questionnaire	Self-Report	*					*			*	
Sleep	Pittsburgh Sleep Quality Index	Self-Report	*					*			*	
Safety & Compliance												
Adverse Events	SAFTEE	Interview			*	*	*	*				
	Columbia Suicide Severity Rating Scale				*	*	*	*				
	Liver Function	Blood		*		*			*			

Medication Compliance	Pill Counts Naltrexone and Bupropion levels	RA Count Plasma				* *		* *				
Vitals	Blood pressure and heart rate		*	*	*	*	*	*	*	*	*	*	
Placebo Rating	Placebo rating by clinician and participant	Self-Report				*		*					
Assays													
	Leptin, ghrelin, estrogen, progesterone	Blood		*					*				

Measures:

Screening Measures

- MINI International Neuropsychiatric Interview-Version 7.0 (**MINI**) [57] is a brief structured interview for Axis I psychiatric disorders. Validation and reliability studies have supported the MINI, including good convergence with SCID [57]. The MINI requires much less time than the SCID and reduces participant burden while providing adequate psychiatric data to characterize patients and determine exclusion criteria.
- Eating Disorder Examination Interview–16th Edition (**EDE**) [58] is an investigator-based interview assesses the features of eating disorders and generates eating disorder diagnoses. The EDE will be our primary method for assessing binge eating and eating disorder psychopathology. The EDE focuses on the previous 28 days, except for diagnostic items, which are rated for additional duration stipulations to address *DSM-5* criteria for BED. The EDE assesses the frequency of different forms of overeating, including objective binge-eating episodes (OBE; i.e., unusually large amounts of food with loss of control). The EDE also comprises four scales (dietary restraint, eating concerns, weight concern, and shape concern) and a global severity score. The EDE has good psychometric properties [59], is the major outcome measure for BED RCTs [44, 60], and has good test-retest reliability.
- Body Mass Index (**BMI**) will be calculated using measured Height (measured once at baseline) and Weight (obtained regularly at assessment meetings).
- Lipid profiles (**Lipids**): total cholesterol, HDL-, LDL-cholesterol, triglycerides will be obtained fasting per established protocols (Anderson et al., 1995).
- Glycemic Control: HbA1c, Glucose and Mean Plasma Glucose, routine measures of average glucose control for a previous (3-month) period.
- Hepatic function panel (**Liver Function**) will be assessed for safety at the first monthly treatment visit and at the end of treatment.
- Thyroid-stimulating hormone (**TSH**) will be assessed if patients report any history of thyroid disease or are taking thyroid medications.
- Urine drug testing for opiates will be completed for all participants.
- Urine pregnancy testing will be assessed for female patients of child-bearing potential.
- Menstrual Cycle Data: Menstrual cycle calendar (updated regularly), hormone use, reproductive and gynecological status
- We will also gather sociodemographic information and clinical data on the patient's medical history and comorbidities prior to the study, which we will update as indicated. If patients begin other treatments, this will allow us to account for this in analyses.

Eating Behavior & Food Craving

- Eating Disorder Examination-Questionnaire Version (**EDE-Q**). The self-report EDE-Q [61] generates the same overeating data and scale scores as the EDE interview. EDE-Q has good test-retest reliability with BED patients [59, 62, 63]. The EDE-Q converges well with the EDE as a measure of "change" [64].
- Eating Loss of Control Scale (**ELOCS**) [65] assesses the complexity of loss of control eating over the past four weeks. The ELOCS has demonstrated good convergent validity and is considered a valid self-report questionnaire that may provide important clinical information regarding experiences of LOC in people with BED and obesity.
- Three Factor Eating Questionnaire (**TFEQ**) [66] measures eating behaviors with 3 factors: cognitive restraint, disinhibition, and hunger. TFEQ has empirical support [67], and shows differential response across treatments consistent with putative mechanisms [68, 69].

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- Yale Food Addiction Scale (YFAS) [70] is a measure of addictive eating behaviors with high fat/sugar foods. Items correspond to the substance dependence diagnostic criteria. The YFAS has demonstrated adequate internal reliability, convergent validity, and incremental validity in predicting binge eating.
- Brief Questionnaire of Food Craving is a measure food craving we developed based on a 10-item Tiffany Questionnaire of Smoking Urges [71] by replacing the word "a cigarette" with "food," and the word "smoke" with "eat."
- Food Craving Inventory (FCI-II) [72] assesses general and specific food cravings and comprises four subscales for different food groups. The FCI has been validated and psychometrically supported in studies with obesity and with obesity/BED groups [72, 73].
- Power of Food Scale (PFS) [74] assesses the psychological impact of and the drive to consume palatable foods in an obesogenic environment. The PFS measures appetite for–rather than the consumption of–palatable foods. The PFS has been validated in large normative (Lowe et al., 2009) and obese samples including weight-loss treatment-seeking obese patients [75]. The PFS comprises 3 scales reflecting food proximity (food available, food present, and food tasted) supported by factor analysis and good test-retest reliability and internal consistency (range 0.81-0.91) [75]. The PFS is a good measure of the hedonic impact of food environment cues; fMRI studies have reported associations with state cravings for desired foods and shifts in brain networks [76].
- Control of Eating Questionnaire is a single item measure to assess perceived control over eating.
- Hunger Ratings is a single item measure 0 to 100 measuring hunger.
-

Health and Behaviors

- Beck Depression Inventory (BDI-II). The BDI [77] is a widely used measure of the symptoms of depression. A voluminous literature has documented good internal consistency (studies range .73 to .95), short-term test-retest reliability, and convergent validity [78].
- Circumplex Scale (Circumplex) [79] was modified to a 10-item scale to assess affective state. Participants are asked to provide ratings on how they feel right now for each affect item on a scale ranging from 0 (Not at all) to 100 (Very) on a visual analog scale, and items are classified into positive and negative affective dimensions.
- Medical Outcomes Study Short-Form Health Survey (SF-12) [80] is widely-used measure of health related quality of life. This measure has well-established reliability and validity [81, 82] for physical health and mental health domains.
- Godin Leisure Time Exercise Questionnaire (Godin) [83] assesses frequency of mild, moderate, and vigorous physical activity. The Godin has good test-retest reliability [83] and has good support from validation studies using various activity measurements such as activity monitors and maximum oxygen consumption [84].
- Pittsburg Sleep Quality Index (PSQI) [85] is a widely used measure of quality and patterns of sleep, assessing namely subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The PSQI has demonstrated good internal consistency and reliability (Cronbach's alpha = .83).
- Alcohol Use Disorders Identification Test (AUDIT-2) [86] is a measure that assesses alcohol use. The AUDIT has been used extensively and demonstrates high internal consistency and good test-retest reliability [87].
- Perceived Stress Scale (PSS) [88] is a measure that assesses how much stress an individual is experiencing. The PSS has a reliable total score (α=.83), 6-week temporal stability (r=.81) and validity associated with health behaviors including eating [89].

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Safety and Compliance

- Blood Pressure (BP) and Heart Rate (HR). BP readings (both systolic and diastolic) and HR will be obtained regularly at assessment meetings.
- Systematic Assessment for Treatment Emergent Effects (SAFTEE) [90] Adverse events will be assessed in person during study related appointments.
- Columbia Suicide Severity Rating Scale (C-SSRS) [91] is a semi-structured assessment intended for administration by clinicians or study staff during scheduled study visits. It explores suicidal ideation and intensity, as well as behaviors and lethality.
- Pill Counts. Participants will be asked to bring their medication to their last appointment and clinicians will count and record the number of pills remaining.
- Naltrexone and Bupropion levels plasma will be collected at weeks 4 and 12 to evaluate plasma trough levels of bupropion, naltrexone, 6-beta-naltrexol levels.

Assays

- Assays will be processed by the Core Laboratory at the Yale Center for Clinical Investigation. These include leptin, ghrelin (octanoylated and des-octanoylated), and estrogen/progesterone. Samples will be stored in -70 freezer, and batched for processing. Medication levels will be processed and stored in a -70 freezer until sent to World Wide Clinical Trials for analysis.

Assessment Training: Independent outcomes assessors will be trained in the study interviews by investigators following well-established protocols from previous grants. Once interviewers are certified in the measures they will receive ongoing supervision to ensure consistent use and prevent drift. Dr. Grilo will do inter-rater reliability studies, as before for BED (Grilo et al., 2004) and psychiatry (Zanarini et al., 2000).

Maintenance of Cohort. Research staff will form on-going relationships and maintain contact with participants. Our experience indicates this improves likelihood of participants' willingness to perform follow-up assessments. In addition: (1) At pre-screening and baseline assessment, participants will be asked whether they will be available for the entire study duration; (2) Participants will be excluded if unable to comply with birth control methods; (3) Participants will provide names and contact information of at least two relatives or friends and permission to contact them if they move without notifying investigators; (4) At each assessment, participants will be asked if they have plans to move; and (5) We will reimburse participants for completion of the assessments.

5. Genetic Testing N/A ☒

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

   Two hundred (N=200) participants with BED with and without obesity (*n*=100 and *n*=100, respectively), and meeting other eligibility criteria as described below, will be randomized to participate in this trial. Previous work with this population suggests participants will be adults, male and female, and represent diverse racial/ethnic and sociodemographic groups.

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

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☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	
☒N/A		

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria:

(1) 18 to 70 years old;
(2) Meet DSM-5 criteria for BED based on semi-structured diagnostic interview (EDE);
(3) BMI in the obesity (BMI >30 and <50) or non-obesity (BMI >21.5 and <29.9) range;
(4) Available for the duration of the treatment and follow-up (15 months).
(5) Read, comprehend, and write English at a sufficient level to complete study-related materials.
(6) Provide a signed and dated written informed consent prior to study participation.

Exclusion criteria:

Main exclusion criteria reflect primarily clinical or medical issues that would indicate different treatment needs or contraindication to NB medication.

(1) Predisposition to seizures (e.g., history or evidence of seizure disorder, febrile seizures during childhood, brain tumor, cerebrovascular disease, or significant head trauma; family history of idiopathic seizure disorder, or is currently being treated with medications or treatment regimens that lower seizure threshold).
(2) Lifetime anorexia or bulimia nervosa, or currently regularly self-inducing vomiting.
(3) Co-existing psychiatric condition that requires hospitalization or more intensive treatment (e.g., bipolar mood disorders, psychotic illnesses, severe depression).
(4) Currently taking a medication that is a contraindication to NB medication (MAOI, opiates, benzodiazepines, CYP2B6 inhibitors, bupropion, naltrexone).
(5) Positive urine drug screen for opiates.
(6) History of allergy or sensitivity to bupropion or naltrexone.
(7) Serious uncontrolled medical conditions (including renal or hepatic impairment, neurological, chronic pulmonary disease, or any other serious, unstable medical disorder).
(8) Breast-feeding or pregnant.
(9) Uncontrolled hypertension with a seated systolic blood pressure > 160 mmHg, diastolic blood pressure > 100 mmHg, or heart rate > 100 beats/minute.
(10) Previous surgical or device intervention for obesity within the past 5 years.
(11) Have not donated blood for 6 weeks prior to the study and agree not to donate blood for 8 weeks following their participation.
(12) History of congenital heart disease, cardiovascular disease, cardiac arrhythmias requiring medication, atherosclerotic disease, or a history of cerebrovascular pathology including stroke.
(13) Current uncontrolled Type I or Type II diabetes mellitus.

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(14) Untreated hypothyroidism with a TSH > 1.5 times the upper limit of normal for the test laboratory with repeat value that also exceeds this limit.
(15) Untreated gallbladder disease.
(16) Current or recent (within 12 months) drug or alcohol dependence
(17) Currently receiving effective treatment for eating or weight loss.
(18) Currently participating in another clinical study in which the participant is or will be exposed to an investigational or a non-investigational drug or device.
(19) Reports active suicidal or homicidal ideation.

Biosensor Arm:

Inclusion Criteria:
(1) 18 to 70 years old.
(2) Willing to wear the Garmin band and interact with the app daily for 6 weeks.
(3) Read, comprehend, and write English at a sufficient level to complete study-related materials.
(4) Provide a signed and dated written informed consent prior to study participation.

Exclusion criteria:
(1) Co-existing psychiatric condition that requires hospitalization or more intensive treatment (e.g., bipolar mood disorders, psychotic illnesses, severe depression).
(2) Serious uncontrolled medical conditions (including renal or hepatic impairment, neurological, chronic pulmonary disease, or any other serious, unstable medical disorder).
(3) Breast-feeding or pregnant.
(4) Previous surgical or device intervention for obesity within the past 5 years.
(5) Currently receiving effective treatment for eating or weight loss.
(6) Current uncontrolled medical condition or medication that could impact weight or eating behavior.
(7) Currently participating in another clinical study in which the participant is or will be exposed to an investigational or a non-investigational drug or device.
(8) Reports active suicidal or homicidal ideation.

9. How will **eligibility** be determined, and by whom? Write here

Participants will be interviewed by a trained research clinician (MINI and EDE) to determine whether they meet criteria for binge-eating disorder. These diagnostic clinical interviews will also determine whether participants have any co-existing psychiatric conditions (including substance use disorders) that require hospitalization or more intensive/different treatment.

The study physician will determine medical eligibility based on results of participants' physical examination (within one year of starting the study), as well as results of the baseline assessment and blood/urine testing. Information obtained from the physical examination will include a list of current medications, which participants will be asked to bring to their baseline assessment.

Biosensor Arm: Eligibility is determined by trained research clinicians. Physical exam and blood/urine testing are not required since the Biosensor is non-invasive and there is no medication administered.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

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NB Pharmacotherapy.

Since participants will undergo a thorough physical evaluation and screening for known contraindications for treatment with the NB medication, potential risks will be minimized. In clinical trials, NB was associated with the following side effects in 10% or more of the time and significantly greater than rate in placebo: nausea, headache, constipation, and vomiting. NB was associated with the following side effects less than 10% of cases but significantly more than placebo: dizziness, insomnia, dry mouth, and diarrhea. Large studies (e.g., Greenway et al., 2010 with N=1742) reported that the proportion of participants reporting a serious adverse event did not differ between NB and placebo (1.6% versus 1.4%) and that none of the observed events were judged to be related to the study. It appears important to evaluate and monitor blood pressure and heart rate because studies have found that patients with obesity treated with NB have significantly lower drops than placebo in systolic BP changes (-0.4 vs. -2.1), diastolic BP (-0.1 vs -1.0), pulse rate (1.0 vs -0.1) (Greenway et al., 2010).

Pill Placebo.

The main risk associated with placebo is failure to improve, although some persons do improve solely on placebo. Although the placebo is inactive, some persons who take the placebo report that they experience some of the side-effects listed above.

Assessments and Interviews.

Participation of the human laboratory component does not add risk above that associated with the clinical trial, with the exception of repeated blood drawing. Risks will be minimized by using trained research nurses. Further, subjects have not donated blood for 6 weeks prior to the study, and they are informed to not donate blood for 8 weeks following their participation.

Participation in the biosensor component does not add risk. De-identified biosensor and smartphone data will be remotely collected by mHealth Core Facility at UMass for data processing.

Research assessments are all noninvasive, and add no substantial risk. The major disadvantages are the time taken to complete them and possible breach of confidentiality. Our past experience with these measures indicates that they are acceptable to participants. Careful efforts aimed at maintaining confidentiality will be made. All identifiable information will be stored in a locked research cabinet. All participants will be assigned a study participant number. A list of numbers and the corresponding names will be maintained by the Principal Investigator and stored in a locked research cabinet. Any identifying information that is collected will be kept in a locked research cabinet in a locked unit. Any information published as a result of the study will be such that it will not permit identification of any participant. All information collected will remain confidential except when we are legally required to disclose such information by law. These circumstances include knowledge of abuse of a child or elderly person, threats of harm to self or others, and plans to harm to property. Data will be stored in locked cabinets for 7 years after the final data are collected. Research records may be the subject of an audit by a regulatory agency within the federal government. Organizations which have a responsibility for protecting human subjects, including the Yale IRB (Human Investigation Committee), may have access to the research records. Additionally, the funding agency (NIH) may have access to the research records. The participant's identity will remain protected except as required for legal or regulatory inquiries. Individually identifiable health information will be protected in accordance with the Health

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Insurance Portability and Accountability Act of 1996. All research personnel will be trained on IRB, ethics, and HIPAA procedures.

There is the possibility that drawing blood might cause a small bruise, mild discomfort, or infection.

Failure to Improve.

There is a chance that the patient's binge eating or obesity may fail to improve or may worsen during the study.

Biosensor- Physical Discomfort from Wristband.

As part of the study, subjects will wear a Garmin wristband and carry a smartphone for the collection of data. While there is potential physical discomfort associated with regular wearing of a wristband, our experience suggests that this has been minimal and subjects have been comfortable wearing the device for extended periods of time. The wristband is adjustable.

Biosensor – Android Cell Phone App

All information collected from both the Garmin wristband and the Android cell phone app will be de-identified. The data from the bands in continuously transmitted o the mHealth Core Facility at UMass through the Garmin service for Academic Researchers. The data from the Android cell phone app will be collected, transmitted, and stored by the mHealth Core Facility at UMass and provided to Yale.

Data Security and Collection.

Security of user information is of paramount importance to us. We have completed a Security Design Review (INC1917498) through Yale ITS and have received approval using this technology (HIC# 2000023970, McKee[PI]). Security of user information is of paramount importance to us. We work to protect security of sensitive information during transmission by using Secure Socket Layer (SSL) software, which encrypts information that is input. Our servers are behind a firewall, and we secure it using the best available methods. This data will not be associated with any personal information of the participant; rather, it will only be associated with a random key associated with the phone. The study organizers at Yale will keep a mapping between the random key and the identity of the individual. We will include privacy safeguards to ensure that participants are comfortable with the data they are revealing. The user will be asked to specify privacy zones where they do not with GPS information to be recorded. This can be done at any point during the study by contacting study organizers or they can explicitly turn on or off GPS logging by using the Settings screen on the app. During periods when location logging is enabled, the system will automatically upload location data to a secure backend database.

We note that Dr. Ganesan has recently completed an NIH R01 (DA033733-01) where we monitored cocaine addicts in out-patient settings with several on-body sensors (wristband, chestband, and smartphone), which had even more extensive data collection than we are proposing in this grant (we collected GPS, respiration, ECG, phone usage patterns, and other signals in the R01 effort). They are also part of several other efforts with similar data collection considerations (NSF 0910706 and NIH 1-U54EB020404-01). Hence, we have extensive experience in mitigating the potential risks, and privacy issues associated with the collection of, and use of sensitive on-body sensor data. Given our experience in this domain, we will follow all the best practices in acquisition and management of subjects' private data.

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11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

Effective screening will exclude all prospective participants who would be at greater risk for complications because of medical or psychiatric illnesses. Subjects will be evaluated repeatedly throughout the study and will be monitored for any adverse reactions. Given the uncertain effects of medication during pregnancy, the following precautions will be taken for women of reproductive age: 1) a female participant of reproductive age must agree to use a reliable method of birth control while she is in the study and to alert the research team if she departs from her birth control plans or if, in spite of adherence to these plans, she thinks she might be pregnant; we will do a urine pregnancy test as needed during the treatment phase of the study, and 2) if a woman becomes pregnant after study entry, her medication will be discontinued.

Screening for opiate use and warning about opioid withdrawal. During the screening process, we will conduct urine drug screens for opiate use as part of the medical evaluation if patients report a lifetime history of substance use disorder with opiates, or if patients report any use of opioid-based pain medications within the past 6 months. Additionally, we will include this advisory pertaining to opioid use and examples of opioid-based medications and drugs in the written consent form as well as the verbal consent process: Naltrexone can cause withdrawal symptoms in individuals who are taking opioid pain medications or drugs. You should not participate and we will not include you in the study if we know or suspect you are using opiate-containing drugs.

Monitoring weight loss. Participants who have a BMI in the healthy-weight or overweight range (i.e., BMI 21.5-29.9 kg/m^2) will be monitored closely for changes in weight. If any participant's weight drops below 20.0 kg/m^2 over the course of the study, this will trigger a discussion amongst investigators and the study physician. Research clinicians will review and/or assess eating behaviors to ensure the patient is not vomiting. This will be discussed with the team along with any reported side effects, and whether the treatment should continue per protocol, dosage decreased, or medication stopped will be considered. We anticipate this will be a rare occurrence; however, the use of this "early signal" (i.e., weight below 20.0 kg/m^2) will greatly reduce the likelihood of adverse events.

Monitoring depressive symptoms. Depressive symptoms will be monitored frequently. To monitor changes in depressive symptoms, patients will be asked to complete the BDI-II at all clinic visits (2x in first month, monthly thereafter). Research clinicians will review BDIs during the clinic visit, and will asked pointed questions pertaining to suicidality/suicidal ideation using the Columbia Suicide Severity Rating Scale. If it appears, based on the clinical judgment of the research clinician, that the participant is experiencing significant adverse effects of the medication, the investigators and study physician will be consulted and a determination of whether to discontinue the medication will be made. The participant will be compensated in full, and will be asked to continue to attend clinic visits and to continue to participate (if applicable) with the behavioral support to ensure remission of any distressing symptoms. If warranted, the participant will be given a referral. There is no assessment of suicidality in the Biosensor Arm.

Blood pressure and heart rate will be measured during all evaluation visits. Two readings will be taken at each assessment. In the event of systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg, or an increase in heart rate of ≥15 bpm (from baseline), the study physician will be notified and will determine whether additional intervention and/or medication discontinuation is warranted.

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Liver function will be measured during baseline, at month-1 clinic visits, and at the end of treatment. The study physician will review results of a full hepatic panel prior to the start of treatment and throughout treatment. Participants with hepatic disease will be excluded if this is detected at baseline, per exclusion criteria. Any changes and out-of-range values will be flagged immediately by research clinicians, and the study physician will determine whether additional intervention and/or medication discontinuation is warranted.

Wallet Safety Card. Each participant will be given a wallet card with the code number for the medication assignment in the event of an emergency and the need for breaking the blind. The research pharmacy has 24-hour service. Participants will be provided with contact information for the study physician and the PI, as well as emergency numbers in case of adverse events or other concerns. Research staff will have cell phones and can be reached 24/7.

Medication Titration & Taper.
Participants will have four weeks of up-titration: one tablet daily (Naltrexone 8mg/ Bupropion 90mg; 1 week), then two tablets daily (Naltrexone 16mg/ Bupropion 180mg; 1 week), then three tablets daily (Naltrexone 24mg/ Bupropion 270mg; 1 week), to reach the full dose of four tablets daily (Naltrexone 32mg/ Bupropion 360mg).

If participants drop out of the study during, we will ask that they return any unused medication. Participants who have been on the study medication for more than 4 weeks, including those who complete the treatment, will be asked to taper off the study medication: two tablets daily (Naltrexone 16mg/ Bupropion 180mg; 4 days), then one tablet daily (Naltrexone 8mg/ Bupropion 90mg; 3 days), to discontinue medications. Participants on placebo will take the same number of tablets as the active group to maintain the blind. Participants will be cautioned against stopping the medication abruptly. Taper off is not medically necessary for participants on the study medication for 4 weeks or less.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Greater than minimal.
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? n/a
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

The principal investigators will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews semi-annually. Although this study qualifies as clinical trial research, it does not meet NIH criteria for Phase III clinical trial research. Nonetheless, this study will be monitored semi-annually by a Data Safety Monitoring Board (DSMB) as the study involves a double-blind placebo controlled evaluation of medication effects that may involve greater than minimal risk. Adequate surveillance and protections will be put in place to discover adverse events promptly and keep their effects to a minimum.
During the review process, the principal investigators and DSMB will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or the DSMB have the authority to stop or suspend the study or require modifications.

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The risks associated with the current study are deemed greater than minimal for the following reasons:

1. We do not view the risks associated with the NB combination medication as minimal risks.
2. Given the now established safety and validity of the current NB combination medication in RCTs and FDA approval, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

DATA AND SAFETY MONITORING PLAN

The treatment interventions and assessment protocols are well-established and pose primarily low risks to subjects. The DSMP focuses on close monitoring by the PIs in conjunction with the study MDs. Excessive adverse events and/or any serious events (should they occur) will be reported promptly to the NIH and to the Yale Human Investigation Committee.

A Data and Safety Monitoring Board (DSMB) will monitor this project. The DSMB is composed of Yale investigators who are independent of the proposed trial and experienced in various aspects relevant to the current proposal including: conduct of clinical trials, biostatistics, primary care, and the clinical management of obesity and BED.

We have developed a standard DSMB report form that summarizes, on a semi-annual basis:

1. Recruitment, retention, and follow-up rates for the study and compares them to target rates.
2. Rates of data completeness and availability of primary outcome data
3. Occurrence of AEs and SAEs
4. Report of study progress since the last report.
5. Rates of recruitment of women and minorities with respect to targets.

These reports are generated by the study coordinator, signed by each study PI prior to their submission to the DSMB. DSMB comments are documented and forwarded to the Yale IRB at the time of the annual review and reapproval. They will also be summarized as part of the annual progress report to NIDDK. However, if adverse events occur in greater magnitude or frequency than expected these will be reported to the DSMB, HIC, and NIH prior to scheduled reports. The Principal Investigators (Grilo & McKee) will assume full responsibility for reporting serious and non-serious and unanticipated adverse events. The DSMB may call an ad-hoc meeting to address emergent safety concerns.

Because the projected effect sizes may not be large enough for detection during interim analyses, we are not proposing a preliminary analysis of accumulating efficacy and safety data by treatment assignment. Instead, we propose to submit semi-annual reports of aggregate data to the DSMB members that contains screening data, baseline demographics, retention data, serious adverse events data, as well as accrual status including projections, times to milestones, and any other data that will help in the assessment of the clinical trial. Based on this report, each DSMB member will complete a form making one of two recommendations: 1) continue recruitment as planned; or 2) schedule formal DSMB meeting immediately. If any DSMB member recommends a meeting, this will be scheduled within one week, minutes will be kept, the report will be

reviewed with the PI, and the committee will vote on whether the study should: 1) continue recruitment unchanged; 2) continue with a protocol amendment; 3) stop recruiting pending further investigation. If, after this meeting, any DSMB member votes to stop recruitment or requests a protocol modification, the Yale IRB will be informed.

Measurement and reporting of adverse events.

Adverse event data will be collected on an on-going basis. These data will be collected and examined with blindness to the medication condition (Naltrexone/Bupropion or placebo). Adverse events data will be reviewed by the PI, co-investigators, and the DSMB throughout this trial (see Table below). A summary of adverse events will be provided to the Yale IRB yearly during the annual renewal review process. Any serious or unanticipated adverse events will be reported to the NIH and to the Yale IRB within 48 hours.

The frequency of data review is summarized in the following table:

Table	Data type	Frequency of Review by PIs and Research Team	Frequency of Review by PI and DSMB
Table 1	Subject accrual	Monthly	Twice-yearly
Table 2	Treatment completion rates (retention/attrition)	Twice-yearly	Twice-yearly
Table 3	Adverse and serious adverse event rates	Twice-yearly	Twice-yearly
Table 4	Checklist for DSMB	NA	Twice-yearly

Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures by the investigators according to the following categories:

a) Definite: Adverse event is clearly related to the investigational procedure/agent.
b) Probable: Adverse event is likely related to the investigational procedure/agent.
c) Possible: Adverse event may be related to the investigational procedure/agent.
d) Unlikely: Adverse event is likely not to be related to the investigational procedure/agent.
e) Unrelated: Adverse event is clearly not related to the procedure/investigational agent.

Plan for Grading Adverse Events:
The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe adverse event

Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events: In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR

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5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

Plan for events to the Yale IRB that are unexpected AND related AND involve risk of harm to subjects or others:

The PIs will report any incident, experience, or outcome that meets all three of these conditions to the IRB immediately:

1. Unexpected (in nature, specificity, severity, or frequency); given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places participants or others at greater risk of harm (physical, psychological, economic, legal, or social) than previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. Adverse events are reportable to the IRB as UPIRSOs only if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the prompt reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review and/or a current DSMB report. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented.

Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitors, e.g., study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies:

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

i. All Co-Investigators listed on the protocol
ii. National Institutes of Health

The investigators will conduct a review of all adverse events upon completion of every study subject. The investigators will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Procedures for providing follow up care:

Medical monitoring will occur at all clinic and follow up visits and medical care will be provided if warranted. If a study participant experiences any psychiatric symptoms or distress (e.g., depressive symptoms or

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suicidality) at any stage of study participation he/she will receive short-term treatment and support from the study treatment team (including psychologists and a psychiatrist) and will be connected to a local emergency department (e.g., the Crisis Intervention Unit at Yale-New Haven Hospital) and his/her physician or therapist for ongoing care.

Measurement and reporting of subject accrual, adherence to inclusion/exclusion criteria.

Review of the rate of subject accrual and adherence to inclusion/exclusion criteria will occur regularly by the PI and co-Investigators and yearly by the DSMB. These reviews will help to assure that participants meet eligibility criteria and ethnic diversity goals outlined in the grant proposal.

Measurement and reporting of participant treatment completion rates.

Participation rates (retention and attrition) will be reviewed on an ongoing basis by the PIs and co-investigators to identify any potential problems, and formally by the PIs and DSMB semi-annually. Any differential dropout across blinded study groups and/or higher than expected dropout will be reviewed by the investigators to determine whether any problems are present and what, if any, corrective action needs to be taken.

During the reviews, if the DSMB has concerns about whether attrition has reached a level that might inhibit the ability of the study to address its primary aims, they will suggest a meeting to discuss methods for improving subject retention. Previous pharmacotherapy studies for BED (with comparable time frames for pharmacotherapy) have reported attrition rates between 20% and 38%. Studies of bupropion for obesity treatment reported attrition of 30% to 38%. Thus, "trigger points" for review and discussion by principal investigator and research staff will be: 35% ("low alert"), 40% ("mid alert"), 45% ("high alert"), 50% ("extreme alert"). With early alerts to problems, action would be taken to avoid higher level alerts; if a higher-level alert should arise, more drastic actions would be taken.

The following actions would be taken at each level of alert:

(1) Low-level alert = Review of potential problems by PI.

(2) Mid-level alert = Meeting with co-investigators to discuss approaches to minimize further losses to follow-up/dropouts.

(3) High-level alert = Meeting with co-investigators to determine further alterations of study protocol to complete the study with no further losses.

(4) Extreme-level alert = In the unlikely event of a 50% dropout rate prior to the mid-study time point, discontinuing the trial would be considered.

Trial Stopping Rules

Given that this study is deemed greater than minimal risk to human subjects but not high risk, it is more likely that attrition or difficulty in recruiting adequate numbers of participants will require stopping the trial than would excess adverse events. However, as outlined, adverse events will be monitored in all participants, and the DSMB, together with the PI, will alert the Yale IRB and the NIH if a larger (or more serious) than

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reasonably expected adverse event rate should occur. Other potential issues relating to stopping rules for this trial include:

1. New Information

It is unlikely that any new information will become available during this trial that would necessitate stopping the trial. If new safety data (i.e., pertaining to short-term use of the study medication) become available, this will be evaluated.

2. Limits of Assumptions

It is possible that baseline differences between the treatment conditions, excessive attrition, and/or missing data could limit the value of data analysis. Baseline differences across blinded treatment groups, if present, will be evaluated yearly and considered in relation to potential effects on the power to detect differences in the primary outcomes. If these effects were to develop and be sizeable, alterations to the randomization schedule would be considered. Any plans to alter the randomization scheme would be communicated to the NIH.

3. Limits of Rules

There are other situations that could occur that might warrant stopping the trial and/or including a section on the safety report entitled "Other situations that have occurred since the last safety report that warrant discussion" to allow for communication of concerns.

Finally, as currently outlined above, the DSMB has the authority to stop the trial following any serious adverse event or following any semi-annual review of adverse events.

13. Statistical Considerations: Describe the statistical analyses that support the study design.

Baseline demographic and clinical characteristics for the randomized groups will be compared using chi-square tests for categorical variables, and ANOVA or Kruskal-Wallis tests for continuous variables. Continuous variables will be examined for normality using normal probability plots and Kolmogorov-Smirnov test statistics. If normality is not satisfied, transformations or nonparametric alternatives will be considered. Dropouts and completers will also be compared. Primary analyses will be based on an intent-to-treat basis. Primary outcomes will be tested at the two-sided alpha 0.05 threshold. Secondary analyses will be adjusted for multiple tests using the Bonferroni correction basing the adjustment on the number of conceptually related statistical tests within each hypothesis.

Overall analysis strategy. Mixed-effects models [92] will be used to compare treatments. These models allow for different numbers of observations per subject, use all available data on each subject, and are unaffected by randomly missing data. A further advantage is the capacity to test and account for individual-difference contributions to the treatment outcomes (Cudeck, 1996; Cudeck & Klebe, 2002; Hedeker et al., 1996; Hedeker & Gibbons, 1996; Singer, 1998). They provide flexibility in modeling the correlation structure of the data. In models for each outcome in Aims 1 & 2, we will include obesity status (obese vs. non-obese) and treatment (NB vs. placebo) as between-subject effects, time (see Aim-specific study time points) as a within-subjects factor, and subject as the clustering factor. Across analysis, time-points associated with the 12-week treatment phase will be considered as primary outcomes, and all analyses will be repeated to examine change

during the 12-month follow-up period. All possible interactions will be modeled and the following primary a priori contrast will be tested: 1) placebo NB vs. active NB. Least-square means will be plotted and compared post-hoc to interpret significant effects. Because we cannot a priori predict the shape of the response over time in each arm of the trial we will first treat time as a categorical predictor and will then test for polynomial trends over time. We will consider different error structures (e.g., AR1, CS, independence) and select the best fitting one based on Schwartz' Bayesian Criterion (BIC). We will compare dropout patterns between groups and if there are concerns of informative dropout or informative intermittent missing data, we will use pattern mixture models [93] to perform sensitivity analyses. Secondary models will include subjects with complete data. To test for assessment reactivity, we will evaluate whether biosensor assessment (yes/no; between-subject variable) moderates our primary outcomes in Aim 1 (as either a main effect, or interacting with medication). If this is found, then all subsequent analyses for Aims 1 & 2 will be limited to the sample (n=140) without the biosensor assessment.

Primary Aim 1. We will use the mixed models described above to test the effectiveness of NB medication for BED patients with and without obesity. The primary aims are to evaluate NB medication for (a) reducing binge eating frequency; and (b) in the patients with obesity, for reducing % weight loss. Significant NB main effects (regardless of obesity status) on frequency of binge eating will be considered supportive of our primary hypothesis. We also expect that NB will be associated with significantly greater reductions in % weight loss among the BED+obese group. In view of the factorial design, we will also be able to assess whether obesity status moderates reductions in binge eating frequency. These analyses will focus on 12-week outcomes. Secondary analysis will be repeated to examine change during the 12-month FU period.

Secondary Aims. (a) Explore effectiveness of NB medication for BED patients with and without obesity on secondary outcomes: eating-disorder pathology (EDE global), eating behaviors (EDE, TFEQ, FCI, PFS), depression (BDI-II), psychosocial functioning (SF-36), metabolic measures (lipid profiles, HbA1c, blood pressure, heart rate) and "remission" and "relapse" from binge eating behaviors. The continuous secondary outcomes (e.g., EDE global, BDI-II, SF-36) will be analyzed using the same approach as for primary aim 1, and logistic regression will be used to compare proportion achieving remission from binge eating or relapse to binge eating. (b) Explore predictors, moderators, and mediators of primary outcomes (i.e., binge eating). In terms of treatment processes, we will attempt to replicate our findings regarding the prognostic significance of rapid response for behavioral and pharmacologic treatments (Grilo et al., 2006, 2012, 2015; Masheb & Grilo, 2008). We will follow Kraemer's (2002) conceptual/statistical models for exploring predictors, moderators and mediators for binge eating. Per Grilo et al. (2012), we hypothesize that overvaluation of shape/weight and depression levels to be significant predictors; such findings would inform future treatment prescription regarding this pharmacologic intervention. Per Kraemer (2002), we will explore if baseline characteristics predict/moderate treatment effects by testing for main effects and interactions in models specified above for primary outcomes. In terms of mediators, we will explore whether differential symptom changes during treatment are associated with subsequent longer-term primary outcomes. Repeated assessments of eating behaviors (EDEQ and TFEQ scales), and food-reward constructs (FCI, PFS) relevant to putative mechanisms of action for NB, will yield relevant change variables for analyses of mediation (i.e. testing subsequent changes in binge eating).

Primary Aim 2. To evaluate potential mechanisms underlying the effect of NB on binge eating behavior, we will first evaluate whether NB treatment changes latency to resist eating, calories consumed, leptin, ghrelin, and food craving employing the mixed models described above. If a potential mechanism demonstrates a significant time x medication effect, we will then evaluate whether improvement in the variable of interest mediates changes in frequency of binge eating over the 12-week treatment period. Following the general analytic framework outlined by Kraemer (2002), we will use the product of the coefficients method to

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evaluate the relationship between the mediator, or indirect effect, and outcome. After running a regression equation to determine (1) the effect of treatment on the mediator (provides beta weight for a), we will evaluate (2) the strength of the relationship between the mediator, treatment, and outcome (provides beta b). Using MacKinnon's software PRODCLIN, we will evaluate the asymmetric confidence intervals for the product of the regression estimates (a*b). Importantly, we note that statistical mediation is not equivalent to causation, and will be sure to appropriately limit our conclusions. Significant NB main effects in latency to resist eating, calories consumed, leptin, ghrelin, and food craving will be considered supportive of our hypothesis. Further, significant mediation of NB-related changes in lab variables on clinical outcomes (reduction in binge eating frequency) will be considered supportive of our hypothesis.

Exploratory Aim 3. To account for the hierarchical structure of the data, linear mixed models will be used to assess differences over time in affect and eating behaviors per day collected over a 6-week period. To evaluate potential mechanisms underlying triggers of binge eating behavior, we will first evaluate whether NB treatment changes eating behavior. We will also evaluate the time course of affect and eating behaviors to identify potential antecedents and consequences of binge eating episodes.

Supplementary analysis: Retention, compliance, and sex. These analyses will provide insight into outcomes which will help us to consider directions for future research. We plan to explore whether medication compliance [plasma bupropion, naltrexone, 6-beta-naltrexol levels, pill counts], and length of time in treatment influenced our primary outcomes. Analyses described earlier will be repeated separately with a) counts of pills taken as a covariate, and b) length of time in treatment as a covariate. In participants taking active medication we will conduct a logistic regression examining area under the curve for the three plasma medication levels as a predictor of our primary outcome (frequency of binge eating) and as predictor of treatment-related change in potential mechanisms. Associations between plamsa medication levels and changes in mechanisms will provide an indication that medication is driving the change in the predictor variable. We also plan to evaluate whether sex moderates medication effects on all study outcomes. Analyses described in D.7.3. will be repeated with sex as between subject variable. We will also explore effects related to laboratory outcomes assessing estrogen and progesterone levels as covariates.

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SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☐N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒
2. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☒
3. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

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Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

☐ Blood grouping serum
☐ Reagent red blood cells
☐ Anti-human globulin

☐ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. Background Information: Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

   In September 2014, the FDA approved ("Contrave") the combination of naltrexone and bupropion to treat obesity consisting of the following empirical support from several RCTs performed with obesity (but not BED). NB medication will combine naltrexone sustained-release (SR, 32 mg/day) combined with bupropion SR (360 mg/day) taken daily (8 mg naltrexone/90 mg bupropion in each tablet – two tablets taken twice daily; matching tablets and frequency for placebo).

   Mechanisms of Action. The putative mechanisms of action for NB seem relevant for binge eating in addition to weight loss. Naltrexone, an opioid receptor antagonist, is approved to treat alcohol and opioid dependence [94]. Naltrexone produces weight loss in lab animals but only minimal weight losses in people [95, 96]. Bupropion operates through dopaminergic, noradrenergic, and nicotinic acetyl-cholinergic mechanisms [51-53]. Bupropion may target reward processes that drive eating behaviors, consistent with its FDA indication for treating nicotine dependence and reduced weight gain during smoking cessation [54, 55]. Bupropion promotes weight loss [56]: in a meta-analysis of five trials of bupropion, the mean difference in weight loss was 2.77 kg (CI, 1.1 to 4.5) between bupropion and placebo groups at 6 months. White and Grilo [97] reported preliminary, modest support for weight loss specifically in patients with obesity and BED.

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NB Combination. The putative mechanisms of action for NB is especially relevant for reducing binge eating and weight per hypothesized effects on brain regions implicated in the regulation of food intake and weight based on research on the mechanisms of action of leptin [96]. The anorectic effects of leptin result from its excitatory effects on pro-opiomelanocorin (POMC) neurons in the hypothalamus melancortin system [98, 99]. Stimulated POMC signaling decreases food intake, increases energy expenditure, but is then inhibited by endogenous feedback [98]. Thus, combining these two drugs will stimulate POMC neurons (bupropion) plus block endogenous feedback that inhibits POMC activity (naltrexone) [47, 96]. This synergistic model received support both in vitro and in vivo studies [47, 100].

Obesity Outcomes. Recently, several large RCTs have reported that the combination of these two medications (Naltrexone/Bupropion) were effective in promoting weight loss in obese patients [47-49, 101]. These RCTs reported significant clinically-meaningful weight losses with sustained-release naltrexone (32 mg/day) plus sustained-release bupropion (360 mg/day) combined in fixed-dose tablets. Most recently, Apovian, Aronne [50], in a study of 1496 obese patients reported significantly greater weight losses relative to placebo (-6.5% vs -1.9% at week 28 and -6.4% vs -1.2% at week 56) and significantly greater likelihood of achieving 5% weight loss (56% vs 18% at 28 weeks and 51% vs 17% at 56 weeks). These findings supporting NB medication are quite consistent with earlier (large) RCTs which reported the following percentage of patients achieving at least 5% weight loss: 56% vs. 18% [48]; 52% vs. 15% [102]. Thus, the proposed RCT study will test the effectiveness of Naltrexone/Bupropion relative to placebo for reducing binge-eating and producing weight loss in obese patients with BED.

Risks. Several large-scale studies have found that this medication is safe and effective for the treatment of obesity [47-49, 101]. The NB combination approved by the FDA (Contrave) is reported to have the following common adverse reactions: nausea (32.5%), constipation (19.2%), headache (17.6%), vomiting (10.7%), dizziness (9.9%), insomnia (9.2%), dry mouth (8.1%), and diarrhea (7.1%). In addition, Contrave will have the FDA warnings and precautions: "Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue Contrave if symptoms develop. Risk of seizure may be minimized by adhering to the recommended dosing schedule and avoiding coadministration with high-fat meal. Increase in Blood Pressure and Heart Rate: Monitor blood pressure and heart rate in all patients, especially those with cardiac or cerebrovascular disease. Hepatotoxicity: Cases of hepatitis and clinically significant liver dysfunction observed with naltrexone exposure. Angle-closure glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. Use of Antidiabetic Medications: Weight loss may cause hypoglycemia. Monitor blood glucose."

3. Source: Identify the source of the drug or biologic to be used.

   NB will be purchased using funds awarded in this grant.

   a) Is the drug provided free of charge to subjects? ☒YES ☐NO
   If yes, by whom? *Write here*

1. Storage, Preparation and Use: Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
   Write here

Check applicable Investigational Drug Service utilized:

☒ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None

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☐ Other:

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

2. Use of Placebo: ☐Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.

Expert opinion [21] and critical quantitative meta-analytic reviews [28] conclude CBT is the best-established treatment for BED; CBT, however, does not produce clinically meaningful weight loss and is not readily available given the need for specialized training. Alternative therapies include other psychological therapies such as interpersonal psychotherapy (which also fails to produce weight loss and is not readily available since it requires intensive training and few practitioners employ it) and self-help versions of CBT (which will be used in this study). Alternative pharmacologic therapies include antidepressant medications (SSRIs) although weight loss is uncertain with those agents.

Pharmacotherapy (medications) for BED has received increased research attention albeit nearly all RCTs have been of short duration and without follow-up period to establish durability [20, 22]. Critical review and meta-analysis show that several drugs – working through varied mechanisms – have short-term efficacy relative to placebo for reducing binge-eating and produce weight loss ranging from modest to none [20]. Placebo-controlled trials of anticonvulsants topiramate and zonisamide [24-26] have reported 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 shown frequent dropout and adverse events which become nearly universal with longer use [27]. SSRI antidepressants, previously regarded as a potential treatment strategy [28] are characterized by small effect sizes relative to placebo [20] and produce no weight loss at all [38] and are inferior to CBT [29, 30].

b) State the maximum total length of time a participant may receive placebo while on the study.

Participants may receive placebo medication for up to 3 months if randomized to placebo.

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.

Without immediate effective treatment, the greatest potential harm is that binge eating and associated eating disorder features may not improve. Placebo-controlled trials have rarely reported worsening and generally report a positive placebo response [22].

d) Describe the procedures that are in place to safeguard participants receiving placebo.

Possible risks include failure of binge eating and associated eating disorder features to improve. Previous experience suggests that the frequency of these situations is rare [22].

To safeguard participants, we plan to assess potential adverse events, side effects, and clinical status. All participants will have monthly visits with research clinicians, who can be expected to detect the clinical

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changes that warrant concern. Participants will be removed from the study if, through the consultation of the PI and study physician, it is determined that participant safety is at risk, including worsening depression, suicidal ideation, intensification of binge eating, or failure to comply with medication. If a participant is removed from the study, a research clinician will provide referrals. If removal is indicated, a referral for appropriate care will be provided.

3. Continuation of Drug Therapy After Study Closure ☐Not applicable to this project

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☒ NO If no, explain why this is acceptable.

Our procedure follows existing pharmacotherapy treatment literature for BED, which has delivered medications in an acute, short-term manner.

B. DEVICES ☐N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No

***If Yes, please be aware of the following requirements*:**

A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request**; AND

Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

We are developing the Biosensor program that facilitates continuous passive monitoring of eating behavior and stress using wristband mounted sensors.

To monitor ambulatory stress levels, we will use Garmin bands. These bands provide a 'stress score' (range 1-100) with a 3-minute granularity. The algorithm is proprietary, but Garmin acknowledges that one of the primary factors in the algorithm is heart rate variability (HRV). HRV is the beat-to-beat variation in heart rate, which has been shown to be associated with emotion regulation and likely contribute to binge eating[101]. The Garmin band also provides daily metrics on steps, distance, heart rate, sleep duration, and sleep level classification. Access to this data is through a Garmin service to academic researchers https://developer.garmin.com/health-api/overview/. Data obtained from bands will be continuously transmitted to the mHealth Core Facility at UMass. The mHealth Core Facility at the University of

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Massachusetts will assist with the collection of electronic data, transmitting and storage of the data, and providing collected and processed data to Yale. This data collection system (which integrates the Garmin Band data collection and the smartphone data collection) is being developed for the Yale-SCORE (HIC#2000023970; PI, McKee). All data collected will be de-identified.

Physical discomfort from wristband. Participants will be outfitted with wrist worn bracelets with integrated sensors. While there is potential physical discomfort associated with regular wearing of a wristband, our experience in the pilot study suggests that this has been minimal and subjects have been comfortable wearing the device for extended periods.

3. Source:

a) Identify the source of the device to be used.

The Garmin bands are available to the public for purchase and will be purchased by the Research Team. A compatible Android phone will be provided by the Research Team for participant use throughout the 6-weeks.

b) Is the device provided free of charge to subjects? ☒Yes ☐No

4. Investigational device accountability: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): All packages shipped to Yale containing equipment will be tracked using the shipper's tracking numbers. A log of materials received will be kept and a corresponding de-identified log will be kept to track items given to each participant. Participants will receive payment for completing the Biosensor portion of the study once the Biosensor has been returned to the Research Team.

b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): A log of materials received will be kept and will include any pertinent information needed to identify each device.

c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: The Biosensor will be stored in a locked cabinet in a locked office.

d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: The locked cabinet where the Biosensors will be stored is located in a locked office within our locked suite. Only members of the Research Team have access to this area.

e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: Subjects will not receive the Biosensor until they have reviewed/agreed/signed a Consent Form, completed the intake process to determine eligibility, and completed the first lab session. Only a subset (n=60) will participate.

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: N=200

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b. If this is a multi-site study, give the total number of subjects targeted across all sites: n/a

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☒ Telephone
☐ Letter	☒ Departmental/Center website	☒ Television
☐ Medical record review*	☐ Departmental/Center research boards	☒ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrails.gov
☒ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☐ Other: EPIC direct to patient		

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Participants will be recruited using ads and flyers placed in local media (newspapers and television), and internet and printed materials throughout the community. We will also work with YCCI using their recruitment strategies, including distribution of materials throughout the community, email and internet solicitation, working with community contacts, and receiving information about potential participants YCCI identified as interested in research related to our topics (obesity, binge eating disorder, mental and physical health).

Biosensor Arm: Participants who are interested in or currently enrolled in any study with the research team can be contacted to see if they are interested in participating in this Biosensor Study alone or in conjunction with the study they are currently enrolled in. Participants will follow the same screening, recruiting and consenting procedures as described below in person or remotely (i.e., Zoom). Participants enrolled in the study will be contacted and offered the biosensor arm. Participants not enrolled in the RCT will only be contacted if we have permission to contact them about future studies.

b. Describe how potential subjects are contacted.

Advertisements will ask participants to contact our research team if they are interested in the study. When potential participants call (or, if preferred by the participant, through the Yale Qualtrics system), they will be screened to determine whether they are likely to be eligible. If they seem potentially eligible and interested, they will be scheduled for an initial assessment.

c. Who is recruiting potential subjects?

After initial contact, research clinicians (who have completed IRB training) will meet with potential participants to discuss the study, the treatments, the assessments, the follow-up period, and the informed consent procedures and forms. Clinicians will answer any questions and obtain written informed consent. A copy of the signed informed consent form will be given to the participants and the original will be kept in the participant's file. All potential subjects and/or participating participants are free to decide whether or not to participate and are free to withdraw from the study at any time. Alternative treatments would be discussed

and/or referrals provided. A decision not to participate or to discontinue participation would not adversely affect future interactions with Yale or the Yale School of Medicine.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?
☐Yes, all subjects
☐Yes, some of the subjects
☒No

If yes, describe the nature of this relationship. *Write here*

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)
Choose one:
☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

Participants will initially call us and/or contact us through an online form in response to advertisements, at which time, if they seem eligible, we will schedule them for an initial assessment and collect contact information. We will also request that patients complete online surveys. If potential participants elect to participate, they would then provide informed consent including HIPAA authorization as described at their initial in-person visit. Names will be removed from surveys if an individual does not provide informed consent.

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: *Write here*

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

At the start of the initial intake evaluation, participants will provide written consent to participate in a research project and treatment. Informed consent will be collected at 301 Cedar Street, 2 Church St South or remotely (via Zoom). Participants will sign the electronic consent via RedCap (Yale's aproved platform). Clinicians will answer any questions that participants may have. Alternative treatments would be discussed and/or referrals provided. Participants will be informed that a decision to not participate or to discontinue participation would not adversely affect future interactions with Yale or the Yale School of Medicine. Participants also will be informed that their participation is strictly voluntary, and that they may withdraw at any time with no penalty.

Participants interested in the Biosensor Arm will complete a separate consent.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   With all participants, we will describe the study verbally during the consent process, and allow participants to ask any questions they might have. To ensure understanding, we will use open-ended questions with all participants to ask that they paraphrase the nature of the research and what they are being asked to do as part of the study, and also summarize the potential risks and benefits of the study.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

   n/a

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. *Please review the guidance and presentation on use of the short form available on the HRPP website.*

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☐Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☒
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☒ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☐ Requesting a waiver of consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

   Height, weight, medical and psychosocial history will be collected and used for research.

2. How will the research data be collected, recorded and stored?

   All participants will be assigned a study number. Subsequently, participants will be identified only by that number. A list of numbers and the corresponding names will be maintained by investigators on a protected research server. Any identifying information that is collected on paper will be kept in locked research cabinets

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within a locked suite. Interviews will be recorded using a digital recorder and recordings will be securely and separately stored and be identified only by a study number and date.

Any information published as a result of the study will be such that it will not permit identification of any participant. All information collected will remain confidential except when we are legally required to disclose such information by law. These circumstances include knowledge of abuse of a child or elderly person, threats of harm to self or others, and plans to harm to property.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   See above, the patients will only be identified by a number on any digital data files. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

   Data will continue to be stored in locked cabinets in limited access areas until the legal requirement for storage has been met. Electronic data files will be password protected. Electronic data files will include code numbers only – i.e., will not contain patient identifying information.

6. If appropriate, has a Certificate of Confidentiality been obtained? *Yes*

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Participation in the study has the potential to result in decreased frequency of binge eating and weight loss for at least some patients through free assessments and treatment. More generally, the low risk is offset by the potential of identifying effective behavioral and pharmacological treatments for reducing binge eating and weight in obese persons with binge eating disorder, which would be beneficial to many persons who experience these conditions.

Participation in the Biosensor Arm carries low risk, which is offset by the potential knowledge to be gained about identifying triggers of binge eating episodes and connections between stress and eating behavior, which would be beneficial to many people who experience binge eating.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   Alternatives include community referrals for cognitive behavioral therapy, behavioral weight loss, or medications.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Clinical trial assessments. Participants will be paid when they complete the assessments at the end of the treatment ($100), 6-Month Follow-up ($100), and 12-Month Follow-up ($100). Participants who drop out of the trial will be invited to return for the follow-up evaluations. At each assessment, conditions for receiving compensation include completion of surveys, bloodwork, and interview.

   Lab sessions. Participants will receive additional payment when they complete human laboratory sessions pre-treatment ($200) and at the end of treatment ($200). Participants can also earn up to $31.50 during each lab session if they chose to delay the full 180 minutes.

   Month 1 Blood Draw. Participants will receive additional payment when they complete their blood draw one month into treatment ($10).

   Biosensor. Participants who are part of the 6-week assessment with biosensor equipment can earn up to $300 if they complete all assessments and return the equipment. Participants can earn up to $300 for wearing the Garmin band and responding to the prompts daily for the 6 weeks (42 days). Participants can earn $6 per day if they respond to all prompts. If they do not respond to 90% of the prompts each day, they will earn $0.50 for each prompt they did respond to that day. The Garmin bands and Android phones must be returned to the Research Team at the end of the 6-weeks. Once the participant has completed the 6-weeks and returned the equipment, they will earn a $48 Completion/Return Bonus. If the Garmin band and/or phone are not returned, the participant will keep the items in lieu of payment and will not receive any additional compensation.

   Therefore, the total payment participants may receive is up to $1073. Our experience with numerous treatment and human laboratory studies has indicated that this incentive results in a high retention rate for follow-ups which is essential for the study.

   Subjects will be compensated for parking for research study appointments at the HRU/CSRU. They must show their parking ticket to the Research Staff for verification. Parking tickets will be returned to the subject so they are able to exit the parking lots and they will sign a Parking Voucher for the money received.

   Biosensor Arm: Participants that complete the 6-week assessment with the biosensor equipment can earn up to $402 if they complete all assessments and return the equipment. Participants will receive $25 for completing the baseline set of questionnaires and $25 for completing the final set of questionnaires. They can earn up to $252 for wearing the Garmin band and responding to the prompts daily for the 6 weeks (42 days). Participants can earn $6 per day if they respond to all prompts. If they do not respond to 80% of the prompts each day, they will earn $0.50 for each prompt they did respond to that day. The Garmin bands and Android

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phones must be returned to the Research Team at the end of the 6-weeks. Once the participant has completed the 6-weeks and returned the equipment, they will earn a $100 Completion/Return Bonus. If the Garmin band and/or phone are not returned, the participant will keep the items in lieu of payment and will not receive any additional compensation.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   Psychological assessment, labwork, and treatment will be provided at no cost to participants, their insurance, health plan benefits nor other third party payer. Participants will be asked to provide information from a recent (within one year) physical with their primary healthcare provider. If they have not had a physical within the past year, we will ask them to obtain a physical prior to participating in the study. A physical exam with their own primary healthcare provider would be at the participant's (or the participant's insurance) cost. (Note: In research we have conducted in the past with patients diagnosed with binge eating disorder, the majority of patients had a physical within the past year.)

   Biosensor Arm: Participants will be provided with the Garmin band and the Android smartphone to use for the 6-week monitoring period at no cost.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs?

      Yes. Referrals for treatment will be made.

   b. Where and from whom may treatment be obtained?

      If the participant is injured as a direct result of participation in this research study, the medical staff at the Yale-New Haven Hospital would be available to provide immediate emergency care, short-term hospitalization and/or short-term outpatient care.

   c. Are there any limits to the treatment being provided?

      If the participant is injured as a direct result of participation in this research study, the treatment will be determined by the medical provider(s).

   d. Who will pay for this treatment?

      The participant or participant's insurance carrier will be billed for the cost of this treatment. There are no plans to compensate the participant for physical or mental disability, lost wages, or any other losses or damages occurring over the long term or if an injury becomes apparent after participation in the study has ended. However, by agreeing to participate in this research study, the participant is not waiving or giving up any legal rights to seek compensation. Participants who believe they have been injured should contact the Principal Investigator, Dr. Carlos Grilo at 203-785-2792 immediately.

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e. How will the medical treatment be accessed by subjects?

Referrals will be provided.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☒ No☐

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☒ No ☐

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes ☒ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☒

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☒

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

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1. Hudson JI, Hiripi, E., Pope., H. G., & Kessler, R. C. The prevalence and correlates of eating disorders in the National Comorbidity Survey and Replication. *Biological Psychiatry* 2007; **61**: 348-58.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Publishing 2013.
3. Stunkard AJ. Eating patterns and obesity. *Psychiatric Quarterly* 1959; **33**: 284-95.
4. Grilo CM, White MA. A controlled evaluation of the distress criterion for binge eating disorder. *Journal of consulting and clinical psychology* 2011; **79**: 509-14.
5. Hudson JI, Hiripi E, Pope HG, Jr., Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatry* 2007; **61**: 348-58.
6. Johnson JG, Spitzer RL, Williams JBW. Health problems, impairment and illnesses associated with bulimia nervosa and binge eating disorder among primary care and obstetric gynaecology patients. *Psychological medicine* 2001; **31**: 1455-66.
7. Wilfley DE, Wilson GT, Agras WS. The clinical significance of binge eating disorder. *The International journal of eating disorders* 2003; **34 Suppl**: S96-106.
8. Kessler RC, Berglund PA, Chiu WT et al. The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. *Biol Psychiatry* 2013; **73**: 904-14.
9. Yanovski SZ. Binge eating disorder and obesity in 2003: Could treating an eating disorder have a positive effect on the obesity epidemic? *Int J Eat Disord* 2003; **34**: S117-20.
10. Hudson JI, Lalonde JK, Coit CE et al. Longitudinal study of the diagnosis of components of the metabolic syndrome in individuals with binge-eating disorder. *Am J Clin Nutr* 2010; **91**: 1568-73.
11. Marques L, Alegria M, Becker AE et al. Comparative prevalence, correlates of impairment, and service utilization for eating disorders across US ethnic groups: Implications for reducing ethnic disparities in health care access for eating disorders. *The International journal of eating disorders* 2011; **44**: 412-20.
12. Striegel-Moore RH, Franko DL. Should binge eating disorder be included in the DSM-V? A critical review of the state of the evidence. *Annu Rev Clin Psychol* 2008; **4**: 305-24.
13. Pope HG, Jr., Lalonde JK, Pindyck LJ et al. Binge eating disorder: a stable syndrome. *Am J Psychiatry* 2006; **163**: 2181-3.
14. Allison KC, Grilo CM, Masheb RM, Stunkard AJ. Binge eating disorder and night eating syndrome: a comparative study of disordered eating. *Journal of consulting and clinical psychology* 2005; **73**: 1107-15.
15. Grilo CM, Masheb RM, White MA. Significance of overvaluation of shape/weight in binge-eating disorder: comparative study with overweight and bulimia nervosa. *Obesity* 2010; **18**: 499-504.
16. Grilo CM, Crosby RD, Masheb RM et al. Overvaluation of shape and weight in binge eating disorder, bulimia nervosa, and sub-threshold bulimia nervosa. *Behaviour research and therapy* 2009; **47**: 692-6.
17. Grilo CM, White MA, Masheb RM. DSM-IV psychiatric disorder comorbidity and its correlates in binge eating disorder. *Int J Eat Disord* 2009; **42**: 228-34.
18. Hudson JI, Lalonde JK, Coit CE et al. Longitudinal study of the diagnosis of components of the metabolic syndrome in individuals with binge-eating disorder. *The American journal of clinical nutrition* 2010; **91**: 1568-73.

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19. Abraham TM, Massaro JM, Hoffmann U et al. Metabolic characterization of adults with binge eating in the general population: the Framingham Heart Study. *Obesity (Silver Spring)* 2014; **22**: 2441-9.
20. Reas DL, Grilo CM. Review and meta-analysis of pharmacotherapy for binge-eating disorder. *Obesity (Silver Spring)* 2008; **16**: 2024-38.
21. Wilson GT, Grilo CM, Vitousek KM. Psychological treatment of eating disorders. *Am Psychol* 2007; **62**: 199-216.
22. Reas DL, Grilo CM. Current and emerging drug treatments for binge eating disorder. *Expert opinion on emerging drugs* 2014; **19**: 99-142.
23. Reas DL, Grilo CM. Pharmacological treatment of binge eating disorder: update review and synthesis. *Expert opinion on pharmacotherapy* 2015; **16**: 1463-78.
24. McElroy SL, Arnold LM, Shapira NA et al. Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. *Am J Psychiatry* 2003; **160**: 255-61.
25. Claudino AM, de Oliveira IR, Appolinario JC et al. Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. *J Clin Psychiatry* 2007; **68**: 1324-32.
26. McElroy SL, Kotwal R, Guerdjikova AI et al. Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial. *J Clin Psychiatry* 2006; **67**: 1897-906.
27. McElroy SL, Kotwal R, Hudson JI et al. Zonisamide in the treatment of binge-eating disorder: an open-label, prospective trial. *J Clin Psychiatry* 2004; **65**: 50-6.
28. National Institutes of Clinical Excellence. Eating disorders—core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders. Clinical Guideline No. 9. National Institutes of Clinical Excellence: London, 2004 <http://www.nice.org.uk/page.aspx?o=101239>. 2004.
29. Grilo CM, Masheb RM, Wilson GT. Efficacy of cognitive behavioral therapy and fluoxetine for the treatment of binge eating disorder: A randomized double-blind placebo-controlled comparison. *Biol Psychiatry* 2005; **57**: 301-9.
30. Ricca V, Mannucci E, Mezzani B et al. Fluoxetine and fluvoxamine combined with individual cognitive-behaviour therapy in binge eating disorder: A one-year follow-up study. *Psychother Psychosom* 2001; **70**: 298-306.
31. McElroy SL, Hudson J, Ferreira-Cornwell MC et al. Lisdexamfetamine Dimesylate for Adults with Moderate to Severe Binge Eating Disorder: Results of Two Pivotal Phase 3 Randomized Controlled Trials. *Neuropsychopharmacology* 2016; **41**: 1251-60.
32. McElroy SL, Hudson JI, Mitchell JE et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry* 2015; **72**: 235-46.
33. Grilo CM, Masheb RM, Crosby RD. Predictors and moderators of response to cognitive behavioral therapy and medication for the treatment of binge eating disorder. *J Consult Clin Psychol* 2012; **80**: 897-906.
34. Appolinario JC, Bacaltchuk J, Sichieri R et al. A randomized, double-blind, placebo-controlled study of sibutramine in the treatment of binge-eating disorder. *Arch Gen Psychiatry* 2003; **60**: 1109-16.
35. Wilfley DE, Crow SJ, Hudson JI et al. Efficacy of sibutramine for the treatment of binge eating disorder: a randomized multicenter placebo-controlled double-blind study. *Am J Psychiatry* 2008; **165**: 51-8.

APPROVED BY THE YALE UNIVERSITY IRB 4/4/2022

36. Vetter ML, Faulconbridge LF, Webb VL, Wadden TA. Behavioral and pharmacologic therapies for obesity. *Nature reviews Endocrinology* 2010; **6**: 578-88.
37. Golay A, Laurent-Jaccard A, Habicht F et al. Effect of orlistat in obese patients with binge eating disorder. *Obes Res* 2005; **13**: 1701-8.
38. Grilo CM, Masheb RM, Salant SL. Cognitive behavioral therapy guided self-help and orlistat for the treatment of binge eating disorder: A randomized, double-blind, placebo-controlled trial. *Biol Psychiatry* 2005; **57**: 1193-201.
39. Grilo CM, White MA. Orlistat with behavioral weight loss for obesity with versus without binge eating disorder: randomized placebo-controlled trial at a community mental health center serving educationally and economically disadvantaged Latino/as. *Behav Res Ther* 2013; **51**: 167-75.
40. Colman E, Golden J, Roberts M et al. The FDA's assessment of two drugs for chronic weight management. *N Engl J Med* 2012; **367**: 1577-9.
41. Miller LE. Lorcaserin for Weight Loss: Insights Into US Food and Drug Administration Approval. *Journal of the Academy of Nutrition and Dietetics* 2013; **113**: 25-30.
42. Smith SR, Weissman NJ, Anderson CM et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010; **363**: 245-56.
43. Grilo CM, Masheb RM, Wilson GT et al. Cognitive-behavioral therapy, behavioral weight loss, and sequential treatment for obese patients with binge-eating disorder: A randomized controlled trial. *J Consult Clin Psychol* 2011; **79**: 675-85.
44. Wilson GT, Wilfley DE, Agras WS, Bryson SW. Psychological treatments of binge eating disorder. *Arch Gen Psychiatry* 2010; **67**: 94-101.
45. Blaine BE, Rodman J, Newman JM. Weight loss treatment and psychological well-being: a review and meta-analysis. *J Health Psychol* 2007; **12**: 66-82.
46. Grilo CM. Psychological and behavioral treatments for binge-eating disorder. *J Clin Psychiatry* 2017; **78 Suppl 1**: 20-4.
47. Greenway FL, Whitehouse MJ, Guttadauria M et al. Rational design of a combination medication for the treatment of obesity. *Obesity (Silver Spring)* 2009; **17**: 30-9.
48. Smith SR, Fujioka K, Gupta AK et al. Combination therapy with naltrexone and bupropion for obesity reduces total and visceral adiposity. *Diabetes Obes Metab* 2013; **15**: 863-6.
49. Greenway FL, Fujioka K, Plodkowski RA et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010; **376**: 595-605.
50. Apovian CM, Aronne L, Rubino D et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)* 2013; **21**: 935-43.
51. Han DH, Hwang JW, Renshaw PF. Bupropion sustained release treatment decreases craving for video games and cue-induced brain activity in patients with Internet video game addiction. *Exp Clin Psychopharmacol* 2010; **18**: 297-304.
52. Stahl SM, Pradko JF, Haight BR et al. A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reuptake Inhibitor. *Primary care companion to the Journal of clinical psychiatry* 2004; **6**: 159-66.
53. Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. *J Pharmacol Exp Ther* 2000; **295**: 321-7.
54. Hurt RD, Sachs DP, Glover ED et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997; **337**: 1195-202.

APPROVED BY THE YALE UNIVERSITY IRB 4/4/2022

55. Farley AC, Hajek P, Lycett D, Aveyard P. Interventions for preventing weight gain after smoking cessation. *Cochrane Database Syst Rev* 2012; **1**: CD006219.
56. Li Z, Maglione M, Tu W et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005; **142**: 532-46.
57. Sheehan DV, Lecrubier Y, Sheehan KH et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; **59 Suppl 20**: 22-33.
58. Fairburn CG, Cooper Z. The Eating Disorder Examination. In: Fairburn CG, Wilson GT, eds. *Binge Eating: Nature, Assessment, and Treatment*. New York: Guilford Press 1993:317-60.
59. Grilo CM, Masheb RM, Wilson GT. Different methods for assessing the features of eating disorders in patients with binge eating disorder: A replication. *Obes Res* 2001; **9**: 418-22.
60. Wilfley DE, Welch RR, Stein RI et al. A randomized comparison of group cognitive-behavioral therapy and group interpersonal psychotherapy for the treatment of overweight individuals with binge-eating disorder. *Arch Gen Psychiatry* 2002; **59**: 713-21.
61. Fairburn CG, Beglin SJ. Assessment of eating disorders: interview or self-report questionnaire? *The International journal of eating disorders* 1994; **16**: 363-70.
62. Grilo CM, Masheb RM, Wilson GT. A comparison of different methods for assessing the features of eating disorders in patients with binge eating disorder. *Journal of consulting and clinical psychology* 2001; **69**: 317-22.
63. Reas DL, Grilo CM, Masheb RM. Reliability of the Eating Disorder Examination-Questionnaire in patients with binge eating disorder. *Behav Res Ther* 2006; **44**: 43-51.
64. Sysko R, Walsh BT, Fairburn CG. Eating Disorder Examination-Questionnaire as a measure of change in patients with bulimia nervosa. *Int J Eat Disord* 2005; **37**: 100-6.
65. Blomquist KK, Roberto CA, Barnes RD et al. Development and validation of the eating loss of control scale. *Psychol Assess* 2014; **26**: 77-89.
66. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *Journal of Psychosomatic Research* 1985; **29**: 71-83.
67. Foster GD, Wadden TA, Swain RM et al. The Eating Inventory in obese women: clinical correlates and relationship to weight loss. *Int J Obes Relat Metab Disord* 1998; **22**: 778-85.
68. Grilo CM, Masheb RM. Correlates of body image dissatisfaction in treatment-seeking men and women with binge eating disorder. *Int J Eat Disord* 2005; **38**: 162-6.
69. Safer DL, Agras WS, Lowe MR, Bryson S. Comparing two measures of eating restraint in bulimic women treated with cognitive-behavioral therapy. *Int J Eat Disord* 2004; **36**: 83-8.
70. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. *Appetite* 2009; **52**: 430-6.
71. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res* 2001; **3**: 7-16.
72. White MA, Whisenhunt BL, Williamson DA et al. Development and validation of the food-craving inventory. *Obes Res* 2002; **10**: 107-14.
73. White MA, Grilo CM. Psychometric properties of the Food Craving Inventory among obese patients with binge eating disorder. *Eat Behav* 2005; **6**: 239-45.
74. Lowe MR, Butryn ML, Didie ER et al. The Power of Food Scale. A new measure of the psychological influence of the food environment. *Appetite* 2009; **53**: 114-8.
75. Cappelleri JC, Bushmakin AG, Gerber RA et al. Evaluating the Power of Food Scale in obese subjects and a general sample of individuals: development and measurement properties. *Int J Obes (Lond)* 2009; **33**: 913-22.

APPROVED BY THE YALE UNIVERSITY IRB 4/4/2022

76. Rejeski WJ, Burdette J, Burns M et al. Power of food moderates food craving, perceived control, and brain networks following a short-term post-absorptive state in older adults. *Appetite* 2012; **58**: 806-13.
77. Beck AT, Steer R. Manual for revised Beck Depression Inventory. New York: Psychological Corporation 1987.
78. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clin Psychol Rev* 1988; **8**: 77-100.
79. Russell JA. A circumplex model of affect. *J Personality Social Psychol* 1980; **39**: 1161-78.
80. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473-83.
81. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993; **31**: 247-63.
82. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994; **32**: 40-66.
83. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci* 1985; **10**: 141-6.
84. Miller DJ, Freedson PS, Kline GM. Comparison of activity levels using the Caltrac accelerometer and five questionnaires. *Med Sci Sports Exerc* 1994; **26**: 376-82.
85. Buysse DJ, Reynolds CF, 3rd, Monk TH et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28**: 193-213.
86. Bohn MJ, Babor TF, Kranzler HR. The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. *J Stud Alcohol* 1995; **56**: 423-32.
87. Reinert DF, Allen JP. The alcohol use disorders identification test: an update of research findings. *Alcohol Clin Exp Res* 2007; **31**: 185-99.
88. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983; **24**: 385-96.
89. Jilcott S, Ammerman A, Sommers J, Glasgow RE. Applying the RE-AIM framework to assess the public health impact of policy change. *Ann Behav Med* 2007; **34**: 105-14.
90. Levine J, Schooler NR. General versus specific inquiry with SAFTEE. *J Clin Psychopharmacol* 1992; **12**: 448.
91. Posner K, Brown GK, Stanley B et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011; **168**: 1266-77.
92. Diggle P, Heagerty P, Liang K, Zeger S. Analysis of Longitudinal Data. *Oxford University Press*. 2nd Edition ed 2002.
93. Hedeker D, Gibbons R. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *psychological Methods* 1997; **2**: 64-78.
94. O'Malley SS, Sinha R, Grilo CM et al. Naltrexone and cognitive behavioral coping skills therapy for the treatment of alcohol drinking and eating disorder features in alcohol-dependent women: a randomized controlled trial. *Alcohol Clin Exp Res* 2007; **31**: 625-34.
95. Malcolm R, O'Neil PM, Sexauer JD et al. A controlled trial of naltrexone in obese humans. *Int J Obes* 1985; **9**: 347-53.
96. Billes SK, Greenway FL. Combination therapy with naltrexone and bupropion for obesity. *Expert opinion on pharmacotherapy* 2011; **12**: 1813-26.

APPROVED BY THE YALE UNIVERSITY IRB 4/4/2022

97. White MA, Grilo CM. Bupropion for overweight women with binge-eating disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2013; **74**: 400-6.
98. Cowley MA, Smart JL, Rubinstein M et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature* 2001; **411**: 480-4.
99. Marsh DJ, Hollopeter G, Huszar D et al. Response of melanocortin-4 receptor-deficient mice to anorectic and orexigenic peptides. *Nat Genet* 1999; **21**: 119-22.
100. Cone RD, Cowley MA, Butler AA et al. The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. *Int J Obes Relat Metab Disord* 2001; **25 Suppl 5**: S63-7.
101. Wadden TA, Foreyt JP, Foster GD et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity* 2011; **19**: 110-20.
102. Greenway FL, Dunayevich E, Tollefson G et al. Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. *J Clin Endocrinol Metab* 2009; **94**: 4898-906.

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