Qsymia Study

Principal Investigator: Jamy Ard, MD

Investigators: Adolfo Fernandez, MD; Elizabeth Krings, NP

Study Manager: Erica Hale, MS

NCT02301416

Version: 9/28/18

Scientific Basis/Rationale

While there is obvious focus on the obesity epidemic that affects approximately one-third of the U.S. population, one subgroup within the epidemic remains on the fringe of scientific study and effective treatment options. The super obese patient, in this instance defined as those with a BMI ≥ 50 kg/m^2, presents a difficult treatment challenge in managing this level of obesity. While bariatric surgery, including Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch, have been shown to be effective in severe obesity (BMI ≥ 40 kg/m^2), the risks involved with surgical intervention in the super obese patient are high. Perioperative morbidity is significantly higher, and mortality is as high as 5.2% at 1 year in some series (Nguyen et al, 2012). To address this issue, surgeons are offering patients a two-stage weight loss process that involves an initial laparoscopic sleeve gastrectomy, followed by the laparoscopic Roux-en-Y gastric bypass after initial weight loss. Some case series have reported improved morbidity and perioperative mortality similar to patients that are in lower BMI categories. A subset of patients using this approach will however not require the second surgery due to success with the first procedure. Alexandrou et al estimated that approximately 30% of patients lost sufficient weight to not require the second procedure in their experience (Alexandrou et al., 2012). Treatment plans that limit the need for the second procedure by promoting effective pre-operative and post-operative weight reduction as an adjunct to the surgical intervention would be valuable. These types of treatment plans would be valuable because they would decrease risk for the patient by eliminating the need for a second surgical procedure and there would be a reduction in cost for the patient and insurer/health system.

Qsymia provides a potential opportunity to develop an effective treatment plan that would be an adjunct to surgical intervention in the super obese patient. Use of Qsymia in addition to a low-calorie dietary prescription pre-operatively would effectively decrease weight prior to surgical intervention, lowering surgical risk to some extent. Additionally, if continued post-operatively, Qsymia as an adjunct to the post-surgical dietary plan would potentially extend the weight loss horizon so that the probability of the typical weight loss plateau at 12-18 months is decreased. The combination of the pre-operative and post-operative weight loss associated with Qsymia use could significantly diminish the need for a second surgical procedure in super obese patients. We have designed a pilot study to examine the use of Qsymia in super obese patients to determine its potential for decreasing the need for a second weight loss surgery.

Primary Objective

The primary objective of the proposed study is to demonstrate the effectiveness of using Qsymia in the superobese (BMI ≥ 50 kg/m^2) as an adjunct to surgical therapy.

Secondary Objectives

Secondary objectives of the proposed study include determining tolerability of Qsymia perioperatively, determining changes in resting metabolic rate postoperatively (3 months and 12 months post-surgery), determining the magnitude of preoperative weight loss and determining the magnitude of weight loss at 12, 18, and 24 months post-surgery.

Treatment Plan

Treatment Group

Patients with a BMI ≥ 50 kg/m^2 that agree to participate in the experimental group will begin their treatment plan with a medical weight loss diet that includes a low-calorie diet and Qsymia at the recommended treatment dose of 7.5/46 mg daily (following initiation of the titration dose for 2 weeks). The low-calorie diet will be individually tailored based on initial resting metabolic rate measurement and co-morbid conditions. Patients will be medically monitored with once monthly medical visits and also have once monthly visits with a dietitian to review the treatment plan. Patients will receive medical weight loss therapy for a minimum of 3 months prior to proceeding to the laparoscopic sleeve gastrectomy. If a patient opts not to proceed to sleeve gastrectomy, they will continue to receive medical therapy for weight reduction including Qsymia and followed for the duration of the study (i.e., for 2 years).

Patients will discontinue Qsymia the week prior to the scheduled operation. The sleeve gastrectomy will be performed by one of the surgeons at the Weight Management Center (Fernandez, McNatt, Powell) using standard laparoscopic technique. Post-operatively, all patients will be provided with dietary counseling and a nutrition prescription for a very low calorie, high protein diet: 500-700 calories, protein goal of 1-1.2g/kg IBW, and 60-75g carbohydrate. Qsymia will be resumed in the second post-operative week at the initial titration dose and increased to the recommended treatment dose of 7.5/46 mg daily. Patients will have standard post-operative surgical follow up at months 1, 3, 6, 9, 12, 18, and 24. During the post-operative phase, all patients will be enrolled in the bariatric support group program that meets on a monthly basis. Patients will also have at least 3 visits with a clinic dietitian to review and update dietary prescriptions. At any point during this course of follow up, a determination can be made that the primary outcome event has occurred if the patient has a weight plateau—defined as weight gain or < 3 lbs weight loss—for 3 consecutive months, remains above a BMI of 39.9 kg/m^2 and continues to have associated co-morbidities. These patients will be evaluated for the possibility of moving forward to the next operative stage (laparoscopic Roux-en-Y gastric bypass) while all other patients will continue on with medication and diet/exercise therapy.

Control Group

Control subjects for the proposed study will be identified from the patient population at the Wake Forest Baptist Health Weight Management Center. They will be matched to subjects in the treatment group on age, sex, ethnicity, and BMI. They will be a historical control group who had surgery prior to the commencement of the proposed study (retrospective review).

Trial Design

Prospective independent historical case control

Inclusion Criteria

Inclusion criteria for the proposed study are:

- BMI ≥ 50 kg/m^2
- Determined to be a good candidate for surgery based on medical and psychological exam.
- Willing to participate in a 3-6 month medically supervised weight loss plan prior to surgery.
- Planning to remain in the reasonable vicinity of the Wake Forest Baptist Health Weight Management Center for the duration of the study.

Exclusion Criteria

- History of prior weight loss surgery (removal/conversion from band to sleeve will not be excluded)
- Pregnant (women of childbearing potential will complete a pregnancy test (blood draw) to make sure they are not pregnant at the time that they initiate the medication). Ongoing monitoring of pregnancy status is the responsibility of the patient and they are instructed as such in the consent form.
- Ongoing use of weight loss medication
- Contraindications to use of Qsymia, including pregnancy, history of glaucoma, unstable cardiac disease (unstable angina, recent heart attack or stroke (in the past 6 months), uncontrolled arrhythmia), hyperthyroidism, taking MAOIs (monoamine oxidase inhibitors) or allergy to either topiramate or sympathomimetic amines like phentermine.

Patients may be removed from the study at any point if they are unable to tolerate the study medication or are less than 50% compliant with the study medication (take less than 50% of the recommended dose). If a patient is removed from the study due to medication intolerance or non-compliance, the study physician will meet with them and instruct them on how to stop the medication.

Primary endpoint

The primary endpoint for this study is the proportion of patients that meet the criteria to move forward with the second surgical procedure (Roux en Y Gastric Bypass). The criteria include all of the following at any point in the 24 month post-surgical follow up period:

1. Weight plateau (defined as weight gain or < 3 lbs weight loss) for at least 3 months
2. Remains above a BMI of 39.9 kg/m^2
3. Continues to have obesity associated co-morbidities (Co-morbidities include hypertension, type 2 diabetes mellitus or pre-diabetes, hyperlipidemia, metabolic syndrome, obstructive sleep apnea, osteoarthritis, non-alcoholic steatohepatitis (NASH), gastroesophageal reflux disease (GERD)).

We hypothesize that the study group treated with Qsymia plus surgery will have a lower rate of occurrence of the primary endpoint at 24 months post-surgery compared to the group with surgery only.

Secondary endpoints

The secondary endpoints for this study are percent weight loss both before and after surgery and changes in percent body fat and resting metabolic rate.

We hypothesize that the study group treated with Qsymia plus surgery will have greater percent weight loss at all time points compared to the group treated with surgery only. We also hypothesize that the study group treated with Qsymia plus surgery will have a higher resting metabolic rate after adjustment for lean body mass compared to the group treated with surgery only.

Other measures obtained by chart review

Height will be measured at all new patient visits and will be repeated at 24 months to account for any changes over the course of participation. Weight is measured at every clinic visit and will be captured for the study at the time points in the table below. Waist circumference will be measured at the level of the umbilicus at the time points reported in the table. Resting metabolic rate will be measured using expired gas analysis via the MEDGem analyzer. This will be measured following the protocol suggested by the manufacturer, including after refraining from eating, drinking, caffeine or exercise for at least 4 hours prior and immediately following a 10 minute period of quiet rest. Body fat percentage will be measured using Bioelectrical Impedance Analysis via the RJL Systems Quantum II. The Quantum II provides body fat percentage as well as a calculation of total lean mass and total fat mass.

Blood Measures

Blood will be drawn at baseline, 3 months, 6 months, 12 months, 18 months and 24 months and stored for use in later analysis.

Boxes marked with UC are tests that are done as part of usual care. Boxes marked with R are tests done for research only.

Test	BL	1m	3m	6m	9m	12m	18m	24m
Resting Metabolic Rate (MEDGem Analyzer)	UC			R		R		R
Body Fat % by Bioelectrical Impedance Analysis (RJL Systems)	UC			R		R		R
Height	UC							R
Weight	UC	UC	UC	UC	UC	UC	UC	UC
Waist Circumference	UC			R		R		R
Blood draw	R		R	R		R	R	R

Monitoring of Side Effects to study medication

Monitoring for side effects will be performed at each visit. Report of suicidal ideation will lead to study discontinuation and withdrawal from medication. Endpoint will be considered reached in this instance.

Increases in heart rate will be monitored. If > 100 beats per minute on 2 consecutive visits, participant will be withdrawn from medication and considered as endpoint reached. Metabolic acidosis will be monitored with basic metabolic panel at each follow up visit. The study clinic questionnaire will be used to monitor problems with the study drug, current dietary plan, vitals and mood changes. Any reports of abnormality on this form will be investigated further by the study physician and further action will be taken if necessary.

Depression and Suicidal Ideation

Change in mood will be assessed at each clinic visit via standard self-report questionnaire (See Clinic Questionnaire). Endorsement by participants of increased depressive symptoms will be reviewed and screened by the treatment provider at the time of the participant's appointment. Should the participant report changes in suicidal ideation, planning, or intent, the participant will be referred to the onsite Clinical Psychologist or referred to the local Emergency room for additional assessment and treatment recommendations. Participants who report significant distress associated with recent onset of mood symptoms will be provided with a list of referrals for local providers who offer counseling and psychopharmacological services. This protocol for assessment and treatment of mood symptoms is above and beyond recommended standard of care for monitoring depression and suicidal thoughts in patients taking Qsymia (topiramate) and other antiepileptic drugs (AEDs).

As a part of standard of care and consistent with guidelines published by the American Society of Metabolic Medicine, all participants will participate in psychosocial evaluation, prior to undergoing weight loss surgery. During this evaluation current/past mood symptoms and suicidal ideation/planning/intent will be assessed via self-report mood measures, a personality inventory, and via clinical interview. Participants will not be cleared to proceed with surgery if they meet criteria for a suicide attempt within the past 12 months or have active suicidal ideation, planning, or intent. Participants who are positive for these criteria will be referred for treatment; they will be reevaluated for bariatric surgery candidacy upon resolution of symptoms.

Safety Monitoring

At each physician visit (monthly during phase one and at months 1, 3, 6, 9, 12, 15, 18, and 24 during phase 2) the participant will complete an adverse events questionnaire in addition to the signs and symptoms clinic questionnaire. All adverse events will be reviewed by the study coordinator to clarify any details or questions about the reported event. The PI will then review each adverse event and determine the likelihood that the event was related to the study and whether or not it was an expected event. Study clinicians will also review the medical record at clinic visits to determine if any event or medical care occurring in the interim was related to safety and/or side effects. Any event requiring immediate reporting will be reported as such. All adverse event data will be recorded in RedCAP and tabulated every 6 months for cumulative review. The PI will be responsible for reporting cumulative frequencies of adverse events for those on study drug. Additionally, any derangements in blood

chemistries that are being monitored as part of this study will be cataloged, and frequencies will be reported for all study participants every 6 months.

Participants will be asked to bring in their pill bottles to count any remaining pills at each visit. Missed doses of medication will be noted and any excess medication will be discarded at the refill visits in the hazardous waste containers per clinic protocol. Participants will be provided with only the medication required to provide daily doses until the next scheduled clinic visit.

Some patients enrolled in the study may have diabetes and be on hypoglycemic medications or insulin prior to surgery. As part of usual care, individuals with diabetes are instructed to reduce all diabetes medication by 50% before leaving the hospital after weight loss surgery and are instructed to follow-up with their primary care provider 2 weeks after surgery in order to monitor or modify medications for diabetes and other comorbid conditions such as blood pressure. In addition, discharge documents are sent to each patient's primary care provider either through Wake One or in paper form. Prior to surgery, patients are expected to develop a relationship with a primary care provider.

Statistical analysis

This is an independent case-control study. Analyses will include completers only. Completers are defined as individuals who enter treatment and continue it (Qsymia and/or gastric sleeve) for at least 24 months without reversal or discontinuation. Participants will be recruited until the sample size of 20 cases is obtained. If a participant consents but does not have surgery, this person will not be counted as a case and thus, recruitment will continue.

Data will be entered into and stored in a REDCap database with access given only to individuals who are part of the study team. Study data uploaded will include information from the weekly clinic questionnaire, adverse events, as well as study outcomes (weight at clinic visits) , demographic information, etc.

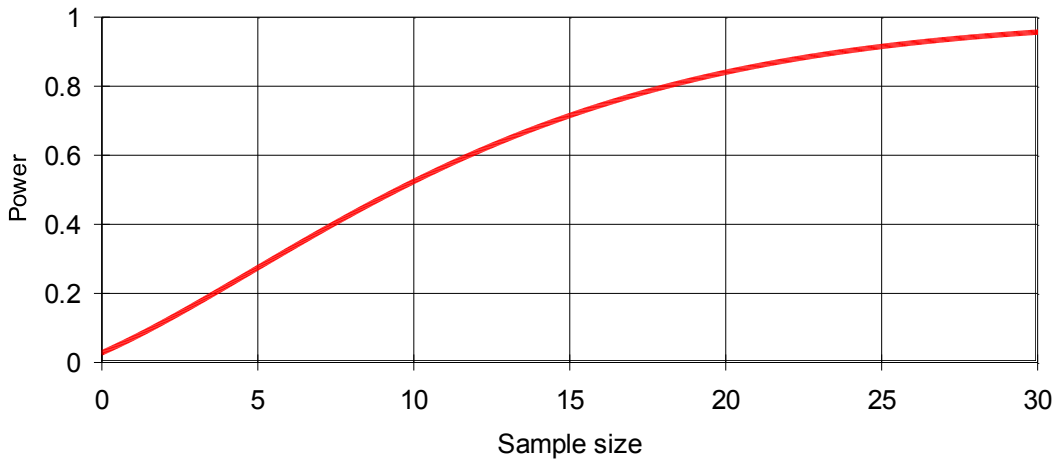
Most of the statistical analyses will be conducted using SPSS or SAS. Prior to testing the specific aims, descriptive statistics will be used to characterize the sample. Next, the groups will be compared using the chi-square statistic and T-test statistic to determine whether differences existed between the groups on key variables that may have an effect on outcomes. The case-control matching procedure should insure balance between the treatment groups on sex, age, BMI and ethnicity, but additional analyses will be used to examine the comparability between groups on baseline body composition, waist circumference, and resting metabolic rate.

The primary endpoint for this study is the proportion of patients that meet the criteria to move forward with the second surgical procedure (Roux en Y Gastric Bypass) at any point during follow up. The proportion of the Qsymia treated group that achieves the primary endpoint will be compared to the surgery only group after 24 months of follow up. Unadjusted and adjusted models will be developed to test for differences in the rate of the primary endpoint occurrence by treatment group.

The secondary outcomes for this study include percent weight loss and changes in percent body fat and resting metabolic rate. The time points of interest include pre-surgery period (baseline to surgery), baseline to 6 months (post-operative), baseline to 12 months, and baseline to 24 months. Independent T-test statistic will be used to test for differences in the changes scores between the groups at each time point for these continuous variables. Given this pilot study design and exploratory nature of this secondary aim, we will not use the conservative approach of Bonferroni adjustment for multiple comparisons. Therefore, alpha will remain at 0.05 for this family of hypotheses.

Sample size justification/statistical power

We are planning a study with 25 experimental subjects and 20 control subjects. Prior data indicate that the approximate failure rate among controls is 0.7 (Alexandrou et al, 2012). If the true failure rate for experimental subjects is 0.25, we will be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) .840. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis.



References

Nguyen, N et al. A review of unmet needs in obesity management. Obes Surg. 2012 Jun;22(6):956-66

Alexandrou et al. What is the Actual Fate of Super-Morbid-Obese Patients Who Undergo Laparoscopic Sleeve Gastrectomy as the First Step of a Two-Stage Weight-Reduction Operative Strategy? Obes Surg (2012) 22:1623–1628