Anti-Obesity Phentermine-Topiramate Extended Release Pharmacotherapy vs Placebo Among Patients Using a Wearable Activity Tracker.

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Protocol

Effect of an anti-Obesity Medication Phentermine-Topiramate Extended Release pharmacotherapy vs placebo among patients with obesity using a wearable activity trackers: Randomized, Double-blinded, Placebo-Control, 1-Year, Single-Center Trial

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IRB approved: Pending

Conflict of Interest: none

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Abstract:

Introduction: Obesity prevalence continues to increase worldwide. Estimated costs to the healthcare system are more than $220 billion annually. Obesity severity is associated with higher cardiovascular mortality. FDA-approved medications, devices and surgeries have shown long-term improvements in obesity and diabetes, however, their use (population penetrance) remains low. On the contrary, and despite of contradicting published literature, numerous wearable technologies specific to physical activity and diet are widely adopted with minimal long-term data or benefits. Little is known about the effect anti-obesity pharmacotherapy among patients undergoing lifestyle intervention that includes a consumer-based wearable activity tracker.

Hypothesis and Aims: We hypothesize that anti-obesity pharmacotherapy (vs placebo) will have an effect on weight loss among patients using an activity tracker as part of a lifestyle intervention. Thus, we aimed to study in a randomized, double blinded, placebo-control, 1-year, single-center trial the effect of Phentermine-topiramate ER (Anti-obesity Pharmacotherapy) vs placebo among patients with obesity using a wearable activity tracker as part of standard lifestyle intervention.

Methods/Study Design: We propose a randomized, single-center trial in 80 patients with obesity to study the Effect of **an** anti-Obesity Medication Phentermine-Topiramate Extended Release vs placebo among patients using a wearable activity tracker in weight loss and obesity related comorbidities in 12 months. All the participants will receive a wearable activity tracker with a Bluetooth scale as part of an intense lifestyle intervention (14 visits total with dietitians, physicians and behavioral therapists (or 6 visits and at least one contact per week virtually with wellness coach) and they will be randomized 1:1 to placebo or Phentermine-topiramate ER (Dosing of 3.75/23 mg daily for 15 days, increased to 7.5/46 mg daily). Participants will be randomized according to a computer generated randomization schedule generated by the study statistician's office and submitted to the Mayo Clinic CTSA research pharmacy. Allocation will be concealed. Study end-points: a) Primary: Total body weight loss at 3 months among the groups; and b) secondary: Total body weight loss at 6, 9 and 12 months among the groups; number of steps (average per week at 3, 6, 9 and 12 months among the groups); calories tracked: number times recorded, calories per day (average per week at 3, 6, 9 and 12 months among the groups), number of exercise sessions (average per week at 3, 6, 9 and 12 months among the groups); hours/week using app/tracker (average per week at 3, 6, 9 and 12 months among the groups); weight loss difference in clinic vs. Bluetooth scale (weight loss difference 3, 6, 9 and 12 months); Quality of life SF36 (at 3, 6, 9 and 12 months among the groups); improvement in obesity-related comorbidities (diabetes/HbA1c, hypertension/SBP-DBP, hyperlipidemia/TC-LDL-HDL-Tg, Sleep apnea/CPAP, Joint Disease/pain).

Protocol

Effect of a Consumer-Based Wearable Activity Tracker in Combination with an Anti-Obesity Pharmacotherapy in Obesity: Randomized, Placebo-Control, 1-Year, Single-Center Trial

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Introduction:

Obesity prevalence continues to increase worldwide[2] and, in the United States, 69% of adults are overweight or with obesity[3]. Estimated costs to the healthcare system are more than $480 billion annually. Increased severity of obesity correlates with a higher prevalence of the associated co-morbidities. Likewise, obesity increases the risk of premature mortality [4]. Obesity affects almost every organ system in the body and increases the risk of numerous diseases including type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and cancer. It is estimated that a man in his twenties with a BMI over 45 will have a 22% reduction (13 years) in life expectancy.

Obesity is defined as the amount of excess of adipose tissue at which health risks increase[5]. Normal weight, overweight and obesity can be measured by Body Mass Index (BMI). BMI is calculated by weight (kg) divided by the square of the height (m^2). The BMI for an adult healthy weight is from 18.5 to 24.9 kg/m^2, overweight is from 25 to 29.9 kg/m^2 and obese is 30 kg/m^2 or above. Obesity is considered morbid or severe when BMI is higher than 40 kg/m^2 (Guidelines 1998). In children, obesity is measured as BMI higher than the 95th percentile related to their age and sex [6,7]. Obesity can also be measured by waist circumference defined as larger than 102 cm in men and 88 cm in women. BMI and waist circumference are associated with health risks and obesity–related co-morbidities.

The Obesity Epidemic: Obesity has reached epidemic proportions in developed countries and its prevalence is increasing in developing countries [7]. In the United States of America (USA), the prevalence of overweight adults is 64%, and obese adults is 30.5% [8]. In children and adolescents, the obesity prevalence has increased to 17.1% [6]. The World Health Organization indicated that globally, in the year 2005, there were approximately 1.6 billion overweight adults, and of those, 400 million were obese [9.] This alarming obesity epidemic poses a heavy burden to the U.S. economy, costing more than $150 billion every year—10 percent of the total health budget—according to the Centers for Disease Control and Prevention (CDC 2012). In 2009, the U.S. Agency for Healthcare Research and Quality reported that overweight and obese people spend 43 percent more each year in medical expenses than those who have normal weight. The Agency also found that obese workers are paid less than their coworkers who have normal weight [10].

Treatment for obesity:

The 2013 Obesity Guidelines suggest that to achieve weight loss, an energy deficit is essential. Reducing dietary energy intake below that required for energy balance can be achieved through a reduction of daily calories to 1200-1500 for women, and 1,500-1800 for men (kilocalorie levels are usually adjusted for the individual's body weight and physical activity levels); or estimation of individual daily energy requirements and prescription of an energy deficit of 500 kcal/d or 750 kcal/d. Recommendations for young children through adolescence vary in order to support normal growth and development occurring during these years. The Academy of Nutrition and Dietetics Evidence Analysis Library recommends no fewer than 900 kcal/day for 6-12 year olds who are medically monitored and no fewer than 1200 kcal/day for 13-18 year olds (Academy of Nutrition and Dietetics Weight Management Position Paper which provides an overview of a nutrition assessment: http://www.eatrightpro.org/resource/practice/position-and-practice-papers/position-papers/weight-management). Evidence supports greatest long-term success with an individualized, structured meal plan in place. A registered dietitian nutritionist can play an important role in designing the nutrition intervention tailored to address each patient's unique needs and circumstances, taking into consideration factors such as insulin resistance. Any diet program that meets this required energy deficit is appropriate to adopt, and comparative trials have shown no long-term superiority between different macronutrient composition or elimination diets. Furthermore, it is important to adhere to a balanced diet that provides a variety of items from all food groups and limits potentially harmful food ingredients like added sugars, sodium and alcohol. Additionally, guidelines recommend limiting or avoiding liquid calories (i.e. sodas, juices, alcohol, etc.). And, finally, the meal plan should be designed in such a way that the individual is likely to follow it.

Along with the prescription for a reduced calorie diet, a comprehensive lifestyle intervention program should prescribe increased aerobic physical activity (such as brisk walking) for ≥150 min/week (equal to ≥30 min/d most days of the week), and a goal of >10,000 steps per day. Higher levels of physical activity, approximately 200 to 300 min/wk., are recommended to maintain the weight lost or minimize weight regain in the long term (>1 year) [11]. The diet and physical activity can be in combination with a hospital/university or commercial behavior program; these are comprehensive

lifestyle interventions that usually provide structured behavior strategies to facilitate adherence to diet and activity recommendations. These strategies include regular self-monitoring of food intake, body weight, physical activity, and food cravings. These same behaviors are recommended to maintain lost weight, with the addition of frequent (i.e., weekly or more frequent) monitoring of body weight[12].

Pharmacotherapy

In addition to diet, exercise and behavioral modification, pharmacotherapies should be considered as an adjunct to lifestyle changes in patients who have been unable to lose and maintain weight with diet and exercise alone. They should also be considered in people whose history or clinical circumstances require expedited weight loss. Medication should not be used alone, but in combination with an intensive lifestyle program.

Pharmacotherapy for the treatment of obesity can be considered if a patient has a body mass index (BMI) ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia and obstructive sleep apnea[12]. Medical therapy should be initiated with dose escalation based on efficacy and tolerability to the recommended dose. An assessment of efficacy and safety at least monthly for the first three months and then at least every three months. In patients who have cardiovascular disease, guidelines recommend against prescribing sympathomimetic agents such as phentermine and phentermine/topiramate extended release (ER). Lorcaserin and orlistat are safer alternatives. In patients with T2DM, the guidelines suggest antidiabetic agents that promote weight loss such as glucagon-like peptide (GLP-1) analogs which reduce hyperglycemia in addition to the first-line agent for T2DM, metformin[13].

Medication / dose	**Clinical data**	**Mean weight change from baseline after 1 year**	**Weight loss after 1 year (Proportion of participants)**			**References**
			>5%	**>10%**	**>15%**	
Orlistat 120 mg TID	Clinical data from three trials	−6.0 to 10.3 Kg vs −2.6 to 6.1 Kg with placebo	**36–67%** (vs.16–43.6%)	**17 - 38.9** (vs. 8.8 – 24.8)	**NA**	[14-16]
Phentermine/ topiramate ER 15 mg/92 mg Q D	1-year trial, people with obesity (BMI ≥35 kg/m^2)	−10.9% vs −1.6% with placebo	**70%** (vs.21%)	**48%** (vs. 7%)	NA	[17]
Lorcaserin 10 mg BID	2-year trial, people with obesity or overweight and ≥1 comorbidity	−5.8% vs −2.5% with placebo	**47%** (vs. 23%)	**22.6** (vs. 7.7)	NA	[18]
Naltrexone/ bupropion SR 32 mg/360 mg	Four 56-week trials, people with obesity and ≥1 comorbidity	−5.4% vs −1.3% with placebo (COR-I)	**42%** (vs. 17%)	**28.3** (vs. 5.7)	**13.5** (vs. 2.4)	[19]
Liraglutide 3.0 mg QD	56-week trial, people with obesity or overweight and ≥1 comorbidity	−7.4% vs −3.0% with placebo	**62%** (vs. 34%)	**33.1%** (vs. 10.6%)	**14.4%** (vs. 3.5%)	[20]

Phentermine-Topiramate Extended Release: When low-dose, controlled-release, phentermine was combined with the glutamatergic and GABA-ergic antiepileptic topiramate in a large phase III study (more than 1400 participants on treatment arms with different doses), subjects lost 10.2 kg on 15/92 mg combination therapy vs. 1.4 kg on placebo over 56 weeks [17]. The most common adverse events were dry mouth, paresthesias, constipation, insomnia, dizziness, and dysgeusia. Depression- and anxiety-related adverse events were also observed. The medication had favorable effects on glycemia, including prevent progression to diabetes, improvements in lipids, blood pressure, sleep apnea, and quality of life measures. There was also, as previously noted, a small but consistent increase in pulse rate [21]. The overall rate of adverse effects decreased in weeks 56–108 compared to weeks 0–56; among which dry mouth, constipation and paresthesias were the most prevalent There were 19 pregnancies carried to term during these studies none of which resulted in congenital abnormalities [21-23].

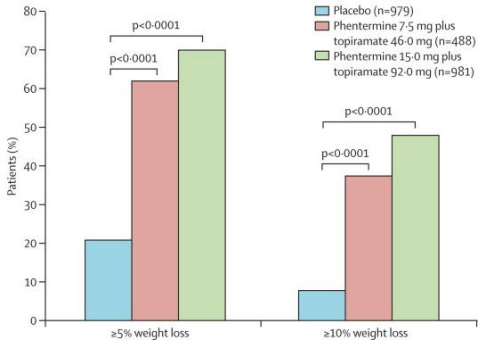

Figure 1. Effects of phentermine plus topiramate on bodyweight. Patients with at least 5% and at least 10% weight loss. [1]

In July 2012, the FDA voted for approval of phentermine (3.75–15mg/d) plus extended release topiramate (23–92mg/d) as an adjunct to diet and physical activity for treatment of obesity among adult individuals with BMI≥30kg/m^2 or BMI≥27kg/m^2 with at least one obesity-related comorbid condition. The drug will carry a warning of potential increased risk for orofacial clefts in neonates exposed to topiramate during the first trimester of gestation and will be subject to a Risk Evaluation and Mitigation Strategy (REMS) that will restrict prescribing to trained clinicians, will require effective contraception and monthly pregnancy tests for reproductive age women, and will restrict dispensing to specific mail-order pharmacies. The company is also required to carry a long-term cardiovascular outcomes trial. No randomized pediatric studies have as yet been reported. Noteworthy, the high dose of PhenTop was associated with a mean weight loss of 9.8%; however, only 48% of patients lost >10% of their body weight, and 30% of patients lost <5% of their body weight (Figure 1).

Wearable Activity Trackers

Consumer-based wearable activity trackers are now readily available and can provide individuals with the ability to objectively monitor their physical activity levels. In addition, when combined with the use of smartphone and computer apps, they may assist users through a range of motivational and tracking tools to better manage their personal health[24]. In addition to providing real-time feedback relating to daily steps and energy expenditure, consumer-based wearable activity trackers have the potential to provide specific, tailored feedback through specifically designed algorithms or by health professionals. This type of emerging technology may provide an alternative means of providing ongoing support and motivation to individuals both looking to increase their activity levels or to maintain activity levels following a structured lifestyle intervention[25]. Moreover, consumer-based wearable activity trackers may assist in reducing the resource and time burden associated with traditional methods of providing ongoing support. Randomized controlled trials have shown that these devices have promise in relation to increasing physical activity participation[26,27]; however, participant numbers in individual studies tend to be low, making it difficult to adequately assess the benefits of these devices. Furthermore, there is limited research relating to their long-term adherence and effectiveness.

A recent systematic review[28] of that aimed to determine the effects of interventions utilizing consumer-based wearable activity trackers on physical activity participation and sedentary behavior when compared with interventions that do not utilize activity tracker feedback, showed that there was a significant increase in daily step count (standardized mean difference [SMD] 0.24; 95% CI 0.16 to 0.33; P<.001), moderate and vigorous physical activity (SMD 0.27; 95% CI 0.15 to

0.39; P<.001), and energy expenditure (SMD 0.28; 95% CI 0.03 to 0.54; P=.03) and a nonsignificant decrease in sedentary behavior (SMD −0.20; 95% CI −0.43 to 0.03; P=.08) following the intervention versus control comparator across all studies in the meta-analyses. In general, included studies were at low risk of bias, except for performance bias. Heterogeneity varied across the included meta-analyses ranging from low (I2=3%) for daily step count through to high (I2=67%) for sedentary behavior. Utilizing a consumer-based wearable activity tracker as either the primary component of an intervention or as part of a broader physical activity intervention has the potential to increase physical activity participation. As the effects of physical activity interventions are often short term, the inclusion of a consumer-based wearable activity tracker may provide an effective tool to assist health professionals to provide ongoing monitoring and support[28].

Online support system: VitalCare (VitalTech Affiliates LLC) is a digital health platform that allows remote collection of date from the wearable tracker and digital wellness devices used as part of this study. It also will allow subjects to document study medication compliance and will allow the remote visits to be conducted through a video conference between subjects and appropriate study team members.

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Methods/Study Design:

We propose a randomized, double blinded, single-center trial in 80 patients with obesity to study the Effect of an anti-Obesity Medication Phentermine-Topiramate Extended Release vs placebo among patients using a wearable activity trackers in weight loss and obesity related comorbidities in 12 months. All the participants will receive a wearable activity tracker and digital wellness devices (Bluetooth scale, Bluetooth pulse oximeter and Bluetooth blood pressure monitor) as part of an intense lifestyle intervention (8 in person visits total with dietitians, physicians and other study team members. At least one contact per month virtually with a member of the study team when an in person visit is not scheduled. Subjects will be randomized 1:1 to placebo or Phentermine-topiramate ER (Dosing of 3.75/23 mg daily for 15 days, increased to 7.5/46 mg daily). Participants will be randomized according to a computer generated randomization schedule generated by the study statistician's office and submitted to the Mayo Clinic CTSA research pharmacy. Allocation will be concealed. Study end-points: a) Primary: Total body weight loss at 3 months among the groups; and b) secondary: Total body weight loss at 6, 9 and 12 months among the groups; number of steps (average per week at 3, 6, 9 and 12 months among the groups); calories tracked: number times recorded, calories per day (average per week at 3, 6, 9 and 12 months among the groups), number of exercise sessions (average per week at 3, 6, 9 and 12 months among the groups); hours/week using app/tracker (average per week at 3, 6, 9 and 12 months among the groups); weight loss difference in clinic vs. Bluetooth scale (weight loss difference 3, 6, 9 and 12 months); Quality of life SF36 (at 3, 6, 9 and 12 months among the groups); improvement in obesity-related comorbidities (diabetes/HbA1c, hypertension/SBP-DBP, hyperlipidemia/TC-LDL-HDL-Tg, Sleep apnea/CPAP, Joint Disease/pain).

Study flowsheet:

Visit schedule:

1. Visit 1-Screening visit
2. Visit 2-Baseline anthroprometric and metabolic studies
3. Visit 3-Counseling / Randomization / wearable tracker, digital wellness devices and Medication assignment and disbursement.
4. Remote visit-2-week follow up (Remote visit)
5. Visit 4-4-week follow up
6. Remote visit-2 month
7. Visit 5-3 month follow up / samples collection / body composition
8. Remote visit-4 month
9. Remote visit- 5 month
10. Visit 6- 6 month follow up
11. Remote visit-7 month
12. Remote visit-8 month
13. Visit 7-9 monthfollow up
14. Remote visit-10 month
15. Remote visit-11 month
16. Visit 8-12 month End of study

				Months											
				1		2	3	4	5	6	7	8	9	10	11	12
Study Procedures	Visit 1 Screening	Visit 2 Baseline Studies	Visit 3 Counseling and Randomization	Remote Study Visit 2-Week (+/- 3 days)	Visit 4 4-Week (+/- 3 days)	Remote Study Visits	Visit 5	Remote Study Visits	Remote Study Visits	Visit 6	Remote Study Visits	Remote Study Visits	Visit 7	Remote Study Visits	Remote Study Visits	Visit 8
Informed Consent	X															
Medical History and Physical Examination	X															
Pregnancy Test	X*	X*	X*		X*		X*			X*			X*			X*
Vital Signs	X	X	X	X	X		X			X			X			X
Metabolic Studies		X														X****
Blood Collection		X					X**			X**			X**			X**
Medication Diary			→	→	→	→	→	→	→	→	→	→	→	→	→	
Dispense medication			X				x			x			x			
Medication Reconciliation			X				X			X			X			

Wearable Tracker and Digital Wellness Devices Given			X													
Randomization and Medication/Placebo Prescription			X													
Behavioral Questionnaires	X***	X[a]														X
Stool Sample		X														
Adverse Event Assessment				X	X	X	X	X	X	X	X	X	X	X	X	X
Review VitalCare Measurments /pregnancy test results				X	X	X	X	X	X	X	X	X	X	X	X	X
Lifestyle Intervention Review			X													
Home Urine Pregnancy Tests Given					X		X			X			X			

* may be done up to 48 hours prior to visit.

**fasting blood draw only (basic metabolic panel, lipid panel, HbA1C, hsCRP, plasma hormones and proteomics.

***HADS, AUDIT-C and Eating disorders questionnaire only

**** Body composition, fasting blood for basic metabolic panel, lipid panel, HbA1C, hsCRP, metabolomics, plasma hormones and proteinomics

[a] All questionnaires except HADS, AUDIT-C and Eating disorders questionnaire

[b] Visit window for visits 5, 6, 7, 8 and all remote visit is +/- 5 days.

Randomization and Allocation

A computer generated randomization schedule generated by the study statistician's office will be submitted to the Mayo Clinic CCaTS Research Pharmacy. Randomization will be based on guiding pharmacotherapy or placebo. Allocations will be concealed. This study will be blinded until data are transmitted to the statistician for data lock. All subjects will be given a verbal explanation of the study, provided time to read and study the written consent form and its information, given opportunities to ask questions and a copy of the consent form. Participants will be informed of their right to withdraw from the study at any time without prejudice to their clinical management now or in the future. Consent will be sought by one of the medical doctor investigators or the study coordinator, and consent will be documented by the participant's signature on the consent form. Mayo's Institutional Review Board will approve the process and protocol. All the members of multidisciplinary team for weight management (i.e. physicians, coordinators, clinical assistants, registered dietitians will remain blinded).

If unblinding is needed for subject safety the Principal Investigator or a Co-Investigator will contact a research Pharmacist or the research pharmacy manager and provide documentation of reason for study unblinding and the subject will be withdrawn from the study. The study team will document and report the reason for unblinding as required by the Mayo Clinic IRB.

Selection Participants

We plan to study a cohort of 80 patients with obesity (BMI>30 kg/m^2). Participants will be recruited from the Mayo Clinic Weight Management and Nutrition Clinic, media advertising, classified ads, and existing databases of patients with obesity, including the phenome registry (Mayo Clinic IRB number [redacted]), the Mayo Clinic biobank and the right-10k cohort.

Inclusion criteria

a) Adults with obesity (BMI >30Kg/m^2); these will be otherwise healthy individuals with no unstable psychiatric disease and controlled comorbidities or other diseases.
b) Age: 18-75 years.
c) Gender: Men or women. Women of childbearing potential will have negative pregnancy tests within 48 hours of enrollment.
d) Women of childbearing potential must agree to use a method of effective contraception during study participation.
e) Subject must have an Apple iPhone 6s or later with iOS 13 or later and be willing to download the VitalCare (VitalTech Affiliates LLC) application from the Apple App Store.
f) Able to provide written informed consent prior to any study procedures, and be willing and able to comply with study procedures

Exclusion criteria

a) History of Abdominal bariatric surgery
b) Weight is greater than 450 lbs (204 kg)
c) Recent use (within the last three months) of any antiobesity medication
d) Recent weight change (gain or loss weight greater than 3% TBW in the last 3 months)
e) Positive history of chronic gastrointestinal diseases, or systemic disease that could affect gastrointestinal motility, or use of medications that may alter gastrointestinal motility, appetite or absorption, e.g., orlistat, within the last 6 months.

f) Significant untreated psychiatric dysfunction based upon screening with the Hospital Anxiety and Depression Inventory (HAD), and the Questionnaire on Eating and Weight Patterns (binge eating disorders and bulimia). If such a dysfunction is identified by an anxiety or depression score >11 or difficulties with substance or eating disorders, the participant will be excluded and given a referral letter to his/her primary care doctor for further appraisal and follow-up.
g) Hypersensitivity or contraindication to the study medication.
h) Participant unable or unwilling to follow protocol including use of the wearable activity tracker, digital wellness devices, VitalCare application, or unwilling to sign consent.
i) Principal Investigator discretion

Anthropometrics and Metabolic Characteristics studies

Anthropometrics Measurements: will be taken of height, weight, blood pressure, pulse, waist and hip ratio, respiration rate and temperature at screening, baseline, randomization day and visit 5, 6, 7, 8 and 9.

Baseline Characteristic studies:

All participants will complete the baseline assessment at the Mayo Clinic after an 8-hour fasting period, and the following characteristics will be measured at baseline: Fasting blood collection, body composition, resting energy expenditure, gastric emptying with meal for breakfast, behavioral questionnaires, exercise capacity and performance and buffet meal test for lunch. Blood will be collected for assessment of metabolomic biomarkers, gastrointestinal hormones, DNA (blood). Stool samples for microbiome and bile acid. Participants will return to the CRTU to pick up medication based on the randomization, the wearable activity tracker and the digital wellness devices.

If participants have already completed the baseline assessment at the Mayo Clinic within the last 3 years, those participants will not need to complete the full baseline assessment. Participants will complete the baseline assessment at the Mayo Clinic after an 8-hour fasting period again, but only the following characteristics will be measured at baseline: Fasting blood collection and body composition. Blood will be collected for assessment of metabolomics biomarkers, gastrointestinal hormones, DNA (blood). Stool samples for microbiome and bile acid. Participants will return to the CRTU to pick up medication based on the randomization, the wearable activity tracker, and the digital wellness devices.

Methods of metabolic studies

a) Body composition will be measured by DEXA (dual energy x-ray absorptiometry).
b) Resting energy expenditure was assessed by indirect calorimetry with a ventilated hood (Parvo Medics, Sandy, UT).
c) Gastric emptying (GE) of solids by scintigraphy: The primary endpoint is gastric half-emptying time (GE $t_{1/2}$) [3, 33, 34]. Images will be acquired at 0, 60, 120 and 240 minutes following the normal clinical gastric emptying testing protocol without a push meal.
d) Appetite (hunger level) by visual analog score fasting and after standard meal for GE and prior to the Satiation test [3].
e) Satiation will be measure by *ad-libitum* buffet meal to measure total caloric intake and macronutrient distribution in the chosen food. Satiation will be reported in calories consumed at fullness (satiation) [3].
f) Satiety by visual analog score postprandial after standard meal for GE and after to the *ad*-libitum buffet meal test for every 30 minutes for 2 hours [3]. Satiety will be measured in length of time of fullness.
g) Samples collection, handling and storage: Samples will be collected after an overnight fast (of at least 8 hours) in the morning. Plasma will be preserved following standard guidelines and protein degradation inhibitors, kalikrein and DPP-IV inhibitors will be added to preserve the samples. Samples will be stored at -80ºC in the PI's laboratory. Fasting samples will be collected and measure on subsequent visits (every 3 months).
    a. Fasting Blood will be collected for basic metabolic panel, lipid panel, HbA1C, hsCRP

b. Plasma hormones and proteomics by radioimmunoassay and/or mass spectrometry measured fasting, and postprandial 15, 45, and 90 minutes, with the primary endpoint being the peak postprandial level (test should be done simultaneously to GE). At the end of study visit (Visit 8), this will be drawn once and not at intervals.
c. Targeted Metabolomics: We will perform quantitative, targeted metabolomics of salient classes of compounds in plasma samples using mass spectrometry.
d. Blood DNA for genome wide association studies (GWAS)
e. Stool will be collected and stored to study microbiome, short chain fatty acids and bile acids.

h) Self-administered questionnaires assessing affect, physical activity levels, attitudes, body image, diet, and eating behavior; details of each questionnaire are provided below. Participants will complete a series of questionnaires.
   a) Hospital Anxiety and Depression Scale: HADS will be used to screen for severe anxiety or depression.
   b) AUDIT-C Alcoholism Screening Test (33) - The AUDIT-C is a 3-item alcohol screening questionnaire that reliably identifies participants who are hazardous alcohol drinkers or have active alcohol use disorders. This score will be used in screening by the study physician/nurse coordinator. The AUDIT-C is scored on a scale of 0-12. Each AUDIT-C question has 5 answer choices. Points allotted are: a=0 points; b=1 point; c=2 points; d=3 points; e=4 points. In men, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. In women, a score of 3 or more is considered positive (same as above).
   c) Eating Disorders Questionnaire - The Questionnaire on Eating and Weight Patterns-Revised (34), is a valid measure of screening for eating disorders which has been used in several national multi-site field trials. Respondents are classified as binge eating disorder, purging bulimia nervosa, non-purging bulimia nervosa, or anorexia nervosa. We have used this instrument to screen for eating disorders in obese populations.
   d) Three Factor eating questionnaire is 21-item questionnaire, validated, to assess for emotional eating disorders and food cravings.
   e) Physical Activity Level - The four-item Physical Activity Stages of Change Questionnaire (38)will be utilized to assess the physical activity level of participants. Mayo Clinic investigators, led by co-investigator Dr. Clark, have used these items to explore the relationship between quality of life and physical activity in an NCI-funded study on long-term lung cancer survivors (38).
   f) Exercise behavior- The Exercise Regulations Questionnaire (BREQ-3)*(39)* and its subsequent modifications have become the most widely used measures of the continuum of behavioural regulation in exercise psychology research. It has been used either as a multidimensional instrument giving separate scores for each subscale, or as a unidimensional index of the *degree* of self-determination.
   g) SF-12v2- a common questionnaire used to measure quality of life
   h) STOP-BANG- questionnaire used to screen for obstructive sleep apnea
   i) WOMAC- questionnaire used to assess osteoarthritis of the knee and hip

Intense Lifestyle Intervention and Behavioral Treatment

All the participants will meet the multidisciplinary team which consists of an Obesity Expert physician, registered dietitian nutritionist as standard of care in our clinical practice. All participants will guided to 1) Nutrition: Reduce dietary intake below that required for energy balance by consuming 1200calories per day for women and 1400calories per day for men; 2) Physical Activity: reach the goal of 10,000 steps or more per day; 3) Exercise: reach the goal of 150 minutes or more of cardiovascular exercise/week; 4) Limit consumption of liquid calories (i.e. sodas, juices, alcohol, etc.). All participants will receive a personal fitness tracker, where their activity and calories will be tracked. This information will be given in a booklet format.

Wearable tracker:

Subjects in the study will be provided with an Apple watch Series 5. The Apple watch will be connected by Bluetooth technology to the subject's personal Apple iPhone. Subjects will be required to use the watch during the study.

Digital Wellness Devices:

Subjects in the study will be provided and a wireless scale, automated blood pressure cuff and pulse oximeter. These digital wellness devices will be connected by Bluetooth technology to the subject's personal Apple iPhone.

Subjects will be allowed to keep the wearable activity tracker and the digital wellness devices if they complete the study. Subjects who withdraw from the study or are withdrawn from the study will be asked to return the digital wellness devices. Subjects will also be provided with a backpack to transport the wellness devices.

Virtual Care:

As part of the study subjects will be asked to download the VitalCare (VitalTech Affiliates LLC) application to the subject's personal Apple iPhone from the Apple App Store. This application will allow the study team to conduct the remote study visits. The application will also be used to monitor subject compliance with taking the study medication and to send reminders to the subject to take the study medication. Additionally this application will record the measurements collected by the digital wellness devices given to the subjects as part of the study. The study subjects will not be required to use the digital wellness devices at any set time points, but it will be encouraged. The digital wellness devices will be used at the subject's discretion. Any measurements recorded by the digital wellness devices will only be reviewed by the study team during the subject's study visits, either in person visits or remote visits. Study team will not monitor the use or results of this study until the next schedule visit or until the participant brings it to our attention.

Medication

Medication Phentermine-Topiramate Extended Release and matching placebo will be provide by Vivus, Inc (California, US). See FDA drug information package.

Pregnancy Testing

Urine pregnancy testing will be done at visits 1, 2, 3, 4, 5, 6, and 8 for women of child bearing potential (WOCBP). Subjects who are WOCBP will be given urine pregnancy test kits (QuickVue+ hCG Combo Test (Quidel Corporation) or similar) along with instructions to complete at home. Subjects will be instructed to complete these home pregnancy test kits and report the results during the remote study visits with the study team. If a subject has a positive urine pregnancy test result at any time the subject will be withdrawn from the study and instructed to stop use of the study medication/placebo immediately. The subject will be given a referral to their primary care provider.

Statistical Considerations

Primary endpoint: Total body weight loss at 3 months

Secondary endpoints:

- Total body weight loss at 6, 9 and 12 months
- number of steps (average per week at 3, 6, 9 and 12 months)
- calories tracked: number times recorded, calories per day (average per week at 3, 6, 9 and 12 months)
- number of exercise sessions (average per week at 3, 6, 9 and 12 months)

- hours/week using app/tracker (average per week at 3, 6, 9 and 12 months)
- weight loss difference in clinic vs. Bluetooth scale (weight loss difference 3, 6, 9 and 12 months)
- Quality of life SF36 (at 3, 6, 9 and 12 months)
- improvement in obesity-related comorbidities (diabetes/HbA1c, hypertension/SBP-DBP, hyperlipidemia/TC-LDL-HDL-Tg, Sleep apnea/CPAP, Joint Disease/pain)

Design: We propose a randomized, double-blinded, placebo-controlled trial of 80 participants with obesity to compare effects of Phentermine-topiramate ER vs placebo in weight loss with 1 year follow up.

Sample size assessment and power calculation: In our recent pilot study [with Liraglutide 3.0 mg vs. placebo], the standard deviation (SD) for the overall weight change (pre-post at12 weeks) observed was 2.8kg [32] and observed weight loss in the control/placebo group was 6.1kg.

Conservatively assuming a standard deviation of 3kg within groups,

Difference to Detect (kg) – reflects greater weight loss in active arm vs placebo	Sample Size per group	TOTAL Sample Size	With 10% dropout at 3 months	With 15% dropout at 3 months	With 20% dropout at 3 months
1kg (ex: 7.1 vs 6.1)	143	286	318	338	358
1.5kg	64	128	142	152	160
2 kg	37	74	82	88	94

Actual power is anticipated to be higher when accounting for baseline weight using Analysis of Covariance (ANCOVA) methods.

Statistical Analysis:

The primary analysis will be conducted under intention to treat (ITT) principles. Since study drug is administered double-blind, all subjects taking at least one dose of study drug will be included in analyses.

Primary endpoint: The primary endpoint is weight at 3 months (12 week visit), compared between groups using Analysis of Covariance (ANCOVA), adjusted for baseline weight. Subjects without follow up (dropouts) will have values imputed using multiple imputation. This approach assumes the distribution of missing data is random after conditioning on observed data in the imputation process. A secondary approach will consider complete case data, though this does not generally adhere to ITT principles.

Weight is recorded longitudinally at several post-baseline timepoints. A secondary analysis will model these longitudinal data using linear mixed effects models, adjusted for baseline weight. Additional adjustment variables will be included based on *a priori* determination by investigators that such variables may be associated with the dropout process. Thus, any dropout is assumed Missing At Random as a function of observed data. Time after randomization will be included as a discrete ordinal variable corresponding to the visit number. The primary comparison is a time by treatment group interaction, so that contrasts of the variables in the model will allow estimation of the treatment effect at each visit.

An interim analysis will be performed after 50% of subjects have completed their 3 month visit. This will allow the study team to review data quality and check assumptions related to the power calculation (including the standard deviation

above). Investigators will remain blinded to group comparisons and while investigators have no intention of stopping the study early (regardless of interim results), the analysis at study completion will be conservatively adjusted using the O'Brien-Fleming boundary (two-sided significance level of 0.0492).

Secondary endpoints will be assessed similarly. Steps, calories, and hours using the app tracker will be collected by the device. These will be aggregated to a weekly total or daily average over the week-long period to smooth out day-to-day variation. Analyses will be performed using linear mixed effects models with these weekly total data, separately for each endpoint. Weight loss as recorded by the Bluetooth scale at home will be analyzed similarly, taking the average of assessments over the course of each week as the outcome [recall, the primary endpoint is weight loss measured in clinic at study visits]. Number of exercise sessions will be evaluated, also as a weekly total number of sessions, using generalized linear mixed effects models with the outcome analyzed as a Poisson count. The distribution of each outcome will be assessed and alternative approaches considered as necessary. Quality of Life questionnaires will be assessed at study visits and analyzed using linear mixed effects models to compare between groups. The primary outcome has been pre-specified and no adjustment will be made for comparisons of these secondary outcomes.

An exploratory aim will evaluate adherent vs non-adherent patients – and further the interaction between adherent (vs non-adherent) and randomized group, to assess whether there is a differential response to Phentermine-Topiramate among exercise adherent patients. Adherence will be defined by 80% use during the first 3 months.

Anticipated results and significance:

Our study will demonstrate the importance of combining a consumer-based wearable activity tracker with an Anti-obesity Pharmacotherapy in Obesity.

Potential pitfalls, precautions taken, and alternative strategies:

a. Feasibility - Given high volume of patients interested in weight loss, we are confident we will recruit sufficient participants for these studies that involve only noninvasive tests and standard of care treatment.
b. Statistical power has been addressed with appropriate sample sizes to demonstrate a difference in weight change vs. placebo.

References

1 Gadde, K. M. *et al.* Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* **377**, 1341-1352, doi:10.1016/s0140-6736(11)60205-5 (2011).

2 Ng, M. *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*, doi:10.1016/S0140-6736(14)60460-8 (2014).

3 Flegal, K. M., Carroll, M. D., Kit, B. K. & Ogden, C. L. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA : the journal of the American Medical Association* **307**, 491-497, doi:10.1001/jama.2012.39 (2012).

4 Hensrud, D. D. & Klein, S. Extreme obesity: a new medical crisis in the United States. *Mayo Clin Proc* **81**, S5-10 (2006).

5 Yach, D., Stuckler, D. & Brownell, K. D. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. *Nat Med* **12**, 62-66, doi:10.1038/nm0106-62 (2006).

6 Daniels, S. R., Jacobson, M. S., McCrindle, B. W., Eckel, R. H. & Sanner, B. M. American Heart Association Childhood Obesity Research Summit: executive summary. *Circulation* **119**, 2114-2123, doi:10.1161/CIRCULATIONAHA.109.192215 (2009).

7 Low, S., Chin, M. C. & Deurenberg-Yap, M. Review on epidemic of obesity. *Ann Acad Med Singapore* **38**, 57-59 (2009).

8 Ogden, C. L., Yanovski, S. Z., Carroll, M. D. & Flegal, K. M. The epidemiology of obesity. *Gastroenterology* **132**, 2087-2102, doi:10.1053/j.gastro.2007.03.052 (2007).

9 World-Health-Organisation. *Fact sheet: obesity and overweight.* , 2012).

10 Tsai, A. G., Williamson, D. F. & Glick, H. A. Direct medical cost of overweight and obesity in the USA: a quantitative systematic review. *Obes Rev* **12**, 50-61, doi:10.1111/j.1467-789X.2009.00708.x (2011).

11 Riebe, D. *et al.* Updating ACSM's Recommendations for Exercise Preparticipation Health Screening. *Med Sci Sports Exerc* **47**, 2473-2479, doi:10.1249/MSS.0000000000000664 (2015).

12 Jensen, M. D. *et al.* 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Journal of the American College of Cardiology* **63**, 2985-3023, doi:10.1016/j.jacc.2013.11.004 (2014).

13 Apovian, C. M. *et al.* Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* **100**, 342-362, doi:10.1210/jc.2014-3415 (2015).

14 Sjostrom, L. *et al.* Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* **352**, 167-172 (1998).

15 Hollander, P. A. *et al.* Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care* **21**, 1288-1294 (1998).

16 Davidson, M. H. *et al.* Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* **281**, 235-242 (1999).

17 Gadde, K. M. *et al.* Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* **377**, 1341-1352, doi:10.1016/S0140-6736(11)60205-5 (2011).

18 Smith, S. *et al.* Multicenter, placebo-controlled trial of lorcaserin for weight management. *The New England journal of medicine* **363**, 245-256, doi:10.1056/NEJMoa0909809 (2010).

19 Apovian, C. M. *et al.* A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity* **21**, 935-943, doi:10.1002/oby.20309 (2013).

20 Pi-Sunyer, X. *et al.* A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *New England Journal of Medicine* **373**, 11-22, doi:10.1056/Nejmoa1411892 (2015).

21 MD, R. *US Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee Clinical Briefing Document February 22, 2012.*, <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM292315.pdf> (February 22, 2012.).

22 Garvey, W. T. *et al.* Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *The American journal of clinical nutrition* **95**, 297-308, doi:10.3945/ajcn.111.024927 (2012).

23 Allison, D. B. *et al.* Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity* **20**, 330-342, doi:10.1038/oby.2011.330 (2012).

24 Lyons, E. J., Lewis, Z. H., Mayrsohn, B. G. & Rowland, J. L. Behavior change techniques implemented in electronic lifestyle activity monitors: a systematic content analysis. *J Med Internet Res* **16**, e192, doi:10.2196/jmir.3469 (2014).

25 Preusse, K. C., Mitzner, T. L., Fausset, C. B. & Rogers, W. A. Older Adults' Acceptance of Activity Trackers. *J Appl Gerontol* **36**, 127-155, doi:10.1177/0733464815624151 (2017).

26 Cadmus-Bertram, L. A., Marcus, B. H., Patterson, R. E., Parker, B. A. & Morey, B. L. Randomized Trial of a Fitbit-Based Physical Activity Intervention for Women. *Am J Prev Med* **49**, 414-418, doi:10.1016/j.amepre.2015.01.020 (2015).

27 Skrepnik, N. *et al.* Assessing the Impact of a Novel Smartphone Application Compared With Standard Follow-Up on Mobility of Patients With Knee Osteoarthritis Following Treatment With Hylan G-F 20: A Randomized Controlled Trial. *JMIR Mhealth Uhealth* **5**, e64, doi:10.2196/mhealth.7179 (2017).

28 Brickwood, K. J., Watson, G., O'Brien, J. & Williams, A. D. Consumer-Based Wearable Activity Trackers Increase Physical Activity Participation: Systematic Review and Meta-Analysis. *JMIR Mhealth Uhealth* **7**, e11819, doi:10.2196/11819 (2019).