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Meal-Replacements followed by Topiramate for the Treatment of Adolescent Severe Obesity: A Pilot Randomized Controlled Trial

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Abstract

Objective—The objective of this pilot study was to assess the safety and efficacy of short-term meal replacement therapy followed by topiramate for body mass index (BMI) reduction in adolescents with severe obesity.

Methods—Adolescents (ages 12-18 years) with severe obesity (BMI ≥1.2 times the 95th percentile or BMI ≥35 kg/m^2) were recruited for this double-blind, randomized, placebo-controlled trial. Participants completed 4 weeks of meal replacement therapy followed by randomization (1:1) to either 24 weeks of topiramate 75 mg/day or placebo. Mean changes were compared between groups.

Results—Thirty adolescents (mean age 15.2 ± 1.7 years, mean BMI 40.3 ± 4.6 kg/m^2) completed the meal replacement phase and were randomized; 21 completed the study. The difference in mean percent change in BMI between the topiramate and placebo groups was not significant (−1.9% [95% CI (−5.2%, +1.5%); P=0.291]). Significant improvements in visceral fat

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Author Contributions: CF, ASK, KR, BN, MA, BS, SK and CB conceived the study and design. CF, ASK, MS, BN, MA, BS, SK recruited patients and executed study. AMK and KR conducted statistical analysis. AP oversaw pQCT data collection and analysis. All authors participated in data interpretation and in writing the paper, and reviewed and approved the final submitted version of the manuscript.

and VLDL-c were observed in the topiramate compared to the placebo group. There were no concerning changes in neurocognitive function or bone health.

Conclusion—In this pilot study, 4 weeks of meal replacement therapy followed by 24 weeks of low-dose topiramate compared to meal replacement therapy alone did not result in significant BMI reduction for adolescents with severe obesity.

Keywords

pharmacotherapy; adolescents; obesity; topiramate; meal replacement

Introduction

Severe pediatric obesity, defined as an age- and gender-specific body mass index (BMI) ≥1.2 times the 95th percentile or BMI ≥ 35 kg/m^2,[1,2] affects approximately 6% of children and adolescents in the United States and the prevalence is rising.[1,3,4] Unfortunately, adolescents with severe obesity often reap little benefit from lifestyle modification therapy, the cornerstone of obesity treatment.[5-9] Thus, novel treatment strategies are desperately needed for this high risk population. Meal replacement therapy, as an adjunct to lifestyle modification therapy, is one such alternative strategy. Specifically, meal replacement therapy consisting of liquid shakes, meal bars, and frozen entrees of a fixed caloric content, can result in meaningful short-term BMI reduction (approximately 6%), yet the effect tends to wane over time.[10] In contrast, meal replacement therapy followed by obesity pharmacotherapy may prove to be a more effective longer term treatment for achieving sustained BMI reduction.

Currently, the only obesity pharmacotherapy approved by the U.S. Food and Drug Administration (FDA) in the pediatric population (age ≥ 12 years) is orlistat. Yet, the use of orlistat is limited by an adverse side effect profile and marginal efficacy.[11] Therefore, identification and evaluation of other pharmacotherapies that have the potential to reduce adiposity and improve cardiometabolic outcomes in youth with severe obesity are needed. Topiramate, an antiepileptic agent FDA-approved for the treatment of seizures in children, may be a candidate medication. Our group conducted a retrospective chart review of patients treated with topiramate in a pediatric weight management clinic and found a 6% average reduction in BMI at 6 months.[12] Although never studied prospectively for the indication of weight loss in the pediatric population to our knowledge, several large randomized, controlled trials examining topiramate for obesity in adults have demonstrated weight reduction of 5-10% over 24-60 weeks.[13-16]

The purpose of this pilot study was to assess the safety and efficacy of short-term meal replacement therapy followed by topiramate for BMI reduction in adolescents with severe obesity in order to inform decisions about a larger clinical trial. Specifically, the primary objective of this randomized, placebo-controlled pilot clinical trial was to compare the percent change in BMI from baseline among participants assigned to meal replacement therapy followed by topiramate versus meal replacement therapy followed by placebo. Our secondary objectives were to a) characterize the safety profile of topiramate for obesity treatment in adolescents, b) evaluate the effect of the intervention on cardiometabolic risk

factors, and c) investigate whether baseline binge eating behavior influences treatment response, given that some studies indicate that topiramate decreases binge eating frequency and weight in people with binge eating disorder.[17-19] We hypothesized that following short-term meal replacement therapy, 24 weeks of topiramate compared to placebo would demonstrate superior reduction in BMI, total body- and visceral fat, systolic blood pressure, fasting triglycerides and insulin. Also, we hypothesized that topiramate would be well tolerated at 75 mg daily and that the presence of binge eating disorder characteristics at baseline would be associated with a greater reduction in BMI with topiramate treatment.

Methods

Trial Design and Eligibility Criteria

This was a 28-week double-blind, randomized, placebo-controlled pilot clinical trial that included 4-weeks of meal replacement therapy followed by 24-weeks of topiramate or placebo without meal replacements. Adolescents 12-18 years old with severe obesity (BMI ≥1.2 times the 95th percentile or BMI ≥ 35 kg/m^2) were recruited from four sites comprising the Minnesota Pediatric Obesity Consortium: University of Minnesota Masonic Children's Hospital Pediatric Weight Management Clinic (Minneapolis, MN), McNeely Pediatric Diabetes Center and Endocrinology Clinic at Children's Hospitals and Clinics of Minnesota (St. Paul, MN), International Diabetes Center at Park Nicollet (St. Louis Park, MN), and Mayo Clinic (Rochester, MN). Exclusion criteria were Tanner stage I, II, or III; type 1 or 2 diabetes mellitus; previous (within 6-months) or current use of medication(s) prescribed primarily for weight loss; if currently using weight altering drug(s), any change in drug(s) or dose within the previous 6 months; previous bariatric surgery; recent initiation (within 3-months) of anti-hypertensive or lipid medication; major psychiatric disorder; females who were pregnant, planning to become pregnant, or unwilling to use 2 or more acceptable methods of contraception when engaging in sexual activity throughout the study; tobacco use; liver/renal dysfunction; glaucoma; obesity associated with genetic disorder (monogenetic obesity); hyperthyroidism or uncontrolled hypothyroidism; medically-documented history of suicidal thoughts/attempts; history of nephrocalcinosis or cholelithiasis; and current use of other carbonic anhydrase inhibitor. The protocol was approved by the University of Minnesota institutional review board. Consent and assent were obtained from parents and participants, respectively. An investigational new drug exemption was obtained from the FDA prior to study initiation and the study was registered on the clinicaltrials.gov website (NCT01859013).

Meal Replacement Intervention

Prior to randomization to topiramate or placebo, all participants engaged in meal replacement therapy for 4 weeks. The regimen was adapted from a previously-published protocol used in adolescents with severe obesity.[10] During the meal replacement period, participants were counseled to strictly follow the prescribed diet, which included three Slim-Fast® shakes (one for breakfast and two for lunch or vice-versa), two pre-packaged frozen entrée meals for dinner (Weight Watchers, Smart Ones®), two servings of fruit, and three servings of vegetables per day (total caloric intake was approximately 1,400 kcals per day). All shakes and frozen entrees were provided to the participants. Participants were

encouraged (but not required) to meet a goal of at least 5% BMI reduction during the meal replacement phase.

Lifestyle Modification/Behavioral Counseling

All participants received lifestyle/behavioral modification counseling throughout the entire study. The curriculum was adapted from the TODAY study lifestyle modification program materials.[20] Study staff delivered the lifestyle modification counseling, which focused on small, successive changes in dietary and physical activity behaviors through the use of evidence-based behavior change strategies such as self-monitoring, goal setting, reinforcement for goal achievement, stimulus control, social support, problem solving, and motivational techniques. Counseling was provided on the transition from meal replacements (initial 4 weeks) to regular dietary habits, per the TODAY program. The educational materials were reviewed and discussed at each face-to-face study visit except week 28 (baseline, weeks 2, 4, 12, and 16) and additionally by phone at weeks 8, 20, and 24.

Topiramate and Placebo Intervention

Following the meal replacement period, participants were randomized (1:1) to either topiramate or placebo capsules, which were identical in appearance. Topiramate was initiated at a dose of 25 mg (taken orally once daily in the evening), escalated to 50 mg (taken orally once daily in the evening) after 1 week, and further escalated to 75 mg (taken orally 25 mg in the morning and 50 mg in the evening) after 2 weeks. The randomization scheme was generated based on randomly permuted blocks of size 2, 4, and 6 and maintained by the University of Minnesota – Fairview Investigational Drug Service Pharmacy.

Measurement of Clinical Variables

All study visits and data collection occurred at a single center (University of Minnesota). Height and weight were obtained with participants in light clothes and without shoes using the same standardized stadiometer and electronic scale, respectively. Three consecutive height and weight measurements were averaged. BMI was calculated as the body weight in kilograms divided by the height in meters, squared. Percent total body- and visceral fat were determined using dual-energy x-ray absorptiometry (iDXA, GE Healthcare, Waukesha, WI, USA). Visceral fat measured with this technique has been previously validated.[21] Seated blood pressure was obtained after five minutes of quiet rest, on the right arm using an automatic sphygmomanometer and appropriately-fitted cuff. The average of three independent blood pressure measurements was used. Tanner stage (pubertal development) determinations were performed by trained registered nurses. Fasting (≥12 hours) blood samples were analyzed for glucose, insulin, and lipids using standard procedures. Binge eating behaviors were measured with the Loss of Control – Eating Disorder Questionnaire and the Eating Disorder Examination Questionnaire − 6.2.[22]

Because of concerns regarding associations between antiepileptic medications and both cognitive effects[23] and bone mineral density,[24] safety outcomes included measures of neurocognitive function and bone health. Changes in neurocognitive function were ascertained with questionnaires and computer-based assessments including the Behavior

Rating Inventory of Executive Function – Self Report (BRIEF-SR), Cambridge Neuropsychological Test Automated Battery (CANTAB) (a computerized test of motor speed, memory, and attention), and the Connors Continuous Performance Test II (CPT II) (a computerized measure of attention and impulsivity). Bone density, geometry, and strength were assessed with peripheral quantitative computed tomography (pQCT) (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany). Images were taken at the distal 4% and along the midshaft (33%) of the non-dominant radius and at the distal 4% and 50% of the tibia. The reference line for both radius and tibia was placed at the proximal end of the distal growth plate using a scout view. Image processing and calculation of bone parameters were completed using the manufacturer's software (version 6.0). Bone outcome measures included volumetric bone mineral density (vBMD, mg/cm^3), trabecular cross-sectional area (CSA, mm^2), total bone strength index (BSI, mg^2/mm^4), cortical thickness (mm), non-weighted polar section modulus (Zp, mm^3), and strength strain index (SSI, mm^3).[25]

Anthropometrics, blood pressure, heart rate, complete metabolic panel, urine pregnancy test and questionnaires were measured at all face-to-face visits (baseline, weeks 2, 4, 12, 16, and 28). Additionally, iDXA, pQCT, glucose, lipids, and insulin were measured at baseline and at week 28. CANTAB, BRIEF-SR, and CPT II were measured at randomization and at week 28.

Statistical methods

The sample size was based primarily on the preliminary nature of the trial (a pilot study), along with limitations of the funding and recruitment timeline associated with the grant support. Baseline characteristics were tabulated with respect to randomized treatment groups using mean (SD) for continuous variables and frequency (%) for categorical variables. The primary endpoint was the mean percent change in BMI from baseline (week 0) to 28 weeks. Secondary efficacy endpoints were defined similarly while secondary safety endpoints were examined from randomization (after 4 weeks meal replacement) to 28 weeks. Analyses of primary and secondary endpoints were based on generalized linear models, adjusting for baseline measurements for added precision.[26,27] Confidence intervals and P-values were evaluated based on robust variance estimation. Due to incomplete follow-up on all participants who entered the study, some final values were imputed based on the most recent prior measurement during follow-up to preserve the pre-specified intent-to-treat analysis. For example, when measurements were available from the week 16 visit but not the final 28 week visit, values from the week 16 visit were carried forward and used. A pre-specified sub-group analysis to examine differential treatment effect based on eating behavior (binge eating) was ultimately not conducted due to insufficient number meeting the criteria at baseline. Data were managed in REDCap[28] and all statistical analyses were performed using R v3.2.0.[29]

Results

Recruitment occurred between July 2013 and May 2015. Thirty-seven participants were assessed for eligibility and 30 were enrolled in the trial (Figure 1). All 30 participants completed the 4-week meal replacement phase. Twelve from the topiramate group and nine

from the placebo group completed the 24-week randomized phase. The intervention was stopped by the study physician for one participant from the topiramate group (see details in "Safety" section, below) but the participant attended all follow-up visits and remained blinded until trial completion.

Baseline (week 0) demographic characteristics, cardiometabolic risk factors, and binge eating score between the topiramate and placebo groups were similar (Table 1a). The mean age of participants was 15.2 years, mean BMI was 40.3 kg/m^2 and 63% were female. Only 3 participants endorsed binge eating, defined as overeating with loss of control at least 4 times in the past month. Randomization visit (week 4) safety measures, including standard scores of learning and memory (CANTAB), executive function (BRIEF), attention, impulsivity, and reaction time (CPT II) were all in the average range (Table 1b). See Supplemental Table 1a for pQCT measures at randomization.

Change in BMI and Cardiometabolic Risk Factors

The primary efficacy endpoint, percent change in BMI from baseline, for all participants is illustrated in Figure 2. At 28-weeks in the intention-to-treat analysis, the difference in the percent change in BMI between the topiramate group and placebo group was −1.85% [95% CI (−5.21% - 1.52%); P=0.291]. Fourteen percent of the placebo group and 25% of the topiramate group experienced ≥5% BMI reduction: difference of 11% [(−45%, 24%); P=0.784]. Each group had 1 participant that experienced ≥ 10% BMI reduction.

Table 2 provides results for the primary efficacy endpoint and secondary outcomes. Visceral fat mass and VLDL-c decreased significantly more in the topiramate group compared to the placebo group and there were trends toward lower triglycerides, insulin and glucose in the topiramate group. The other cardiometabolic risk factors were largely unchanged.

Safety

The most common adverse event was paresthesia, reported by 25% in the topiramate group and none in the placebo group (Table 3). One participant from each group experienced worsening depressive symptoms during the trial. The participant randomized to the topiramate group had a history of mild depression, which was stable prior to enrollment in the study but re-emerged 2 days after randomization. For this reason, the intervention was stopped but this participant completed all study visits, blinded. The participant randomized to the placebo group reported transient depressed mood, which resolved on its own. Two participants in the topiramate group experienced concussions; one was hit in the head with a softball and the other fell while skiing. There were no significant differences between the topiramate and placebo group on any of the CANTAB subscales or the BRIEF subscales. For the CPT II, only the hit reaction time was different indicating a faster reaction time in the topiramate group compared to placebo (Table 4). No significant changes in bone density, strength, or geometry were observed between the groups (Supplemental Table 1b). None of the participants withdrew from the trial due to adverse events.

Discussion

In this double-blind, randomized, placebo-controlled pilot clinical trial, we observed a marginal and statistically insignificant effect on percent BMI reduction from meal replacement therapy followed by topiramate compared to meal replacement alone for adolescents with severe obesity. However, there were reductions in visceral fat mass and VLDL-c favoring the treatment arm, and though the other changes in cardiometabolic disease risk factors were not statistically significant, the magnitude of improvement in triglycerides, insulin and glucose were notable and clinically meaningful. Importantly, topiramate at 75 mg daily had an acceptable safety profile compared to placebo and was generally well-tolerated.

At least ten randomized controlled clinical trials have examined topiramate for weight reduction in adults.[30] The first was a dose-ranging study which found that at 24 weeks, the placebo-subtracted mean weight reduction from topiramate was 2.4%, 2.2%, 3.7%, and 3.7% at doses of 64, 96, 192, and 384 mg/day, respectively.[14] The longest trial was a 60-week randomized, double-blind placebo-controlled study which found that compared to placebo, the mean weight reduction from topiramate was 5.3%, 7.4%, and 8.0% at topiramate doses of 96, 192, and 256 mg/day, respectively.[16] Our findings are not directly comparable to these adult trials given that our study design utilized meal replacement therapy for the initial period of treatment before topiramate/placebo was started. However, if we consider only our 4 to 28 week randomization period, after the meal replacement therapy ended, we showed a 2.4% (95% CI: −5.4%, +0.6%) difference in BMI favoring topiramate, which is comparable to the aforementioned adult dose ranging study outcomes.

Although the adult randomized controlled trials suggested that the weight loss efficacy of topiramate improves with increasing dose, up to 400 mg/day,[30] we had two primary reasons for utilizing a 75 mg/day dose in this pilot trial. First, we previously reported significant BMI reduction (about 6%) among adolescent patients treated with topiramate for severe obesity in a weight management clinic based on retrospective chart review (80% were treated with a dose of 75 mg/day).[12] Second, the studies in adults identified that adverse events, primarily neurologic, were dose-dependent, and that these in turn led to study withdrawal.[30] Nevertheless, if we used a higher dose, we may have observed greater BMI reduction, though possibly at the risk of prompting neurologic (albeit reversible) side effects.

The duration of the adult topiramate trials was also a predictor of response, with study durations longer than 28 weeks eliciting more weight loss than shorter studies.[30] For this pilot study, we used a 28 week duration (including 4 weeks of the meal replacement therapy before randomization) in order to minimize subject drop out. We recognize that the FDA recommends that obesity pharmacotherapy studies include at least 1 year duration, yet 28 weeks may be considered reasonable for this pilot study.

Few other medications have been studied for the indication of weight loss in the pediatric population using randomized controlled trials.[31] Orlistat, a gastrointestinal lipase inhibitor, is currently the only FDA approved medication for weight reduction in youth ≥ 12 years old. In the largest randomized, controlled study of orlistat, the placebo subtracted mean BMI

decrease was 0.8 kg/m^2 (less than 3% BMI reduction) favoring orlistat at 52 weeks.[11] Metformin, although only FDA approved for diabetes in adolescents, has also been widely studied for the indication of obesity in the pediatric population. In a systematic review of 14 randomized clinical trials, metformin resulted in a BMI reduction of 1.38 kg/m^2 (95% CI, −1.93 to −0.82 kg/m^2) from baseline (equating to approximately 3% BMI reduction) compared to controls at 6 months. However, the pooled estimate from studies, which included one year of treatment, was not statistically significant.[32] Our group has also examined exenatide, a glucagon like peptide-1 agonist, for BMI reduction in adolescents with severe obesity. In a small randomized controlled crossover trial we observed a 4.9% (95% CI, −8.61% to −1.23%) decrease in BMI with 3 months of treatment with exenatide.[33] In a separate randomized placebo controlled pilot study we observed a 2.7% (95% CI, −5.02% to −0.37%) decrease in BMI at 3 months.[34] Again, it should be noted that the results of the current pilot trial may not be directly comparable to these other pediatric outcomes because we utilized a meal replacement initial period. Yet, the degree of change that we observed with topiramate was relatively comparable to these other medications.

The most common side effects observed in the adult studies of topiramate for weight reduction were related to the peripheral and central nervous systems. These included paresthesia, difficulty with concentration/attention, psychomotor slowing, difficulty with memory, and mood problems such as depression. Most of these adverse events were dose dependent.[16] In our study, the most common adverse event was paresthesia, reported by 25% of the topiramate group and none in the placebo group. We found no concerning changes in memory, motor speed or attention, which is consistent with other reports of topiramate use in adolescents for migraine up to a dose of 100 mg/day.[35] Further, there was no meaningful difference in executive function or impulsivity between treatment groups. The relevance of the participant who developed a re-emergence of his depression symptoms 2 days into the topiramate treatment arm is unclear but warrants discussion. All antiepileptic medications increase the risk of depression symptoms in patients taking these medications for any indication, and should be monitored for the emergence or worsening of such symptoms. Nevertheless, in interpreting this outcome, it is important to note that one participant in the placebo group also experienced transient depression symptoms.

In line with one of our secondary aims, we attempted to examine the effect of baseline binge eating behavior on the treatment efficacy of topiramate. Binge eating is characterized by consuming a large amount of food in a discrete time period accompanied by a sense of loss of control over the eating episode,[36] and prior randomized controlled trials suggested that topiramate decreases binge eating episodes in adults with this disorder.[17-19] Because only three participants in our pilot study endorsed binge eating, we were unable to appropriately evaluate this question. Therefore, future trials of topiramate could attempt to address this important issue.

Strengths of this study include the double-blind, randomized, placebo-controlled design and the practical and translatable nature of the intervention. Limitations include the relatively small number of participants and the short duration of treatment (28 weeks). Further, we did not report on participant fidelity to the lifestyle modification therapy and introduction of a medication may influence adherence.

Conclusion

In summary, this randomized placebo-controlled pilot clinical trial of 4 weeks of meal replacement therapy followed by 24 weeks of topiramate at a dose of 75 mg/day demonstrated limited efficacy for BMI reduction in adolescents with severe obesity compared to meal replacement followed by placebo. Importantly, topiramate at 75 mg/day appeared to be well-tolerated, had an acceptable safety profile, and had a beneficial impact on visceral adiposity. Adult studies suggest that higher doses of topiramate may be effective for weight reduction, though at the expense of the potential for neurocognitive side effects. For adolescents, this still needs to be explored. As with any intervention, the risks and benefits have to be measured against each other. Since severe obesity in adolescents is associated with considerable physiological, psychological, and social morbidity, perhaps relative risk in treatment is warranted. This pilot study suggests that studies using higher doses of topiramate may be justified to examine the risk/benefit profile of this medication for use in severe adolescent obesity, an otherwise recalcitrant disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is Already Known About this Subject

- Meal replacement therapy results in modest, albeit transient, weight reduction in adolescents with severe obesity.
- Topiramate promotes weight reduction in adults with obesity, but has not yet been studied prospectively for weight reduction in adolescents with obesity.

What this Study Adds

- In this double-blind, randomized, placebo-controlled pilot clinical trial, four weeks of meal replacement therapy followed by 24 weeks of low-dose (75 mg/day) topiramate compared to meal replacement therapy alone did not produce significantly better body mass index (BMI) reduction.
- Low-dose topiramate for weight reduction in adolescents was safe and well-tolerated.
- Significant improvements in visceral fat and VLDL-c were observed in the topiramate compared to the placebo group.
- Studies using higher doses of topiramate for obesity in adolescents may be warranted.

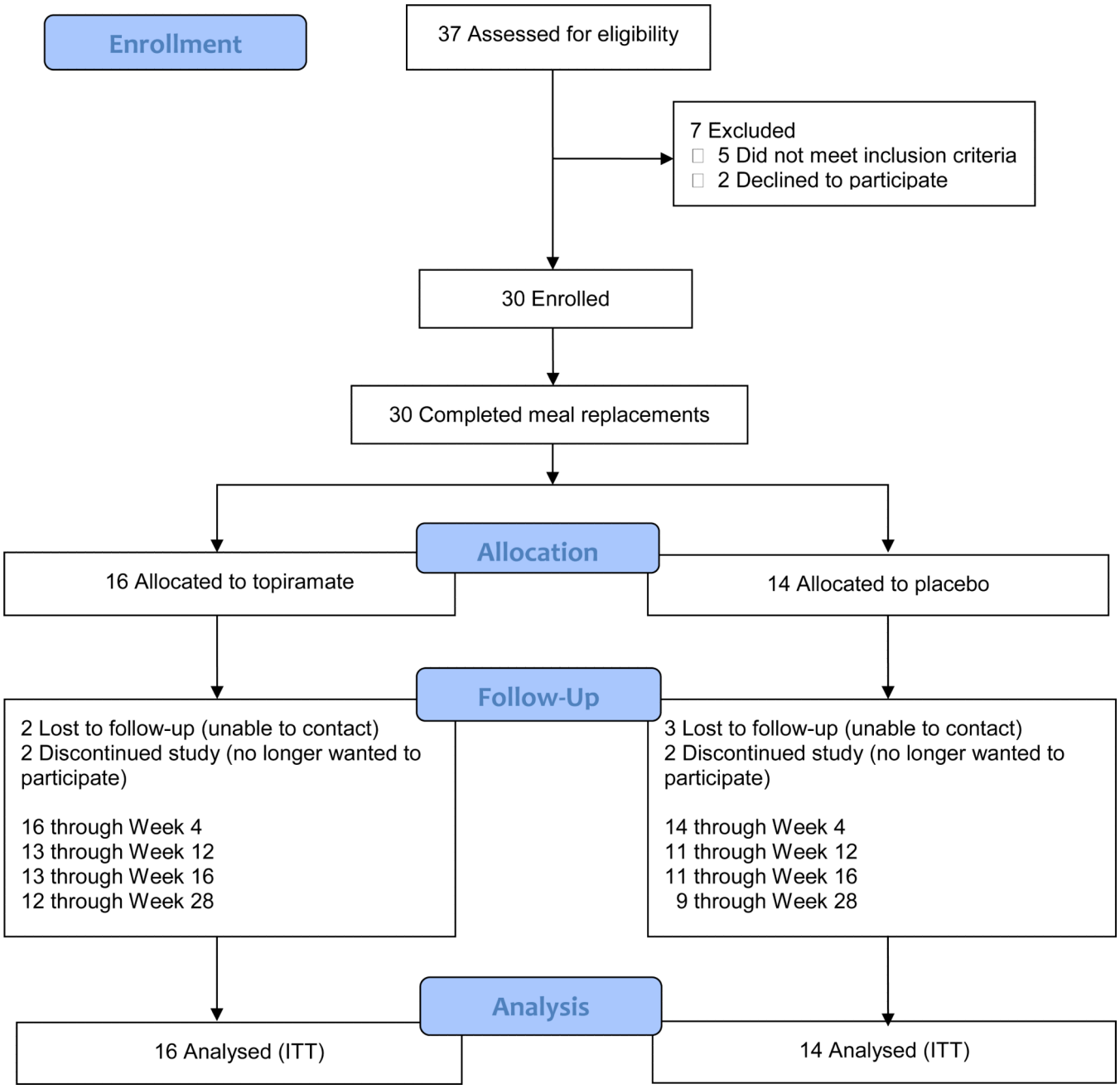

Figure 1.
CONSORT Diagram.

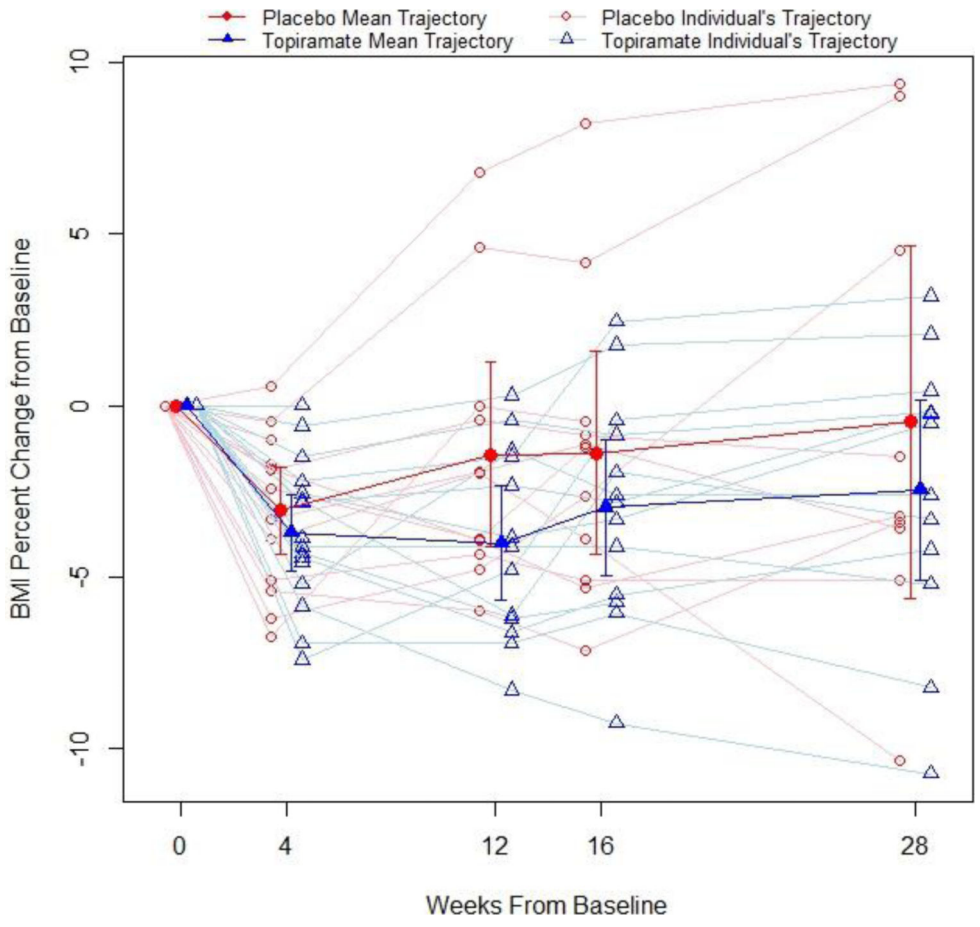

Figure 2.
Percentage change in BMI from baseline for the topiramate and placebo groups, unadjusted analysis.

Table 1a

Participant characteristics at baseline. Values expressed are mean (SD) or N (%) where indicated.

Covariate	Overall (N=30)	Placebo (N=14)	Topiramate (N=16)
Female	19 (63.3%)	9 (64.3%)	10 (62.5%)
African American/Black	4 (13.3%)	1 (7.1%)	3 (18.8%)
White	18 (60.0%)	8 (57.1%)	10 (62.5%)
Other	8 (26.7%)	5 (35.7%)	3 (18.8%)
Age (years)	15.2 (1.7)	15.7 (1.8)	14.9 (1.6)
Height (cm)	168 (8.0)	169 (7.5)	168 (8.7)
Weight (kg)	115 (19.9)	112 (15.3)	117 (23.5)
BMI (kg/m^2)	40.3 (4.6)	39.5 (4.0)	41.0 (5.0)
BMI z-score	2.5 (0.26)	2.5 (0.24)	2.6 (0.26)
Percent of the 95^{th} BMI Percentile	146 (17.1)	141 (15.6)	150 (17.7)
Total Fat Mass (kg)	54.8 (12.0)	51.2 (10.3)	57.9 (12.9)
Percent Body Fat (%)	49.0 (4.8)	47.0 (5.6)	50.8 (3.2)
Visceral Fat Mass (g)	1320 (626.9)	1189 (680.0)	1434 (573.5)
Lean Body Mass (kg)	56.7 (10.4)	57.5 (9.2)	56.0 (11.7)
Systolic BP (mmHg)	121 (12.3)	120 (11.3)	122 (13.6)
Diastolic BP (mmHg)	67.9 (8.6)	67.3 (6.2)	68.4 (10.4)
Heart Rate (bpm)	75.9 (9.4)	74.2 (8.0)	77.4 (10.5)
Glucose (mg/dL)	80.7 (10.2)	79.4 (8.9)	81.9 (11.3)
Insulin (mg/dL)	21.6 (11.4)	18.6 (9.2)	24.3 (12.6)
Total cholesterol (mg/dL)	162 (31.7)	167 (40.3)	157 (22.0)
LDL-c (mg/dL)	95.2 (27.1)	100 (34.8)	90.3 (17.0)
HDL-c (mg/dL)	42.2 (11.0)	44.7 (13.4)	40.0 (8.2)
VLDL-c (mg/dL)	23.1 (11.3)	21.8 (10.6)	24.3 (12.1)
Triglycerides (mg/dL)	129 (92.8)	109 (53.1)	147 (116.1)
ALT (mg/dL)	37.7 (19.1)	41.6 (24.1)	34.2 (13.3)
AST (mg/dL)	24.5 (8.9)	26.6 (10.0)	22.7 (7.8)
Binge eating ≥ 4 times in past month	3 (10.0%)	0 (0.0%)	3 (18.8%)

Table 1b

Safety variables at randomization.

Covariate	Overall (N=30)	Placebo (N=14)	Topiramate (N=16)
CANTAB			
Standard PAL	0.51 (0.58)	0.61 (0.46)	0.43 (0.67)
Standard PAL Shapes	0.43 (0.81)	0.60 (0.34)	0.28 (1.00)
Standard PRM	0.54 (0.62)	0.44 (0.78)	0.62 (0.46)
Standard SSP*	0.62 (1.10)[2]	0.71 (0.99)[1]	0.54 (1.30)[1]
CPT-II*			
Omissions %	54.9 (23.6)[3]	59.8 (31.0)[1]	50.4 (13.4)[2]
Commissions %	47.3 (14.2)[3]	47.8 (15.7)[1]	46.8 (13.3)[2]
Hit Reaction Time	51.9 (14.4)[3]	52.2 (15.2)[1]	51.7 (14.3)[2]
BRIEF-SR*			
BRI T-score	47.5 (15.1)[10]	43.4 (19.0)[5]	50.7 (10.8)[5]
MI T-score	54.2 (12.8)[12]	55.3 (15.3)[5]	53.0 (10.4)[7]
GEC T-score	51.8 (12.2)[12]	52.1 (14.2)[5]	51.6 (10.8)[7]

PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; SSP, Spatial Span; BRI, Behavior Regulation Index; MI, Metacognition Index; GEC, Global Executive Composite.

*superscript denotes number of subjects missing given observation

Table 2

Primary and secondary outcomes from baseline, with differences adjusted for baseline values using intention-to-treat analyses with last observation carried forward.

Outcome	N	Placebo Δ [mean (SD)]	Topiramate Δ [mean (SD)]	Mean Difference [Topiramate-Placebo] (95% CI)	P-value
Percentage Change in BMI	30	−0.85 (5.31)	−2.74 (3.74)	−1.85 (−5.21, 1.52)	0.291
Change in BMI	30	−0.30 (2.05)	−1.16 (1.58)	−0.81 (−2.15, 0.53)	0.244
Change in BMI z-score	30	−0.04 (0.11)	−0.07 (0.07)	−0.04 (−0.11, 0.02)	0.206
Change in Percentage of the 95th BMI Percentile	30	−2.55 (6.99)	−6.20 (5.65)	−3.78 (−8.55, 0.99)	0.132
Change in Weight (kg)	30	−0.46 (5.63)	−2.89 (4.92)	−2.07 (−5.80, 1.65)	0.285
Percentage Change in Weight	30	−0.37 (5.45)	−2.18 (4.00)	−1.54 (−4.94, 1.85)	0.380
Change in Total Body Fat Mass (kg)	30	0.32 (4.07)	−1.51 (3.81)	−1.30 (−4.21, 1.61)	0.388
Change in % Body Fat	30	0.32 (1.82)	−0.63 (1.46)	−0.57 (−1.83, 0.68)	0.377
Change in Visceral Fat Mass (g)	30	70.57 (168.36)	−95.75 (197.02)	−160.09 (−296.93, −23.25)	0.030
Change in Lean Body Mass (kg)	30	−0.36 (1.80)	−0.06 (2.19)	0.22 (−1.38, 1.83)	0.787
Change in Systolic BP (mmHg)	30	−1.86 (8.70)	−2.63 (10.71)	−0.18 (−5.83, 5.47)	0.951
Change in Diastolic BP (mmHg)	30	0.00 (9.32)	0.94 (6.87)	1.45 (−3.76, 6.66)	0.590
Change in Heart Rate (bpm)	30	3.71 (9.62)	2.25 (10.53)	0.09 (−6.60, 6.79)	0.978
Change in Glucose (mg/dL)	30	3.07 (12.55)	−4.69 (12.35)	−6.23 (−14.09, 1.62)	0.131
Change in Insulin (mg/dL)	30	7.36 (18.02)	−3.94 (10.28)	−10.16 (−20.91, 0.59)	0.075
Change in Total Cholesterol (mg/dL)	30	−10.79 (17.65)	−7.94 (17.78)	1.25 (−11.33, 13.83)	0.847
Change in LDL-c (mg/dL)	29 *	−12.36 (14.60)	−4.60 (13.60)	7.27 (−3.33, 17.88)	0.190
Change in HDL-c (mg/dL)	30	−1.29 (6.46)	1.38 (5.99)	1.76 (−2.62, 6.14)	0.438
Change in VLDL-c (mg/dL)	29	6.21 (14.02)	−3.53 (8.16)	−9.40 (−17.81, −0.99)	0.038
Change in Triglycerides (mg/dL)	30	13.64 (56.14)	−28.88 (51.19)	−29.01 (−60.67, 2.65)	0.084
Change in ALT (mg/dL)	30	−3.21 (12.72)	−2.69 (12.28)	−0.61 (−9.65, 8.43)	0.896
Change in AST (mg/dL)	30	−2.29 (9.14)	−1.81 (6.27)	−0.66 (−6.14, 4.81)	0.814

* unable to measure one participant due to high triglycerides

Table 3

Adverse event summary.

Adverse Event	Placebo (N=14)	Topiramate (N=16)
Amenorrhea	0 (0%)	1 (6.2%)
Concussion	0 (0%)	2 (12.5%)
Dizziness	0 (0%)	1 (6.3%)
Drowsiness	2 (14.3%)	3 (18.8%)
Dysgeusia	0 (0%)	1 (6.2%)
Insomnia	1 (7.1%)	0 (0%)
Mood problems	1 (7.1%)	1 (6.2%)
Paresthesia	0 (0%)	4 (25.0%)
Pharyngitis	2 (14.3%)	1 (6.2%)
Sinusitis	1 (7.1%)	1 (6.2%)
Fever due to pharyngitis	0 (0%)	1 (6.2%)
Tendon injury	0 (0%)	1 (6.2%)
Diarrhea	1 (7.1%)	2 (12.5%)
Nausea	0 (0%)	1 (6.2%)
Vomiting	0 (0%)	1 (6.2%)

Table 4

Change in safety variables from randomization using completers only.

Outcome	N	Placebo Δ [mean (SD)]	Topiramate Δ [mean (SD)]	Mean Difference [Topiramate-Placebo] (95% CI)	P-value
CANTAB					
Standard PAL	21	−0.24 (0.23)	0.04 (0.60)	0.26 (−0.16, 0.69)	0.238
Standard PAL Shapes	21	−0.24 (0.53)	0.11 (1.62)	0.07 (−0.74, 0.88)	0.863
Standard PRM	21	0.24 (0.80)	−0.64 (2.00)	−0.70 (−2.13, 0.73)	0.348
Standard SSP	19	0.11 (0.79)	0.36 (1.21)	0.16 (−0.80, 1.11)	0.750
CPT-II					
Omissions %	20	−0.09 (18.09)	0.34 (4.62)	−3.81 (−13.72, 6.09)	0.461
Commissions %	20	2.20 (7.29)	1.55 (11.04)	−0.30 (−8.01, 7.42)	0.941
Hit Reaction Time	20	6.37 (10.38)	−2.67 (7.44)	−11.13 (−18.32, −3.93)	0.008
BRIEF-SR					
BRI T-score	15	1.17 (10.96)	−1.00 (8.80)	−1.97 (−10.57, 6.62)	0.661
MI T-score	14	0.33 (13.38)	0.00 (5.32)	−0.64 (−10.50, 9.21)	0.900
GEC T-score	14	1.00 (12.81)	−1.00 (7.52)	−2.02 (−11.74, 7.71)	0.692

PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; SSP, Spatial Span; BRI, Behavior Regulation Index; MI, Metacognition Index; GEC, Global Executive Composite