The use of a virtual weight management program for prescription of phentermine in patients with overweight or obesity compared to standard face-to-face visits

Background and significance

Obesity is a major healthcare problem in the United States affecting over one-third of the population, often increasing the risk of other comorbidities like hypertension, dyslipidemia, type 2 diabetes mellitus (1) and is also associated with increased risk of all-cause mortality and cardiovascular death. Modest weight loss of 5% has been associated with improvement in obesity as well as obesity related comorbidities and quality of life. (2) The cornerstone for treatment of obesity is behavioral modification and lifestyle changes including dietary modification and physical activity. (3) Adaptive physiologic responses due to increased appetite makes it difficult to achieve weight loss with lifestyle intervention alone. Anti-obesity medications (AOM) are often required as adjuvant therapy for weight loss induction and maintenance, and have the potential to augment further weight loss. (4)

Obesity is a chronic disease that often requires chronic treatment and the use of FDA-approved medications to reduce the appetite set-point in the hypothalamus. Currently, the United States Food and Drug Administration (FDA)-approved medications include: phentermine, phentermine-topiramate (Qsymia), bupropion-naltrexone (Contrave), orlistat (Xenical, Alli) and liraglutide (Saxenda). AOMs remain underutilized and just a minority of patients receive prescription treatment due to cost of therapy, lack of insurance coverage, old requirements of frequent face-to-face visits, lack of physician training, among others. Phentermine is the most affordable and the most commonly prescribed pharmacotherapy for weight loss; however, FDA approval is only for the short-term use (90 days), and in the State of Ohio, face-to-face visits every 30 days were required until recently during the course of treatment. (5) A recent study from our group found that in real-world practice AOMs are associated with clinically meaningful additional weight loss and phentermine therapy was associated with the most weight loss (3.7% weight loss in 12 weeks and an average of 7-12% when enhanced to our current weight management program. (6). Another study has demonstrated that phentermine is one of the most cost-effective pharmacologic weight-loss strategies. (7)

A barrier to successful weight loss is patient attrition, as often more than half of patients do not complete lifestyle-based weight loss intervention. (8) Scalable methods for the delivery of obesity treatment that encourages patient participation are needed. A potential way to improve patient participation and weight loss outcomes is through the use of virtual medical visits, remote monitoring, and e-Health. Telemedicine is a growing segment of medical field with the potential to improve access to care removing geographic barriers, extending care to home with the introduction with new technology capabilities that patients are already using on their personal lives. These new modalities have the potential to decrease costs, provide scalable and more accessibility and provide the same quality of care. Several studies have shown the utility of e-Health in the management of chronic conditions, concluding the behavioral changes can be achieved using technological innovation. (9, 10)

More recently, the emergency COVID-19 pandemic presented an unprecedented challenge to the current healthcare system, and all institutions are rapidly changing their health care delivery model and quickly adopting telemedicine and remote monitoring and very soon this type of care may become standard. Frequent visits have been shown to be effective-facilitating changes in lifestyle, while also addressing psychological aspects. During the last few months, the Endocrinology and Metabolism Institute (EMI) has completely switched the obesity care to essentially 90% virtual visits. In addition, the federal government and the State of Ohio recently relaxed standards for prescribing controlled substances so providers are now able to prescribe phentermine (and other anti-obesity medications) via telemedicine. If we are able to demonstrate that a meaningful and safe weight loss can also be achieved via virtual care, we may be able to make the current relaxed recommendations of the State of Ohio permanent, which would represent a significant shift in the current laws and would greatly benefit the care of patients suffering with obesity.

Our weight management clinic provides an ideal environment to investigate the impact of virtual weight management program for the prescribing of phentermine. The proposed trial will afford the opportunity to study the effects of a well-established weight management program associated with the prescription of phentermine in a virtual setting, comparing its effects with standard face-to-face visit. At the present time, there are no studies which have demonstrated that the use of phentermine, prescribed via telemedicine, will lead to the same outcomes in terms of weight loss. This gap in the literature needs to be rapidly answered in order to shift the current standard of weight management care from face-to-face to virtually provided care. This trial has the potential to lead to major impact on how we manage patients with obesity. If we show that a virtual weight management program may be as effective as face-to-face encounters for prescription of anti-obesity mediation (initially with phentermine due to feasibility) this will pave the way for future clinical trials leveraging virtual care as standard of care for management of obesity and prescription of anti-obesity medications.

Specific aims and hypothesis

Specific aim 1:
To demonstrate that the use of a virtual weight management program for prescription of phentermine (anti-obesity medication) in patients with BMI ≥ 27 with comorbidities or BMI ≥ 30 is non inferior to the standard face-to-face approach to achieve weight loss during a 90 day course of treatment
Hypothesis: in a population of patients with BMI ≥ 27 with comorbidities or BMI ≥ 30, the virtual weight management approach for the prescription of phentermine will prove to be non-inferior in achieving weight loss when compared to standard face to face medical care.
Specific aim 2:
To demonstrate that the use of a virtual weight management program for prescription of phentermine in patients with BMI ≥ 27 with comorbidities or ≥ 30 is as efficacious as the standard face-to-face approach to achieve > 5% weight loss during a 90 day course of treatment
Hypothesis: in a population of patients with BMI ≥ 27 with comorbidities or BMI ≥ 30, the virtual weight management approach for the prescription of phentermine will prove to be non-inferior in achieving greater than 5% weight loss when compared to standard face to face medical care.
Specific aim 3:
To demonstrate that the use of a virtual weight management program for prescription of phentermine in patients with BMI ≥ 27 with comorbidities or ≥ 30 leads to more adherence to the weight management program and to the medication when compared to face-to-face visits.
Hypothesis: in a population of patients with BMI ≥ 27 with comorbidities or BMI ≥ 30, the virtual weight management approach for the prescription of phentermine will prove to show that patients are more adherent to the program and to the course of phentermine therapy alone when compared to standard face to face medical care

Research design and methods
Study Type: Interventional
Study Design: Allocation: Prospective, Randomized by site, Single-center, Parallel-group trial comparing the use of virtual visit for prescription of phentermine versus standard face-to-face visits for weight management
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Randomization, Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment.

The primary overall objectives and specific aims of this project include:

1) To demonstrate that the use of a virtual weight management program for prescription of phentermine (anti-obesity medication) in patients with BMI ≥ 27 with comorbidities or BMI ≥ 30 is non-inferior to standard face-to-face approach to achieve weight loss during a 90 day course of treatment

The secondary objectives and aims of this project include:

1) To demonstrate that the use of a virtual weight management program for prescription of phentermine in patients with BMI ≥ 27 with comorbidities or BMI ≥ 30 is non-inferior to the standard face-to-face approach to achieve > 5% weight loss i during a 90 day course of treatment
2) To demonstrate that the use of a virtual weight management program for prescription of phentermine in patients with BMI ≥ 27 with comorbidities or BMI ≥ 30 leads to more adherence to the weight management program and to the medication when compared to face-to-face visits

Enrollment

The enrollment process will include identifying potential study subjects by screening patients who are scheduled to the Weight Management Clinic at the Department of Endocrinology at the Cleveland Clinic. Plan is to recruit patients from Main Campus, Women's Health Program, Lyndhurst Campus (our weight management center), the Solon Family Health Center, and Bariatric Metabolic Institute. The Endocrinology department has more than 40 endocrinologists, six of them practice obesity as a subspecialty. Patients with documented BMI ≥ 27 with comorbidities or BMI ≥ 30 will be pre-screened with a documented telephone encounter, or MyChart message on EPIC by the Research coordinators for inclusion/exclusion criteria prior to their scheduled visit. Patients who meet study criteria will be complete and sign the informed consent in their scheduled visit with provider(s). This visit will be their baseline visit. IRB approval of the study will be obtained.

Study Population/Sample

Inclusion Criteria:

1. Gender: men and women
2. Ethnicity: all ethnic groups
3. Language: English
4. Age: 18-65 years old
5. Obesity, Body mass index (BMI) BMI ≥ 27 with comorbidities (hypertension, diabetes, sleep apnea, fatty liver disease, PCOS, dyslipidemia, congestive heart failure, osteoarthritis) or BMI ≥ 30
6. Able to log in to an online platform or have a smartphone, and willing to join a virtual weight management program

Exclusion Criteria:

1. Contraindication for the use of phentermine
2. Female who is pregnant, breast-feeding or intends to become pregnant
3. Participation in another clinical trial within 30 days before screening
4. Cardiovascular disease including uncontrolled hypertension or history of arrhythmias
5. Treatment with any medication with the intention of weight loss within 180 days before screening
6. Use of Topiramate within 180 days before screening
7. Previous history of bariatric surgery or use of minimally-invasive weight loss devices

Sample Size

Sample size calculations were performed on weight change (%) at 12 weeks. In the Qsymia trial, at 12 weeks, patients taking phentermine showed a mean change of approximately 5%. The standard deviation was not explicitly stated but, based on presented confidence intervals, appears to be between 4% and 6% at 12 weeks. In the present population, low variability in response is expected based on investigator experience, so power calculations were performed assuming a standard deviation of 4.5%. Assuming no mean difference between the two groups, and a standard deviation for change of 4.5%, a total of 29 patients per group will be required to achieve 80% power to detect non-inferiority assuming a 3% non-inferiority region. Note that if larger improvements are seen in favor of the virtual weight management program, this sample size will be able to detect 3% or larger mean weight changes in tests of superiority under the same assumptions. After accounting for 15% dropout, 35 patients will be recruited in each arm to detect non-inferiority effect size differences in the primary endpoint between groups.

Assumptions for sample size calculations included:

- Two sample one sided t-test with equal variances.
- Calculations assume use of one-sided tests with significance levels of 0.05.
- Overall 5% significance level for non-inferiority, and 5% significance level for superiority testing. Superiority will be tested only if non-inferior is demonstrated and will be claimed only if estimated difference in mean weight loss favors the virtual weight management program
- 1:1 randomization by site
    - 30% of subjects in all arms are expected to be non-compliant with assigned treatment
    - Among subjects who were non-compliant, 50% are expected to return for last visit (12 week) assessment.
    - Therefore, 15% loss-to-follow-up rate is expected.

Table 1. Sample Size Per Group Required for 80% Power. Sample size numbers do not account for loss-to-follow-up

Wt. Difference (%)	0			1			2		
Wt. SD (%)	4	4.5	5	4	4.5	5	4	4.5	5
Non-inferiority region									
0% (Superiority)	NA	NA	NA	199	252	310	51	64	78
1%	199	252	310	51	64	78	23	**29**	36
2%	51	64	78	23	**29**	36	14	17	21
3%	23	**29**	36	14	17	21	9	11	14
4%	14	17	21	9	11	14	7	8	10

Interim Analysis

No interim analysis is planned for this study

Study Period

Recruitment period: planned duration of recruitment is 9 months. During this period of time it will be required to recruit an average of 8 patients per month to complete the cohort of 70 patients. On average more than 20 new patients for weight management are seen on a weekly basis and around half of them will start an anti-obesity medication. Of those the majority will be prescribed phentermine. Study period: 12 weeks with final weight check at final visit (12 week visit). If unavailable, weight at any other encounter in EPIC within +/- 7 days of that scheduled final visit (within visit window), and third, if both of the above are unavailable, have patients to take a weight from home scale and report.

Primary endpoints

The primary endpoint is mean change in body weight (%) from baseline (visit 1) to 12 weeks (visit 4) in body weight. All variables will be assessed at baseline, 4, 8, and 12 weeks.

Secondary endpoints

1) Weight will be assessed at baseline, 4, 8, and 12 weeks
    a) Weight: Mean change in body weight (lbs) from baseline to week 12
    b) BMI: Mean change in BMI from baseline to week 12
    c) Percentage of patients that lose > 5% body weight
    d) Calculated as the percentage of subjects achieving a weight loss of >5% of starting body weight at week 4, 8, and 12 weeks
2) Weight: Mean change in body weight from baseline to week 12 (weight check only)
3) Adherence to weight management program will be assessed as numbers of missed visits at the end of the trial

4) Adherence to medication use will done by the providers inquiring the patient at each of the follow-up visits as they take their interim history, their medication dosage, tolerance and overall medication compliance will be documented on the patient's visit note.

Protocol

Patients determined to meet the study inclusion/exclusion criteria will be consented, baseline characteristics will be recorded. Patients will be randomized to one of the following two study arms:

1) Virtual Weight Management Program

A comprehensive weight management program comprised of one to one virtual visit every four weeks with an obesity-medicine specialist provider, associated with an initial virtual visit with dietitian, exercise physiologist with subsequent visit on an as needed basis. Issues related to nutrition, physical activity, stress, mental health, appetite control, medication side effect will be addressed in all visits. See schedule of events for details.

All patients independently of the randomization arm will be seen face to face on visit 1. Patient will be evaluated by one of our obesity-medicine specialist in a 1:1 consultation. Since Phentermine is an FDA approved medication and pregnancy testing is not part of the usual standard of care practice, a pregnancy test will not be required but strong counseling will be provided to female patients that are of child-bearing potential to avoid becoming pregnant during the time they are on phentermine. A pregnancy test may be ordered per physician discretion.

During the first month, the patient will also be seen face to face by a registered dietitian and exercise physiologist via telemedicine. Plan of care will be personalized, subjects will choose between two dietary programs (Mediterranean or Ketogenic). Patients will be prescribed Phentermine 37.5 mg for 28 days, at baseline visit, and they will start on half a pill during the first two weeks. If they tolerate medication with no side effects, they will increase to a full tablet during thereafter. If at any point, there is a change in the toleration of the medication, the dosage will be reduced or modified as needed. Weight and vital signs will need to be monitored remotely and patients will receive a remote scale and a remote blood pressure cuff.

Subjects will then initiate a series of one to one virtual visits with the obesity specialist (for a total of 3 visits after initial face to face visit).On each of this visit the five pillars of weight management will be discussed including nutrition, physical activity, appetite control, sleep issues, and anxiety/depression/stress. Other topics related to nutrition plan, emotional eating, weight set point, hunger/fullness, food preparation, exercise topics, healthy sleeping habits, behavioral modification will be discussed. During the nutrition and exercise physiologist visit we will provide a personalized nutrition and exercise program. In addition to that, if felt relevant by the provider, subjects may also be referred to a mental health specialist and/or sleep clinic. Specific questions regarding well-being, social support, increased stress levels due to social isolation will be conducted. All this medical care will be provided virtually.

The use of phentermine will be monitored on each visit and in the interim for any possible side effects. Vitals signs including heart rate, blood pressure will be monitored remotely. In order for the trial to remain as close as possible to real world condition, subjects will still have to pay for the use of phentermine. Prescription will be sent directly to pharmacy of choice electronically.

2) Face-to-face Weight Management Program (standard of care)

A comprehensive weight management program comprised of 1:1 face-to-face visit every four weeks with an obesity-medicine specialist provider, and an initial visit with dietitian, exercise physiologist with subsequent visits as needed. Issues related to nutrition, physical activity, stress, mental health, appetite control, medication side effect will be addressed in all visits. See schedule of events for details.

All patients independently of the randomization arm will be seen face to face on visit 1. Patients will be seen and evaluated by one of our obesity-medicine specialist in a 1:1 face-to-face consultation. Since, Phentermine is an FDA approved medication and pregnancy testing is not part of the usual standard of care practice, a pregnancy test will not be required but strong counseling will be provided to female patients that are of child-bearing potential to avoid becoming pregnant during the time they are on phentermine. A pregnancy test may be ordered per physician discretion.

During the first month, the patient will also be seen face to face by a registered dietitian and exercise physiologist. Plan of care will be personalized and subjects and subjects will chose between two dietary programs (Mediterranean or Ketogenic). Patients will be prescribed Phentermine 37.5 mg for 28 days, at baseline visit, and they will start on half a pill during the first two weeks. If they tolerate medication with no side effects, they will increase to full tablet during thereafter. If at any point, there is a change in toleration of the medication the dosage will be reduced or modified as needed.

Subjects will then initiate a series of visits with the obesity specialist provider every 4 weeks. On each of this visit and also during the visit with the dietitian and exercise physiologist the five pillars of weight management will be discussed including nutrition, physical activity, appetite control, sleep issues, and anxiety/depression/stress. Other topics related to nutrition plan, emotional eating, weight set point, hunger/fullness, food preparation, exercise topics, healthy sleeping habits, behavioral modification will be discussed. The nutrition and exercise physiologist will provide a personalized nutrition and exercise program. In addition to that, if felt relevant by the provider, subjects may also be referred to a mental health specialist and/or sleep clinic. Specific questions regarding well- being, social support, increased stress levels due to social isolation will be conducted. All medical care will be provided via a face–to-face manner.

The use of phentermine will be monitored on each visit and in the interim for any possible side effects. Vitals signs including heart rate, blood pressure will be checked on each of the visits. In order for the trial to remain as close as possible to real world condition, subjects will still have to pay for the use of phentermine.

Schedule of Events
Schedule of Events

	Physician Encounter (virtual or face to face)			
Visit (V)	V1 (first visit: face to face)	V2	V3	V4
Timing of visit (weeks)	0	4	8	12
Visit window (days)		±7	±7	±7
Assessment	Inclusion and Exclusion Criteria Informed consent Screening and Randomization Randomization Demographics Schedule and referral to exercise physiologist and nutritionist Baseline Assessment Complete medical history 1st Phentermine prescription	Interim History Adverse Event Phentermine renewal	Interim History Adverse Event Phentermine renewal	Interim History Adverse Event
Weight and VS	X	X	X	X

	Physician Encounter (virtual or face to face)			
Visit (V)	V1 (first visit: face to face)	V2	V3	V4
Timing of visit (weeks)	0	4	8	12
Visit window (days)		±7	±7	±7
Nutritionist and Exercise Physiologist	X (up to 7 days)			

Data Collection

A file database will be created for data collection accessible only by authorized study personnel. Information will be entered into the database as it is collected and patients finish the study. Each patient will be assigned a study number consecutively as they are enrolled. Only the study number will be used to identify all study-related documents such as case report forms. A master list of study numbers linked to patient identifiers will be maintained by the study coordinator in a secured location. Study data will be collected and managed using REDCap (Research Electronic Data Capture); this will include patient identification number, medical record number, age, gender, and ethnicity.

Statistical Analysis

The primary analysis will be performed using the intent-to-treat cohort. Categorical factors will be described using frequencies and percentages, while continuous measures will be summarized using means, standard deviations, and percentiles of interest. Changes in primary continuous measures from baseline to the pre-specified times during the follow-up periods will be compared using linear mixed effect models that include baseline levels of these variables as well as stratification factors as covariates. In these models, all study times will be used, and interactions between time and group will be included. For the primary endpoint, non-inferiority will be tested at the 0.05 level at 12 weeks. If the endpoint is non-inferior, superiority testing at the 0.05 error level for each endpoint at 12 weeks will be performed, also based on a one-sided test. Analysis of other secondary endpoints will be performed using similar models, but determination of whether to evaluate time points separately will depend on model fit. If the interactions in these mixed effect models are not significant, overall differences in each endpoint over time will be evaluated. Otherwise, contrasts will be used to compare groups at pre-specified time points. If necessary, transformations of continuous measures will be performed prior to analysis to meet assumptions of the models. These mixed effect models account for data missing at random through maximum likelihood estimation, and do not require additional imputation approaches. Select categorical variables will be compared between groups using mixed effect Poisson regression and logistic regression models, as appropriate. These models will also incorporate multiple time points and evaluate overall and time specific differences between groups. Compliance, measured as the time from randomization to early medication stoppage, will be analyzed using Kaplan-Meier estimation and Cox proportional hazards models. Each endpoint will be tested assuming an overall 0.05 significance level. Secondary endpoints will be each evaluated independently with error level control being employed at the Aim level, such that for each aim, the error will be controlled at the 0.05 level. As a sensitivity analysis, a per-protocol analysis, among those patients that meet minimum compliance standards with their assigned treatment will be performed as above.

Adverse events and data monitoring committee

A Data Monitoring Committee is planned for the study to monitor adverse events and safety.

Safety

Phentermine abuse or psychological dependence (addiction) does not occur in patients treated with phentermine for obesity. Phentermine treatment does not induce phentermine drug craving, a hallmark sign of addiction. Amphetamine-like withdrawal does not occur upon abrupt treatment cessation even at doses much higher than commonly recommended and after treatment durations of up to 21 years (11)

For the purposes of this study, adverse events (AEs) will only be required to be collected if they meet the definition of an SAE. An SAE is defined as any AE which results in at least one of the following outcomes:

- Initial inpatient hospitalization or prolongation of existing inpatient hospitalization
- A life-threatening event, i.e., an event in which the subject was at immediate risk of dying at the time of the event; not an event that hypothetically could have caused death had it been more severe
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect in offspring
- Death
- Is deemed serious for any other reason, i.e., if it is an important medical event based on appropriate medical judgement which may jeopardize the subject and may require medical or surgical intervention to prevent one of the other listed outcomes.

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