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CLINICAL STUDY PROTOCOL

A Behavioral Treatment with Sequenced Adjunctive Pharmacotherapy for Weight Regain After Bariatric Surgery: A Pilot Study

Protocol Number

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Sponsor

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Confidentiality Statement:

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Synopsis

Primary Objective

This study aims to evaluate the feasibility and acceptability of adding a specific pharmacological treatment (Naltrexone+Bupropion combination [NB]) to behavioral treatment for non-responders among adults experiencing weight regain following metabolic and bariatric surgery (MBS). A behavioral treatment will be given to all subjects as the primary treatment. After one month of behavioral treatment, patients who do not show a "response" (based on weight-loss data) will begin a trial of a specific medication (in addition to continuing the behavioral therapy); repeated multi-modal assessments will assess whether the combined approach augments the behavioral therapy.

We hypothesize that the treatments will be feasible and acceptable to subjects, and that subjects will experience significant weight loss and improvements in psychosocial functioning. More specifically, it is hypothesized that early responders to BWL will show weight loss during the trial, while the addition of NB will aid early non-responders in achieving weight loss.

Secondary Objectives (if applicable)

This pilot will also examine whether augmenting behavioral treatment with NB results in improvements in psychosocial functioning.

Study Duration

Study duration will be three months.

Study Design

The proposed clinical trial will pilot the feasibility and acceptability of delivering behavioral weight loss treatment (BWL) to adults struggling with weight regain after MBS. All participants will receive BWL treatment. Early weight loss responders will continue with BWL for the duration of treatment, while early non-responders will be given NB as an adjunct to BWL. The pilot will also examine whether augmenting behavioral treatment with NB results in weight loss and improvements in psychosocial functioning.

Study Population

N=25 adults (aged 18-65) who experience weight regain after MBS will participate in the study. Weight regain will be defined by the recommended definition of weight regain in the field, that is, weight regain defined as the percentage of maximum weight lost ([100*(post-nadir weight — nadir weight)]/(pre-surgery weight — nadir weight). Weight regain based on this definition was the best indicator of poor clinical outcomes.

Number of Participants

N=25

Number of Study Sites 1
Primary Outcome Variables Primary outcomes will include: 1) feasibility, 2) acceptability, and 3) weight loss. 1) Feasibility will be determined by examining enrollment, number of sessions attended, compliance, and retention. 2) Treatment credibility and satisfaction will be examined via self-report. 3) To examine weight changes, we will examine percent total weight loss for the entire participant group. We will also compare percent weight loss for the two responder groups.
Secondary and Exploratory Outcome Variables (if applicable) Secondary outcomes include changes in psychosocial functioning including eating-disorder psychopathology, depressive symptoms, and food cravings.

Abbreviations

Abbreviation	Explanation
NB	Naltrexone+Bupropion
MBS	Metabolic and Bariatric Surgery
RYGB	Roux-en-Y gastric bypass
LSG	Sleeve gastrectomy
BMI	Body Mass Index
BWL	Behavioral Weight Loss

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1 - Introduction

1.1 Introductory Statement

Metabolic and bariatric surgery (MBS) is the most effective treatment for severe obesity and associated sequalae. Despite MBS' overall efficacy, weight regain with recurrence and/or onset of medical and psychological comorbidities is common and a matter of great concern. Very little is known about post-MBS treatments for weight regain. The goals of this proposal are to evaluate the feasibility and acceptability of evidence-based obesity treatments in post-MBS patients. All eligible subjects who experience weight regain after MBS will be given behavioral treatment (BWL). After one month of BWL treatment, "treatment response" will be determined based on early weight loss status because of its strong prognostic significance for optimal weight loss outcomes. Early weight-loss responders will continue BWL treatment, while *non*-responders will be given a pharmacologic agent to augment BWL treatment. This study aims to explore whether the addition of specific pharmacotherapy to BWL amongst initial non-responders improves outcomes. The study will compare the two treatment conditions and will examine within-group weight and psychosocial changes over time in the combined treatment condition; these data will serve as pilot data and represent effect-size estimates to design and power larger definitive treatment trials testing combined behavioral and pharmacological interventions and stepped-care approaches to prevent weight regain after MBS.

2 - Background

2.1 Background/prevalence of research topic

Individuals with obesity suffer from increased risk of cardiovascular morbidity and mortality, as well as type 2 diabetes, obstructive sleep apnea, dyslipidemias, asthma, and several cancers (1). Rates of obesity (defined as body mass index (BMI) ≥ 30) have steadily increased over the last few decades to a staggering 39.8% (2). Alarmingly, obesity prevalence in the general adult population is expected to rise to over 51%, with a 130% increase in severe obesity (BMI ≥ 40) by 2030 (3). These rates and projected future increases are deeply concerning given the substantial disease and economic burden of obesity (4). As severe obesity rates continue to rapidly rise, MBS is expected to increase. MBS is the most effective and enduring treatment for severe obesity and results in impressive acute and long-term weight loss and improvement and/or remission of medical comorbidities (5)and psychosocial sequalae (6). Currently, laparoscopic Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (LSG) are the most commonly performed MBS procedures (7).

Despite these impressive data, weight trajectories following both forms of MBS have significant variability. Data from the NIH-funded Longitudinal Assessment of Bariatric Surgery (LABS) consortium found substantial average weight loss by 3 and 7 years post-RYGB, with most of the weight loss occurring during the first year post-surgery (8). Nonetheless, weight outcomes have marked heterogeneity in both RYGB and LSG. Lowest maximal weight loss was as low as -1.1% for LSG and -4.1% for RYGB, with ranges of 1.1-58.3% for LSG and 4.1-60.9% for RYGB (9). Even for those with optimal outcomes, weight regain is not uncommon and there exists marked variability in weight losses achieved after MBS (9). Additionally, worsening or recurrence of medical and psychological comorbidities, is of great concern (10).

Post-MBS Treatment is Needed.

Behavioral Treatment. Although the field recognizes the need for post-operative behavioral or psychosocial allied treatments, there is little guidance as to what should be provided based on empirical data. Of the limited research to date which has examined pre- and post-MBS interventions to improve weight outcomes, results suggest that pre-surgical interventions have largely been ineffective at producing significant weight differences post-surgically (11); however, behavioral treatments may have utility post-surgery (12).

Pharmacologic Treatment. Another promising, yet understudied, avenue involves the use of weight-loss medications after MBS. Emerging research suggests utility in weight-loss medications after MBS (13). The combination of Naltrexone and Bupropion (**NB**), also known as "Contrave," is an optimal starting point due to its consistent weight-loss evidence base, affordable costs, tolerable side-effects, safety profile, and putative mechanisms of action. In 2014, the FDA approved NB for obesity following empirical support from several RCTs performed with obesity (14). These RCTs reported significant clinically-meaningful weight losses with naltrexone plus sustained-release bupropion combined in fixed-dose pills. These

findings supporting NB medication are consistent with large RCTs which reported greater weight loss with NB than placebo (-6.5 vs -1.2% (14)). Although the name brand (Contrave) is expensive, the combination of Naltrexone and Bupropion are available at affordable prices. Putative mechanisms of action for NB seem relevant for post-MBS patients who might also be struggling with maladaptive eating behaviors, such as loss-of-control (LOC) eating. LOC eating and related eating-disorder psychopathology are consistent predictors of poor outcomes after MBS (15). As reviewed in the preliminary data section below, NB may be helpful in both reducing problematic eating such as LOC eating (i.e., binge eating) and weight loss. Putative mechanisms of action for NB is especially relevant for reducing LOC eating and weight per hypothesized effects on brain regions implicated in the regulation of food intake and weight based on the mechanisms of action of leptin (16).

Early Weight Loss. Meaningful early weight loss, ranging from 0.5 to 3% weight loss during the first 1-2 months of treatment, is a consistent predictor of weight loss by the end of treatment and longer-term (17). Earlier work has found that at least 1% weight loss early in treatment was associated with meaningful weight loss at the end of treatment (17).

Collectively, the lack of evidence-based treatments after MBS remains a critical and concerning gap in the field. An evidence base is urgently needed to direct the field in managing obesity after surgical intervention. Given that BWL and NB are both empirically-based weight-loss treatments, the proposed study will pilot the feasibility and acceptability of delivering behavioral treatment (BWL) to adults struggling with weight regain after MBS. Early weight loss responders will continue with BWL for the duration of treatment, while early non-responders will be given NB as an adjunct to BWL. The pilot will also examine whether augmenting behavioral treatment with NB results in weight loss and improvements in psychosocial functioning. These data will inform designs and provide effect size data to power larger definitive trials examining stepped care approaches with behavioral and pharmacological interventions for post-MBS.

3 - Rationale/Significance

3.1 Problem Statement

MBS is the most effective treatment for severe obesity and associated sequalae. Despite MBS' overall efficacy, weight regain with recurrence and/or onset of medical and psychological comorbidities is common and a matter of great concern. Very little is known about post-MBS treatments for weight regain.

3.2 Purpose of Study/Potential Impact

The goals of this proposal are to evaluate the feasibility and acceptability of evidence-based obesity treatments in post-MBS patients. All eligible subjects who experience weight regain after MBS will be given BWL. After one month of BWL treatment, "treatment response" will be determined based on early weight loss status because of its strong prognostic significance for optimal weight loss outcomes. Early weight-loss responders will continue BWL treatment, while *non*-responders will be given a pharmacologic agent to augment BWL treatment. This study aims to explore whether the addition of specific pharmacotherapy to BWL amongst initial non-responders improves outcomes. The study will compare the two treatment conditions and will examine within-group weight and psychosocial changes over time in the combined treatment condition; these data will serve as pilot data and represent effect-size estimates to design and power larger definitive treatment trials testing combined behavioral and pharmacological interventions and stepped-care approaches to prevent weight regain after MBS.

3.3.1 Potential Risks

The primary risks of this study are the BWL therapy, the pharmacologic therapy with NB, the assessment procedures, and lack of efficacy.

BWL: BWL is an established and widely-used intervention for obesity. The only foreseeable risks include some mild discomfort or embarrassment when discussing eating patterns or body image concerns. Previous controlled clinical trials with similar interventions with large numbers of similar patients have not reported problems. Any troublesome effects would be readily identifiable by the experienced research clinicians during the repeated evaluations. Thus, the risks of BWL are judged to be minimal.

NB: NB combination is FDA-approved for the treatment of obesity. Both medications will be used in the present study. NB has demonstrated safety, tolerability, and efficacy for patients with obesity treated over much longer periods of time (>12 months) than in the present study (Greenway et al., 2010). 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. Less common side effects include risk of seizure, increase in blood pressure and heart rate, hepatotoxicity, and angle-closure glaucoma. 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 none of the observed events

were judged to be related to the study. In keeping with the FDA advisory pertaining to antidepressants, including bupropion, the following information will be included in the study consent forms:

"The U.S. Food and Drug Administration (FDA) has issued an Advisory cautioning health care providers, patients, and families to closely watch individuals taking bupropion for signs of their depression getting worse and for thoughts of killing or harming themselves, especially during the first several weeks that bupropion is being taken. Patients and their families should watch for and promptly report new symptoms. For example, report to the study doctor as soon as possible any signs of impulsivity (taking action or saying something without thinking first), agitation (feeling nervous or finding sitting still very difficult), and panic attacks (extreme fear without apparent reason)."

To monitor changes in depressive symptoms, patients will be asked to complete the PHQ-9 at monthly clinic visits. The research clinicians, who are trained and supervised by licensed psychologists in suicidal assessment, will review PHQ-9s during the clinic visit, and will asked pointed questions pertaining to suicidality/suicidal ideation (i.e., suicidal thoughts, plan, means, and intent) 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. If warranted, the participant will be given a referral and safety planning will be implemented. If any participant experiences adverse reactions, or if side effects are too severe, the medication will be discontinued.

Assessments: Completion of the assessment procedures may cause some mild anxiety or embarrassment to some patients. Drawing blood from a vein to perform necessary laboratory tests is quite safe. Sometimes a bruise will occur at the puncture site and on very rare occasions a blood clot or infection may occur. If this occurs, appropriate treatment will be instituted immediately.

Failure to Improve: There is a chance that the patients will not lose weight or will gain weight during the study. Patients will be withdrawn from the study if their clinical condition deteriorates to a significant degree. Our experience with numerous RCTs is that this is quite rare.

3.3.2 Potential Benefits

Subjects will receive potentially beneficial weight loss treatment(s) that are empirically-supported. There is substantial importance in the knowledge to be gained in this study. Finding ways to identify, understand, and improve treatments for weight regain after MBS is critically important to address this important health problem. The dearth of treatment research with this subgroup, particularly with pharmacological methods, is strikingly at odds with the public health significance and prevalence of obesity and MBS. Given the modest risks associated with the treatments and study procedures and the substantial potential knowledge to be gained, the benefit to risk ratio is very favorable.

4 - Study Objectives

4.1 Hypothesis

We hypothesize that the treatments will be feasible and acceptable to subjects, and that subjects will experience significant weight loss and improvements in psychosocial functioning. More specifically, it is hypothesized that early responders to BWL will show weight loss during the trial, while the addition of NB will aid early non-responders in achieving weight loss.

4.2 Primary Objective

This study aims to evaluate the feasibility and acceptability of adding a specific pharmacological treatment to behavioral treatment for non-responders among adults experiencing weight regain following MBS. A behavioral treatment will be given to all subjects as the primary treatment. After one month of behavioral treatment, patients who do not show a "response" (based on weight-loss data) will begin a trial of a specific medication (in addition to continuing the behavioral therapy); repeated multi-modal assessments will assess whether the combined approach augments the behavioral therapy.

We hypothesize that the treatments will be feasible and acceptable to subjects, and that subjects will experience significant weight loss and improvements in psychosocial functioning. More specifically, it is hypothesized that early responders to BWL will show weight loss during the trial, while the addition of NB will aid early non-responders in achieving weight loss.

4.3 Secondary Objectives (if applicable)

This pilot will also examine whether augmenting behavioral treatment with NB results in improvements in psychosocial functioning.

5 - Study Design

5.1 General Design Description

A behavioral treatment will be given to all subjects as the primary treatment. After one month of behavioral treatment, patients who do not show a "response" (based on weight-loss data) will begin a trial of a specific medication (in addition to continuing the BWL); repeated multi-modal assessments will assess whether the combined approach augments the behavioral therapy.

5.1.1 Study Date Range and Duration

Subjects will participate in the treatment trial for three months starting with an initial evaluation. If eligible, subjects will receive three months of BWL treatment (early non-responders will be given an adjunct medication). When treatment ends, subjects will participate in a post-treatment evaluation. Duration of the entire study will be three months. Anticipated start date is February 1, 2021 with an end date of January 31, 2023.

5.1.2 Number of Study Sites

1

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

Primary outcomes will include: 1) feasibility, 2) acceptability, and 3) weight loss.

1) Feasibility will be determined by examining enrollment, number of sessions attended, compliance, and retention.

2) Treatment credibility and satisfaction will be examined via self-report.

3) To examine weight changes, we will examine percent total weight loss for the entire participant group. We will also compare percent weight loss for the two responder groups.

5.2.2 Secondary and Exploratory Outcome Variables (if applicable)

Secondary outcomes will include psychosocial functioning such as eating-disorder psychopathology measured by the Eating Disorder Examination, depressive symptoms measured by the Patient-Health Questionnaire 9, and food craving measured by the Food Craving Inventory.

5.3 Study Population

Adults (aged 18-65) who experience weight regain after MBS (RYGB or LSG) will be recruited to participate in the study. Weight regain will be defined by the recommended definition of weight regain in the field, that is, weight regain defined as the percentage of maximum weight lost ([100*(post-nadir weight — nadir weight)]/(pre-surgery weight — nadir weight). Weight regain based on this definition was the best indicator of poor clinical outcomes.

5.3.1 Number of Participants

N=25 adults who underwent MBS at the Yale bariatric surgery center will be recruited to participate in the study.

5.3.2 Eligibility Criteria/Vulnerable Populations

Inclusion criteria: To be included in the trial, a prospective participant must:

1. Be in the age range ≥18 years of age and ≤65 years of age.
2. Have a BMI ≥30 (or BMI ≥27 with a medical comorbidity) and BMI ≤ 50
3. Have had laparoscopic Roux-en-Y gastric bypass or sleeve gastrectomy at a Yale bariatric surgery center
4. Experience weight regain after surgery
5. Had a physical during the past year
6. Be an otherwise healthy subject without uncontrolled medical problems, as determined by the study physician and medical co-investigators (physical examination, laboratory studies).
7. Read, comprehend, and write English at a sufficient level to complete study-related materials.
8. Provide a signed and dated written informed consent prior to study participation.
9. Be available for participation in the study for up to 3 months.

Exclusion criteria: To enhance generalizability, exclusion criteria will be minimal, but consistent with study medication prescribing guidelines. A prospective participant will be excluded if he or she:

1. Has a predisposition to seizures (e.g., subject with a history or evidence of seizure disorder, febrile seizures during childhood, brain tumor, cerebrovascular disease, or significant head trauma; has a family history of idiopathic seizure disorder or is currently being treated with medications or treatment regimens that lower seizure threshold).
2. Has a history of anorexia nervosa or history of bulimia nervosa or current regular self-induced vomiting.
3. Is currently taking a medication that is a contraindication to NB medication (e.g., MAOI, opiates).
4. Is currently using other medications for weight loss.
5. Has a history of allergy or sensitivity to bupropion or naltrexone.
6. Has a co-existing psychiatric condition that requires hospitalization or more intensive treatment (such as bipolar mood disorders, psychotic illnesses, or severe depression)
7. Has untreated hypertension with a seated systolic blood pressure > 160 mmHg, diastolic blood pressure > 100 mmHg, or heart rate > 100 beats/minute.

8. Has a history of congenital heart disease, cardiovascular disease, cardiac arrhythmias requiring medication, or a history of cerebrovascular pathology including stroke.
9. Has current uncontrolled hypertension.
10. Has current uncontrolled Type I or Type II diabetes mellitus.
11. Has 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.
12. Has gallbladder disease.
13. Has a history of severe renal, hepatic, neurological, chronic pulmonary disease, or any other unstable medical disorder.
14. Has a recent history of drug or alcohol dependence.
15. Is currently in active treatment for eating or weight loss.
16. Is currently participating in another clinical study in which the subject is or will be exposed to an investigational or a non-investigational drug or device.
17. Is breast-feeding or is pregnant or is not using a reliable form of birth control.
18. Reports active suicidal or homicidal ideation.
19. History of poor eye health.

6 - Methods

6.1 Treatment - Drug

6.1.1 Identity of Investigational Product/New Drug

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. NB medication will combine naltrexone (50 mg/day) combined with bupropion (300 mg/day) taken daily.

Mechanisms of Action. Naltrexone, an opioid receptor antagonist, is approved to treat alcohol and opioid dependence [Marsh et al., 1999]. Naltrexone produces weight loss in lab animals but only minimal weight losses in people [Lavori & Dawson, 2007; Almirall et al., 2014]. Bupropion operates through dopaminergic, noradrenergic, and nicotinic acetyl-cholinergic mechanisms. 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 [Kalarchian et al., 2013; Krimpuri et al., 2018]. 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 [Almirall et al., 2012] reported preliminary, modest support for weight loss specifically in patients with obesity and binge-eating disorder.

NB Combination. The putative mechanisms of action for NB is especially relevant for reducing weight per hypothesized effects on brain regions implicated in the regulation of food intake based on research on the mechanisms of action of leptin [Almirall et al., 2014]. The anorectic effects of leptin result from its excitatory effects on pro-opiomelanocorin (POMC) neurons in the hypothalamus melancortin system [Chen et al., 2017; McElroy et al., 2015]. Stimulated POMC signaling decreases food intake, increases energy expenditure, but is then inhibited by endogenous feedback [Chen et al., 2017]. Thus, combining these two drugs will stimulate POMC neurons (bupropion) plus block endogenous feedback that inhibits POMC activity (naltrexone) [Rusch & Andris, 2007; Almirall et al., 2014]. This synergistic model received support both in vitro and in vivo studies [Rusch & Andris, 2007, McElroy et al., 2016].

Obesity Outcomes. Recently, several large RCTs have reported that the combination of these two medications (Naltrexone/Bupropion) were effective in promoting weight loss in individuals with obesity [Rusch & Andris, 2007; Elder et al., 2018; Mond et al., 2010; Citrome, 2015]. 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 pills. Most recently, Apovian, Aronne, 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% [Elder et al., 2008]; 52% vs. 15% [Gasior et al., 2017].

Risks. Several large-scale studies have found that this medication is safe and effective for the treatment of obesity [Rusch & Andris, 2007; Elder et al., 2008; Mond et al., 2010; Citrome, 2015]. 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 medication if symptoms develop. Risk of seizure may be minimized by adhering to the recommended dosing schedule and avoiding co-administration 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. Warning about Opioid Withdrawal: 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 if you are taking opioid medications of any kind and we will not include you in the study if we know or suspect you are using opiate-containing drugs.* In addition to structured clinical diagnostic interviews with our clinical-research staff and medical record reviews, we will perform lab urine test at Quest with potential subjects suspected of opiate usage.

6.1.2 Dosage, Admin, Schedule (if applicable)

NB Pharmacotherapy Treatment Protocol. Participants who do not respond to the first month of BWL treatment will have NB added to their treatment for the remaining two months of treatment. NB medication will comprise naltrexone (50 mg/day) combined with bupropion (300 mg/day) taken daily. In a previously conducted pilot study, the NB final dosage consisted of 50 mg/day naltrexone combined with 300 mg/day bupropion XL, which closely approximates the newly approved NB combination (Contrave) dosage for weight loss [Greenway et al., 2009; Greenway, Fujioka & Plodkowski, 2010; Smith et al., 2013; Wadden et al., 2011], but with advantages. One advantage is that the formulations of both medications used in this study are already available at substantially lower cost than Contrave (75% savings for retail purchase) and the smaller size of pills (in blinding) is better for patients following MBS. Importantly, the immediate release (IR) version of Bupropion will be used in the present study as recommended by clinical guidelines for MBS populations. Because MBS can lead to changes in medication absorption due to alterations of gut anatomy, clinical practice guidelines recommend avoiding extended-release formulations of medications and using immediate release formulations (de Sousa Prado Geraldo et al., 2014; Lorico, 2020, Vouri et al., 2021). Additionally, using normal-release naltrexone rather than the sustained release formulation available only in Contrave is not seen as a pharmacokinetic disadvantage in any way. Despite a short initial serum half-life, the pharmacologic activity of naltrexone is long-lived, with an effective half-life of over 3 days, consistent with the terminal phase of plasma clearance [Lee et al., 1988]. For this reason, naltrexone has been used effectively in clinical treatment using daily or less frequent dosing.

In the proposed RCT, our dosage follows standard and long-standing dosage for both naltrexone and bupropion used for related psychiatric problems. Per previous RCTs, a dosing escalation approach will be used [Greenway, Fujioka & Plodkowski, 2010; Wadden et al., 2011]. This dosing will continue for the remainder of the RCT unless a 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, they will be discontinued from the medication. Physician visits will be brief (10 -15 minutes), focusing on compliance with dosing and evaluating side effects. For participants taking medication for greater than 4 weeks, a 7-day taper will be provided.

Month 2	**NB Medication**	
Study Day	*Naltrexone Capsule*	*Bupropion IR Capsule*
1-7	--	150 mg once a day
8-study end	50 mg	150 mg twice a day

6.1.3 Method of Assignment/Randomization (if applicable)

NA

6.1.4 Blinding and Procedures for Unblinding (if applicable)

Participants will not be blind to behavioral and medication treatments. There is no placebo for this trial because NB is an evidence-based weight loss treatment.

6.1.5 Packaging/Labelling

Refer to medication package insert.

6.1.6 Storage Conditions

The medication will be stored and dispensed at the Yale Investigational Drug Services pharmacy.

6.2 Assessments

Assessment Procedures. Table 1 summarizes the assessment schedule and measures. Assessments will be done by *independent* evaluators *not* involved in the treatment delivery and *blind* to early weight loss responder status.

Assessment of Treatment Outcome and Time Course.

Percent total weight loss (%TWL) (measured weight across time points). Per standard reporting guidelines, %TWL will be determined by the following formula: [(Initial Pre-Treatment Weight) — (Post-Treatment Weight)] / [(Initial Pre-Treatment Weight)]*100.

Psychosocial/Behavioral Functioning listed below.

Informed consent will be obtained after complete study description, followed by interviews and surveys.

Interviews:

Eating Disorder Examination Interview — Bariatric Surgery Version (EDE-BSV) (18) an investigator-based interview will be the primary method for assessing loss-of-control eating, as well as severity of eating-disorder psychopathology.

Mini International Neuropsychiatric Interview-Version 7.0 (MINI) (19) is a brief structured interview for psychiatric disorders, which will provide data to characterize subjects.

Anthropometrics: Weight and **height** will be measured to calculate body mass index.

Self-Report Measures (baseline and repeated per Table 1):

Demographics: ethnicity/race, age, sex, education, and socio-economic status.

Eating Disorder Examination-Questionnaire Version with Instructions (**EDE-Q-I**) (20), which generates the same eating behavior and pathology data as the interview version, will be used across *all assessment points* given its low burden (*in addition to the EDE-BSV given during major assessment points*).

Food Craving Inventory (**FCI)** (21) assesses general and specific food cravings (**relevant for NB**) and comprises four subscales for different food groups. The FCI has been validated and psychometrically supported in studies with obesity and BED. The use of this craving instrument will allow direct comparison to the leading NB non-surgical obesity trials (14).

Patient Health Questionnaire-9 (PHQ-9) is a brief and widely-used measure of depression in diverse medical settings (22). Post-MBS depression was associated with poorer MBS outcomes in some studies and is relevant to the study medication.

Treatment Variables: Credibility ratings will be examined before beginning treatments and again after completing treatments. Treatment Compliance for BWL will include session attendance and self-monitoring compliance and counts, and pill count method for medication.

Adverse Events will be collected during clinic visits using adverse event checklist of the most commonly reported adverse events for NB to monitor safety.

6.2.1 Efficacy. NB is an FDA-approved medication for weight loss among individuals with obesity.

6.2.2 Safety/Pregnancy-related policy

Given the uncertain effects of medication during pregnancy, the following precautions will be taken for women of reproductive age who are sexually active and non-responders (those who will be starting NB medication) : 1) a pregnancy test will be required; 2) will be required 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, and 3) if a woman becomes pregnant after study entry, her medication will be discontinued.

6.2.2.1 Adverse Events Definition and Reporting

Adverse event data will be collected on an on-going basis. Adverse events data will be reviewed by the PI and co-investigators throughout this trial. 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 Yale IRB within 48 hours.

6.2.3 Pharmacokinetics (if applicable)

6.2.4 Biomarkers (if applicable)

6.3 Study Procedures

Subjects will participate in an initial evaluation to determine eligibility. Eligible participants who provide written informed consent will start BWL treatment which last for three months. The BWL treatment is a mixture of the published LEARN behavioral lifestyle weight control treatment developed by Brownell (2000) and the Diabetes Prevention Program (Knowler et al., 2002); the PI and research team has extensive experience administering BWL with patients with obesity, binge-eating disorder, and histories of bariatric surgery. BWL will be delivered weekly by research-clinicians according to treatment manuals that detail session-by-session procedures. These manuals closely parallel patient-version BWL self-care materials for the entire course of treatment and follow closely that used by Wadden et al. (2011) in the COR-BMOD Trial testing BWL and NB/placebo medication for obesity, but modified for post-MBS patients. Behavioral strategies (goal-setting, self-monitoring, stimulus control problem-solving) will be taught within a lifestyle approach for achieving dietary goals (augmented by portion size and caloric goals) and physical activity goals (to achieve 180 min/week of moderate physical activity). Research-clinicians will be trained in BWL by the research team and will be supervised and monitored over the course of treatment delivery to ensure quality adherence. After one month of BWL treatment, "treatment response" will be determined based on early weight loss status because of its strong prognostic significance for optimal weight loss outcomes. Early weight-loss responders will continue BWL treatment, while *non*-responders will be given a pharmacologic agent (NB) to augment BWL treatment for the remaining two months of treatment. Outcomes assessments will be done by independent evaluators not involved in the treatment delivery and blind to responder status. Participants will be asked to complete self-report surveys at the baseline evaluation, monthly during treatment, and at the end of treatment. For participants starting NB medication, they will be asked to have labs drawn to examine liver values for safety before starting medication and again after being on the medication for one month.

6.3.1 Study Schedule

Assessment Points	Baseline	during rx 1-Month	during rx 2-Month	POST rx 3-Month
Medical History, Height, MINI Psychiatric Interview,Demographics (i.e., sex, race)	▪			
EDE-BSV Interview, Treatment Credibility/Satisfaction	▪			▪
EDE-Q-I, FCI, PHQ-9, GPAQ, Weight, Adverse Events, Compliance	▪	▪	▪	▪

6.3.2 Informed Consent

Research clinicians (who have completed IRB and ethics training) will meet with potential participants to discuss the study and all procedures, treatments, and risks and obtain written informed consent. All potential participants will be free to decide whether or not to participate and are free to withdraw from the study at any time. Alternative treatments (both psychosocial and pharmacological options) will be discussed and referrals offered if requested. The written informed consent will be obtained after opportunity to discuss and address all questions. 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. A decision to not participate or to discontinue participation would not adversely influence future interactions with Yale, Yale School of Medicine, or the investigative group. The process of informed consent may be completed in-person or remotely. If completed remotely, the consent process will be conducted by one of two methods: 1) a consent form will be mailed or emailed to the participant. The participant will then mail back (or email back) the signed consent form to the study team for signature or 2) the consent form will be completed using the validated Part 11 version of REDCap. A copy of the final consent (signed by both parties) will be mailed or emailed to the participant for his/her records. For all consenting, a meeting will be held in-person or remotely (e.g., via Zoom) to discuss the study and informed consent process.

6.3.3 Screening

Pre-Screening: Participants responding to recruitment efforts will be screened by telephone. If participants prefer to answer some of the screening questions through the Yale Qualtrics system, participants will indicate their consent to the recruitment/screening process in the online system. Potentially eligible participants will be consented and evaluated in-person or remotely by trained supervised research clinicians (doctoral level and/or advanced trainees).

6.3.4 Recruitment, Enrollment and Retention

Participants will be recruited from the Yale Bariatric/Gastrointestinal Surgery Center of Excellence via flyers and posters at the bariatric center, provider referral, and patient mailings. Specifically, the bariatric team agreed to identify potential subjects during routine medical post-surgical evaluations and support group meetings. In addition, flyers and posters alerting potential subjects to the treatment study will be placed in the Yale Gastrointestinal Surgery/Bariatric Center. Flyers will also be placed on our program's website. Letters will be mailed to individuals who had MBS within the past five years at Yale. For the mailing, we will utilize the Yale Joint Data Analytics Team (JDAT) to identify potential subjects. JDAT creates updated list of individuals who have recently had bariatric surgery at Yale and ensures that letters are not sent to subjects who have opted out of research at Yale. Yale JDAT is able to identify potential subjects by specific parameters related to inclusion criteria such as age (18-65), and MBS (laparoscopic Roux-en-Y gastric bypass or sleeve gastrectomy) performed at Yale. A study flyer and letter describing the study (approved by the Yale IRB) will be mailed. If interested, individuals will have the opportunity to contact the study team for screening. *Previous experience with this recruitment process has been very successful and without adverse reactions (i.e., for NIH/NIDDK-funded bariatric trial R01 DK098492).* Participants who opted out of research will not be contacted.

Advertisements will ask participants to contact our research team if they are interested in the study. When potential participants call and/or respond to an online form, 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 in-person or remote (e.g., via Zoom) assessment.

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.

6.3.5 On Study Visits.

Participants may attend visits in-person at the Yale Program for Obesity, Weight, and Eating Research or remotely.

6.3.6 End of Study and Follow-up

Participants will be asked to attend a post-treatment (end of study) assessment, which will consist of an interview, measured weight, and completion of self-report surveys as indicated in the assessment schedule grid.

6.3.7 Removal of subjects

Withdrawal/attrition from treatments will be examined. Use of other treatments during the study will be assessed and considered in analyses. Patients will be asked about all forms of treatments during major assessments. Criteria for removal of patients from the study may include worsening depression, suicidal ideation, or failure to comply with medication. Previous experience suggests that worsening clinical status is rare; in such cases, Dr. Ivezaj and study physician would determine whether to remove the person from the study and provide referrals.

6.4 Statistical Method

6.4.1 Statistical Design and Analyses

To examine weight changes, we will examine percent total weight loss for the entire participant group. We will also compare percent weight loss for the two responder groups. We will use linear mixed effects models with treatment (BWL or BWL+NB medication), time and the interaction between treatment and time to examine percent weight loss. We will construct a 95% confidence interval for percent weight loss within the non-responder arm based on the mixed model above.

7 - Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

A compound consent form will be used (see attached).

7.2 Institutional Review Board (IRB) Review

IRB approval will be required prior to study enrollment.

7.3 Subject Confidentiality

Protecting Confidentiality: To ensure confidentiality, all participant research records will be kept in locked files in the Department of Psychiatry at the Yale University School of Medicine or on secure server at Yale. All research forms, interviews, measures, audiotapes, and computer data will be coded to ensure anonymity and will be kept in separate locked files. Data analysis and reporting will not allow for identification of any individual participants. All research personnel will be trained and supervised around confidentiality issues. The training will include formal Yale IRB modules with testing certification as well as HIPAA guidelines to follow around confidentiality. 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. Research records may be the subject of an audit by a regulatory agency. Organizations which have a responsibility for protecting human subjects, including the Yale Human Investigation Committee (HIC), may have access to the research records. Additionally, the funding agency (APF) may have access to the research records. The

subject'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 Insurance Portability and Accountability Act of 1996. All research personnel will be trained on HIC and HIPAA procedures.

7.4 Deviations/Unanticipated Problems

Deviations/unanticipated problems will be reported to the IRB.

7.5 Data Collection

Data collection is done by study staff who received and completed Yale trainings in human subjects, HIPAA, and good clinical practice and are approved by the HIC.

7.6 Data Quality Assurance

Data is cleaned and monitored by the study team.

7.7 Study Records

All participants will be assigned a study ID. Subsequently, participants will be identified only by that ID. 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 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 ID and date. Data will be saved on a secure server. 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.

7.8 Access to Source

7.9 Data or Specimen Storage/Security

Data are stored on a secure server and in locked file cabinets on a secure floor and building.

7.10 Retention of Records

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.

7.11 Study Monitoring

Monitoring for data integrity and safety will be the responsibility of the investigators and the Yale IRB (Human Investigation Committee). The data safety monitoring plan (DSMP) for this clinical trial focuses on close monitoring by the principal investigator and co-investigators.

7.12 Data Safety Monitoring Plan

The investigators will perform study oversight and monitoring including data quality, storage, confidentiality, and issues covered in good clinical practice. In addition, the principal investigator will promptly report excessive adverse events and any serious adverse events to the APF and to the IRB at the Yale University School of Medicine. Other (less serious) adverse events will be reported to the IRB periodically during regular reporting periods.

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews quarterly. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator and co-investigators will review the following:

1. Recruitment and retention for the study and compare 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 each quarter (reviewed by PI and co-investigators). If adverse events occur in greater magnitude or frequency than expected these will be reported to the APF and HIC prior to scheduled reports. The Principal Investigator will assume full responsibility for reporting serious and non-serious and unanticipated adverse events.

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 will review twice-yearly aggregate data that contains screening data, baseline demographics, retention data, serious adverse events data, as well as accrual status, and any other data that will help in the assessment of the clinical trial.

Risk Assessment:

The risks associated with the current study are deemed greater than minimal. Although we do not view the risks associated with the study medication as minimal risk, the established safety and validity of the Naltrexone/Bupropion (FDA-approval of Contrave for obesity) RCTs suggest that the study procedures and medications are not 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:

Measurement and reporting of adverse events.

Adverse event data will be collected on an on-going basis. Adverse events data will be reviewed by the PI and co-investigators 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
Table 1	Subject accrual	Monthly
Table 2	Treatment completion rates (retention/attrition)	Quarterly
Table 3	Adverse and serious adverse event rates	Quarterly
Table 4	Checklist for DSMB	NA

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:

1. Definite: Adverse event is clearly related to the investigational procedure/agent.
2. Probable: Adverse event is likely related to the investigational procedure/agent.
3. Possible: Adverse event may be related to the investigational procedure/agent.
4. Unlikely: Adverse event is likely not to be related to the investigational procedure/agent.
5. 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 resulting in inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
4. Severe adverse event that may jeopardize the participant's health and requires medical or surgical intervention to prevent death, disability/incapacity, or congenital anomaly.
5. Fatal adverse event

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

The PI will report any incident, experience, or outcome that meets all three of these conditions to the IRB immediately: a) unexpected (in nature, specificity, severity, or frequency); b) related (probably or definitely); and c) places participants or others at greater risk of harm (physical, psychological, economic, legal, or social) than previously known or recognized. Following immediate reporting, an event will be reported using Form 710 FR 4 (Unanticipated Problem Involving Risks to Subjects or Others Reporting Form) to the IRB within 5 calendar days of it becoming known to the PI.

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:

1. All Co-Investigators listed on the protocol
2. American Psychological Foundation

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 suicidality) at any stage of study participation he/she will receive short-term treatment and support from the study treatment team (including

psychologists) 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. These reviews will help to assure that participants meet eligibility criteria and ethnic diversity goals.

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 twice-yearly. Any differential dropout 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 investigators have 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 binge-eating disorder and obesity (with comparable time frames for pharmacotherapy) have reported attrition rates between 20% and 38%. Studies of NB for obesity treatment reported attrition of 30% to 45%. 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.

Trial Stopping Rules

Given that this study is deemed greater than minimal risk to human subjects, 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 PI will alert the Yale IRB and the APF if a larger (or more serious) than 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.

1. Limits of Assumptions

It is possible that excessive attrition and/or missing data could limit the value of data analysis. This will be evaluated yearly and if present, considered in relation to potential effects on the power to detect differences in the primary outcomes.

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.

1. 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.

7.13 Study Modification

Study modifications will be submitted to the HIC for review and approval.

7.14 Study Discontinuation

The HIC will be notified if study discontinuation is warranted.

7.15 Study Completion

Study completion is expected 1-2 years after first enrollment.

7.16 Conflict of Interest Policy

The study team declares no conflicts of interest.

7.17 Funding Source

American Psychological Foundation

7.18 Publication Plan

The PI (Dr. Ivezaj) ensured that the clinical trial is registered on ClinicalTrials.Gov before enrollment of the first participant. Initial registration data will include information about the study, including the grant title and number, the local IRB number and contact information, responsible party, description of study intervention and primary outcomes, study location and inclusion/exclusion criteria. Data submitted as study results will include participant flow, demographic characteristics, clinical characteristics at baseline, outcomes, statistical plan and findings, adverse events, the study protocol, and administrative information. The following statement will be included in the informed consent document for this study: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov

(http://www.ClinicalTrials.gov), as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time." Yale University has an internal policy to ensure that clinical trials are registered and results are reported in compliance with policy requirements.

In addition, results will be reported at national/international conferences and published in peer-reviewed journals. Finally, data will be used as pilot data for larger, definitive NIH RCTs.

Appendices

Appendix #	Title	Section	Topic

NA

List of Tables

References

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