Use of pharmacotherapy to improve weight loss in early non-responders to behavioral treatment

Jena Tronieri (jenatronieri@pennmedicine.upenn.edu)
University of Pennsylvania https://orcid.org/0000-0003-3587-4130

Thomas Wadden
University of Pennsylvania https://orcid.org/0000-0002-0438-4609

Method Article

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Abstract

The original protocol was approved on December 19, 2018 during the funding application process (NIH/NIDDK 1K23DK116935). Two protocol amendments were made prior to the start of recruitment. First, the study medication was changed from liraglutide (the medication proposed in the original K23 funding application) to phentermine, and medication-specific sections of the protocol, including medication-related inclusion/exclusion criteria, were modified accordingly (IRB-approved May 13, 2019). The second amendment included the following minor changes (IRB-approved July 18, 2019): replacing cholecystokinin (CCK) with insulin in a neuropeptide hormone panel; adding a prespecified secondary analysis of changes in past-week VAS ratings of appetite, adding exploratory questionnaires (Philadelphia Mindfulness Questionnaire, Yale Food Addiction questionnaire, sleep hours/week); specifying that the electrocardiogram (ECG) would occur at screening and that the first BT session would start immediately after the baseline assessment visit; updating the portion size of the liquid test meal for males vs. females; and specifying that only randomized participants would complete a cardiometabolic and lipid panel at the randomization visit.

Three minor protocol amendments were made during the trial: 1) in order to reduce in-person contact in response to COVID-19, we allowed the ECG to take place any time prior to randomization (rather than only at screening) and specified that all lifestyle counseling sessions (not just make-up sessions) could be conducted remotely via videoconferencing or phone (IRB-approved July 27, 2020); 2) we replaced the term “nurse practitioner” with “research nurse” due to a change in the Center’s staff (IRB-approved April 13, 2021); and 3) we amended that HbA1c could be substituted for fasting blood glucose for the second, confirmatory assessment of diabetes at screening (IRB-approved May 14, 2021).

Introduction

A substantial minority of patients treated with behavioral treatment (BT) for obesity fail to achieve clinically meaningful losses of $\geq 5\%$ of initial weight. Medications approved by the Food and Drug Administration (FDA) for weight management enhance average weight losses when combined with BT; however, their use among patients with suboptimal response to BT has never been tested in a randomized controlled trial. This study seeks to identify behavioral and biological phenotypes predictive of poor response to BT and test whether providing pharmacotherapy with phentermine 15.0, as compared to placebo, improves the induction of weight loss for subjects who lose minimal weight with 4 weeks of BT alone (a strong predictor of later failure to lose $\geq 5\%$ of initial weight with that treatment).

1.1 Background and Relevant Literature

1.1.1 Obesity and Its Treatment.
Obesity, defined by a BMI \( \geq 30 \text{ kg/m}^2 \), is the most common nutritional disease in the United States, affecting about 36% of adults age 20 years and over. An additional 33% of American adults are overweight, as judged by a BMI of 25.0-29.9 kg/m². Obesity is associated with a number of co-morbidities including type 2 diabetes (70% of people with type 2 diabetes are obese) and cardiovascular disease.

Current treatment guidelines\(^1\) recommend that patients with obesity be offered comprehensive behavioral treatment that includes a reduced calorie diet, increased physical activity, and behavioral strategies to facilitate adherence to diet and activity goals. On average, patients achieve losses of 5-8% of initial weight with 6 months of high intensity BT (i.e., \( \geq 14 \) individual or group sessions in 6 months).\(^1\) (Providing more than 16 visits in 6 months [e.g., weekly visits] does not appear to significantly increase weight loss.\(^2\) A loss of \( \geq 5\% \) of initial weight is commonly used as a criterion for clinically meaningful weight loss and is associated with improvements in cardiometabolic risk factors.\(^3\) However, 35-50% of patients fail to lose this amount in high intensity BT programs.\(^4,5\)

1.1.2 Non-response to BT.

Numerous studies have shown that slow early weight loss (e.g., < 0.5% of body weight per week) in the first 1-2 months of BT is a strong predictor of limited total weight loss after 6-12 months of treatment.\(^4,6-13\) Approximately one third of participants fail to lose \( \geq 0.5\% \) of body weight per week in the first month of BT, and the majority of these early non-responders do not achieve a loss of \( \geq 5\% \) body weight after 6 months of treatment (53-70%).\(^4,7,8\)

1.1.3 Factors Influencing Weight Loss Success.

Obesity-related phenotypes, consisting of clusters of behavioral, psychological, and physiological characteristics, may facilitate or limit response to BT.\(^14,15\) The most consistent behavioral phenotypes associated with poor weight loss include low satiety and high hunger,\(^16-19\) as well as a high reinforcing value of food\(^20,21\) and high impulsivity.\(^21-26\) Lower satiety ratings after consuming a standard meal predict higher short- and long-term energy intake and less weight loss with BT.\(^e.g.,16,17,27\) Higher fasting hunger has also been associated with greater energy intake and poor weight loss\(^16,18,19\). A high relative reinforcing value of food (RRV\(_{food}\)) is associated with higher food intake and body weight.\(^27-31\) Delay discounting (DD) is conceptualized as an aspect of impulsivity that reflects difficulty with inhibiting responses to rewarding stimuli.\(^24,28,32\) In a meta-analysis, individuals with a steeper rate of DD, or those with the greatest preference for immediate rewards over larger, delayed rewards, were more prone to
obesity.\textsuperscript{24} Individuals who have both a high $R_{RV_{food}}$ and steep DD may have the greatest difficulty regulating their intake in order to lose weight\textsuperscript{21,28,32-34} because weight loss participants are asked repeatedly to choose low-calorie foods that will produce long-term weight loss over palatable high-calorie foods that offer a more immediate reward.\textsuperscript{26,28}

Behavioral phenotypes are presumed to be linked to biological mechanisms that control hunger and food responsiveness.\textsuperscript{20,26,35-38} Several neuropeptides are involved in the detection of long- (e.g., leptin) and short-term energy needs (e.g., glucagon-like-peptide-1 [GLP-1], ghrelin, insulin, peptide YY [PYY]), and they influence perceived palatability and reward-motivated eating (e.g., GLP-1, leptin, ghrelin). e.g.\textsuperscript{39,40} The rate of gastric emptying both influences and is influenced by several of these neuropeptides and may also affect food consumption and body weight.\textsuperscript{39,41-43} However, few studies have examined whether pre-treatment neuropeptide levels or gastric emptying predict weight loss with BT. The majority of these studies have examined the role of pre-treatment leptin and ghrelin levels in predicting weight loss, with mixed success.\textsuperscript{39,44-49}

Individual predictors typically explain only a small amount of the variance in weight loss outcomes, suggesting high inter-individual variability in mechanisms of non-response.\textsuperscript{50} In some cases, obesity phenotypes may be mutually exclusive (e.g., high hunger and low satiety), while in others, the combination of several traits may best characterize a mechanism of non-response (e.g., high $R_{RV_{food}}$ and high impulsivity). The ability of most studies to detect distinct phenotypes that predict weight loss has been limited by their inclusion of only a small number of self-report measures.\textsuperscript{14,50,51} Simultaneously examining multiple behavioral traits using laboratory-based assessments, along with neuroendocrine biomarkers and gastric emptying, may enhance our ability to identify phenotypes associated with poor response to BT. Better characterizing these non-responders will in turn facilitate the development of tailored treatments that can address different biopsychosocial barriers.

1.2 Treating BT Non-responders.

In addition to identifying mechanisms of non-response, it is important to evaluate whether alternative treatments improve the weight losses of BT non-responders. Several researchers have recommended that non-responders be provided with a different treatment method as early as possible, rather than spending 3-6 months in a treatment program that is unlikely to facilitate a clinically significant weight loss.\textsuperscript{4,6-9} Early non-responders to BT are also likely to become discouraged about reaching their desired weight loss goals and are more likely to drop out of treatment.\textsuperscript{10,52,53}

Several studies have examined the efficacy of stepped-care approaches in which BT is intensified for patients who do not meet early weight loss milestones. The baseline treatment offered in these programs has been of low intensity, consisting of self-help\textsuperscript{54}, internet-based BT\textsuperscript{55}, or monthly BT visits\textsuperscript{56}, and treatment has primarily been intensified by increasing provider contact. The effect of offering a
categorically different treatment to early non-responders in an intensive BT program has not been tested in an RCT.

1.2.1 Pharmacotherapy for Weight Management.

Expert panels recommend that individuals with a BMI \textsuperscript{³} 30 kg/m\textsuperscript{2} (or BMI \textsuperscript{³} 27 kg/m\textsuperscript{2} with comorbidity) be offered adjunctive treatments such as FDA-approved medications for chronic weight management if they are unable to lose weight or sustain weight loss with BT alone.\textsuperscript{1,57} Multiple studies have demonstrated that combining BT with medication produces greater weight loss (and reduces weight regain), compared to BT with placebo.\textsuperscript{e.g., 58-68} Wadden and colleagues\textsuperscript{59} have shown that the effects of BT and medication are additive. Participants prescribed medication alone (sibutramine 10-15 mg/day) lost 5 kg of initial weight at 1 year, those provided high-intensity BT alone lost 6.7 kg, and those given the combination of these two therapies lost 12.1 kg.\textsuperscript{59}

Phentermine 15.0 mg.

Phentermine hydrochloride is a sympathomimetic amine thought to reduce appetite and food intake by increasing norepinephrine and possibly catecholamine levels in the hypothalamus. Phentermine was approved by the Food and Drug Administration (FDA) in 1959 for “short-term” use, commonly interpreted as 12 or fewer weeks. In 2012, the FDA approved the combination of phentermine (7.5 – 15.0 mg/d) plus topiramate for long-term weight management (e.g., ≥12 months). Phentermine (monotherapy) is the most widely used weight loss medication in the U.S. and is frequently prescribed in clinical practice for periods longer than 12 weeks.\textsuperscript{69-71} The FDA did not require an Investigational New Drug (IND) application for the use of phentermine in the present study. Patients without diabetes achieve average placebo-subtracted weight losses of 4.0 to 7.4 kg with 12 to 28 weeks of treatment with phentermine (15.0-30.0 mg/d).\textsuperscript{72-77} In a recent representative study, subjects who received BT plus phentermine 15.0 mg/d lost 6.0 kg (6.1% of initial weight), whereas those who received BT with placebo lost 1.5 kg (1.7% of initial weight).\textsuperscript{77}

Higher fasting hunger and lower dietary restraint have been shown to predict a greater likelihood of achieving a 5% weight loss among patients treated with 8 weeks of phentermine.\textsuperscript{18} In another study, low satiety was associated with reduced weight loss at 2 weeks in patients assigned to placebo, but with greater weight loss in those who received phentermine-topiramate.\textsuperscript{78} These findings suggests that
phentermine will be particularly beneficial for individuals with the very phenotypes (e.g., high hunger, low satiety) that may predict non-response to BT.

Studies of the efficacy of weight loss medication have either initiated medication simultaneously with low- to moderate-intensity BT, 61,63-65,68 or have only randomized patients to medication or placebo if they succeeded in achieving a certain weight loss criterion (e.g., 5%) during an initial BT run-in. 58,66,67,79 Remarkably, the recommendation to offer weight loss medication to individuals who are unable to successfully lose weight with BT alone has not been tested.

Reagents

Equipment

Procedure

1 Investigational Plan

1.1 General Design

This is a two-phase study. Phase 1 will evaluate obesity-related behavioral and biological characteristics as potential mechanisms of non-response to BT. Phase 2 is a double-blind, placebo-controlled, RCT to test whether augmenting BT with weight loss medication improves 24-week weight loss, as compared to BT with placebo, in subjects identified as early non-responders to 4 weeks of individual behavioral weight control. Subjects will be a total of 150 adults, aged 21-70 years, with a body mass index (BMI) of 31 kg/m$^2$ or above (28 kg/m$^2$ with an obesity-related comorbidity). Subjects will attend a screening visit in which they will complete a behavioral evaluation with a psychologist and a medical history. In phase 1, eligible subjects will complete questionnaires and an in-person baseline assessment of obesity-related behavioral characteristics (satiety, hunger, RRV$_{food}$, and impulsivity), neuropeptides, and gastric emptying. Within 2 weeks of this assessment, they will begin an initial 4-week BT “run-in” delivered individually in 20-30 minute sessions. The primary goal of phase 1 will be to evaluate baseline postprandial satiety, postprandial change in GLP-1, and gastric emptying as predictors of early weight loss after 4 weeks of BT. We will also examine whether these variables predict categorization as an early non-responder to BT who loses < 2.0% of initial weight (vs. early responders who lose $\geq$ 2.0%; approximately 33% vs. 66% of the sample, respectively).

In phase 2, early non-responders (who lost < 2.0% during the BT run-in) will be randomly assigned to 24 weeks of: 1) BT plus placebo (BT+P); or 2) BT plus medication (BT+M; phentermine 15.0 mg). Both treatment groups will continue to attend 20-30 minute individual BT sessions, weekly for the first 12 weeks and every other week for the last 12 weeks (total of 18 visits). Both treatment groups will also take
once daily study medication (placebo or phentermine 15.0 mg) for the duration of the intervention period (with titration between randomization and week 2). Early BT responders identified during the run-in will receive the same 24-week BT program, but will not receive study medication or be included in the randomized trial. The assessments administered at baseline – questionnaires, including behavioral testing, blood draws, and measurements of body weight – will be repeated at randomization (week 0) and at week 24.

Comment. The use in phase 2 of an adaptive design, in which hypotheses only include participants who do not lose \( \geq 2\% \) with 4 weeks of BT, minimizes the size of the randomized sample treated in the current study. However, the initial sample size of 150 participants needed to assess weight loss predictors and identify at least 50 early non-responders is large for a K23 award. To limit treatment burden, we considered offering early responders no further treatment or a less intensive intervention following the 4-week diet run-in. However, we thought that offering responders a low-intensity treatment (or no treatment), which is known to produce suboptimal weight loss,\(^1\) would not be ethical, and that doing so also would likely de-incentivize success during the 4-week run-in. We therefore decided to offer the same 24-week BT program to all participants who complete the run-in, regardless of responder status. Continuing to treat responders also allows us to conduct an exploratory analysis comparing the weight losses of these individuals to non-responders treated with BT + M. We also considered enrolling both early non-responders and early responders in the RCT. However, in consultation with program officers at NIDDK, we ultimately decided that it would be inappropriate to expose individuals to drug who were already successful with BT alone. Although we believe that the selected design provides the best balance between maintaining focus on the study’s primary aim of improving treatment for early non-responders and the ethical care of all enrolled participants, the ongoing treatment of responders with BT limits our ability to recruit a larger initial sample with the aim of powering the study with enough non-responders to test secondary aims.

1.2 Allocation to Interventional Group

After completing 4 weeks of BT, subjects will attend a randomization visit (described to subjects as a “progress assessment visit”) at which their weight will be measured, and they will be categorized as an early non-responder (loss of < 2.0% of initial weight) or early responder (loss of \( \geq 2.0\% \)). After early non-responders’ eligibility is confirmed via a medical assessment, they will be randomly assigned in a 1:1 ratio, in randomly permuted blocks of 2 to 4 subjects, to one of the two treatment conditions. To maintain investigator blinding, randomization will be carried out by Penn’s Investigational Drug Services who will purchase phentermine and package the study medications (phentermine or placebo) in blinded capsules. The first subject to meet the randomization criteria will be assigned the first number in the sequence; each subsequent subject to meet randomization criteria will be assigned the next number in the sequence.

1.3 Study Endpoints
1.3.1 Primary Study Endpoints

The primary endpoints of phase 1 are percent weight loss from the start of the BT run-in (week -4) to randomization (week 0), as well as categorization as an early non-responder who lost < 2.0% of initial weight at randomization (co-primary outcomes), as predicted by postprandial satiety ratings (measured by visual analogue scales (VAS) during a test meal), postprandial change in GLP-1, and gastric emptying (measured using an acetaminophen test) at baseline.

The primary endpoint of phase 2 is change in body weight (i.e., % reduction in initial weight), as measured from randomization to week 24.

1.3.2 Secondary Study Endpoints

Secondary endpoints of phase 1 are percent weight loss from the start of the BT run-in (week -4) to randomization (week 0) and categorization as an early non-responder who lost < 2.0% of initial weight at randomization, as predicted by additional behavioral characteristics (hunger as measured by VAS ratings, $RR_{food}$ as measured using a computer task, and impulsivity as measured using a delay discounting computer task) and neuropeptides (higher fasting ghrelin, lower fasting leptin, and lower postprandial changes in insulin and PYY).

Secondary endpoints of phase 2 will include change in body weight in kg from randomization to week 24, as well as the portion of early non-responders who achieve a post-randomization loss of ≥ 5% and ≥ 10% of initial body weight. We will also examine differences between non-responders treated with BT+M vs. BT+P in changes in hunger, satiety, the reinforcing efficacy of food, and impulsivity (measured as described above) between randomization and week 24. The groups also will be compared on changes in past week VAS ratings of hunger, fullness, food preoccupation, food liking, and cravings as measured at treatment visits. A comparison will also be made in percent weight loss from randomization to week 24 between early non-responders treated with BT+M and early responders treated with BT alone.

1.3.3 Exploratory Endpoints

An exploratory analysis will compare the two randomized groups (BT+M vs. BT+P) on changes from randomization to week 24 in CVD risk factors (i.e., blood pressure, triglycerides, LDL and HDL cholesterol, and waist circumference), glycemic control (i.e., fasting blood sugar), quality of life (as measured by the Short Form Health Survey (SF-36), mood (as measured by the Patient Health Questionnaire (PHQ-9)), and physical activity (Paffenbarger Physical Activity Questionnaire).
An exploratory factor analysis will be used to determine whether primary and secondary predictor variables cluster into phenotypes. Exploratory endpoints will also include additional potential predictors of early response to BT. These will include measures of hunger (i.e., Eating Inventory [EI], past-week visual analogue scale [VAS] ratings), RRV\textsubscript{food} (i.e., Power of Food Scale [PFS]), the reinforcing efficacy of food, general sensitivity to reward (i.e., the Behavioral Inhibition/Activation Scale [BIS/BAS]), impulsivity (i.e., the Barratt Impulsiveness Scale [BIS-15]), appetite (past-week VAS ratings), cognitive restraint (EI), disinhibition (EI), binge eating (i.e. the Questionnaire on Eating and Weight Patterns [QEWP-5]), food craving (i.e., Food Craving Questionnaire – Trait – reduced [FCQ-Tr]), emotional eating (Dutch Eating Behaviour Questionnaire [DEBQ]), perceived barriers to healthy eating and physical activity, diet and exercise self-efficacy (i.e., Weight Efficacy Life-Style Questionnaire [WEL], SCI Exercise Self Efficacy Scale [ESES]), social support for healthy eating and physical activity (i.e., Ball and Crawford Social Support Scale), hours of sleep per week, mindfulness and acceptance (Philadelphia Mindfulness Questionnaire [PHLMS]), food addiction (Yale Food Addiction Scale [YFAS]), indicators of withdrawal (Highly Processed Food Withdrawal Scale [ProWS]), perceived stress (i.e., Perceived Stress Scale), anxiety (i.e., GAD-7), and mood (i.e., PHQ-9).

2 Study Population and Duration of Participation

2.1 Inclusion Criteria

1. BMI $\geq 31$ kg/m$^2$ (or 28 kg/m$^2$ with obesity-related comorbidity)

2. Age $\geq 18$ years and $\leq 70$ years

3. Eligible female patients will be:
   - non-pregnant, evidenced by a negative urine pregnancy test
   - non-lactating
   - surgically sterile or postmenopausal, or they will agree to continue to use an accepted method of birth control during the study. Acceptable methods of birth control are: hormonal contraceptives; double barrier method (condom with spermicide or diaphragm with spermicide); intrauterine device; surgical sterility; abstinence; and/or postmenopausal status (defined as at least 2 years without menses).

4. Subjects must:
   - have a primary care provider (PCP) who is responsible for providing routine care
· understand and be willing to comply with all study-related procedures and agree to participate in the study by giving written informed consent
· plan to remain in the Philadelphia area for the next 9 months or more

2.2   **Exclusion Criteria**

1. Pregnant or nursing, or plans to become pregnant in the next 9 months.

2. Uncontrolled hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg)

3. Type 1 diabetes

4. Type 2 diabetes

5. A fasting blood glucose >126 mg/dL (on second assessment after first elevated value, patients are excluded if they have both fasting blood glucose > 126 mg/dL and HbA1c ≥ 6.5)

6. History of cardiovascular disease (e.g., coronary artery disease, stroke, arrhythmias, congestive heart failure, or heart block greater than first degree)

7. Clinically significant hepatic or renal disease

8. Hyperthyroidism

9. Other thyroid disease, not controlled.

10. History of malignancy (except for non-melanoma skin cancer) in past 5 years

11. Narrow angle glaucoma

12. Presence or history of marked agitation

13. Current severe major depressive episode (BDI-II score ≥ 29), current active suicidal ideation, or history of suicide attempts within the past 5 years.

14. Any severity of thought or bipolar disorder, or bulimia nervosa.

15. Psychiatric hospitalization within the past 6 months

16. Self-reported alcohol or substance abuse within the past 6 months, including at-risk drinking (current consumption of ≥ 14 alcoholic drinks per week)

17. Past year history of drug abuse.
18. Use in the past 2 weeks of monoamine oxidase inhibitors.

19. Current use of serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, duloxetine, desvenlafaxine, milnacipran, levomilnacipran).

20. Use in past 6 months of medications known to induce significant weight loss (i.e., prescription weight loss medications) or weight gain (e.g., chronic use of oral steroids, second generation antipsychotics).

21. Loss of $\geq 5\%$ of initial body weight within the past 6 months

22. History of (or plans for) bariatric surgery (e.g., roux en y gastric bypass, sleeve gastrectomy, gastric banding), endoscopic intragastric balloon, or aspire assist.

23. Inability to walk 5 blocks comfortably or engage in some other form of aerobic activity (e.g., swimming)

24. Known or suspected allergy to sympathomimetic amines or related products

25. The receipt of any investigational drug within 6 months prior to this trial

26. Previous participation in this trial (e.g., randomized and failed to participate)

27. Changes to any chronic medication (type or dosage) within the past 3 months.

28. Any serious or unstable medical or psychological condition that, in the opinion of the investigator, would compromise the patient’s safety or successful participation in the study

Other Therapy: Subjects will be expected to use medications (prescribed by their PCP) to control traditional cardiometabolic risk factors (e.g., hypertension, hypercholesterolemia, etc) and other co-morbid conditions, with the exception of medications listed above under “exclusions.” In all cases, the subjects’ PCP will be asked at the study’s outset to keep medication does constant throughout the study, whenever possible. Subjects will be expected to have been on their medication regimen (including the dose) for 3 months prior to beginning the BT program.

2.3 Randomization Criteria

To be eligible to participate in the randomized phase of the trial, subjects must also:

1. Complete at least 3 out of 4 treatment sessions during the 4-week BT run-in and attend a randomization visit. Attending an in-person makeup session within one week of a missed visit will count as having attended the run-in visit.

2. Lose $< 2.0\%$ of initial weight during the 4-week BT run-in.
Subjects who complete at least 3 out of 4 treatment sessions during the 4-week BT run-in and have lost ≥ 2% of initial weight at the randomization visit will be provided with 24 weeks of BT during phase 2 of the study, but will not be eligible for randomization to a study medication.

2.4 Subject Recruitment

Subjects will be recruited from the greater Philadelphia area via flyers and online, radio, and print advertisements, through referrals from Penn primary care practices, and through Penn’s iConnect system. All recruiting materials used in the study will have IRB approval.

2.5 Duration of Study Participation

The total duration of the study subjects’ participation is expected to be 8 months. This includes a screening visit, baseline visit, 28 total weeks of BT (4 weeks before and 24 weeks after the randomization visit), and a post-treatment assessment.

2.6 Total Number of Subjects and Sites

Recruitment will end when 150 subjects are enrolled. It is expected that approximately 50 of these subjects (33%) will become classified as early non-responders to BT and enrolled in the randomized trial.

2.7 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

3 Study Interventions

3.1 BT Run-in

All subjects will complete an initial 4-week BT program in which they will attend weekly individual weight loss sessions of 20-30 minutes led by practitioners with training and experience in the delivery of BT (e.g., registered dietitians (RDs), NPs, psychologists). Subjects will be instructed to consume a self-selected diet of 1200-1500 kcal/day (for those who weigh < 250 lb) or 1500-1800 kcal/day (for those who weigh ≥ 250 lb) and be asked to begin to gradually increase their physical activity levels. Subjects will be counseled on how to consume a well-balanced diet and will be taught to use calorie counting and self-monitoring (e.g., Myfitnesspal, paper diaries) to meet their goals.
3.2 BT Intervention

Following randomization, all subjects will continue to attend individual (20-30 minute) BT sessions weekly for 12 weeks, then every other week until week 24 (total of 18 sessions). Subjects will be instructed to continue to follow their calorie goal and to engage in low-to-moderate intensity physical activity (e.g., walking), gradually building to a goal of $\geq 180$ minutes per week (spread across 5 days) by week 24. They will be provided a curriculum on behavioral weight control, based on prior studies,\(^{80,81}\) that includes self-monitoring, stimulus control, goal-setting, problem-solving, cognitive restructuring, and relapse prevention. Subjects will continue to monitor their food intake, physical activity, and weight online (e.g., Myfitnesspal) unless they prefer paper diaries. Subjects who miss a treatment visit will be contacted by the research coordinator and invited to complete a make-up session with study staff.

Initially, BT sessions were primarily provided in-person (make-up sessions were conducted in person or by phone). Consistent with University policy, all BT sessions will be provided by telehealth (phone or secure teleconferencing system) while recommendations to maintain remote activities due to COVID-19 remain in place.

BT interventionists will include RDs, NPs, and psychologists who are experienced in delivering lifestyle modification. Before beginning the study, interventionists will receive a 2-hour overview of obesity and its behavioral management, followed by ongoing weekly group clinical supervision. The PI will observe each provider delivering a treatment session at least once every 6 months to provide individualized feedback and ensure protocol adherence.

3.3 Medication and Placebo Interventions

In addition to attending BT sessions, non-responders will take a once daily study medication (phentermine or placebo) beginning at the randomization visit. The study medication will be provided in capsule form, and participants will be encouraged to take the medication in the morning upon awakening. Subjects will receive a 30-day supply of the study medication on each of 6 occasions. Phentermine will be provided as $8.0\text{mg/d}$ for the first 2 weeks to facilitate its acceptance to participants. The dose will be increased at week 2 to $15\text{mg/d}$ (or further placebo) in all participants. Phentermine (or placebo) will be down-titrated (back to $8.0\text{mg/d}$) or terminated in patients who report that they cannot tolerate the medication after a prolonged effort to do so. Down-titration will be managed in a blinded manner by Penn’s Investigational Drug Service (IDS), in response to notification from the principal investigator (or study co-investigators) of patients’ complaints of symptoms. (With IDS, we successfully used this titration method in prior randomized placebo-controlled trials of sibutramine for weight loss\(^{82}\) and of the addition for 12 weeks of phentermine or placebo to liraglutide 3.0 mg.\(^{83}\)) Participants in whom phentermine (or placebo) is terminated will continue to receive BT for the remainder of the 24-week treatment period.

3.4 Preparation and Packaging of Study Medications
Phentermine (and placebo) will be purchased and then packaged in blinded capsules by Penn’s Investigational Drug Service (IDS). IDS has prepared medications before for our Center in this manner, including the preparation of phentermine and placebo for a recent 12-week trial. IDS will store all phentermine-placebo at the hospital, to be picked up on a weekly or every-other-week basis by study coordinators and distributed to study patients.

3.5 Medication Storage

Drug supplies will be kept in a secured enclosure with limited access, both at the IDS where the medication is packaged, and at the Center for Weight and Eating Disorders (the Center), where it will be dispensed to subjects. The PI and research coordinator will ensure the availability of proper storage conditions at the Center. We will maintain adequate drug inventory and security at all times. Unused medication(s) will be stored separately from used trial medication(s). The PI will take appropriate precautions to prevent theft or diversion of the study drug.

3.6 Blinding

A master file of subject assignments will be kept by the pharmacists at IDS. Once a subject is randomized, the research team will receive a medication blister pack or container labeled with the subject identification number from IDS. The research team and the subject will be blinded and will not know the investigational product contained in the container. The blind may be broken in the case of an emergency. To request unblinding, the PI or a member of the study team who has been authorized by the PI will contact IDS to receive the relevant subject(s)’ information.

3.7 Administration and Accountability

A record of product administration will be maintained by IDS and in the subject’s file by the study team, including the medication identification number, date of distribution, and date that the product was returned by the subject. A standard form will be utilized to document this information throughout the study period.

3.8 Subject Compliance Monitoring

BT interventionists will briefly review the subject’s medication adherence at each visit, determining the number of days the medication was used each week and identifying reasons for missed doses. The number of doses of medication taken each week will be tracked. Interventionists will help subjects to problem solve barriers to adherence to the medication regimen and will refer subjects to the study physician or NP on an as needed basis. Subjects will be asked to return used medication containers,
which will allow the study team to obtain an objective measure of the subject’s adherence to the medication regimen.

1.1 Screening Procedures

Phone screens will be conducted by trained staff to assess preliminary eligibility. Individuals who appear to be eligible will be invited for an in-person screening visit that will include a behavioral evaluation conducted by a psychologist (including the PI). Prior to their screening visit, applicants will complete questionnaires that are administered as part of standard clinical practice at the Center for Weight and Eating Disorders: the Beck Depression Inventory-II (BDI-II) to assess symptoms of depression; and the Weight and Lifestyle Inventory (WALI) to provide information about the individual’s weight history, disordered eating behaviors, and other health behaviors (e.g., food intake, alcohol consumption).

The in-person interview will be conducted by a psychologist, who will obtain informed consent and evaluate subjects’ behavioral eligibility (i.e., willingness and appropriateness to participate). This will include our assessment of the applicant’s mood (as measured by interview and the BDI-II) and suicidality (including history of suicidal ideation and behavior, as assessed at screening by interview and the Columbia-Suicide Severity Rating Scale). Subjects who remain interested and pass this portion of the assessment will provide a medical history and physical examination to determine medical eligibility. Persons who continue to remain eligible will proceed to have a fasting blood test to determine that final eligibility criteria are met. Safety screening labs will include a comprehensive metabolic panel (CMP) and lipid panel, and a urine pregnancy test (for females of child-bearing age). An electrocardiogram (EKG) also will be performed to confirm medical eligibility prior to any participant’s enrollment in the randomized trial. We anticipate completing 180 in-person screenings to obtain an initial sample of 150 subjects.

1.2 Randomization Visit

Following the 4-week BT run-in, subjects will attend a randomization visit (week 0, described to subjects as a “progress assessment visit”) at which their percent weight loss from the start of the BT program (week -4) will be calculated. Subjects who have lost ≥2% of initial weight at this time will be categorized as early responders and will not be eligible for participation in the randomized trial. These subjects will be offered an additional 24 weeks of BT but will not receive a study medication.

Subjects who have lost <2% of initial weight at the randomization visit will be categorized as early non-responders. Trained research staff will review with randomization-eligible subjects information related to the study medication, including possible risks and benefits, and will confirm applicants’ willingness to participate prior to enrolling them in the randomized phase of the trial. Interested subjects will then have their eligibility confirmed by trained research staff, including completion of a urine pregnancy test. Non-
responders who remain eligible will be randomly assigned in double blinded fashion in a 1:1 ratio to receive either phentermine 15.0 mg or placebo, combined with an additional 24 weeks of BT. They will then meet with trained research staff who will instruct them in the use of the study medication and provide the first month's supply of medication.

All subjects will then complete an outcome assessment, as described below.

### 1.3 Outcome Assessments

All subjects will be asked to attend 3 outcome assessments, which will occur at baseline (week -5), randomization (week 0) and week 24. These assessments will include an evaluation of potential predictors of weight loss and assessment of the primary outcome measures used to judge the effectiveness of the treatments in inducing weight loss (described below). BT responders (who do not participate in the randomized trial) will provide weight, CVD, and questionnaire outcome measures at week 24, but will not be asked to complete the other portions of the in-person assessment at that time.

Each in-person outcome assessment visit will take approximately 2 hours. Subjects will be asked to fast for 8 hours prior to the in-person visit (overnight fast). Questionnaire measures will be completed online within 2 weeks of the in-person visit. A paper version of these measures will be provided to subjects upon request.

### 1.4 Treatment Visits

As described above, subjects will attend 4 initial, once weekly, 20-30 minute, individual BT sessions (“BT run-in;” week -4 to week -1). The first BT session will be scheduled immediately following the baseline outcome assessment. After completing the randomization visit (week 0), all subjects will continue to attend BT sessions, provided in the same treatment format, weekly for the first 12 weeks (12 sessions) and every-other-week for the last 12 weeks (6 sessions).

### 1.5 Missed Visits

Subjects who miss a treatment visit will be contacted by the research coordinator and invited to complete a make-up session with study staff, in person or by phone (except for visits at which medication is distributed). Subjects who do not attend a randomization visit within 2 weeks of the end of the BT run-in will not be eligible to continue participation in the study. All subjects who complete a randomization visit will be invited to complete the week 24 assessment, even if they have discontinued the study medication or attendance of BT visits.

### 1.6 Subject Withdrawal
A subject may voluntarily withdraw from the study at any time for any reason. The investigator or sponsor also may withdraw the subject from further participation at any time, if it is considered in the best interest of the subject or the study, without prejudice to the subject’s future medical care. It will be documented whether or not each subject completes the clinical study.

The primary reason for a subject’s premature discontinuation from the study will be selected from the following standard categories and documented in the source documents:

**Adverse event (AE):** One or more clinical or laboratory events which, in the medical judgment of the investigator, are grounds for discontinuation, even if the event does not appear to be related to study drug. The subject may withdraw because of an AE even if the investigator does not feel that it is grounds for discontinuation. This category includes subject death.

**Withdrawal of consent:** The subject desires to withdraw from further participation in the study.

**Lost to follow-up:** In the case of subjects who do not return to the center for study procedures and cannot be contacted, study personnel will make vigorous and repeated attempts (minimum of 3) to contact the subject. If all attempts to contact the subject fail, that subject will be considered to be lost to follow-up and discontinued from the study.

**Protocol violation:** The subject’s laboratory or other findings or conduct fail to meet the protocol entry criteria or fail to adhere to the protocol requirements.

**Subject pregnancy or intention of becoming pregnant**

The **Stopping Criteria** for individual subjects include:

1. The Principal Investigator and/or Medical Monitor conclude it is unsafe for the subject to continue.
2. A new diagnosis is made of a significant medical condition which could influence the response to phentermine (e.g., congestive heart failure).
3. A medication is begun that could alter the subject’s responses to phentermine.

Subjects meeting individual stopping criteria will be withdrawn from the trial.

1.7 Early Termination Visits

Whenever possible, subjects who withdraw early or who are asked by the investigator to cease participation in the study will have one final visit to collect study medication and to follow up regarding adverse events.

2 Study Evaluations and Measurements

The following measures will be collected during all outcome assessments, unless otherwise specified.

2.1 Primary Outcome Measure: Body Weight

Body weight will be measured at screening and at all clinic visits. However, for purposes of the primary outcome, weight will be assessed during outcome assessments at baseline (at the start of the BT run-in); at randomization (week 0); and at week 24. Weight will be measured on a digital scale (to the nearest 0.1 kg) with subjects dressed in light clothing, without shoes. Two measurements will be taken on each occasion.

2.2 Phase 1 Predictor Variables

2.2.1 Appetite, Neuropeptides, and Gastric Emptying

During the two-hour in-person outcome assessment at baseline (week -5), randomization (week 0) and week 24, subjects will first complete measures of appetite, neuropeptides, and gastric emptying before and for 60 minutes after consumption of a liquid test meal (e.g., Muscle Milk). The test meal size (oz and kcal will vary by sex with women consuming 70% of the amount provided to men. Subjects will be asked to fast for 8 hours prior to the in-person assessment (overnight fast), and research staff will confirm the timing of the subject’s last ingestion prior to beginning the assessment.

Appetite measures are perceived ratings of hunger, fullness, and satiety that reflect both objective (e.g., physiological) and subjective (e.g., learned) components of appetite. They will be assessed using 100-mm visual analog scales (VAS) with opposing anchors (e.g., “extremely full” to “not at all full”). The satiety quotient (SQ) will be the primary measure of perceived satiety and reflects the extent to which the liquid test meal reduces appetite sensations per unit of intake (e.g., kcal), calculated as: SQ (mm/kcal) = [(fasting rating before preload – 60 min post-preload rating)] / (energy content of preload) x 100. Physiological appetitive response will be measured as: 1) fasting levels of circulating neuropeptides
associated with appetite (GLP-1, insulin, PYY, leptin, and ghrelin); 2) postprandial changes in these neuropeptides, calculated as the 60-minute area under the curve (AUC); \(^{45}\) and 3) gastric emptying as assessed by an acetaminophen test (60-minute AUC). \(^{87-89}\) Because acetaminophen is minimally absorbed by the stomach but quickly enters the bloodstream in the small intestine, gastric emptying is considered to be the primary factor influencing its appearance in the blood. \(^{87-89}\) Maximum blood concentration of acetaminophen is reached in 30 to 60 minutes; therefore, the 60-minute AUC is thought to represent rapidity of gastric emptying. \(^{89}\)

Blood samples and VAS scales will first be completed in a fasted state. Subjects will be given 1.5g of acetaminophen with 50 ml of water. \(^{87-89}\) They will then be asked to consume a liquid test meal within a 10-minute period. Subjects will repeat VAS ratings at 10-minute intervals after consumption of the test meal. \(^{27}\) Postprandial blood samples will be collected at 30- and 60-minutes post-ingestion to evaluate changes in circulating neuropeptides and acetaminophen absorption. Protease inhibitors and DPP4 inhibitors will be added to samples to be assayed for GLP-1, PYY, and ghrelin to prevent enzymatic breakdown. Samples will be centrifuged at 4°C, separated, and frozen at −80°C for later analysis.

2.2.2 Impulsivity

After completion of the final blood draw and appetite ratings, subjects will complete measures of impulsivity (delay discounting; DD), reinforcing efficacy (questionnaire), and the relative reinforcing value of food (RRV\textsubscript{food}; baseline [week -5] only). The completion of these tasks following consumption of the liquid meal is designed to reduce the effect of hunger on food reinforcement. \(\text{e.g.}, \) \(^{33}\)

DD is conceptualized as an aspect of impulsivity that reflects difficulty with inhibiting responses to rewarding stimuli. The measure indicates the degree to which delaying an outcome reduces its perceived value. DD will be assessed via a computer program in which subjects are offered choices between small, immediate rewards and larger, delayed rewards. \(\text{e.g.}, \) \(^{28,32}\) The size of the larger amount is fixed, while the size of the smaller reward and length of delay vary between trials. Indifference points are calculated as the point at which the subject switches preference from the immediate to the delayed reward, and the AUC (representing the ratio of immediate reward size to time delay) will be used as the primary outcome. \(^{28,32}\)

2.2.3 Relative Reinforcing Value of Food

RRV\textsubscript{food} refers to how hard a person is willing to work to gain access to a food reinforcer. Subjects are allowed to work to earn points from a slot machine task at either of two computer stations, one of which provides points towards obtaining a preferred high-calorie food, and the other points towards a preferred low-calorie food. \(\text{e.g.}, \) \(^{29,30}\) Points are earned on a progressive ratio scale that increases at fixed intervals. The primary outcome is the number of food reinforcer points earned, which is thought to reflect the subject’s willingness to allocate time and effort to obtaining desired foods.
2.3  Cardiometabolic Risk

To evaluate exploratory outcomes, cardiometabolic risk factors will be assessed at screening, randomization (week 0) and week 24. Fasting blood samples (i.e., following an overnight fast of at least 8 hours) will be drawn on each occasion and assayed for a CMP and lipid panel. (Samples will be analyzed by Quest Diagnostics.) Responders who are not randomized will not complete the CMP and lipid panel at randomization (week 0). All participants will complete these analyses at screening and at week 24.

Blood pressure and pulse will be measured on each occasion using an automated monitor (Dinamap, model 9300). Two readings will be taken on each occasion (at 1-minute intervals), after subjects have been seated for at least 5 minutes. Waist circumference (measured horizontally halfway between the lowest rib and the top of the hipbone) to the nearest 0.1 cm will be assessed on the same schedule. Two waist measurements will be obtained at each assessment visit.

2.4  Questionnaire Measures

**Eating characteristics.** Self-report measures of hunger, impulsivity, and the relative reinforcing value of food will be administered to all subjects at all three outcome assessments. The Eating Inventory (EI – hunger subscale 90) and one-week VAS ratings will be used to assess hunger. \( \text{RRV}_{\text{food}} \) will be assessed by the Power of Food Scale (PFS 91) and general sensitivity to reward will be assessed by the Behavioral Inhibition/Activation Scale (BIS/BAS). 92 The Barratt Impulsiveness Scale (BIS-15) 93 will be used to assess impulsivity. We will also collect measures of additional eating characteristics for use in exploratory analyses, including past-week VAS appetite ratings 94, cognitive restraint (EI), disinhibition (EI), and binge eating (Questionnaire on Eating and Weight Patterns [QEWP-5] 95). Craving frequency will be assessed using the Food Craving Questionnaire – Trait – reduced (FCQ-Tr) 96 and emotional eating using the Dutch Eating Behavior Questionnaire (DEBQ) 97 Emotional Eating subscale. Perceived barriers to health behavior change 98, diet and exercise self-efficacy (i.e., Weight Efficacy Life-Style Questionnaire [WEL] 99, SCI Exercise Self Efficacy Scale [ESES] 100), social support for healthy eating and physical activity (i.e., Ball and Crawford Social Support Scale) 101, will also be assessed. Reinforcing efficacy of high- and low-energy density snack foods and active and non-active activities will be assessed using a computerized questionnaire during the in-person assessment. 114 Food addiction will be assessed using the Yale Food Addiction Scale (YFAS). 115

The Highly Processed Food Withdrawal Scale (ProWS) 116 will be administered on a separate timeline from the questionnaires described above. Participants will first complete the ProWS at their screening visit (week -5) and will be sent an email every other day with a link to complete this questionnaire until the second intervention visit (week -2). This timeline will allow us to assess indicators of withdrawal that may develop early in treatment when an individual attempts to cut down on highly processed foods.
Psychosocial characteristics. Psychosocial characteristics will be assessed on the same schedule as the primary outcomes. Mood will be assessed using the PHQ-9\textsuperscript{102} and the C-SSRS\textsuperscript{86}. Perceived stress will be assessed using the Perceived Stress Scale (PSS)\textsuperscript{103} and anxiety using the GAD-7. Quality of life will be assessed using SF-36.\textsuperscript{104} The Philadelphia Mindfulness Scale (PHLMS) will be used to assess general mindfulness and acceptance.\textsuperscript{117} Physical activity will be assessed by the Paffenbarger Physical Activity Survey.\textsuperscript{105} A brief questionnaire will assess hours of sleep per week.\textsuperscript{118}

Troubleshooting

Time Taken

Anticipated Results

1.1 Sample Size and Power Determination

A total sample size of 150 subjects will provide at least 80% power to detect all three primary outcomes. All power analyses were conducted using G*Power 3.1 at an alpha of .05. A correction for multiple comparisons is not proposed due to the preliminary nature of this research.

Phase 1: For the co-primary outcome - percent weight loss at the end of the BT run-in as predicted by baseline satiety, postprandial GLP-1, and gastric emptying - an estimated effect size for each predictor of $f^2 = .042$ was selected as the lower estimate from studies predicting weight loss from VAS satiety ratings and GLP-1 ($r's \geq .20$).\textsuperscript{16, 106} (We did not find studies using gastric emptying to predict weight loss, and the effect sizes for comparisons between BMI categories of $f^2 = .07 - .30$ were less conservative.\textsuperscript{43, 78}) Based on this estimate, a sample size of 150 subjects would yield 80% power to detect statistical significance for the three individual predictor variables. The second co-primary outcome - non-responder status as predicted by these three predictors in discriminant analysis - would have 90.1% power with this sample size, based on power analysis for a 2-group MANOVA for 3 response variables\textsuperscript{107, 108} with an estimated combined effect size of $f^2 = .10$.

Phase 2: For the primary outcome - percent weight change from randomization to week 24 among early non-responders - estimated group means, variances, and attrition rates were derived from data from prior studies conducted at our Center and from previous research in early non-response to BT e.g.\textsuperscript{4}. The estimated treatment effect is based on the placebo-subtracted effect of 28 weeks of phentermine 15.0 mg of 4.5 kg (4.4% of initial weight), as determined by a multi-arm RCT that enrolled 219 total patients in the placebo and phentermine 15.0 mg groups.\textsuperscript{77} We selected this result as the basis of our power analysis because it most closely matched the phentermine dose and duration used in the present study. Other previous RCTs examining the effect of phentermine monotherapy have typically administered a 30.0 mg dose for 12 to 16 weeks. The majority of these trials have achieved larger placebo-subtracted weight losses of 5.4 to 7.8 kg.\textsuperscript{72, 74-76} (One randomized trial reported a 4.0 kg placebo-subtracted loss
with a different formulation, phentermine resin 30.0 mg, and one reported a 3.3% placebo-subtracted loss when both phentermine 37.5 mg and placebo were combined with a 900-1100 kcal/day meal replacement diet, resulting in large mean weight losses in both groups. An additional study suggested that the difference in mean weight loss between phentermine 15.0 mg and phentermine 30.0 mg (both when combined with lorcaserin) is small (0.6 kg mean difference). We therefore believe that participants provided with 24 weeks of phentermine 15.0 mg are likely to achieve a placebo subtracted loss of ≥4.5% of initial weight. (Most early phentermine studies reported results in kg, which is roughly equivalent to percent weight loss in populations with obesity.)

We predict a 24-week post-randomization weight loss among early non-responders of 6.5% in BT+M and 2.0% in BT+P, with expected standard deviations of 5.5%. We expect 33% of the initial baseline sample of 150 subjects to be categorized as early non-responders following the BT run-in. Based on these estimates, a randomized sample size of 50 non-responders (25 per group), assuming a 20% attrition rate, will give us 81.5% power to detect between-treatment group differences at week 24 of 4.5% (effect size: d = 0.82).

**References**


85. Wadden TA, Foster GD. Weight and Lifestyle Inventory (WALI). Obesity. 2006;14(3S):99S-118S.


**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- FinalProtocolMedforNonrespondersRevisionv6.05.5.21clean.pdf