IRB: 2000022480

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

**Protocol Title:** Cognitive-Behavioral and Pharmacologic (LDX) Treatment of Binge Eating Disorder and Obesity

**Principal Investigator:** Carlos M. Grilo, Ph.D.

**Version Date:** May 18, 2022

(*If applicable*) **Clinicaltrials.gov Registration #:** NCT03924193; NCT03926052; NCT03946111

| INSTRUCTIONS |
| --- |
| This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:**<br>1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.<br>2. If a section or question does not apply to your research study, type "Not Applicable" underneath.<br>3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system. |



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## SECTION I: RESEARCH PLAN

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

   STAGE 1 RCT – Primary Outcomes Aim # 1:
   Compare the effectiveness of CBT, LDX, and CBT+LDX for BED on primary outcomes (1a) reducing binge-eating and (1b) reducing weight.

   STAGE 1 RCT – Secondary Aims:
   (2a) *Examine the effectiveness of* CBT, LDX, and CBT+LDX for BED on secondary outcomes: categorical remission (zero binges/ 28 days), eating-disorder pathology, and depression.
   (2b) *Explore predictors*, *moderators*, and *mediators* of primary treatment outcomes (reductions in binge-eating and weight) and in secondary categorical outcome (binge-eating remission).

   STAGE 2 RCT – Primary Outcomes Aim # 1:
   (3) Among *Responders* to Stage 1 acute treatments with LDX (i.e., LDX and CBT+LDX), *compare the effectiveness of LDX versus Placebo* for enhancing maintenance and longer-term outcomes. *Primary outcome will be "relapse"* and secondary outcomes will be binge-eating frequency, weight loss, eating disorder pathology, and depression.

   STAGE 2 RCT – Secondary Aims:
   (4a) *Examine* LDX and CBT effects, alone and in combination, for longer-term BED outcomes. *Our two-stage design will allow comparison of CBT (i.e., Stage 1 CBT-only short-term) versus the Stage 2 LDX/placebo maintenance treatment (i.e., Stage 2 LDX/placebo following Stage 1 LDX or Stage 1 CBT+LDX) for longer-term outcomes through 18 months.* This will inform clinical questions regarding whether LDX maintenance treatment following either acute LDX treatment or acute combined CBT+LDX differ and whether it offers any additional benefits over acute CBT-only.

   (4b) Among *Non-responders* to Stage 1 acute treatments with LDX (i.e., LDX and CBT+LDX), *explore the effectiveness of switching to an alternative medication NB vs placebo* for primary outcomes (reducing binge-eating and reducing weight) and secondary outcomes (binge remission, ED pathology, depression).

   (5) Secondary Aims: Generate *cost-effectiveness* estimates of treatments. Incremental cost effectiveness ratios (ICERs) will be computed for LDX vs CBT and LDX+CBT vs CBT (using quality-adjusted life years).

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   September 1, 2018- August 31, 2025

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

   SIGNIFICANCE: Obesity (OB) is an increasingly prevalent, refractory, and serious public health problem, with estimates that 34% of U.S. adults are obese (Flegal, Carroll et al. 2010). Obesity is considered one of the most serious public health problems of the 21st century. Economic consequences of OB are staggering; associated annual medical costs were estimated at $147 billion (roughly 10% of all medical spending) (Finkelstein et al. 2009), which reflects continued escalation since estimates of $75 billion five years earlier (Finkelstein et al.



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2004). This study focuses on testing treatments for a high-risk subgroup with binge-eating disorder (BED) (Hudson, Hiripi et al. 2007; Kessler et al., 2013).

Binge Eating Disorder (BED) – An Important Clinical Subgroup of Persons with Obesity

Obesity is a heterogeneous problem and research has highlighted the particular significance of a subgroup with BED. Recognized as a serious problem by Stunkard (1959), only recently has BED become a research focus and established as a formal diagnosis in the DSM-5 (APA, 2013). BED is defined by recurrent episodes of binge-eating without compensatory weight control methods that characterize bulimia nervosa. Binge-eating is defined as eating an unusually large amount of food given the context coupled with a subjective sense of loss of control and diagnosis requires binge-eating to be associated with marked distress (Grilo and White 2011). Epidemiologic studies have found that BED is more prevalent than the other two formal eating disorders (Hudson, Hiripi et al. 2007; Kessler, Berglund et al. 2013). The prevalence of BED in the National Co-morbidity Survey Replication (Hudson, Hiripi et al. 2007) was 3.5% among women and 2.0% among men. Estimates of BED are higher in obese adults (8%) and are much higher in most clinical settings (Wilfley, Wilson et al. 2003). Compared to other eating disorders, BED is prevalent across gender and ethnic/racial groups (Marques, Alegria et al. 2011). BED has diagnostic validity (Striegel-Moore and Franko 2008), is a stable construct (Pope, Lalonde et al. 2006), differs from other eating disorders and obesity (Allison, Grilo et al. 2005; Grilo, Crosby et al. 2009; Grilo, Masheb et al. 2010) and is strongly associated with obesity (Kessler et al., 2013) and elevated risk for medical, psychiatric, and psychosocial problems (Hudson et al. 2007; Hudson et al., 2010).

Treatment for BED: Overall Current Status and Future Needs Overall, the BED literature suggests that several medications have short-term efficacy relative to placebo (Reas & Grilo 2008, Reas & Grilo, 2014, 2015) and certain psychological treatments have efficacy both short-term and longer-term (Wilson et al., 2007). The few relevant studies performed to date suggest that certain psychological treatments hold important advantages over the few medications tested thus far (alone or in combination) (Grilo, Reas, & Mitchell, 2016; Reas & Grilo 2014, 2015; Grilo et al., 2012). This application focuses on two "leading" and distinct treatments that have yet to be compared: a specific "specialist" psychological - cognitive-behavioral therapy (CBT) - and the first and only FDA-approved medication for BED - lisdexamfetamine dimesylate (LDX).

Cognitive Behavioral Therapy (CBT) is the best-established treatment (Grilo, 2017; Iacovino, Gredysa, Altman, & Wilfley, 2012; National Institutes of Clinical Excellence, 2004, 2017; Wilson, Grilo, & Vitousek, 2007). Randomized clinical trials (RCTs) testing CBT generally report roughly 50% - 60% remission rates from binge-eating (Grilo, Masheb et al. 2005; Grilo, Masheb et al. 2011; Wilfley et al., 2002; Wilson, Wilfley, Agras, & Bryson, 2010). RCTs have demonstrated that CBT has short-term effectiveness and "treatment specificity" (i.e., superiority to a variety of control and active treatments) (Grilo, Masheb, & Wilson, 2005; Wilson et al., 2010), demonstrated longer-term superiority to fluoxetine (Grilo, Crosby, Wilson, & Masheb, 2012) and other medications (Ricca et al., 2001), and longer-term durability of outcomes (Hilbert et al., 2012; Wilson et al. 2010). CBT also produces significant and robust improvements in associated features of eating disorder pathology and depression (Grilo et al., 2011; Wilson et al., 2010). Importantly, however, CBT fails to produce weight loss (Grilo et al., 2005; 2011, Wilfley et al., 2002; Wilson et al., 2010) as is the case with other empirically-supported psychological treatments (Grilo, 2017) such as interpersonal therapy and dialectical behavioral therapy) (Wilfley al., 2002; Safer et al., 2012). CBT does appear to reliability stabilize and prevent future weight gain (Hilbert et al., 2012; Wilson et al., 2010) which is important in light of the concerning steep weight-gain trajectories characteristic of persons with BED prior to treatment (Barnes, Blomquist, & Grilo, 2011; Blomquist et al., 2011; Ivezaj, Kalebjian, Grilo, & Barnes, 2014; Masheb, White, & Grilo, 2013)



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The strong association between BED and obesity (Hudson, Hiripi et al. 2007; Kessler et al., 2013) and heightened risk for developing future metabolic problems (Hudson, Lalonde et al. 2010) highlight the need to find methods to effectively reduce weight - in addition to binge-eating - in this subgroup of obese persons.

Behavioral Weight Loss (BWL) for BED, has received less research support than CBT for BED. Recent rigorous RCTs have found BWL may be more effective than CBT for producing weight loss in BED (Grilo, Masheb et al. 2011), although longer-term follow-up suggests that the improvements in binge-eating and weight losses are less durable in BWL (Wilson, Wilfley et al. 2010). Longer-term effectiveness of BWL combined with (a different) pharmacotherapy is the focus of an on-going RCT by Dr. Grilo (HIC #1506016065).

Pharmacotherapy (medications) for BED has received increased research attention albeit nearly all RCTs have been of short duration and without follow-up to establish durability. Critical review and meta-analysis show that several drugs – working through varied mechanisms – have short-term efficacy relative to placebo for reducing binge-eating and produce weight loss ranging from modest to none (Grilo et al., 2016; Reas & Grilo, 2008, 2014, 2015). Placebo-controlled trials of anticonvulsants (McElroy et al. 2003; McElroy et al. 2006; Claudino et al. 2007) have reported effects for reducing both binge-eating and weight (mean weight loss of roughly 3-4 kg), but have high dropout and frequent adverse events which become nearly universal and troubling with longer use (McElroy, Kotwal et al. 2004). SSRIs, initially regarded as a potential treatment strategy (e.g., NICE, 2004) are characterized by small effect sizes relative to placebo (Reas & Grilo, 2008) and produce no weight loss at all (Grilo et al., 2005) and are inferior to CBT (Grilo et al., 2005; Ricca et al 2001).

FDA-Approved LDX (CNS Stimulant) Medication for BED An important recent development was the FDA approval in January 2015 of a CNS stimulant, lisdexamfetamine dimesylate (LDX), for the treatment of moderate-to-severe BED based on findings from an integrated series of studies funded by Shire (the manufacturer). The phase II (11-week) RCT demonstrated dosing response and that 50mg and 70mg were superior to placebo (McElroy et al., 2015). Two identically designed phase III RCTs testing LDX (50–70 mg dose optimization) for moderate-to-severe BED in adults (McElroy et al., 2016) found LDX superior to placebo for reducing binge-eating days and reported binge-eating abstinence rates of LDX versus placebo (Study 1: 40% versus 14%; Study 2: 36% versus 13%) at the end of 11 weeks of treatment. Primary analyses of reduction in binge-eating frequency significantly favored LDX over placebo in both phase-III RCTs, with effect-size of 0.83 and 0.97 (McElroy et al., 2016). Another much smaller RCT with N=50, also funded by Shire, reported weaker advantage of LDX over placebo (ES = 0.50), suggesting the need for further and continued investigation by other researchers. McElroy et al (2017) reported time-course data for binge-eating and associated outcomes to expand upon the McElroy et al (2015) report regarding the significant reductions (over 80%) in binge-eating with LDX; these analyses suggest an early and rapid response (and are supportive of our proposed definition of "response" (see Research Design section). The efficacy and safety data were reviewed and appear to represent a favorable benefit-to-risk ratio (Citrome, 2015).

LDX was also associated with significant acute weight loss relative to placebo (mean 4.9 kg) (McElroy et al., 2015, 2016); weight loss was examined as a safety measure. The FDA-approval and manufacturer product labeling include a "Limitation of Use" highlighting that LDX is not indicated for weight loss. In the present study, we anticipate that LDX will produce short-term weight loss and the key and novel research goals will involve the questions of the utility of maintenance LDX treatment and longer-term follow-up.

More recently, two Shire-funded studies have been reported, both providing further support for the proposed research. A Phase III open-label 12-month extension safety and tolerability trial of LDX for BED with N=604 patients who completed previous Shire RCTs (McElroy et al., 2015, 2016) was completed (Gasior et al., 2017). Gasior et al (2017) reported the safety/tolerability profile with 12-months of LDX was consistent with



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short-term (12-week) BED trials and with established profile of LDX for ADHD (FDA-approved); 9% of patients reported treatment emergent side-effects resulting in medicine discontinuation. Hudson et al (2015 ACNP conference), in a double-blind RCT, reported LDX was significantly superior to placebo for preventing relapse following clinical response to open-label LDX (3.7% vs 32.1% relapsed, respectively). These findings suggest short-term treatment extension with LDX may be effective for decreasing relapse amongst initial responders to LDX. Importantly, Hudson et al (2015) did not report follow-up data after discontinuing the maintenance treatment and whether LDX enhances maintenance for responders to other treatments is unknown.

Putative mechanisms of action for LDX. LDX (l-lysine-dextroamphetamine), is a prodrug of d-amphetamine covalently linked to l-lysine, that when metabolized to d-amphetamine (active form) is a moderately potent inhibitor of DAT, NET, and VMAT2, with little affinity for SERT; its net effect is increased catecholamine availability (Guerdjikova et al., 2016; Hutson et al., 2014; Pennic, 2010; Comiran et al., 2016). LDX seems relevant for reducing binge-eating per preclinical and clinical (Vickers et al., 2015; Wang et al., 2011), and neurobiologic (fMRI) findings suggestive that binge-eating is related to dysfunctions in the dopamine and norepinephrine systems (Balodis, Grilo, & Potenza, 2015; Balodis, Grilo et al., 2013), which play important roles in regulating eating behaviors and reward (Wellman, 2005; Palmiter, 2007).

LDX Research Needs: Longer-term follow-up data are needed for this FDA-approved LDX medication for BED. There exists no empirical guidance for practitioners regarding (1) whether or not to combine with CBT, (2) whether maintenance treatment with LDX, which reduced relapse over the short-term amongst LDX responders (Hudson et al., 2015), has utility for enhancing outcomes with other treatments (e.g., CBT) and has any durability or shows any benefit over time after discontinuation; (3) what are longer-term outcomes and what is the risk/timing for relapse, and (4) what factors predict outcomes and moderate outcomes (i.e., for whom the LDX and CBT work best). Furthermore, there is a dearth of knowledge regarding mediators for how CBT and LDX (or other BED treatments) achieve (or fail to achieve) either short- or longer-term outcomes (which may reflect different processes). The integration of repeated behavioral measures tapping putative constructs associated with these two distinct treatments (CBT vs LDX) offers an important novel opportunity to explore possible mediators of therapeutic action in addition to the primary aims of providing important new information about the comparative effectiveness – both short- and longer-term – of these two "leading" treatments, alone and in combination.

What About Non-Responders?: In addition to the important need to test maintenance treatments (e.g., LDX) to enhance outcomes amongst initial treatment responders, studying treatment "non-responders" is also especially needed. To date, this issue - and "SMART" or "adaptive" integrative treatment designs tested in other psychiatric problems (e.g., depression) (Guidi, Tomba, & Fava, 2016) – has received very little attention in BED. Grilo et al (2017 IJED plenary) reported new findings that non-responders to BWL (a "generalist" treatment) failed to derive any further benefit from CBTgsh but did derive some benefit from anti-obesity medications. How to help non-responders to CBT (a leading "specialist" treatment), however, seems challenging. Agras et al (1995) reported that IPT failed to benefit Non-responders to CBT and Grilo et al (2011) found that sequencing BWL after CBT failed to enhance outcomes (except for some modest weight loss). The failure of IPT and BWL to enhance limited CBT response is striking in light of their documented effectiveness as initial treatments (Wilson et al., 2010). In this application, we will propose a different and novel strategy for treating patients with BED who fail to benefit from LDX and CBT+LDX being compared in the Stage 1 RCT. Specifically, following the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) clinical trials (Rush et al., 2006; Rush et al., 2008; Olbert et al., 2016), we will test whether switching to a second (alternative) medication produces benefits. We propose to explore the utility of naltrexone/bupropion.



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Pharmacotherapy with Naltrexone/Bupropion (FDA-Approved for Obesity). In 2014, the FDA approved combination of naltrexone and bupropion for obesity following empirical support from several RCTs performed with obesity (non-BED) (Greenway et al., 2009; Greenway et al., 2010; Smith et al., 2013; Wadden et al., 2011). 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 ("NB32", which we will refer to as NB medication). For example, Apovian et al (2013), 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). These findings supporting NB medication are quite consistent with earlier large RCTs which reported greater weight loss with NB than placebo (-6.5 vs -1.2% (Greenway et al. 2013); -8.2% vs -2.1% (Smith et al., 2013)) Overall, NB has been well tolerated with the most common adverse event being nausea.

Putative mechanisms of action for Naltrexone and Bupropion seem relevant for binge eating in addition to weight loss. Naltrexone, an opioid receptor antagonist, is approved for treatment of alcohol and opioid dependence (O'Malley, Sinha, Grilo, et al., 2007). Naltrexone produces weight loss in lab animals but only minimal weight losses in humans (Malcolm et al. 1985; Billes & Greenway, 2013). Bupropion is thought to operate through dopaminergic, noradrenergic, and nicotinic acetyl-cholinergic mechanisms (Slemmer, Martin et al. 2000; Stahl, Pradko et al. 2004; Han, Hwang et al. 2010), may target reward processes that drive eating behaviors, consistent with its FDA indication for treating nicotine dependence and reduced weight gain during smoking cessation (Hurt et al., 1997; Farley et al., 2012). Bupropion has been found to promote weight loss in obesity (Li et al., 2005). White & Grilo (2013) first reported preliminary support for a possible (albeit modest) weight loss benefit specifically in obese BED patients.

Putative mechanisms of action for the COMBINATION NB is especially relevant for reducing binge eating and weight per hypothesized effects on brain regions implicated in the regulation of food intake and weight based on the mechanisms of action of leptin (Billes & Greenway, 2011). Leptin's anorectic effects result from its excitatory effects on pro-opiomelanocorin (POMC) neurons in hypothalamus melancortin system (Crowley et al, 2001; Marsh et al, 1999). Stimulated POMC signaling decreases food intake, increases energy expenditure, but is then inhibited by endogenous feedback (Crowley et al., 2001). Thus, combining these two drugs is to stimulate POMC neurons (bupropion) plus block endogenous feedback that inhibits POMC activity (naltrexone) (Greenway et al., 2009; Biles & Greenway, 2013). This synergistic model received support both in vitro and in vivo studies (Greenway et al., 2009; Cone et al., 2001). Billes and Greenway (2013) noted that NB was associated with ability to control food intake and reduced food craving and, in turn, weight loss.

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



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| Pre-Randomization | Stage 1 | Stage 2 | Follow-Up |
|---|---|---|---|
| • Response to Recruitment<br>• Pre-Screening<br>• Baseline Assessment | • Initial Randomization<br>• Participation in Stage 1<br>• Stage 1 Post Assessment Classification as Responder or Non-Responder | • Response-based Randomization<br>• Participation in Stage 2<br>• Stage 2 Post Assessment | • 6-Month Follow-Up Assessment<br>• 12-Month Follow-Up Assessment |

Pre-Screening: Participants responding to recruitment efforts (see pages 35-36) 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 by trained supervised research clinicians (doctoral level and/or advanced trainees). Participants will complete survey measures of eating behaviors and psychopathology and psychosocial functioning around the time of the in-person appointment.

Participants who provide informed consent and are determined to be eligible (see page 15-16) will then participate in the study as depicted and described in the following paragraphs. See also Figure 1 (page 8).

Stage 1, N=180 patients with BED and obesity will be randomized to one of three 12-week treatments: CBT, LDX, or CBT+LDX.

In Stage 2, patients who received pharmacotherapy (Stage1 LDX or CBT+LDX) and were "Responders" (defined as 65% or more decrease in binge eating) will be randomly assigned in equal proportions (blocked randomization stratified by first treatment) to LDX or placebo (double blind) for 12 weeks.

"Non-responders" to Stage 1 pharmacotherapy (LDX or CBT+LDX) will be randomized to a second medication (NB or placebo) in double-blind fashion for 12 weeks. Stage 1 CBT patients will be followed without further treatment; this will allow controlled comparison of Stage 1 RCT and context for Stage 2 RCTs.

Independent assessments will determine outcomes after discontinuation of treatments through 18 months. Secondary aims are to produce important new data regarding predictors of outcomes and moderators of treatment effects to inform prescription (i.e., for whom LDX vs. CBT work best), and exploration of potential mediators through which the distinct treatments achieve outcomes, and cost-effectiveness estimates.



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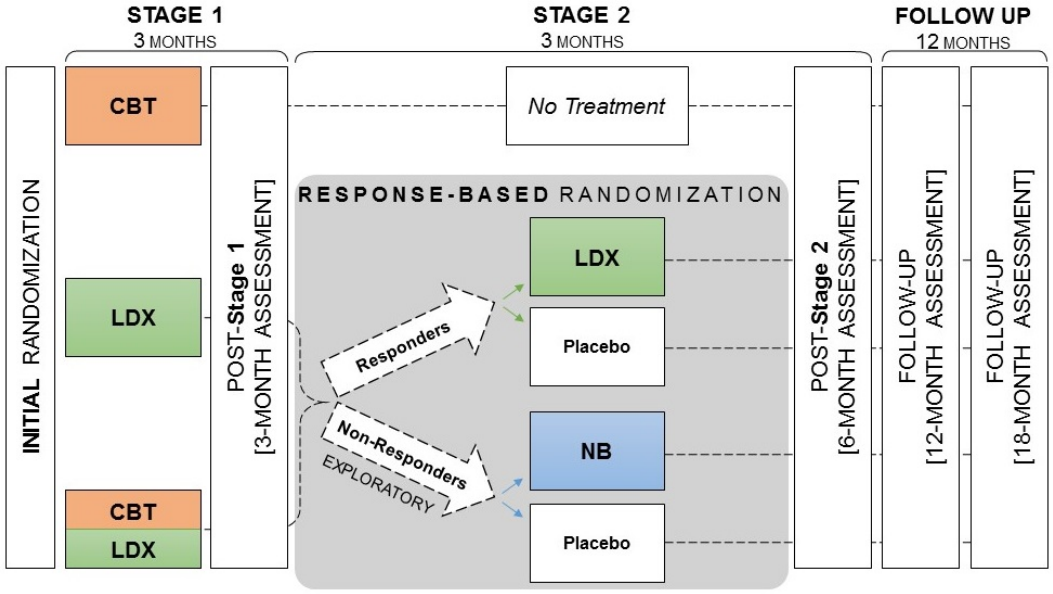
*Figure 1.* *Study design*




Potential participants will be screened by telephone and potentially eligible patients will be consented and evaluated in-person by trained supervised research clinicians (doctoral level and/or advanced trainees). (see page 36).

Randomization to Stage 1 Treatment. Eligible participants who provide written informed consent will be randomized in equal proportions to one of three treatments (blocked randomization with random block sizes of 3 and 6 for Stage 1 to obviate any secular trends). Randomization will be stratified by two variables to be tested as moderators (overvaluation of shape/weight (based on ≥4 EDE item scores) and depression (based on >16 BDI-II score) (Grilo, Masheb, Crosby, 2012).

Randomization to Stage 2 Treatments for LDX and CBT+LDX (Stage 1) "Responders".
"Responders" to Stage 1 LDX (i.e., LDX and CBT+LDX) treatments will be defined as 65% or greater reduction in binge-eating. This cut-point is based on reliable findings regarding prognostic significance of such reductions (Grilo et al., 2006; 2012) and supported by recent report on "time course of the effects of LDX" (McElroy et al., 2017). "Responders" will be randomized in equal proportions (using stratified blocked randomization with Stage 1 treatment as a stratifying variable) to LDX or placebo (double-blind) for 12 weeks.

CBT Treatment Protocol. CBT will be delivered by trained and monitored research clinicians following manualized protocols we have used successfully in previous RCTs (e.g., Grilo et al., 2005, Grilo et al., 2011). CBT will be delivered in individual sessions weekly for 12 weeks following CBT manuals based on Fairburn et al (1993) used in our RCTs (Grilo et al., 2005, 2011) which are similar to those used in major RCTs testing CBT delivered via 12-24 weeks (Wilfley et al., 2002; Wilson et al., 2010). The CBT manuals provide detailing session-by-session procedures for clinicians and parallel guides are provided to the patients to facilitate homework and mastery of the material. CBT, a specialist focal treatment, consists of



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three overlapping phases. Phase one involves establishing a collaborative therapeutic relationship while focusing on educating the patient about the nature of binge-eating and factors thought to maintain the problem. Specific behavioral strategies (e.g., self-monitoring) are used to help patients identify problematic eating patterns while establishing a normal structured eating pattern. Phase two integrates cognitive restructuring procedures, where patients learn to identify and challenge maladaptive cognitions regarding eating and weight/shape and thoughts that trigger binge-eating. Phase three focuses on maintenance of change and relapse prevention.

LDX Pharmacotherapy Treatment Protocol. Medication will be double-blind; patients and study staff, physicians and investigators will be blind to medication assignment. LDX, *FDA-approved for BED*, will be prescribed per procedures found to be superior to placebo in two large-scale phase 3 RCTs (McElroy et al., 2015). The LDX (dose-optimization at 50-70mg per day) protocol followed the McElroy et al (2015) RCT findings that 50-70mg/day dosing was significantly superior to 30mg/dosing and to placebo.

During week 1, LDX will be 30 mg/day for initial titration. During week 2, LDX will be titrated to 50mg/day. During weeks 3-4, LDX increases to 70mg will be made based on acceptable tolerability and clinical need. If 70mg is not tolerated, downward titration to 50mg/day can occur. For the remaining treatment (weeks 4-12), the optimized LDX dose (50 or 70 mg/day) will be maintained.

For the Stage 2 randomized maintenance (double-blind) treatment, a similar approach to dose-optimization will be followed for responders. "Responders" re-randomized to LDX will continue taking LDX at the same dose as Stage 1. "Responders" randomized to placebo will be switched from LDX to placebo. Participants will be instructed to take the medication (active or placebo) once daily in the morning.

Safety and tolerability will be assessed during study clinic visits as will clinical compliance with the study medication. During the dose-optimization period, if the patient develops tolerability concerns, dosing can be reduced once to achieve tolerability. If the patient cannot tolerate the medication, has adverse effects, or is non-compliant with medication for > 7 consecutive days, s/he will be discontinued from the medication arm. Physician visits will be brief (10-15 minutes) and focus on compliance with dosing and evaluating side effects without integrating dietary, behavioral, or CBT techniques.

In Stage 1 or Stage 2, participants taking medication for greater than 4 weeks, a taper will be provided (Refer to Minimizing Risk section on page 20 for details).

Naltrexone/Bupropion (NB) Pharmacotherapy Treatment Protocol. During Stage 2, "non-responders" will be randomized to NB or placebo. Medication will be double-blind; patients and study staff, physicians and investigators will be blind to medication assignment. NB will be prescribed per FDA-approval for obesity and previous RCTs demonstrating effectiveness for weight loss in obese patients (Greenway et al., 2009, 2010, 2013; Smith et al., 2013; Wadden et al., 2011). "Non-responders" will start talking NB or placebo one week following discontinuation of LDX. NB medication will comprise naltrexone (50 mg/day) combined with bupropion (300 mg/day) taken daily ( matching frequency for placebo). Per previous RCTs, a dosing escalation approach will be used(Greenway et al., 2010; Wadden et al., 2011). See below.

| **Study Day** | **Active Group** | | **Placebo Group** | |
|---|---|---|---|---|
| | *Naltrexone Capsule* | *Bupropion XL Capsule* | *Naltrexone Capsule* | *Bupropion XL Capsule* |
| 1-2 | Placebo | 150mg | Placebo | Placebo |
| 3-4 | Placebo | 300mg | Placebo | Placebo |
| 5-study end | 50mg | 300mg | Placebo | Placebo |



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This dosing will continue for the remainder of 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 medication arm. Physician visits will be brief (10 -15 minutes), focus on compliance with dosing and evaluating side effects, without using CBT or dietary/behavioral methods. Participants taking medication for greater than 4 weeks, a 7-day taper will be provided (Refer to Minimizing Risk section on page 20 for details).

Withdrawal From Treatment and Other Treatments. *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, intensification of binge eating, or failure to comply with medication. Previous experience suggests that worsening clinical status is rare; in such cases, Dr. Grilo and study physician would determine whether to remove the person from the study and provide referrals.

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

Assessment Procedures. Figure 2 below shows assessment schedule and measures. Major assessment at: baseline, during Stage 1 treatment (month 1, 2), post-Stage 1 treatment (month 3), during Stage 2 treatment (month 4, 5), post-Stage 2 treatment (month 6), and follow-ups at 6- and 12-months after completing Stage 2 treatment (i.e., 18 months after starting treatment). Outcomes assessments will be done by independent evaluators not involved in the treatment delivery and blind to treatment assignments.

Assessment Training. Independent assessors will receive training in diagnostic interviews from investigators following established protocols. Interviewers, once certified, will receive ongoing supervision to ensure consistent use and prevent drift. Dr. Grilo will do inter-rater reliability studies, which he has published for BED (Grilo et al., 2004) and psychiatry (Zanarini et al., 2000).

Eligibility and Baseline Assessment. Potential subjects will be assessed by clinicians who describe the treatment study and procedures, and obtain informed consent. Baseline assessment (two meetings) will include two interviews, the MINI (Sheehan et al., 2014) and EDE (Fairburn et al., 1993), to generate lifetime and current psychiatric diagnoses and detailed current eating disorder features and (BED) diagnoses.

Assessment of Treatment Outcome and Time Course.



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Primary Measures: (1) Binge-eating frequency (EDE); (2) weight (measured weight and height and BMI); for Stage 2 LDX vs Placebo test: "Relapse" to DSM-5 threshold of once-weekly binge eating on EDE

Secondary Measures: (1) "remission" (zero binges past 28 days on EDE; eating disorder pathology (EDE global), depression (BDI-II); for exploration of mediators: (2) eating behaviors (EDE, TFEQ, FCI-II), executive control and impulsivity (BIS-11, DDT, Trails) and selected metabolic measures (lipid profiles, HbA1c, blood pressure, HR) to characterize metabolic outcomes and allow comparison with RCTs for LDX and NB.

***Figure 2****. Grid depicting when each measurement is obtained*

| Assessment Points | BASELINE (2 MTG) | DURING RX STAGE 1 1-MONTH | DURING RX STAGE 1 2-MONTH | POST RX STAGE 1 3-MONTH | DURING RX STAGE 2 4-MONTH | DURING RX STAGE 2 5-MONTH | POST RX STAGE 2 6-MONTH | 6 AND 12-MO FOLLOW-UP (18 MONTH TOTAL) |
|---|---|---|---|---|---|---|---|---|
| MINI Psychiatric Interview, Height, Credibility, | • | | | | | | | |
| EDE Interview, SF-12, GPAQ, Lipid Profile, HbA1C, Glucose | • | | | • | | | • | • |
| EDE-Q-I, BDI-II, GLTEQ, Weight, BP, HR | • | • | • | • | • | • | • | • |
| TFEQ-Restraint | • | • | | • | | | • | • |
| DDT | • | • | | • | | | • | |
| FCI-II, PFS | • | • | | • | • | | • | |
| BIS-11 | • | • | | • | • | | • | • |
| ELOCS | • | • | | • | | | | |
| Trails, YFAS, BRS, Amphetamine Testing | • | | | • | | | • | |
| Placebo Ratings | | | | | • | | • | |
| Start of New Treatments | | | | • | | | • | • |
| Medical History **Creatinine w/ EGFR PSQI** | • | | | • | | | | |
| Adverse Events | | • | • | • | • | • | • | |
| Insulin | • | | | • | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Liver Function | • | | | • | • (Non-responders only) | | | |
| Pregnancy Test | • | | | • | | | | |

Clinical Assessments:

- MINI International Neuropsychiatric Interview-Version 7.0 (**MINI**) (Sheehan et al., 2014) is a brief structured interview for Axis I psychiatric disorders. Validation and reliability studies have supported the MINI, including good convergence with SCID (Sheehan et al 2014). The MINI requires much less time than the SCID and reduces subject burden while providing adequate psychiatric data to characterize patients and determine exclusion criteria. We will use the MINI-7 (based on *DSM-5)*.

- Eating Disorder Examination Interview–16th Edition (**EDE**; Fairburn & Cooper, 2008) investigator-based interview assesses the features of eating disorders and diagnoses. The EDE will be our primary assessment method for binge eating and ED pathology at baseline, post-treatment(s), and follow-ups. EDE focuses on past 28 days, except for diagnostic items (rated for durations stipulated in DSM-5). EDE assesses frequency of different forms of overeating, including objective bulimic episodes (OBE) (binge eating, i.e., unusually large amounts of food with loss of control). EDE also comprises four scales (restraint, eating concerns, weight concern, and shape concern) and a global severity score. EDE has good psychometric properties (Grilo et al., 2001a, 2001b), is the major outcome measure for BED RCTs (Wilfley et al., 2002; Wilson, Wilfley, et al. 2010), and has good test-retest reliability in obese and BED groups (Grilo et al, 2004, 2005).
- Trail Making Test, Parts A & B (**Trails**). Trails is a measure of executive attention and relevant to LDX models (Kessler et al., 2016). In Part A, participants connect numbered dots consecutively as quickly as they can and In Part B, participants connect dots labeled with numbers and letters, alternating between number and letter. Trails can be administered in <5 minutes (Gaudino et al., 1995; Strauss, Sherman, & Spreen, 2006).
- We will also gather clinical data on the patient's medical history prior to the study, which we will update as indicated in Figure 2. If patients begin other treatments, this will allow us to account for this in analyses.

Self-Report Questionnaires:

- EDE-Questionnaire Version with Instructions (**EDE-Q-I**; Fairburn & Beglin 1994; Celio, Wilfley et al. 2004) generates the same eating data and scale scores as EDE interview, has good test-retest reliability with BED (Grilo, Masheb et al. 2001; Reas, Grilo et al. 2006). EDEQ will be used across all assessment points given its low burden (in addition to EDE at major assessment points). EDEQ converges well with EDE as a measure of "change" (Sysko, et al. 2005). In N=200 BED patients, alphas for the four scales ranged .71 to .75.
- Three Factor Eating Questionnaire (**TFEQ**; Stunkard & Messick, 1985) taps eating behaviors with 3 factors: cognitive restraint, disinhibition, and hunger; however, we will be using the restraint subscale for this study. TFEQ has validity (Foster et al., 1998), and shows differential response across treatments consistent with putative CBT mechanisms (Blomquist & Grilo, 2011; Grilo & Masheb, 2005; Safer et al., 2004). In N=200 BED patients, alphas for the 3 scales ranged .67 to .76.
- Food Craving Inventory (**FCI-II;** White et al., 2002) assesses general and specific food cravings (relevant for NB) and comprises 4 subscales for different food groups. FCI-II is validated and



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psychometrically supported in studies with obese and with BED groups (White et al., 2002; White & Grilo, 2005). Internal consistency was 0.93 for total score and ranged 0.70-0.85 for subscale items in N=464 BED patients.

- The Power of Food Scale (**PFS;** Lowe et al., 2009) assesses psychological impact of and drive to eat palatable foods. PFS measures appetite for – rather than consumption of – palatable foods. PFS has been validated in normative (Lowe et al., 2009) and treatment-seeking obese patients (Cappelleri et al., 2009). PFS comprises 3 scales reflecting food proximity (food available, food present, and food tasted) supported by factor analysis and good test-retest reliability and internal consistency (range 0.81-0.91) (Cappelleri et al., 2009). The PFS is a good measure of the hedonic impact of food environment cues; fMRI studies have reported associations with state cravings for desired foods and shifts in brain networks (Rejeski et al., 2012).
- Eating Loss of Control Scale (**ELOCS**; Blomquist et al., 2014) assesses the complexity of loss of control eating over the past four weeks. The ELOCS has demonstrated good convergent validity and is considered a valid self-report questionnaire that may provide important clinical information regarding experiences of loss-of-control eating in persons with obesity and BED.
- Godin Leisure Time Exercise Questionnaire (**GLTEQ;** Godin et al., 1985) assesses mild, moderate, and vigorous physical activity, has good test-retest reliability (Jacobs et al., 1993) and has been validated using various activity measurement methods (Miller et al., 1994).
- Global Physical Activity Questionnaire (**GPAQ;** Armstrong et al., 2006) is recommended by the NIH ADOPT guidelines for the assessment of physical activity and sedentary behavior when actigraphy is not used (Lytle et al., 2018).
- Beck Depression Inventory (**BDI-II**; Beck & Steer, 1987) 21-item version is a widely used measure of the symptoms of depression. A voluminous literature has documented good internal consistency (studies range .73 to .95), short-term test-retest reliability, and convergent validity (Beck, Steer, & Garbin, 1988). In a recent consecutive series of N=200 obese BED patients at Yale, alpha coefficient was .87.
- Barratt Impulsiveness Scale (**BIS-11**; Patton et al., 1995). The BIS-11 is a well established and widely scale of impulsivity; BIS-11 yields three second-order factors: attentional (consisting of the first-order factors attention and cognitive instability), motor (consisting of the first-order factors motor and perseverance) and non-planning (comprised of the first-order factors self-control and cognitive complexity) (Patton et al., 1995. These measures are relevant to disordered eating and reward systems (Carver & White, 1994), neurobiology of BED (Balodis et al., 2013), and to models of BED and possible LDX effects (Kessler et al., 2016).
- Delayed-Discounting Task (**DDT**), related to impulsivity, occurs when individuals choose smaller, more immediate rewards over larger rewards that would occur after a time delay (Green & Myerson, 2004). Analysis of responses with varied time delays and varied rewards indicates individuals' selections fall into a hyperbola-shaped pattern balancing delay and size of rewards (Green & Myerson, 2004) including obesity (Thomas et al., 2015). Individuals with BED show steeper responses than participants with obesity (Manwaring et al., 2011). Kirby is a DDT that asks participants to choose between two hypothetical rewards, one of which is after a delay. Amount of the short-term reward, long term reward, and time delay vary across 27 items, allowing for the computation of a "discounting rate" (i.e., when participants do not have a preference between smaller immediate reward and the larger but delayed reward) fitted to a hyperbolic discount curve (Kirby, 2009). These discounting rates have shown evidence of stability over 5-week (r=.77) and 57-week (r=.63) test-retest periods. DDT is relevant to neurobiologic models of BED (Balodis, Grilo, & Potenza, 2015) and models of LDX (Kessler et al., 2015).



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- Short-Form-12 MOS Health Survey (SF-12; Ware & Sherbourne, 1992) taps health-related quality of life, with established reliability and validity (McHorney et al., 1993, 1994), and will be used to calculate quality-adjusted life years (QALY) per established methods (Revicki et al., 2005; Tsai et al., 2005) used in recent BED research on cost-effectiveness of LDX (Agh et al., 2016) and CBTgsh (Lynch et al., 2010; Dickerson, 2011).
- The Yale Food Addiction Scale 2.0 (YFAS 2.0 and YFAS-S 2.0) (Gearhardt et al., 2016) is a self-report questionnaire that adapted the 11 symptoms of substance dependence (as listed in the DSM-5 to assess addictive-type eating behaviors.
- Pittsburgh Sleep Quality Index (PSQI) is a widely used 19-item self-report measure which assesses sleep quality during the prior month (Buysse et al., 1989). The PSQI generates a global score ranging from 0 to 21; scores greater than five are indicative of poor sleep quality.
- Brief Resilience Scale is a psychometrically-sound brief measure assessing a person's ability to thrive and recover from stress.

Physical Assessment:

- Pregnancy test: All women of reproductive age who are sexually active will be required to have a pregnancy test before Stage 1 randomization. Women of reproductive age who are sexually active who are randomized to Stage 1 medication groups (CBT+ LDX or LDX ONLY) will also require a pregnancy test before Stage 2 treatment.
- Lipid profiles will be obtained following established protocols (12-hr overnight fast, no exercise for 48 hr, a.m. draw) (Anderson et al., 1995).
- Glycemic Control will be determined with HbA1c, a routine measure of average glucose control for a previous (3-month) period.
- Hepatic function panel (Liver Function) will be assessed for safety.
- Creatinine w/ EGFR (Renal Function) will be assessed for safety.
- Glucose, Mean Plasma Glucose, and Insulin levels will be obtained.
- Thyroid-stimulating hormone (TSH) will be assessed if patients report any history of thyroid disease or are taking thyroid medications.
- Body weight measured (no shoes) on high-capacity equilibrated digital scales and height measured on stadiometer to nearest 0.1 cm will be used to calculate BMI ($kg \cdot m^{-2}$). Weight will be measured at all assessment points and will also be measured every two weeks throughout treatments.
- Blood Pressure (BP) and Heart Rate (HR). BP readings (systolic and diastolic) and HR will be obtained regularly at clinic meetings.
- Urine drug testing: For non-responders in Stage 2 (those eligible for the NB versus placebo arm), participants will receive urine drug testing for opiates.

Perceptions of Treatment:

- Treatment Credibility ratings will be examined before beginning each stage of treatment.
- Placebo/Med Ratings Patients and clinicians will provide *medication versus placebo ratings*.
- Treatment Compliance *for CBT* will include session attendance and self-monitoring compliance and counts. Compliance for medication treatment(s) will include pill count method and will supplemented by additional "objective" method. Medication compliance with LDX will be monitored through evaluation of urine levels of amphetamine. In addition, we will be able to explore the relationships between compliance for CBT and LDX with the primary outcomes.
- Adverse Events will be collected during clinic visits using standard adverse event checklists of commonly reported adverse events for the LDX and the NB medications. Research-clinicians will ask open-ended and follow-up questions as needed.



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5. Genetic Testing N/A ☒
   **A.** Describe
      i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*
      ii. the plan for the collection of material or the conditions under which material will be received *Write here*
      iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*
      iv. the methods to uphold confidentiality *Write here*

   B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*
   C. Is widespread sharing of materials planned? *Write here*
   D. When and under what conditions will materials be stripped of all identifiers? *Write here*
   E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*
      i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*
   F. Describe the provisions for protection of participant privacy *Write here*
   G. Describe the methods for the security of storage and sharing of materials *Write here*

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

   N=180 participants with BED (DSM-5; APA, 2013) and with obesity (BMI≥30 or BMI ≥27 if with metabolic comorbidity), ages 18-64 years, and meeting other eligibility criteria as described below will be randomized to participate in this trial. Previous work with this population suggests participants will be male and female, and represent diverse racial/ethnic and sociodemographic groups.

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

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

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

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

   Inclusion Criteria:

1. Be in the age range ≥18 years of age and <65 years of age.
2. Have a BMI ≥30 and ≤50 (or BMI≥27 with a metabolic disorder associated with obesity).
3. Meet diagnostic criteria for binge eating disorder (per DSM-5).
4. Be an otherwise healthy subject (except for obesity-related metabolic problems that are not deemed uncontrolled), as determined by physical examination and EKG, medical history and treatment, and lab testing which will be reviewed by the study physician.
5. Read, comprehend, and write English at a sufficient level to complete study-related materials.
6. Provide a signed and dated written informed consent prior to study participation.
7. Be available for participation in the study for up to 18 months (3 month + 3 month treatment plus 12 month follow up).

Exclusion Criteria:

1. Previous history of problems with LDX or other stimulants.
2. Any current psychostimulant use or any medication for ADHD.
3. Current use of study medications including Bupropion (also known as Wellbutrin or Zyban), Naltrexone, or the combination of Bupropion and Naltrexone (also known as Contrave).
4. History of congenital heart disease, known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, cerebrovascular pathology including stroke, exertional chest pain, uncontrolled high blood pressure, and other serious heart problems.
5. Has a history of severe renal, hepatic, neurological, or chronic pulmonary disease.
   Out-of-range tests will be reviewed with the medical doctor. For hepatic functioning, a diagnosis of cirrhosis, hepatic failure or 3 times the normal AST and ALT (AST>144; ALT>165) will be exclusionary. For renal functioning, eGFR ≤ 30 will be exclusionary.
6. Current *uncontrolled* medical problems, including hypertension, type I or II diabetes mellitus, thyroid illness.
7. Has psychotic or bipolar disorders or reports active suicidal or homicidal ideation.
8. History or current alcohol or substance use disorder (smoking will not be exclusionary)
9. Is currently receiving evidence-based effective therapy or using medications for weight loss or eating/weight issues.
10. 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; or has a family history of idiopathic seizure disorder
11. Is currently taking MAOI medication, SSRI medication, or strong inhibitors of CYP2D6 (i.e., Bupropion, Cinacalcet, Fluoxetine, Paroxetine, Quinidine).
12. Has a history of allergy or sensitivity to LDX or other stimulant medications
13. Has untreated hypertension with a seated systolic blood pressure > 160 mmHg, diastolic blood pressure > 100 mmHg, or heart rate > 100 beats/minute.
14. 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.
15. Has gallbladder disease.
16. Is breast-feeding or is pregnant, or is not using a reliable form of birth control.
17. Current medication contraindicated with study medications.
18. Current regular self-induced vomiting
19. History of bruxism due to medication
20. For Stage 2 non-responders only, history of anorexia nervosa or history of bulimia nervosa will be exclusionary for that stage; however, history of anorexia nervosa or history of bulimia nervosa will not exclude individuals from Stage 1, Stage 2 “Responder” treatment (LDX), or any of the follow-ups.”



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21. For Stage 2 non-responders only, history of allergy or sensitivity to bupropion or naltrexone will be exclusionary for that stage; however, history of allergy or sensitivity to bupropion or naltrexone will not exclude individuals from Stage 1, Stage 2 "Responder" treatment (LDX), or any of the follow-ups.
22. Non-responders, during Stage 2, currently taking Tramadol or opioid pain medications or drugs.

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

Participants will be interviewed by a trained research clinician (MINI and EDE) to determine whether they meet criteria for binge-eating disorder. These diagnostic clinical interviews will also determine whether participants have any co-existing psychiatric conditions (including substance use disorders) that require hospitalization or more intensive/different treatment. The study physician will determine medical eligibility based on results of participants' physical examination (within one year of starting the study), as well as results of the baseline assessment. Information obtained from the physical examination will include an EKG and a list of current medications, which participants will be asked to bring to their baseline assessment. For otherwise healthy participants, an EKG during the past two years will be acceptable. Medical review is required for all participants. Therefore, communication with treating physicians occurs for each patient. If the study physician requires additional information, the study physician will contact the treating physician.

Source of Research Materials

Data will be collected in the form of standardized clinical interviews, self-report questionnaires, clinical interviews, and traditional medical methodologies including standard laboratory blood tests. All the assessments are described in the previous section (Research Design). The data will be used for clinical and research purposes only.

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

The primary risks of this study are the cognitive behavioral therapy (CBT), the pharmacologic therapy with LDX, the pharmacotherapy with NB, placebo during Stage 2 RCT, the assessment procedures, and lack of efficacy.

1) **CBT**: Cognitive behavioral therapy (CBT) is an established and widely-used psychological therapy for BED (and for other forms of eating disorders and obesity). The only foreseeable risks include some mild discomfort or embarrassment when discussing binge-eating, 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 CBT are judged to be minimal.

2) **LDX**: Lisdexamfetamine (LDX) is the only FDA-approved medication for the treatment of BED. LDX has demonstrated short-term effectiveness relative to placebo and safety in one phase 2 and two phase 3 RCTs. An additional Phase 3 open-label 12-month extension safety and tolerability trial of LDX for BED with N=604 patients who completed previous Shire RCTs (McElroy et al., 2015, 2016) reported the 12-month safety/tolerability profile of LDX was consistent with short-term (12-week) BED trials and with established profile of LDX for ADHD (FDA-approved); 9% of patients reported treatment emergent side-effects resulting in medicine discontinuation (Gasior et al., 2017).



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LDX was associated with the following side effects 10% or more of the time and twice as often as placebo: dry mouth and insomnia. LDX was associated with the following side effects in less than 10%, but twice as often as placebo: decreased appetite, increased heart rate, feeling jittery, constipation, anxiety, diarrhea, decreased weight, hyperhidrosis, vomiting, gastroenteritis, paresthesia, pruritis, upper abdominal pain, energy increased, urinary tract infection, nightmare, restlessness, and oropharyngeal pain.

Serious risks of LDX include psychiatric problems and heart complications, including sudden death in people who have heart problems or heart defects, and stroke and heart attack in adults. Central nervous system stimulants, including lisdexamfetamine, may cause psychotic or manic symptoms, such as hallucinations, delusional thinking, or mania, even in individuals without a history of psychotic illness.

LDX is associated with increased risk of serotonin syndrome when co-administered with serotonergic agents, but also during overdosage situations. The potential for a pharmacokinetic interaction exists with co-administration of CYP2D6 inhibitors which may increase the risk with increased exposure to the active metabolite dextroamphetamine.

This study will provide LDX following the same dosing and procedures and time frame (12-weeks) as the large phase 2 study demonstrating safety and optimal dosing and two large phase 3 trials reporting safety and efficacy for BED over 12-week treatments. The same optimal dosing strategy will be used in the Stage 2 maintenance RCT; this delivery safety is further supported by the Hudson et al (2017) report of LDX vs placebo maintenance. LDX is also classified as a DEA-controlled substance and product labeling includes a "Warning" that CNS stimulants have high potential for abuse/dependence.

Bruxism is also a potential rare side effect. History of bruxism in response to a medication will be exclusionary.

NB: Naltrexone/Bupropion combination (NB) is FDA approved for the treatment of obesity. 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 Naltrexone/Bupropion and placebo (1.6% versus 1.4%) and none of the observed events were judged to be related to the study. Since one of the study's (Stage 2) medication may be a combination Naltrexone/Bupropion, 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)."*



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3) Placebo: Placebo, which is a risk only during the Stage 2 treatment, is considered a generally inert comparison condition and participants may not improve or sustain improvements with the passage of second 12-week treatment stage. Such placebo controls have been utilized in numerous published trials with BED without problems and RCTs have reported that some persons do improve solely on placebo.

4) 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.

5) Failure to Improve: There is a chance that the patient's BED may fail to improve or may worsen 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. In the case of non-responders to Stage 1 treatments (with the "leading" active treatments), if warranted due to clinical status and/or if participants request, appropriate referrals will be provided.

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

CBT and Interviews: The research clinicians in this study and additional research staff will be carefully trained and supervised by the Investigators in their procedures, assessments, and evaluations. The clinical evaluators are carefully trained and supervised research clinicians (doctoral level and/or advanced trainees). All of these clinical-research staff who have multiple contacts with the participants can reasonably be expected to identify potential problems. They are expected given their experience and training to identify any problems or distress and to take appropriate action as medically indicated. The study investigators will be continuously available to the research clinicians and to the independent evaluators to discuss any problems and to implement any needed interventions or offer appropriate referrals. The repeated detailed assessments during the course of treatment (and the two follow-up assessments) will allow for additional and ample opportunity to identify difficulties. In the event that a participant experiences undue distress, ample resources at Yale are available.

LDX: Effective screening will exclude all prospective participants who would be at greater risk for complications because of medical or psychiatric illnesses. LDX is classified as a DEA-controlled substance and product labeling includes a "Warning" that CNS stimulants have high potential for abuse/dependence. Thus, potential participants with a history of drug and alcohol problems will be excluded and all participants in the RCT will be evaluated carefully at all clinic visits for any signs of medication misuse in addition to structured assessments of potential side-effect or adverse events per the published procedures (McElroy et al., 2015). The LDX pharmacologic treatment protocol follows the evidence-based dose-optimization protocol that has demonstrated safety, tolerability, and efficacy in the same patient group during the 12-week duration of treatment. Subjects will be evaluated repeatedly throughout the study and will be monitored for any signs of medication misuse and for side-effects and adverse reactions using structured assessments at all clinic visits. If any participant experiences adverse reactions, or if side effects are too severe, the medication will be discontinued. Regarding the risk of serotonin syndrome, all SSRI medication and strong inhibitors of CYP2D6 will be excluded for this study. Regarding risk of heart complications, individuals with a history of cardiac disease will be excluded. Participants will be required to have an EKG before enrolling. Subjects with a baseline EKG that is assessed and determined to be indicative of one of the cardiac disorders listed in the exclusion criteria will be excluded. Regarding psychiatric symptoms, such as mania and psychosis: At monthly follow-ups during Stage 1 and Stage 2, study clinicians will assess manic and psychotic symptoms using structured questions from the Mini International Neuropsychiatric Interview (MINI), a well-established interview used to assess psychiatric disorders. This added specific assessment will be conducted with



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participants aged 30 years or less (given previous LDX trial report that 0.1% of those patients might have developed such symptoms). Any older patients assessed who are suspected of having such symptoms would also be assessed carefully. We note that subjects with history of psychotic or bipolar illness are excluded from participating and this should minimize such risks. Study clinicians are supervised by licensed psychologists trained and experienced in psychiatric assessment. If participants endorse manic or psychotic symptoms (or any of the other potential symptoms of concern), clinicians will consult with the study investigators for safety management and treatment planning. Monitoring of depressive symptoms is described below.

NB: The NB pharmacologic treatment protocol (Stage 2 for non-responders to Stage 1) follows the evidence-based dosing that has demonstrated safety, tolerability, and efficacy for obesity treated over much longer periods of time (>12 months) than the present study. 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 Naltrexone/Bupropion and placebo (1.6% versus 1.4%) and none of the observed events were judged to be related to the study. 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 and we will not include you in the study if we know or suspect you are using opiate-containing drugs.* In addition to structured MINI and clinical diagnostic interviewing and medical record reviews, we will perform lab test with potential subjects suspected of opiate usage.
Monitoring of Depressive Symptoms. In response to the FDA advisory described above on page 17, depressive symptoms will be monitored frequently. To monitor changes in depressive symptoms, patients will be asked to complete the BDI-II at monthly clinic visits. The research clinicians, who are trained and supervised by licensed psychologists in suicidal assessment, will review BDIs 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. The participant will be will asked to continue to follow-up assessments (if applicable). 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.

Finally, 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.

Wallet Safety Card. Each participant will be given a wallet card with the code number for the medication assignment in the event of an emergency and the need for breaking the blind. Participants will be provided with contact information for the study physician and the PI, as well as emergency numbers in case of adverse events or other concerns.

Medication Titration & Taper.
LDX: Participants will have up to three weeks of up-titration: one pill daily (30 mg/day; 1 week), then one pill daily (50 mg/day; 1 week), then one pill daily (70 mg; 1 week) based on acceptable tolerability and clinical need). If 70 mg is not tolerated, downward titration to 50 mg/day can occur. For the remaining treatment



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(weeks 4-12), the optimized LDX dose (50 or 70 mg/day) will be maintained. For the Stage 2 randomized maintenance (double-blind) treatment, a similar approach to dose-optimization will be followed. LDX down-titration for Stage 1 and Stage 2: 70 mg to 50 mg for 2 days, then 30 mg for 2 days, to discontinue medications. At the end of Stage 2, participants on placebo will take the same number of pills as the active group to maintain the blind.

Non-responders NB: NB titration is described on pages 9-10 of the protocol. Participants on placebo will take the same number of pills as the active group to maintain the blind. Participants will be cautioned against stopping the NB abruptly. For NB, taper off is not medically necessary for participants on the study medication for 4 weeks or less.

Assessments: We will evaluate and monitor blood pressure and heart rate because studies have found that patients with obesity treated with NB have significantly lower drops than placebo in systolic BP changes (-0.4 vs. -2.1), diastolic BP (-0.1 vs -1.0), pulse rate (1.0 vs -0.1) (Greenway et al., 2010). Blood pressure and heart rate will be measured during all evaluation visits. Two readings will be taken at each assessment. In the event of systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg, or an increase in heart rate of ≥15 bpm (from baseline), the study physician will be notified and will determine whether additional intervention and/or medication discontinuation is warranted. Liver function. Participants with severe hepatic disease will be excluded if this is detected at baseline, per exclusion criteria. Liver function will also be repeated in the Stage 2 RCT for non-responders who are randomized to NB or placebo at month-1 clinic visits. The study physician will review results of a hepatic panel prior to the start of treatment and throughout treatment. Any changes and out-of-range values will be flagged immediately by research clinicians, and the study physician will determine whether additional intervention and/or medication discontinuation is warranted.

Given the uncertain effects of medication during pregnancy, the following precautions will be taken for women of reproductive age who are sexually active: 1) a pregnancy test will be required at Stage 1 and Stage 2 (but only for those who will be re-randomized to treatment in Stage 2), 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.

Failure to Improve: There is a chance that the patient's BED may fail to improve or may worsen 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. In the case of non-responders to Stage 1 treatments (with the “leading” active treatments), Stage 2 RCT will test another pharmacologic treatment strategy. If warranted due to clinical status and/or if participants request, appropriate referrals will be provided.

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. 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 NIH or 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



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of an audit by a regulatory agency within the federal government. 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 (NIH) 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.

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.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
    Greater than minimal risk
    Although this study qualifies as clinical trial research, it does not meet NIH criteria for Phase III clinical trial research. Nonetheless, this study will be monitored twice yearly by a Data Safety Monitoring Board (DSMB) as the study involves double-blind placebo controlled evaluation of medication effects that may involve greater than minimal risk. Adequate surveillance and protections will be put in place to discover adverse events promptly and keep their effects to a minimum. The treatment interventions and assessment protocols are well-established and pose primarily low risks to subjects. The DSMP focuses on close monitoring by the PI (Grilo) in conjunction with the study MD (Dr. Tek). Excessive adverse events and/or any serious events (should they occur) will be reported promptly to the NIH and to the IRB (Human Investigation Committee) at the Yale University School of Medicine. In addition to the DSMP, the Yale IRB reviews all aspects of the study protocol (including progress and problems) minimally once per year.

    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? NA

    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews semi-annually. Although this study qualifies as clinical trial research, it does not meet NIH criteria for Phase III clinical trial research. Nonetheless, this study will be monitored semi-annually by a Data Safety Monitoring Board (DSMB) as the study involves a double-blind placebo

controlled evaluation of medication effects that may involve greater than minimal risk. Adequate surveillance and protections will be put in place to discover adverse events promptly and keep their effects to a minimum. During the review process, the principal investigator and DSMB will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or the DSMB have the authority to stop or suspend the study or require modifications.

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 LDX (FDA-approval of Vyvanse for BED) and Naltrexone/Bupropion (FDA-approval of Contrave for obesity) medications in 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:

## DATA AND SAFETY MONITORING PLAN

The treatment interventions and assessment protocols are well-established and pose primarily low risks to subjects. The DSMP focuses on close monitoring by the PI in conjunction with the study MDs. Excessive adverse events and/or any serious events (should they occur) will be reported promptly to the NIH and to the Yale Human Investigation Committee.
A Data and Safety Monitoring Board (DSMB) will monitor this project. This board is already in place at Yale for HIC 2000021769. The DSMB is composed of Yale investigators who are independent of the proposed trial and experienced in various aspects relevant to the current proposal including: conduct of clinical trials, biostatistics, primary care, and the clinical management of obesity and BED.

We have developed a standard DSMB report form that summarizes, *on a twice-yearly basis*:

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

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

Because the projected effect sizes may not be large enough for detection during interim analyses, we are not proposing a preliminary analysis of accumulating efficacy and safety data by treatment assignment. Instead, we propose to submit a twice-yearly report of aggregate data to the DSMB members that contains screening data, baseline demographics, retention data, serious adverse events data, as well as



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accrual status, and any other data that will help in the assessment of the clinical trial. Based on this report, each DSMB member will complete a form making one of two recommendations: 1) continue recruitment as planned; or 2) schedule formal DSMB meeting immediately. If any DSMB member recommends a meeting, this will be scheduled, minutes will be kept, the report will be reviewed with the PI, and the committee will vote on whether the study should: 1) continue recruitment unchanged; 2) continue with a protocol amendment; 3) stop recruiting pending further investigation; and 4) the Yale IRB will be informed.

Measurement and reporting of adverse events.

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

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

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

Attribution of Adverse Events:

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

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

Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

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

Plan for Determining Seriousness of Adverse Events:

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

1. Death;

2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

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

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

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

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

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

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

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

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

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

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



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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 a psychiatrist) and will be connected to a local emergency department (e.g., the Crisis Intervention Unit at Yale-New Haven Hospital) and his/her physician or therapist for ongoing care.

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

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

During the reviews, if the DSMB has concerns about whether attrition has reached a level that might inhibit the ability of the study to address its primary aims, they will suggest a meeting to discuss methods for improving subject retention. Previous pharmacotherapy studies for BED (with comparable time frames for pharmacotherapy) have reported attrition rates between 20% and 38%. Studies of 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 safety officer, together with the PI, will alert the Yale IRB and the NIH 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.

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



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randomization schedule would be considered. Any plans to alter the randomization scheme would be communicated to the NIH.

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.

3. Limits of Rules

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

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

d. For multi-site studies for which the Yale PI serves as the lead investigator: NA

1. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
2. What provisions are in place for management of interim results? *Write here*
3. What will the multi-site process be for protocol modifications? *Write here*

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

DATA ANALYSIS

Baseline demographic and clinical characteristics for randomized groups will be compared using chi-square tests for categorical variables, and ANOVA or Kruskal-Wallis tests for continuous variables. Continuous variables will be examined for adherence to normal distribution using normal probability plots and Kolmogorov-Smirnov tests. If normality not satisfied and transformations do not help with achieving normality, alternative analytic strategies will be considered such as generalized estimating equations or nonparametric methods. Dropouts and completers will be compared. Analyses will be intent-to-treat; patients will be followed regardless of treatment completion to minimize missing data. Primary outcomes will be tested at two-sided 0.05 significance level. Secondary analyses will be adjusted for multiple tests using Bonferroni correction.

Overall Data Analysis Strategy will involve MIXED EFFECTS MODELS (Diggle et al, 2002, Gueorguieva & Krystal, 2004) to compare treatments. These models allow for different numbers of observations per subject, use all available data on each subject, and are unaffected by randomly missing data. Further advantage is capacity to test and account for individual-difference contributions to treatment outcomes (Cudeck, 1996; Cudeck & Klebe, 2002; Hedeker et al., 1996; Hedeker & Gibbons, 1996; Singer, 1998). They provide flexibility in modeling the correlation structure of data. In models for each outcome, we will include fixed effects of time, treatment, and interaction between time and treatment, and random subject-level effects. Because we cannot a priori predict the shape of responses over time in each arm of the trial we will first treat time as a categorical predictor and will then test for polynomial trends over time. We will consider different error structures (e.g., AR1, independence) and select the best fitting one based on information criteria. We will



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compare dropout patterns between groups and if there are concerns of informative dropout or informative intermittent missing data, we will use pattern mixture models (Hedeker & Gibbons, 1997) to perform sensitivity analyses.

(1) STAGE 1 – Primary Outcomes Aim 1 and Secondary Outcomes Aim 2a: Compare LDX and CBT effects, alone and in combination, for acute BED outcomes. Analyses examining the co-primary outcomes (reduction in binge-eating and percent weight loss) and examining the secondary outcomes (binge remission, eating disorder psychopathology, depression, metabolic variables) will be intent-to-treat using mixed-effects models per the overall strategy described above. Mixed-model analyses on continuous (or pseudo-continuous) data will use SAS PROC MIXED; mixed-model analyses on binary variables will use SAS PROC GLIMMIX. Logistic regression will be used for categorical outcomes (i.e., remission from binge-eating (defined as 0 binges/past 28 days on EDE interview). Significantly greater reductions in binge eating in CBT and CBT+LDX groups compared to LDX, and weight loss in LDX and CBT+LDX compared to CBT will be considered supportive of our primary aim hypotheses. We do not anticipate significant differences between CBT and CBT+LDX on binge eating and between LDX and CBT+LDX on weight loss but the mixed model approach will allow us to estimate the magnitude of the effects with associated confidence intervals.

(2) STAGE 1 – Secondary Outcomes Aim 2b: Explore conceptually and empirically supported predictors, moderators, and mediators for the primary outcomes (reductions in binge-eating and weight loss) and secondary categorical outcome (binge-eating remission). We will use the Kraemer et al (2002) approach to assess predictor, moderator and mediator effects by adding potential predictor, moderator and mediator variables to the models above. Predictors will be identified as variables with significant main effects on the outcome, moderators as variables with significant interactions with treatment on the outcome, and mediators will need to be significantly affected by treatment, to be related to the outcome and have main or interactive effects with treatment on the outcome. We will explore two empirically-supported predictors and moderators of BED outcomes – overvaluation of shape/weight (EDE) and depression (BDI-II) (Grilo, Masheb et al., 2012; Grilo et al., 2013). It is necessary to test previous findings to establish them specifically for CBT and LDX treatments to inform prescription (i.e., for whom these "leading" treatments work best).

Finally, we expect that "rapid response" will have differential prognostic significance for CBT and LDX. Based on our prior methods (Grilo et al., 2006; Grilo, White, et al., 2012; Masheb & Grilo, 2007), we hypothesize that overall rapid response will predict superior outcomes in both treatments (i.e., greater weight losses in LDX and greater reductions in binge-eating in both CBT and LDX) and that non-rapid-response will predict no further improvement in LDX but not for CBT (where gradual improvement is expected). In terms of mediators, per Kraemer et al (2002) models, we will explore whether differential symptom changes during treatment are associated with subsequent longer-term primary outcomes (binge-eating and weight loss). Repeated (and early) assessments of eating behaviors and cognitions (EDE-Q-I, TFEQ) constructs relevant to CBT, food-reward constructs (FCI-II, PFS) and executive control (Trails, BIS, DDT) constructs relevant to LDX, food-reward (FCI-II, PFS) constructs relevant to NB, and more general conceptually supported constructs (depression (BDI-II)), will yield relevant change variables for analyses of mediation (i.e., testing subsequent changes in binge-eating and weight). These analyses are exploratory and hence may be underpowered. However, they will provide valuable information in the form of variability estimates and effect size estimates for future more definitive studies.

(3) STAGE 2 – Primary Aim 1: Among Responders to Stage 1 treatments with LDX (i.e., LDX and CBT+LDX), compare LDX to placebo as a treatment maintenance strategy. The primary outcome will be "relapse" to DSM-5 level of once-weekly binge-eating and secondary outcomes will be binge-eating frequency, weight loss, eating-disorder pathology, and depression. For the primary outcome (predicting relapse), we will follow



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analytic strategy of studies testing medication for maintenance (i.e., fluoxetine) for bulimia nervosa (Romano et al (2002) and for anorexia nervosa (Walsh et al (2006) which was recently used in the Shire maintenance study of LDX for BED (Hudson et al., 2015). Stage 2 LDX and placebo will be compared on the proportion of Stage 1 responders who "relapse" using chi-squared tests and Cox Proportion Hazards Tests; we will explore further using survival analyses to estimate whether time to relapse differs between LDX and placebo. For the secondary outcomes, we will use mixed effects models to assess whether there is significant change in binge eating or weight loss between the group who continue LDX treatment and the group who receive placebo. We anticipate that subjects randomized to LDX maintenance will maintain better outcomes than patients randomized to placebo. We will also perform parallel analyses on all three groups (CBT, LDX, CBT+LDX) to compare outcomes at the 6-month time point (i.e., comparing 3-month CBT and 6-month two-stage treatments).

(4a) STAGE 2 – Secondary Aim 1: Explore LDX and CBT effects, alone and in combination, for longer-term BED outcomes. Our two-stage design will also allow us to also compare CBT (i.e., Stage 1 CBT-only short-term) versus the Stage 2 LDX/placebo maintenance treatment (i.e., Stage 2 LDX/placebo following Stage 1 LDX or Stage 1 CBT+LDX) for longer-term outcomes through 18 months. This will inform clinical questions regarding whether LDX maintenance treatment following either acute LDX treatment or acute combined CBT+LDX differ and whether it offers any additional benefits over acute CBT-only (4b).

STAGE 2 – Secondary Aim 2: Among Non-responders to Stage 1 treatments with LDX, Explore the effectiveness of switching to an alternative medication (NB versus placebo). Primary outcomes will be reducing binge-eating and reducing weight and secondary outcomes will be binge-eating remission, eating-disorder pathology, and depression. We will use similar analyses to Primary Aim 1: mixed models for the continuous outcome variables and logistic regression for categorical (remission) variable.

(5) Secondary Aim: Generate estimates of cost-effectiveness. We will compute within-study costs for CBT, LDX, CBT+LDX and SMART Stage 2 interventions. Repeated assessments will track additional clinician visits and medication use in our RCT as well as outside treatment contacts through the 18-months. SF-12, administered pre- and post-treatments and at follow-ups, will be used to calculate quality-adjusted life years (QALY) following established methods (Revicki et al., 2005) also used in BED studies of cost-effectiveness specifically of LDX (Agh et al., 2016) and CBTgsh (Lynch et al., 2010; Dickerson et al., 2011), as well as for obesity (Tsai et al., 2005; Malone et al., 2005) including obesity medications (Ara et al., 2012), and for similar SMART designs (switching medication for initial non-responders) in depression (Singh et al 2017). We will calculate incremental cost-effectiveness ratios (ICERs) for the various arms; in these ICERs, the numerator will be the incremental medical cost and the denominator will be the incremental effectiveness of the specific treatment compared to CBT. Confidence intervals for the ICERs will be determined using non-parametric bootstrapping. These ICERS will be compared to the two previous BED (Agh et al., 2016; Lynch et al., 2010) analyses and inform subsequent more definitive larger-scale effectiveness studies.

POWER ANALYSIS: We calculated our sample size to have at least 80% power at 2-tailed alpha level 0.025 (adjust for 2 outcomes) to detect clinically meaningful effects in Stage 1 for co-primary outcomes (binge eating and weight loss) and Stage 2 for primary outcome (relapse by initial Responders) at 2-tailed level of 0.05 according based on documented effects of the two treatment components (LDX and CBT). In Stage 1, with 180 subjects total (60 per treatment group), accounting for up to 20% dropout, we can detect medium effect sizes (d=0.64, f=0.32) for the between group comparisons with more than 80% power at two-sided alpha level of 0.025. These effect sizes are smaller than the effect sizes calculated based on data (Telch et al., 1990; Grilo et al., 2005; McElroy et al., 2015, McElroy 2016) which ranged d=0.69 to d=0.78 for the comparison of CBT to LDX on binge-eating and was d=1.53 for LDX vs CBT on percent weight loss. Dropout



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rate estimated based on completion rates for Dr. Grilo's RCTs with BED: 87% in Grilo & Masheb, 2005; 84% in Grilo, White et al., 2014; and previous grant 2R01 DK49587-15 testing stepped care multi-modal treatment and obesity medication along with the LDX RCTs (McElroy et al., 2015, 2016). For binary outcomes (remission), we can detect the following clinically meaningful differences in proportions (63% vs 35%, 66% vs 38%) at 2-tailed alpha of 0.025 in Stage 1. These are in line with observed proportions for CBT (62% by Wilson et al (2010); 64% by Striegel-Moore et al. (2010); LDX (40% and 36% by McElroy et al (2015; 2016) in BED subjects uncomplicated by co-morbidity. Thus, we are well powered for realistic and meaningful effect sizes for both primary and secondary outcome variables. In Stage 2, we expect to randomize 65-70% of subjects as Responders (per McElroy et al 2017); thus we anticipate to have about 80 subjects from the LDX and CBT+LDX groups for the comparisons of interest. Assuming further 20% dropout, we will have 64 subjects with complete data at the end of Stage 2. With this sample size, we have 89% power at two-sided alpha level of 0.05 to detect differences in relapse reported by Hudson et al (2015) of 4% vs 32% (LDX vs placebo). We would have over 80% power to detect differences for the following rates between placebo and LDX: 10% vs 39%, 15% vs 46%, 25% vs 58%.

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

*If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.*

A. RADIOTRACERS ☒N/A

4. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

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

4. **Source:** Identify the source of the radiotracer to be used. *Write here*

5. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.
*Write here*

B. DRUGS/BIOLOGICS ☐N/A



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

| **Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:** | |
|---|---|
| 1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. | ☒ |
| 2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. | ☒ |
| 3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product | ☒ |
| 4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). | ☒ |
| 5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. | ☒ |

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

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

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

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

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

**Exempt Category 3**

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



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Exempt Category 4

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

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

LISDEXAMFETAMINE DIMESYLATE

An important recent development was the FDA approval in January 2015 of a CNS stimulant, lisdexamfetamine dimesylate (LDX), for the treatment of moderate-to-severe BED based on findings from an integrated series of studies funded by Shire (the manufacturer). The phase II (11-week) RCT demonstrated dosing response and that 50mg and 70mg were superior to placebo (McElroy et al., 2015). Two identically designed phase III RCTs testing LDX (50–70 mg dose optimization) for moderate-to-severe BED in adults (McElroy et al., 2016) found LDX superior to placebo for reducing binge-eating days and reported binge-eating abstinence rates of LDX versus placebo (Study 1: 40% versus 14%; Study 2: 36% versus 13%) at the end of 11 weeks of treatment. Primary analyses of reduction in binge-eating frequency significantly favored LDX over placebo in both phase-III RCTs, with effect-size of 0.83 and 0.97 (McElroy et al., 2016). Another much smaller RCT with N=50, also funded by Shire, reported weaker advantage of LDX over placebo (ES = 0.50), suggesting the need for further and continued investigation by other researchers. McElroy et al (2017) reported time-course data for binge-eating and associated outcomes to expand upon the McElroy et al (2015) report regarding the significant reductions (over 80%) in binge-eating with LDX; these analyses suggest an early and rapid response (and are supportive of our proposed definition of "response". The efficacy and safety data were reviewed and appear to represent a favorable benefit-to-risk ratio (Citrome, 2015).

LDX was also associated with significant acute weight loss relative to placebo (mean 4.9 kg) (McElroy et al., 2015, 2016); weight loss was examined as a safety measure. The FDA-approval and manufacturer product labeling include a "Limitation of Use" highlighting that LDX is not indicated for weight loss (because other CNS stimulant medications for weight loss have been associated with cardiovascular problems and the safety and efficacy of LDX for obesity remains uncertain). In the present study, we anticipate that LDX will produce short-term weight loss and the key and novel research goals will involve the questions of the utility of maintenance LDX treatment and longer-term follow-up.

More recently, two Shire-funded studies have been reported, both providing further support for the proposed research. A Phase III open-label 12-month extension safety and tolerability trial of LDX for BED with N=604 patients who completed previous Shire RCTs (McElroy et al., 2015, 2016) was completed (Gasior et al., 2017). Gasior et al (2017) reported the safety/tolerability profile with 12-months of LDX was consistent with short-term (12-week) BED trials and with established profile of LDX for ADHD (FDA-approved); 9% of patients reported treatment emergent side-effects resulting in medicine discontinuation. Hudson et al (2015 ACNP conference), in a double-blind RCT, reported LDX was significantly superior to placebo for preventing relapse following clinical response to open-label LDX (3.7% vs 32.1% relapsed, respectively). These findings suggest short-term treatment extension with LDX may be effective for decreasing relapse amongst initial responders to LDX. Importantly, Hudson et al (2015) did not report follow-up data after discontinuing the maintenance treatment and whether LDX enhances maintenance for responders to other treatments is unknown.



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Putative mechanisms of action for LDX. LDX (l-lysine-dextroamphetamine), is a prodrug of d-amphetamine covalently linked to l-lysine, that when metabolized to d-amphetamine (active form) is a moderately potent inhibitor of DAT, NET, and VMAT2, with little affinity for SERT; its net effect is increased catecholamine availability (Guerdjikova et al., 2016; Hutson et al., 2014; Pennic, 2010; Comiran et al., 2016). LDX seems relevant for reducing binge-eating per preclinical and clinical (Vickers et al., 2015; Wang et al., 2011), and neurobiologic (fMRI) findings suggestive that binge-eating is related to dysfunctions in the dopamine and norepinephrine systems (Balodis, Grilo, & Potenza, 2015; Balodis, Grilo et al., 2013), which play important roles in regulating eating behaviors and reward (Wellman, 2005; Palmiter, 2007).

Risks. LDX is classified as a DEA-controlled substance and product labeling includes a "Warning" that CNS stimulants have high potential for abuse/dependence. Thus, as previously mentioned, potential participants with a history of drug and alcohol problems will be excluded and all participants in the RCT will be evaluated carefully at all clinic visits for any signs of medication misuse in addition to structured assessments of potential side-effect or adverse events per the published procedures (McElroy et al., 2015). Research has found that 9% of patients reported treatment emergent side-effects resulting in medicine discontinuation (Gasior et al., 2017). In addition, the following side effects were reported in adults with BED taking LDX and at least twice as often as the placebo: dry mouth (36%), insomnia (20%), decreased appetite (8%), increased heart rate (7%), feeling jittery (6%), constipation (6%), anxiety (5%), diarrhea (4%), decreased weight (4%), hyperhidrosis (4%), and the following side effects occurred at 2% (vomiting, gastroenteritis, paresthesia, pruritis, upper abdominal pain, energy increased, urinary tract infection, nightmare, restlessness, and oropharyngeal pain.

NALTREXONE/BUPROPION (Stage II Medication for Non-Responders)

In September 2014, the FDA approved ("Contrave") the combination of naltrexone and bupropion to treat obesity consisting of the following empirical support from several RCTs performed with obesity (but not BED). NB medication will combine the generics naltrexone (50 mg/day) combined with bupropion (300 mg/day) taken daily; matching frequency for placebo).

Mechanisms of Action. The putative mechanisms of action for NB seem relevant for binge eating in addition to weight loss. Naltrexone, an opioid receptor antagonist, is approved to treat alcohol and opioid dependence [92]. Naltrexone produces weight loss in lab animals but only minimal weight losses in people [93, 94]. Bupropion operates through dopaminergic, noradrenergic, and nicotinic acetyl-cholinergic mechanisms [51-53]. Bupropion may target reward processes that drive eating behaviors, consistent with its FDA indication for treating nicotine dependence and reduced weight gain during smoking cessation [54, 55]. Bupropion promotes weight loss [56]: in a meta-analysis of five trials of bupropion, the mean difference in weight loss was 2.77 kg (CI, 1.1 to 4.5) between bupropion and placebo groups at 6 months. White and Grilo [95] reported preliminary, modest support for weight loss specifically in patients with obesity and BED.

NB Combination. The putative mechanisms of action for NB is especially relevant for reducing binge eating and weight per hypothesized effects on brain regions implicated in the regulation of food intake and weight based on research on the mechanisms of action of leptin [94]. The anorectic effects of leptin result from its excitatory effects on pro-opiomelanocorin (POMC) neurons in the hypothalamus melancortin system [96, 97]. Stimulated POMC signaling decreases food intake, increases energy expenditure, but is then inhibited by endogenous feedback [96]. Thus, combining these two drugs will stimulate POMC neurons (bupropion) plus block endogenous feedback that inhibits POMC activity (naltrexone) [47, 94]. This synergistic model received support both in vitro and in vivo studies [47, 98].



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Obesity Outcomes. Recently, several large RCTs have reported that the combination of these two medications (Naltrexone/Bupropion) were effective in promoting weight loss in obese patients [47-49, 99]. 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 [50], in a study of 1496 obese patients reported significantly greater weight losses relative to placebo (-6.5% vs -1.9% at week 28 and -6.4% vs -1.2% at week 56) and significantly greater likelihood of achieving 5% weight loss (56% vs 18% at 28 weeks and 51% vs 17% at 56 weeks). These findings supporting NB medication are quite consistent with earlier (large) RCTs which reported the following percentage of patients achieving at least 5% weight loss: 56% vs. 18% [48]; 52% vs. 15% [100]. Thus, the proposed RCT study will test the effectiveness of Naltrexone/Bupropion relative to placebo for reducing binge-eating and producing weight loss in obese patients with BED.

Risks. Several large-scale studies have found that this medication is safe and effective for the treatment of obesity [47-49, 99]. The NB combination approved by the FDA (Contrave) is reported to have the following common adverse reactions: nausea (32.5%), constipation (19.2%), headache (17.6%), vomiting (10.7%), dizziness (9.9%), insomnia (9.2%), dry mouth (8.1%), and diarrhea (7.1%). In addition, Contrave will have the FDA warnings and precautions: Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue Contrave if symptoms develop. Risk of seizure may be minimized by adhering to the recommended dosing schedule and avoiding 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.

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

   Both NB and LDX will be purchased using funds awarded in this grant.

   a) Is the drug provided free of charge to subjects? ☒YES ☐NO
   If yes, by whom? Both NB and LDX are purchased by the study PI using funded awarded in this grant.

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

Check applicable Investigational Drug Service utilized:

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

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

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

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



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

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

Pharmacotherapy (medications) for BED has received increased research attention albeit nearly all RCTs have been of short duration and without follow-up period to establish durability [20, 22]. Critical review and meta-analysis show that several drugs – working through varied mechanisms – have short-term efficacy relative to placebo for reducing binge-eating and produce weight loss ranging from modest to none [20]. Placebo-controlled trials of anticonvulsants topiramate and zonisamide [24-26] have reported effects for reducing both binge-eating and weight (with a mean improvement in weight loss of approximately 3-4 kg compared to placebo), but have also shown frequent dropout and adverse events which become nearly universal with longer use [27]. SSRI antidepressants, previously regarded as a potential treatment strategy [28] are characterized by small effect sizes relative to placebo [20] and produce no weight loss at all [38] and are inferior to CBT [29, 30].

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

During Stage 1, participants will not receive placebo. During Stage 2, participants who are non-responders or responders may receive placebo medication for up to 3 months if randomized to placebo.

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

Without immediate effective treatment, the greatest potential harm is that binge eating and associated eating disorder features may not improve. Placebo-controlled trials have rarely reported worsening and generally report a positive placebo response (Reas & Grilo, 2014).

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

Possible risks include failure of binge eating and associated eating disorder features to improve. Previous experience suggests that the frequency of these situations is rare (Reas & Grilo, 2014). To safeguard participants, we plan to assess potential adverse events, side effects, and clinical status. All participants will have monthly visits with research clinicians, who can be expected to detect the clinical changes that warrant concern. Participants will be removed from the study if, through the consultation of the PI and study physician, it is determined that participant safety is at risk, including worsening depression, suicidal ideation, intensification of binge eating, or failure to comply with medication. If a participant is removed from the study, a research clinician will provide referrals. If removal is indicated, a referral for appropriate care will be provided.

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

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



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

☒ **NO** If no, explain why this is acceptable.

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

B. DEVICES ☒N/A

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

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

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

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

3. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
   *Write here*
4. **Source:**
   a) Identify the source of the device to be used. *Write here*
   b) Is the device provided free of charge to subjects? ☐Yes ☐No

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

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): *Write here*

   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): *Write here*

   c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*

   d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*

e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: *Write here*

## SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. Targeted for enrollment at Yale for this protocol: N=180
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: NA

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

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

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

3. **Recruitment Procedures:**

a. Describe how potential subjects will be identified.

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

EPIC Direct to Patient MyChart confidential messaging will be utilized for recruitment of subjects meeting specific parameters (Adults meeting obesity or binge-eating disorder criteria). The following template will be utilized:

Title of study, Phase or type of study: Cognitive-Behavioral and Pharmacologic (LDX) Treatment of Binge Eating Disorder and Obesity

Principal Investigators: Carlos Grilo, Ph.D.

Study Contact: Valentina Ivezaj, Ph.D. Phone # 203-785-7210

Description:
If you are 18 to 64 years old with binge eating, you may be eligible to participate in a free and confidential study that may help improve your eating behaviors. No cost treatment provided (FDA-Approved medication or behavioral therapy). Participants will receive up to $400 compensation. To learn more or see if you are eligible to participate, please call the Yale Program for Obesity, Weight, and Eating Research at: (203) 785-7210.

Please indicate how often you would like to receive new names of potential participants ☐ daily ☒ weekly

b. Describe how potential subjects are contacted.

Advertisements will ask participants to contact our research team if they are interested in the study. When potential participants call 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 assessment.

c. Who is recruiting potential subjects?

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

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☐Yes, some of the subjects

☒No

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

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

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

Participants will initially call us and/or fill out an online interest form in response to advertisements, at which time, if they seem eligible, we will schedule them for an initial assessment and collect contact information. We will also request that patients complete online surveys. If potential participants elect to participate, they would then provide informed consent including HIPAA



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authorization as described at their initial in-person visit. Names will be removed from surveys if an individual does not provide informed consent.

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

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

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

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

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

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

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

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

   NA

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

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



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

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

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

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

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

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

10. Use of Hospital Research Unit (HRU/CSRU)

Participants who have not had an EKG in the past year (or two years if otherwise healthy) or who are unable to obtain an EKG by their provider, will obtain an EKG through the HRU or the CSRU.

Subjects who have not had a physical or EKG in the past year (or two years if otherwise healthy) and are unwilling or unable to obtain a physical and/or EKG from their provider will be given the option to have a physical and/or EKG at the CSRU. The cost of these services at the CSRU and HRU will be covered by study funds.

For a waiver of signed consent, address the following:

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

OR

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

☐ Requesting a waiver of consent:

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

☐ Entire Study



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

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

## SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

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

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

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

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

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

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

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

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



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

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

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

## SECTION V: POTENTIAL BENEFITS

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

Subjects will receive potentially beneficial treatment for BED. There is substantial importance in the knowledge to be gained in this study. BED is the most prevalent formal eating disorder (a diagnosable mental disorder) associated strongly with obesity and is associated with substantial psychiatric and medical co-morbidity and with functional impairment. Finding ways to identify, understand, and improve treatments for BED is critically important to address this important health problem. The dearth of treatment research, particularly with pharmacological methods and longer-term outcomes, is strikingly at odds with the public health significance and prevalence of BED. 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.

## SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

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

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

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

   Subjects will be paid $100 for each of the primary outcome assessments (post-treatment Stage 1, post-treatment Stage 2, 6-month follow-up, and 12-month follow-up) for up to a total of $400. Subjects who drop out of the trial will be invited to return for the follow-up evaluations. Our experience with numerous treatment studies has indicated that this incentive results in a high retention rate for follow-ups which is essential for the study.

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

   Psychological assessment, labwork, and treatment will be provided at no cost to participants, their insurance, health plan benefits nor other third party payer. Participants will be asked to provide information from a



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recent (within one year) physical with their primary healthcare provider. If they have not had a physical within the past year, we will ask them to obtain a physical prior to participating in the study. A physical exam with their own primary healthcare provider would be at the participant's (or the participant's insurance) cost. (Note: In research we have conducted in the past with patients diagnosed with binge eating disorder, the majority of patients had a physical within the past year.)

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

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

    Yes. Referrals for treatment will be made.

    b. Where and from whom may treatment be obtained?

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

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

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

    d. Who will pay for this treatment?

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

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

    Referrals will be provided.

## IMPORTANT REMINDERS

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

*A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by*

*professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects*.

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

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

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

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

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

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

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

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

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

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