Topiramate for Weight Loss in Adults with Obesity and Loss of Control Eating after Bariatric Surgery

Amanda Faxon

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TOPIRAMATE FOR WEIGHT LOSS IN ADULTS WITH OBESITY AND LOSS OF CONTROL EATING AFTER BARIATRIC SURGERY

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Amanda Faxon, PA-SII
Class of 2022
Yale Physician Associate Program

Valentina Ivezaj, PhD
Assistant Professor
Yale School of Medicine
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Abstract

Diagnostic criteria for binge eating disorder may preclude a diagnosis in post-bariatric surgery patients because they require consumption of abnormally large quantities. Loss of control eating is considered the salient feature of binge eating disorder in some eating disorder literature, and some of the field is moving towards excluding the quantity of food criterion. Loss of control eating is associated with poorer weight outcomes post-surgery. Topiramate, an anticonvulsant, has been shown to improve weight outcomes in patients with binge eating disorder after surgery, therefore its evaluation in patients with loss of control eating and obesity post-surgery is warranted. We aim to identify whether topiramate increases weight loss and reduces loss of control eating in patients with obesity and loss of control eating after bariatric surgery via a randomized, double-blind, placebo-controlled trial. This study will enhance our understanding of topiramate for weight loss and loss of control eating in this population.
Chapter 1: Introduction

1.1 Background

Binge eating disorder (BED) is an eating disorder included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). BED is characterized by recurring episodes of binge eating, which involve consuming abnormally large amounts of food within a short period of time and experiencing a sense of loss of control. Binge eating episodes must be associated with three of the following five symptoms to meet DSM-5 criteria for BED: eating more rapidly than usual, eating until feeling uncomfortably full, eating large amounts of food when not physically hungry, eating alone because of embarrassment, and feeling disgusted with oneself, depressed, or guilty after overeating. People with BED feel marked distress about binge eating and experience binge episodes an average of at least one day per week for three months. Binge eating must not be associated with regular use of compensatory behaviors such as purging, excessive exercise, or fasting (unlike some other eating disorders, such as bulimia nervosa) to meet DSM-5 criteria for BED.

According to a study published by Udo and Grilo in 2018, the lifetime prevalence estimate (standard error) of BED is 0.85% (0.05%) and the 12-month estimate is 0.44% (0.04%). In comparison, the lifetime prevalence estimates (standard error) of anorexia nervosa (AN) and bulimia nervosa (BN) are 0.80% (0.07%) and 0.28% (0.03%), respectively. Lifetime and 12-month prevalence estimates for BED were significantly higher for women than men, at 1.25% for women vs 0.42% for men and 0.60% for women vs 0.26% for men, respectively. BED is associated with several comorbidities including obesity, mood disorders, anxiety disorders, social functioning impairment, and
substance use disorders. Patients with BED are faced with a multitude of challenges that are centered around the emotional stress associated with the cyclic nature of binge eating episodes, sometimes followed by attempts to diet, resulting in feelings of guilt and shame that further exacerbate binge eating and distress. Furthermore, many patients with co-occurring BED and obesity or excess weight struggle with issues related to both body image and physical well-being. Udo and Grilo published a study in 2019 that evaluated a sample of 36,309 adults to compare the lifetime prevalence of psychiatric and somatic conditions across groups with AN, BN, BED, and those without a specific eating disorder. They found that 93.8% of those with BED met criteria for at least one lifetime psychiatric disorder. Specifically, BED is significantly associated with mood disorders (major depressive disorder, persistent depression, and bipolar disorder), anxiety disorders (agoraphobia, social anxiety disorder, specific phobia, and general anxiety disorder), post-traumatic stress disorder (PTSD), alcohol use disorder (AUD), personality disorders (antisocial, borderline, and schizotypal) and conduct disorder. BED was also significantly associated with somatic conditions, including diabetes, hypertension, high cholesterol, and high triglycerides. BED is also associated with remarkable social and economic costs. It is estimated that the total economic costs associated with eating disorders in fiscal year 2018-2019 was $64.7 billion, equivalent to $11,808 per affected individual. BED was the second most costly eating disorder, accounting for 30% of total economic costs associated with eating disorders. Moreover, the “substantial reduction in wellbeing associated with eating disorders” was valued at $326.5 billion. Treatment of patients with BED should strive to address both emotional and physical aspects of the disease to optimize overall health.
Current treatment options for BED include psychotherapeutic and pharmacologic approaches, both as monotherapy and as combination therapy. Cognitive behavioral therapy (CBT) as a treatment for BED has been studied more than any other psychological therapy. CBT strives to disrupt the pattern of binging and dieting to achieve a more normal eating schedule and healthier habits, as well as improve self-image to reduce binging behaviors. Interpersonal therapy (IPT) has also been studied as a treatment for BED. IPT postulates that BED is a means of coping with social issues which, in turn, are worsened by the detachment from relationships that is associated with BED, further worsening the eating disorder and social functioning. Wilfley and colleagues found that CBT and IPT successfully induced recovery after treatment in 79% and 73% of participants, respectively. Even more promising are the recovery rates after one year of follow-up (59% for CBT and 62% for IPT). It is now recommended that CBT be offered to adults with BED. Behavioral weight loss (BWL), which focuses on gradual lifestyle modifications, including moderate caloric decreases and moderate increases in physical activity, has also been shown to benefit those with BED and excess weight, as described in a study published in 2020 by Grilo et al. They found that 74.4% of patients treated with BWL achieved binge eating abstinence, as defined by zero episodes in the past 28 days, and an average weight loss of 5.1%.

Pharmacologic treatment options for BED are limited. In January of 2015, the United States Food and Drug Administration (FDA) approved lisdexamfetamine dimesylate (LDX), a prodrug stimulant, as the first drug to treat moderate-to-severe BED after it was originally approved for the treatment of attention deficit hyperactivity disorder (ADHD). A double-blind, randomized control trial (RCT) conducted in 2015
found that LDX contributed to a significant reduction in binge eating episodes per week and weight compared to placebo. It is worth noting, however, that in this study weight was assessed as a safety measure rather than a primary or secondary outcome. At the time of LDX FDA approval, a “Limitation of Use” was appended, recommending that LDX not be used for weight loss purposes. Moreover, due to its sympathomimetic properties, LDX should not be used in patients with BED and uncontrolled hypertension or cardiovascular disease, a known comorbidity of BED. Patients and clinicians should also consider LDX classification as a controlled substance and its high potential for abuse and dependence prior to treatment initiation.

Though CBT has demonstrated sustained improvement in BED pathology and associated depressive symptoms, it has not shown to be effective in providing significant weight loss, an outcome desired by many patients with BED and obesity. Combination treatments comprised of CBT in addition to various pharmacotherapies have yielded varying rates of success with regard to BED outcomes. Grilo and Reas published a review in 2021 stating that BED outcomes have not been shown to improve long-term with the addition of antidepressants or weight loss medications (sibutramine and orlistat) to psychotherapy. Antiepileptic medications, namely zonisamide and topiramate, showed promise in improving BED outcomes. Zonisamide, when added to CBT, significantly decreased both depressive symptoms and BMI in adults aged 18 to 60 with BED and subthreshold BED, defined as at least one episode of binge eating per week over the past six months. After one year, patients who received this combination treatment experienced less binge eating episodes than patients who received only CBT. These patients also did not regain weight during the follow-up period while patients in the CBT-only arm did.
Topiramate, in combination with CBT, produced greater binge eating abstinence and weight loss after treatment compared to placebo plus CBT as treatment. A randomized, double-blind, placebo-controlled trial found that topiramate, in addition to CBT, was associated with statistically significant weight loss, fewer binge episodes per week, and greater rates of binge eating remission. CBT and topiramate combination therapy was found to be safe and well-tolerated, as demonstrated by an 81% completion rate and only one withdrawal due to side effects. A 2011 meta-analysis of 10 RCTs provided data regarding the safety and efficacy of topiramate for weight loss with data from 3,320 participants. All studies reported significant weight loss in the topiramate group versus placebo group regardless of dosage and duration of treatment. Data regarding the safety of topiramate was available for 6,620 individuals, and pooled meta-analysis reported increased risk for paresthesia (pooled OR 8.70, 95% CI 6.90-11.0, P <0.001). However, there was no report of cardiovascular or major adverse events in any of the studies.

BED is strongly associated with obesity. The 2017-2018 age-adjusted prevalence of obesity (defined as a body mass index (BMI) ≥30 kg/m²) in the United States (U.S.) among adults was 42.4%. Obesity is associated with an array of adverse health outcomes, including metabolic diseases (type 2 diabetes and fatty liver disease), cardiovascular diseases (hypertension, myocardial infarction, and stroke), osteoarthritis, Alzheimer’s disease, depression, and cancers of the breast, prostate, ovaries, liver, kidneys, and colon. It is estimated that obesity can decrease life expectancy by five to twenty years, therefore treatment is of paramount importance. Obesity may also be associated with decreased productivity, lower quality of life, social disadvantages, and
unemployment\textsuperscript{22}. Therefore, obesity contributes to physical health challenges and rising economic costs.

Bariatric surgery is indicated in patients with a BMI $\geq 40$ kg/m\textsuperscript{2}, or patients with a BMI $\geq 35$ kg/m\textsuperscript{2} with at least one obesity-related comorbidity such as type 2 diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, non-alcoholic fatty liver disease, asthma, and venous stasis disease\textsuperscript{23}. Several bariatric surgery methods exist. The Roux-en-Y gastric bypass (RYGB) involves multiple anastomoses to reroute the path of ingested food, decreasing absorption of nutrients and, subsequently, weight\textsuperscript{24}. Sleeve gastrectomy (SG) is an alternative form of bariatric surgery and is a restrictive technique that reduces the stomach capacity to 60-110 mL\textsuperscript{24}, is easier and faster to perform than RYGB, and is thought to be safer than RYGB\textsuperscript{25}. Spaniolas et al. published a study\textsuperscript{26} in 2015 that looked at changes in trends of bariatric procedures performed in the U.S. using a cohort of 74,790 bariatric patients. They found that the rate of SG increased from 9.6\% (95\% CI 9.13-10\%) of all bariatric surgeries performed in 2010 to 49.4\% (95\% CI 48.8-50.1\%) in 2013, while rates of both open and laparoscopic RYGB decreased significantly during the same period. SG is now the most common bariatric procedure performed in the U.S\textsuperscript{26}.

Meany and colleagues conducted a review of literature in 2014 and found that while bariatric surgery often ameliorates disordered eating, namely binge eating and BED, this is not always the case. Fourteen of the fifteen studies reviewed showed that BED or loss of control (LOC) eating, the central feature of binge eating, after bariatric surgery is correlated with less weight loss or increased weight regain following surgery\textsuperscript{27}. 


It is important to acknowledge the physical limitations to eating that patients experience after bariatric surgery that may preclude a BED diagnosis. For example, as SG reduces stomach capacity by up to 80%\textsuperscript{24}, the patient may no longer be able to ingest the abnormally large quantities of food required for diagnosis of BED, despite the presence of other eating disorder psychopathology. Mitchell and colleagues studied the status of 100 patients after bariatric surgery over a period of 13-15 years and found that only 6.4\% of subjects met the complete criteria for BED. After removal of the quantity of food criterion, 12\% of patients met criteria for BED\textsuperscript{28}.

Because of this limitation of diagnostic criteria, LOC eating can be used as an alternative means of defining disordered eating among post-bariatric surgery patients. LOC eating is “a subjective sense of loss of control while eating (regardless of the amount consumed), difficulty stopping eating, or difficulty preventing oneself from eating\textsuperscript{29}”. This definition allows for assessment of disordered eating among those who physically cannot consume an abnormally large amount food to meet criteria for BED due to the physical restraints imposed upon patients after surgery. Though the DSM-5 specifies consumption of a large quantity of food as a criterion for the diagnosis of BED, some of the eating disorder literature recognizes LOC eating as the salient feature of BED\textsuperscript{1,30}. Colles, Dixon, and O’Brien published a cross-sectional study in 2007 that evaluated the relationship between core behaviors of binge eating and markers of psychological distress in over 400 adults who were either bariatric surgery candidates, general community respondents, or members of non-surgical weight loss support groups\textsuperscript{30}. They found that the feeling of LOC surrounding eating behavior was the factor most closely associated with psychologic disturbance. The frequency and size of binges
were less strongly associated with psychological disturbance, therefore the authors concluded that those who do not meet all DSM-5 criteria for BED may still be at risk for psychological upset and may benefit from clinical intervention. A 2018 study published by Ivezaj and colleagues studied 431 adults seeking treatment for eating and weight concerns and found that both participants who met all DSM-5 criteria for BED (without bariatric surgery) and those who met all criteria for BED except for the “unusually large” criterion for BED (the “Bariatric BED” group) did not differ in various forms of eating disorder psychopathology and functioning. It is imperative that healthcare providers recognize this particular subset of patients who experience LOC eating without necessarily meeting the requirement for consuming abnormally large quantities of food, as they can still experience eating-disorder psychopathology, marked distress, and suboptimal weight outcomes after bariatric surgery.

Mitchell et al. conducted a study in 2015 that aimed to describe eating patterns and the prevalence of certain eating behaviors before bariatric surgery. Among the 2,266 adults that participated in the study, 43.4% reported LOC eating before surgery. Smith and colleagues studied 2,156 patients who underwent bariatric surgery between 2006 and 2009 and were followed for up to seven years until 2015 in the Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) study. They found that LOC eating was most prevalent before surgery (35.0%), with the greatest decrease in prevalence occurring in the first postoperative year (prevalence 24.6% twelve months after surgery). However, despite this initial decrease, prevalence peaked again at 31.7% three years after surgery. Following surgery, 25.6% of subjects reported new LOC eating, 25.4% reported recurrent LOC eating, and 9.7% reported remitted LOC eating. Although LOC eating was not
shown to be related to prolonged or subsequent weight loss outcomes, it was associated with less concurrent weight loss. Those who reported LOC eating over the past six months experienced 1.7% less weight loss since prior assessment compared to those who did not report LOC eating \( (p < 0.05) \). Therefore, LOC eating has the potential to persist after bariatric surgery and arise in de novo cases. Given the association between LOC eating after surgery and suboptimal weight loss outcomes, assessment and treatment of disordered eating behaviors rather than diagnosis is of great clinical importance.

### 1.2 Statement of the Problem

There have been no studies published investigating the use of pharmacotherapy in patients with obesity and LOC eating following bariatric surgery, though it has already been established that such a population exists\(^ {31} \). More research is needed to study treatments that reduce both weight and LOC eating in these patients to help optimize outcomes following bariatric surgery.

Topiramate, an FDA approved anticonvulsant medication, has been shown to improve weight and binge eating outcomes among those with BED\(^ {19, 34, 35} \). Low to moderate doses of topiramate have been shown to be well-tolerated by patients while still providing statistically significant weight loss\(^ {36} \). Thus, evaluation of topiramate for weight loss and eating disorder symptomatology in LOC eating is warranted.

### 1.3 Study Goal and Objectives

The primary aim of this study is to investigate the effect of topiramate versus placebo on mean percent weight change in adults with obesity and LOC eating after bariatric surgery. Percent weight change will be defined as change from baseline (enrollment) to the end of the 16-week intervention and change from baseline to a six
month follow-up after treatment ends (see Appendix A for visual aid). Secondary outcomes include LOC eating frequency and achievement of LOC eating remission, as defined by zero episodes of LOC eating in the past 28 days, at the end of treatment and at six months following completion of the intervention period. The objective of this study is to understand the effect on weight and LOC eating of pharmacotherapeutic use of topiramate in adults with obesity and LOC eating following bariatric surgery.

1.4 Hypothesis

The use of topiramate in adults with obesity and LOC eating after bariatric surgery is associated with a different mean percent weight change since baseline at the end of treatment and at six months following completion of the intervention period compared to placebo.

1.5 Definitions

- **Binge eating disorder (BED):** recurring episodes of binge eating, which involve consuming abnormally large amounts of food within a short period of time and experiencing a sense of loss of control; must meet three of the following five symptoms to meet DSM-5 criteria for BED: 1) eating more rapidly than usual; 2) eating until feeling uncomfortably full; 3) eating large amounts of food when not physically hungry; 4) eating alone because of embarrassment; 5) feeling disgusted with oneself, depressed, or guilty after overeating
- **Obesity:** body mass index (BMI) $\geq 30$ kg/m$^2$
- **Loss of control (LOC) eating:** a subjective sense of LOC while eating (regardless of amount consumed), difficulty stopping, or difficulty preventing oneself from eating
- **LOC eating remission:** zero episodes of LOC eating in the past 28 days
1.6 References

Chapter 2: Review of the Literature

2.1 Introduction

There are currently no studies evaluating the effect of topiramate on weight loss in adults with obesity and LOC eating following bariatric surgery in the U.S. A thorough review of literature was conducted from July to December of 2021 with the intent to summarize and critically appraise earlier research on pertinent topics related to this area of medical research. The aforementioned summary and analyses will also serve to provide justification for the proposed study methods, discussed in detail in Chapter 3.

PubMed, Ovid, Embase, and the ClinicalTrials.gov registry were used in this search. Systematic reviews, meta-analyses, RCTs, case series, and retrospective cohort studies were incorporated into this literature review, but only papers written in English were accepted. The medical subject headings (MeSH) used are listed in Appendix B.

2.2 Overview of the Implications of LOC Eating on Various Measures of Mental and Physical Health Following Bariatric Surgery

As discussed at length in Chapter 1, current methods of classifying binge eating fail to appropriately represent the problematic eating behavior in the bariatric surgery population due to patients’ limited ingestive capacities resulting from surgery. In addition, consumption of large quantities or overly-rich or fatty foods may induce vomiting or dumping syndrome postoperatively, decreasing the likelihood of ingestion of abnormally large quantities\(^1\). As such, the subjective sense of LOC may be a more telling indicator than BED in this particular subset of patients. In a cross-sectional study published in 2018, Ivezaj and colleagues found that post-bariatric surgery patients who met all DSM-5 criteria for BED, except for consumption of an “unusually large” amount
of food, closely resembled patients who met all criteria for BED with regard to overall eating disorder psychopathology and depressive symptoms\(^2\). Furthermore, they found no significant difference between the aforementioned groups in terms of overvaluation of weight and shape concerns, a key cognitive feature of disordered eating. These findings call for an increased awareness among medical professionals to properly diagnose LOC eating in the bariatric surgery population regardless of the amount of food consumed. Patients in this study were limited to those who had undergone SG, potentially decreasing generalizability, however SG is currently the most common bariatric procedure performed in the US\(^3\). Strengths of this study include the use of relevant patient comparison groups and a well-established, semi-structured interview to measure eating disorder psychopathology and BED.

The psychological and physical effects of LOC eating is highlighted in a 12-month observational study\(^4\), published by Colles et al in 2008, in which a range of eating behaviors, including BED and LOC eating, were assessed before and one year after laparoscopic adjustable gastric banding (LAGB) in 129 subjects. Postoperatively, 22.5% (n=29) reported LOC and 3.1% (n=4) met diagnostic criteria for BED. Together, these 33 participants were termed “uncontrolled eaters” and achieved a significantly lower mean weight loss (21.6 kg) compared to the remainder of the cohort (26.7 kg). This equates to a mean percent weight loss of 17.4 ± 8.2 in the uncontrolled eaters compared to the remainder of the cohort, whose mean percent weight loss was 22.0 ± 8.3 (p = 0.008)\(^4\). Uncontrolled eaters also reported less restraint (10.9 ± 3.7 versus 13.7 ± 4.1, p < 0.01) and more hunger (6 (3–9) versus 2 (1–4), p < 0.001 [data presented as median (IQR)]) and disinhibition (10.1 ± 3.1 versus 4.8 ± 3.2, p < 0.001) compared to the rest of the
cohort. A higher percentage of their diet was fat (34.3 ± 5.6 versus 30.3 ± 6.4, \( p < 0.01 \)), and they consumed more calories per day (4370 ± 1544 versus 3807 ± 1356, \( p < 0.05 \)). Uncontrolled eaters experienced greater depression and poorer mental health-related quality of life. Importantly, analyses showed similar results when the four BED subjects were excluded. After 12 postoperative months, uncontrolled eaters and the subset with a high level of emotional disturbance related to feelings of LOC reported eating in response to anxiety, depression, fatigue, boredom, stress, and anger compared to the rest of the cohort. Additionally, they continued to eat when full and feared weight gain. Patients lost to follow-up were more likely to have reported presurgical BED\(^4\), potentially distorting the data to show less postoperative eating pathology than was actually present. Moreover, 80% of participants were female, decreasing external validity and potentially hindering generalization to other populations. This study’s relatively large sample size and assessment of emotional markers of distress deem it an important contributor to current knowledge regarding the postoperative effects of LOC eating. However, the generalizability of this study is significantly limited in that it only included those who had undergone LAGB, which is no longer recommended in those with a BMI \( \geq 35 \) kg/m\(^2\) because it is associated with poorer short- and long-term outcomes, higher failure rates, and a lower safety profile compared to other surgical procedures such as SG and RYGB\(^5\).

Whereas the previously mentioned study\(^4\) assessed eating pathology and postsurgical outcomes at 12 months, White et al. assessed the clinical effects of LOC eating in 361 post-bariatric surgery patients during a 24-month follow-up period\(^1\). Mixed models analyses revealed that post-operative LOC was a significant predictor of weight loss at 12 months (\( F(1, 272) = 7.595, \ p = .006 \)) and 24 months (\( F(1,156) = 4.298, \ p = .040 \))
post-surgery. Moreover, LOC eating at 6 months was shown to significantly predict weight loss at 12 and 24 months ($F(1, 252) = 4.748, p = .03$). Those with LOC eating at 6 months lost significantly less weight at 12 months (34.6 vs. 37.2% BMI loss) and 24-months (35.8% vs. 39.1% BMI loss). These subjects also experienced more depressive symptoms and decreased quality of life, as measured by the Beck Depression Inventory (BDI) and the Medical Outcomes Study Short Form-36 Health Survey (SF-36), respectively, emphasizing the importance of early intervention in those who continue to experience LOC eating after surgery. Participants in this study had a mean BMI of 51.1 kg/m$^2$. 86% were female and 81% were Caucasian, so these results may not generalize to patients who do not fit these descriptions. Although mixed-models was used to analyze data, a limitation of this study is missing data due to dropout before the 24 month follow-up appointment. However, few differences were found between those who provided data at 24 months compared to those who did not. The authors did not report the dropout rate or values regarding attrition.

Ivezaj and colleagues published a study in 2016 that evaluated LOC eating severity and weight loss after laparoscopic SG surgery$^6$. Participants were adults 18-65 who reported at least once weekly LOC eating over the past 28 days four to nine months after SG. Importantly, LOC eating criteria did not require consumption of a minimum quantity of food. Participants were divided into two study groups using modified BED criteria. The “Bariatric BED” (Bar-BED) group met all BED criteria (weekly LOC eating over the past three months, three of five associated symptoms, marked distress, and lack of regular compensatory behaviors), except for the large quantity of food criteria. Participants with LOC eating but without at least 3 associated symptoms, marked levels
of distress, or lack of compensatory behaviors were deemed the “LOC-Only” group. Among the 71 participants, 49.3% (n=35) were categorized as the Bar-BED group and 50.7% (n=36) were classified as the LOC-Only group. The Bar-BED group reported significantly greater LOC eating episodes (without an unusually large quantity of food), significantly more associated symptoms, and greater levels of distress than the LOC-Only group. Moreover, the Bar-BED group reported significantly greater eating disorder psychopathology, including restraint, eating, weight, and shape concerns. The Bar-BED group also had significantly less percent total weight loss by six months post-surgery than the LOC-Only group (19.0 vs 22.4, \( p = 0.033 \))^6. These findings are consistent with those reported by the Longitudinal Assessment of Bariatric Surgery Research Consortium (LABS), which found that post-surgical BED and LOC eating are associated with poorer weight loss outcomes after gastric bypass and laparoscopic banding surgeries^7,8. Ivezaj and colleagues’ study contributed to the literature by evaluating outcomes after SG.

A study^9 published by Wiedemann and colleagues in 2018 evaluated the frequency of LOC eating and its relationship with eating psychopathology and weight loss after SG in 131 patients who had undergone SG in the previous 4 to 9 months at the Yale Bariatric/Gastrointestinal Surgery Center of Excellence. A higher frequency of LOC eating was associated with poorer weight outcomes 6 months after surgery. This particular study highlights the importance of recognizing “triple recall bias”, first described by Evers et al in 2009, which states that participants are required to recall their negative emotions, food intake, and the association between the two in order to identify emotional eating^10. By using the Yale Emotional Eating Questionnaire (EOQ) to assess the frequency of overeating due to negative emotions, triple recall bias may be
minimized. Because this was a cross-sectional study, causality between the frequency of LOC eating and weight outcomes cannot be inferred. Only SG patients were included in this study, so it is possible that results may not generalize to those who have undergone other types of bariatric surgery. Although participants were of more diverse ethnic backgrounds (53% were white) than the previously mentioned study\textsuperscript{1}, 85.1\% of participants were female, so results may not generalize to the male population.

This section highlights that LOC eating is associated with poorer weight outcomes and increased eating disorder psychopathology after bariatric surgery.

2.3 Review of Empirical Studies Involving Topiramate

2.3.1 Studies Evaluating the Effects of Topiramate on Weight Loss and Eating Disorder Pathology

As discussed at length in Chapter 1, evaluation of LOC eating may be a more appropriate measure of certain eating disorder pathologies than BED, which requires consumption of an abnormally large amount of food for diagnosis, a criterion that is likely to exclude many who have undergone bariatric surgery\textsuperscript{1,11}, but still experience subjective feelings of LOC while eating. Because the similarities between BED and LOC eating among bariatric surgery patients has only recently been explored\textsuperscript{2}, this section will include studies published in recent decades that assess the use of topiramate in BED, though the proposed study will use LOC eating rather than BED as an inclusion criterion. LOC is the salient feature of binge eating, and the International Classification of Diseases (ICD) diagnosis of BED does not require binges to be large, but does require LOC\textsuperscript{12,13}.

Among the first studies to evaluate the use of topiramate in patients with BED and obesity is a case study of eight subjects published in 2002 by Appolinario et al\textsuperscript{14}. This
was a 16-week open-label trial in which 150 mg of topiramate was administered daily to patients with both obesity and BED. Outcomes included the number of days per week with binge eating episodes, binge eating behavior (assessed using Binge Eating Scale (BES) scores), depressive symptoms (assessed using BDI), and body weight. Six subjects completed the trial, all of whom experienced reduced binge eating behavior at the end of the intervention period. The mean number of days per week with binge eating episodes decreased from 4.3 (SD 1.7) at baseline to 1.1 (SD 2.4) at the end of the study (t = 4.4, df 7, p = 0.03), and mean BES scores fell from 31.8 (SD 7.5) to 15.3 (SD 9.2) (t = 4.2, df = 7, p = 0.04). Subjects also experienced fewer depressive symptoms, demonstrated by a drop in mean BDI scores from 25.3 (SD 7.5) to 15.8 (SD 5.7) (t = 3.0, df = 7, p = 0.02) at the end of treatment. A statistically significant drop in weight also occurred, with a mean weight loss of 4.1 kg (t = 2.4, df = 7, p = 0.04). This study is limited by its very small sample size and its open-label nature. Authors of this study note that patients with BED have shown to have a high placebo response rate, shown to be as high as 44% in a run-in period for a study evaluating a different antiepileptic, d-fenfluramine. Therefore, it cannot be ruled out that the results of this study are due to placebo response. Regardless, the reported findings helped justify a placebo-controlled trial evaluating the use of topiramate in BED associated with obesity.

 Schmidt do Prado-Lima and Bacaltchuck also published a case study in 2002 that investigated the use of topiramate in a 32 year old female patient with an 11-year history treatment-resistant depression, obesity (BMI of 34 kg/m²), and BED. Despite aggressive pharmacotherapy with carbamazepine, risperidone, venlafaxine, methylphenidate, and others for several years, she continued to have binge eating
episodes associated with significant weight gain, and later experienced worsening of her depressive symptoms, including new suicidal ideation. Topiramate was then introduced at 25 mg daily and titrated to 300 mg daily. After three months on topiramate, the patient said she “had never felt so well” and reported increased concentration, happiness, interest, energy, and work performance and decreased fatigue. Her BMI decreased to 20 kg/m$^2$ in 10 months and she achieved binge eating remission$^{16}$. This case study is greatly limited by its sample size of one subject, and the use of other medications in addition to topiramate. It cannot be determined with certainty whether or not it was topiramate or another drug, such as venlafaxine, prescribed to the patient that caused the reported effects. Furthermore, the authors did not define “binge eating remission”, so while this suggests improvement in the patient’s BED symptoms, the exact results are unknown.

A multicenter, randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity was conducted in 2003 by Bray et al$^{17}$. Participants included 385 “healthy obese” subjects between the ages of 18 and 75 with a BMI of $\geq 30$ to $<50$ kg/m$^2$, or $\geq 27$ to $<50$ kg/m$^2$ if the subject also had controlled hypertension and/or dyslipidemia, who were recruited from 17 centers in the U.S. Patients were randomized to receive either placebo or topiramate at 64, 96, 192, or 384 mg daily, which was continued for 24 weeks and then tapered off by 50% per week for two weeks. All subjects took part in the same lifestyle program. Subjects were evaluated two weeks after the completion of the 24-week treatment period, during which weight and blood pressure were measured. Analyses of the intent-to-treat (ITT) population using last-observation-carried-forward (LOCF) revealed mean percent weight loss since baseline was 2.6% in the placebo group and 5.0%, 4.8%, 6.3%, and 6.3% in the 64 mg, 96 mg, 192 mg, and
384 mg topiramate groups, respectively. Moreover, there was a statistically significant increase in the percentage of participants who achieved 5% and 10% among those receiving 64, 96, and 192 mg of topiramate compared to placebo. The increase was greatest at 192 mg of topiramate, in which 53% of subjects achieved 5% weight loss compared to 19% of those taking placebo \((p = 0.001)\), and 29% achieved 10% weight loss compared to 7% of those taking placebo \((p = 0.002)\). This study boasts a very large sample size and is placebo-controlled, improving its internal validity. Because this was the first randomized, prospective clinical trial involving topiramate use in patients with obesity, only healthy participants were recruited\(^\text{17}\). However, this greatly decreases the external validity of the study, because obesity is often associated with comorbidities\(^\text{18}\). It is unclear whether or not the results of this study would generalize to patients with obesity who also have comorbid conditions. Finally, due to the titration schedule, the time needed to reach the target dose of topiramate was two, three, six, or 12 weeks for the 64, 96, 192, and 384 mg daily dose groups, respectively. Therefore, the time that each group remained on the target dose varied from 12 to 22 weeks, so it is possible that the differences between groups were underestimated and would have been larger if the time spent at target doses was longer. The most common side effect was mild to moderate paresthesia, which was dose-dependent. Topiramate doses of 64 and 96 mg were tolerated better than the 192 and 384 mg doses. Cognitive side effects, including difficulty concentrating, memory impairment, somnolence, and psychomotor slowing, were more frequently reported at higher doses and during the titration phase of the study. These adverse effects usually resolved without discontinuation or dose reduction of topiramate. Discontinuation of topiramate due to side effects occurred in 21% of the
topiramate group and 11% of the placebo group ($p < 0.05$). There was one case of moderately severe hyperchloremic acidosis in one patient who was asymptomatic and on 192 mg of topiramate and no other medications; it resolved within two weeks of discontinuing topiramate. Serious adverse events occurred in 12% (four subjects) of the topiramate group, including nephrolithiasis (patient continued treatment), increased hepatic enzymes (patient discontinued treatment), and motor vehicle accident injury (patient discontinued treatment), all of which resolved. Nephrolithiasis is a known rare but serious side effect of topiramate, as is narrow-angle glaucoma, which was not reported in this study$^{19,20}$. This trial is particularly useful as it highlights the effects of topiramate at varying doses and associated side effects. Because lower doses of topiramate were associated with weight loss and better tolerated, perhaps they should be favored in long-term obesity management.

In 2003, McElroy and colleagues published a 14-week, single-center, randomized, parallel-group, placebo-controlled, flexible-dose study$^{21}$ to investigate the use of topiramate in 61 adults with obesity and BED. Topiramate doses ranged from 50 to 600 mg daily; the median dose was 212 mg per day. The primary outcome was the number of binge episodes (binge frequency) during the seven days before each office visit throughout the trial. Secondary outcomes were mean weight loss since baseline and the number of days in which binge eating episodes occurred (binge day frequency). Topiramate was associated with a significant reduction in binge frequency compared to placebo (94% vs 46%, $p < 0.02$), as well as binge day frequency (93% vs 46%, $p < 0.02$) in the ITT group. Results were also significant among the completer group for both measures. Mean weight loss since baseline was significant at week 14, measuring 5.9 kg
and 1.2 kg in the topiramate and placebo group, respectively. Importantly, no adverse effects or withdrawal symptoms during the taper and discontinuation phase were reported among patients receiving topiramate. The greatest limitation of this study is its dropout rate; only 35 participants (57%) completed the 14 weeks of topiramate treatment. The most common reason for noncompletion was nonadherence to study protocol, numbered at 13 participants, six randomized to receive topiramate and seven randomized to receive placebo. Indeed, we will clearly explain and emphasize study protocol to participants prior to and during this proposed trial.

Completers (n=35) of the previously mentioned study by McElroy et al. were offered participation in a 42-week, open-label extension trial of topiramate. Participants included 31 subjects who completed the previous double-blind trial. Data from 13 participants of the double-blind only trial were also used in ITT analyses using LOCF method. Of these 44 participants, 43 provided outcome data (one subject was lost to follow-up). The primary outcome was change from baseline to final visit in weekly binge frequency, which significantly declined for all 43 patients (−3.2; p < .001), as well as for those (n=15) who received topiramate in the open-label extension trial only (−2.5; p = .044) and those (n=15) who received topiramate in both the double-blind and open-label trials (−4.0; p < .001). Moreover, patients taking topiramate experienced statistically significant weight loss. Among those who received placebo during the double-blind trial and topiramate during the open-label trial, mean weight loss since baseline after a mean topiramate treatment time of 19.3 weeks was 14.5 kg (p = .002), which was similar to the mean weight loss since baseline of those who took topiramate during both the double-blind and open-label trials, which was 14.1 kg (p = .023) after a mean 23.0 weeks of
treatment. Importantly, among those who received placebo during both trials, mean weight loss since baseline was 6.7 kg at week 20 and 14.1 kg at week 56 (the end of both the 14-week double-blind trial and the 42-week open-label trial). Mean weekly binge frequency was 5.0 at baseline, 1.1 at week 20, and 0.3 at week 56. Those treated with placebo during the double-blind study and topiramate during the open-label extension trial also saw a significant difference in mean weight loss since baseline, which was 6.4 kg at week 36 and 14.5 kg at week 56. Their mean binge frequency was 4.1 at baseline, 1.4 at week 36, and 0.7 at week 56. Thus, topiramate was effective in producing long-term reductions in weight and binge frequency among adults with BED and obesity. The results of this trial are imperative as they demonstrate the sustained effect of topiramate in reducing weight and binge eating behaviors. However, this was a nonrandomized and uncontrolled trial so it is possible that the observed results were due to placebo response. Recall that patients with BED have been shown to have a high placebo response rate\textsuperscript{15}. Another limitation of this study is its attrition rate. Of the 61 individuals who entered the double-blind trial, only 10 (16\%) completed the 42-week extension trial. This is a major limitation of this study. Nonadherence to study protocol (n=17) and adverse effects (n=14) were the most common reasons for discontinuation. It is possible that participants did not tolerate the medication well, which could impact both adherence and adverse effects data. Despite this point, LOCF method was used to analyze results with missing data, so it is possible that the results were an underestimation of the effects of topiramate on weight change and binge behaviors.

The previously mentioned 14-week double-blind, randomized, placebo-controlled study\textsuperscript{21}, published in 2003 McElroy et al., was replicated in 2007 at a larger scale\textsuperscript{23}. The
former was a single-center study with a sample size of 61 patients, and the latter included 407 patients from 19 centers in the U.S. Similarly, the objective of the study was to evaluate topiramate for the treatment of BED associated with obesity. Topiramate was started at 25 mg per day and was titrated to 400 mg per day or the maximum tolerated dose over eight weeks. The primary outcome measure was the number of binge eating days per week, and secondary outcomes included weight and the number of binge eating episodes per week. The study length was 16 weeks. The mean number of binge eating days per week decreased by 3.7 (from 4.6 to .9, or 72% +/- 38%) in the topiramate group over the 16 weeks, compared to 2.4 (from 4.6 to 2.2, or 47% +/- 41%) in the placebo group (p <0.001). The mean number of binge eating episodes per week decreased by 5.3 (from 6.6 to 1.3, or 73% +/- 37%) and by 3.5 (from 6.3 to 2.8, or 47% +/- 41%) in the placebo group (p <0.001). Those taking topiramate also experienced statistically significant weight loss, with a mean weight reduction of 4.5 kg +/- 5.1 kg compared to 0.2 kg +/-3.2 kg lost in the placebo group (p <0.001). The results of this trial, as well as the 2003 trial, support the hypothesis that topiramate is effective at reducing weight and binge eating behavior in adults with BED and obesity. Because those with certain lifetime psychiatric disorders such as bipolar disorder were excluded in this study, it remains unknown whether or not the results would generalize to those populations. The discontinuation rate was 29% for this study, compared to the 43% discontinuation rate for the 2003 study. This is likely because the maximum dose of topiramate was 400 mg in this study, compared to 600 mg in the previous study. This evidence suggests that lower doses of topiramate should be favored in the treatment of BED associated with obesity.
because they are tolerated better than higher doses while still providing statistically significant weight loss and reduction in certain eating disorder pathologies.

Topiramate has also been evaluated for the treatment of BED in conjunction with CBT. A 21-week, double-blind RCT\textsuperscript{24} was conducted by Claudino and colleagues in 2007 at four centers in the U.S. Participants included 73 adults (aged 18-60) with obesity and BED who were randomized to receive CBT and either topiramate (200 mg target daily dose) or placebo. Those who completed treatment (n=56) experienced a mean percentage weight loss since baseline of 6.8\% (SD = 5.2), which was significantly more than that of the placebo group (4.1\%, SD = 4.3\%, \textit{p} = 0.04). Additionally, the percentage of those who achieved greater than 10\% weight loss was 33.3\% and 11\% for the topiramate + CBT group and placebo + CBT group, respectively (\textit{p} = 0.05). The mean frequency of binge eating days per week was significant in both the topiramate and placebo groups (\textit{p} < 0.001), falling from 4.2 (SD = 3.4) to 0.0 (SD = 0.2) and from 3.4 (SD = 1.3) to 0.3 (SD = 0.6), respectively. A significantly greater percentage of patients taking topiramate achieved binge eating remission, as defined by zero episodes of binge eating during the final week of the study (83.8\% vs 61.1\%, \textit{p} = 0.03). Completion rates between treatment arms were not statistically significant, and tolerability was good, as demonstrated by the study’s 76.7\% completion rate. Only one patient in the topiramate arm withdrew due to adverse effects, including paresthesia and confusion, however the patient inadvertently took the wrong dose and did not wish to continue with the trial. The mean dose of topiramate was 205.8 mg (SD = 35.8) (range, 100–300 mg), suggesting this may be a tolerable dose for the treatment of BED associated with obesity. Most study participants (n=70, 96\%) of participants were female, so it is possible that these results do
not generalize to the male population. Another limitation of this study is its exclusion of patients with clinically significant comorbid psychiatric or medical conditions, which includes many patients with obesity, further reducing external validity. Nevertheless, these results support the use of topiramate in certain eating disorders for weight loss and reduction of eating disorder symptoms.

Topiramate has been studied in patients with disordered eating and severe obesity before bariatric surgery. In 2016, Guisado-Macías and colleagues published a clinical trial in which 75 patients (mean BMI 45.4 kg/m², SD +/- 9) were randomized to receive fluoxetine (40 mg/day), topiramate (200 mg/day), or a combination of both (fluoxetine 40 mg/day + topiramate 200 mg/day) for six months before bariatric surgery to stabilize disordered eating behaviors. The prevalence of disordered eating behaviors in this study were as follows: food snacking (n=61, 81%), abundant intake (n=39, 52%), binges as a symptom (n=32, 42%), nighttime eating (n=10, 13%). Eighteen participants (24%) met criteria for BED. The primary outcomes were mean percent weight loss since baseline at three and six months. The fluoxetine, topiramate and combination groups significantly differed in mean weight loss at six months, which was 2.90%, 4.75%, and 6.08%, respectively. The differences in mean weight loss since baseline three months before surgery were not statistically significant. Topiramate was associated with more weight loss at six months than fluoxetine as monotherapy. Regarding patients with BED, there was no significant difference in weight loss at three or six months. However, 80% of patients with BED received combination therapy with fluoxetine and topiramate while 20% received fluoxetine monotherapy (no patients with BED were randomized to receive topiramate monotherapy). These results would have been useful in determining the effect
of topiramate monotherapy in patients with BED and morbid obesity before bariatric surgery. The greatest limitation of this study is its lack of a placebo-controlled group to compare results. Moreover, 80% of participants were female, similar to other studies\textsuperscript{17,21,23}. There is great need for research regarding the use of topiramate for weight loss and disordered eating in the male population. Another limitation of this study is that the percent with BED was very small, especially when splitting across groups.

### 2.3.2 Studies Evaluating the Effects of Topiramate after Bariatric Surgery

A 2018 retrospective cohort study\textsuperscript{26} conducted by Toth et al. compared the effects of three medications (topiramate, phentermine, and metformin), on weight loss in 37 young adults (21-30 years of age) who experienced weight regain or inadequate weight loss after bariatric surgery. Primary efficacy measures included median percent change in weight after medication and the proportions of patients who achieved 5\%, 10\%, and 15\% of postsurgical weight loss. There was no significant difference in median percent weight change between those on topiramate and the rest of the cohort ($p = 0.3197$). However, 54.6\% of patients achieved 5\% postsurgical weight loss, and 34.3\% and 22.9\% achieved 10\% and 15\% postsurgical weight loss, respectively. No difference was seen in median percent weight loss when medications were started at weight plateau (6\%) compared to after weight regain (5.4\%) ($p = 0.5304$). Thus, there seems to be some flexibility with regard to when weight loss medications are started while still providing patients with optimal results. This study is of particular interest because the study population is only composed of young adults, whereas other studies have included older adults up to 75 years\textsuperscript{17,21-25}. However, this study is limited by its small sample size.
The results of the previously mentioned study\textsuperscript{26} were similar to those published in 2017 by Stanford et al. from a retrospective cohort study\textsuperscript{27} of 319 individuals (aged 20-73; mean age 45 years) who had undergone bariatric surgery between 2000 and 2014 who were subsequently placed on weight loss medications for inadequate weight loss or weight regain. Fifteen different weight loss medications were evaluated in this study, and the average number of medications for participants was two. The four coprimary endpoints were relative change in weight, and the proportions of patients who achieved 5\%, 10\%, and 15\% of postsurgical weight loss, measured at the weight plateau after medication administration. Similar to findings by Toth and colleagues\textsuperscript{26}, 56\% of patients achieved 5\% weight loss, and 30.1\% and 16\% of patients achieved 10\% and 15\% postsurgical weight loss, respectively. The results of these studies\textsuperscript{26, 27} suggest that pharmacotherapy is an effective weight loss intervention in adults after bariatric surgery.

Of the 15 medications evaluated by Stanford et al., topiramate was the only one associated with statistically significant weight loss, with patients being twice as likely to achieve 10\% postsurgical weight loss compared to those not on topiramate (odds ratio 1.9, \( p = 0.018 \))\textsuperscript{27}. Lack of a control group in this retrospective study is a substantial limitation. Perhaps even more limiting is the inability to control for confounding variables such as diet, exercise, length of time that patients took medications, and concurrent use of other medications. Strengths of this study include a large sample size, compared to the study by Toth et al., in which the study population was only 37 individuals\textsuperscript{26}. However, because this study was retrospective, the time at which participants started medications in relation to surgery was not standardized. This is a limitation that must be considered.
Zilberstein and colleagues published a case series in 2004 of 16 individuals between the ages of 15 and 60 with binge eating episodes or BED and inadequate weight loss after adjustable gastric banding (AGB), a type of bariatric surgery. Patients were followed prospectively for 90 days while receiving topiramate in varying doses between 12.5 and 50 mg daily. Among participants, mean age was 36.4 years and mean BMI was 43.5 kg/m². Fourteen participants were female and two were male. The primary outcome was mean increase in percent excess weight loss, which increased from 20.9% to 34.1% ($p = 0.0139$) after 90 days, without the need for band readjustment. Two patients experienced somnolence as a side effect of topiramate and opted to discontinue the drug. The results of this trial suggest that topiramate may be an effective adjuvant after AGB in those who are struggling with inadequate weight loss. Because this study only included patients who had undergone AGB, however, results may not generalize to those who have undergone other types of bariatric surgery, including RYGB or SG, which is now the most common bariatric procedure performed in the U.S.

More recently, the use of topiramate has been studied in a large cohort of individuals (n=760) who underwent RYGB between 2004 and 2015 at Boston Medical Center. The 11-year cross-sectional analysis, published by Istfan et al. in 2020, studied the rate of rapid weight regain among patients who took no antiobesity medications or were prescribed topiramate, phentermine, or a combination of both. Rapid weight regain was defined as a rate of increase in body weight of $\geq1.22\%$ per month relative to nadir weight. Cox regression analysis revealed a proportional hazard ratio of 0.729 (CI: 0.556-0.957, $p = 0.023$) for the adherent antiobesity medication users compared with the nonusers of antiobesity medications, suggesting that the antiobesity medications are
effective in preventing rapid weight regain among subjects. This study did not compare the antiobesity medications to one another, but rather looked at their use collectively. Therefore, it cannot be determined whether phentermine monotherapy, topiramate monotherapy, or combination therapy is more effective at reducing weight regain after RYGB. The findings of this study imply that phentermine, topiramate, and combination phentermine/topiramate were effective in reducing risk of weight regain after RYGB. Strengths of this study include its large sample size and diverse ethnic backgrounds of participants; 30.8% of participants identified as African American and 14.6% identified as Hispanic. Because this study only included those who had undergone RYGB, it is unclear whether or not the results are generalizable to a population that has undergone other types of bariatric surgery. This is of particular concern because SG is now the most common bariatric procedure performed in the U.S.3.2.4 Methodology Considerations 2.4.1 Choice of Intervention Group

A thorough review of the literature regarding pharmacotherapeutic approaches for the treatment of disordered eating associated with obesity after bariatric surgery has revealed the promise of topiramate as an effective medication to treat both LOC eating and obesity, as outlined in Section 2.3.

Reas and Grilo published a comprehensive review30 in 2015 on the pharmacological treatments for BED. Although the proposed study will investigate LOC eating rather than BED, results from this review are thought to be an adequate surrogate in the absence of trials that specifically investigate pharmacotherapies in LOC eating associated with obesity after bariatric surgery. Reas and Grilo reviewed 22 RCTs
evaluating antidepressant, antiobesity, antiaddiction, stimulant, and antiepileptic medications for the treatment of BED. Five RCTs evaluated fluoxetine against placebo\textsuperscript{31}, against sertraline\textsuperscript{32}, against fluvoxamine\textsuperscript{33}, and against CBT alone or against CBT plus either fluoxetine or fluvoxamine\textsuperscript{33-35}. However, fluoxetine did not appear to confer any obvious benefit over placebo in terms of binge eating behavior\textsuperscript{30}. Similarly, other RCTs studying fluvoxamine\textsuperscript{36}, escitalopram\textsuperscript{37}, and duloxetine\textsuperscript{38} did not report statistically significant or clinically significant outcomes compared to placebo.

Orlistat, an antiobesity medication, has been studied in patients with BED and obesity\textsuperscript{30}. One RCT found that Orlistat reduced weight, but not binge eating behavior, compared to placebo\textsuperscript{39}. Orlistat has also been studied as an adjunct to CBT, and was found to cause significant weight loss but not significant reductions in binge eating behavior compared to placebo\textsuperscript{40}. Orlistat has also failed to provide significant reductions in weight and binge eating behavior compared to placebo when use in adjunct to behavioral weight loss\textsuperscript{41}.

Acamprosate, a glutamate receptor modulator used for the treatment of alcohol dependence, and ALKS-33, an oral opioid modulator with potential for use in alcohol dependence\textsuperscript{42}, have been studied in the treatment of BED\textsuperscript{30}. Acamprosate has not been shown to reduce weekly binge eating episode frequency or weight compared to placebo\textsuperscript{43}. Similarly, ALKS-33 has not been shown to produce significant changes in binge eating frequency, binge eating remission, or weight compared to placebo\textsuperscript{42}.

As outlined in Chapter 1, LDX, a prodrug stimulant used to treat ADHD, was approved in 2015 as the first drug to treat moderate-to-severe BED\textsuperscript{30}. A 2015 RCT\textsuperscript{44} found that LDX significantly reduced the number of binge eating days per week among
260 adults with moderate-to-severe BED. There was also a significantly higher percentage of participants who achieved 4-week binge eating cessation among patients who took LDX compared to placebo. LDX was also associated with statistically significant weight loss, though it was assessed as a safety variable rather than as a primary or secondary efficacy measure\textsuperscript{44}. Despite its potential effectiveness at reducing weight and binge eating behavior, we opted not to select it as the intervention drug for this proposed study because of its classification as a schedule II controlled substance and its potential for abuse\textsuperscript{45}.

Zonisamide, lamotrigine, and topiramate are antiepileptic medications that have been studied in the treatment of BED associated with obesity\textsuperscript{30}. Zonisamide was found to significantly reduce binge eating frequency, body weight, and BMI, but was not well-tolerated\textsuperscript{46}. Lamotrigine proved to be well-tolerated, however it was not associated with statistically significant reductions in binge eating frequency or weight compared to placebo\textsuperscript{47}. Topiramate is arguably the most promising drug for use in BED associated with obesity, as it is the only medication that has provided significant weight loss in patients with BED\textsuperscript{30}. Three RCTs have assessed the use of topiramate in this population, which were discussed in Section 2.3.1. To summarize, two RCTs\textsuperscript{21,23} reported significantly faster reductions in binge eating frequency and weight compared to placebo, as well as greater achievement of binge eating remission among patients on topiramate compared to placebo. Another RCT\textsuperscript{24} found that a significantly greater percentage of patients taking topiramate as an adjunct to CBT achieved binge eating remission and a significantly higher mean percentage weight loss since baseline compared to those taking placebo as an adjunct to CBT. Topiramate’s success in producing significant reductions
in weight and binge eating pathology warrant its use in the intervention group in this proposed study.

2.4.2 Choice of Topiramate Dosage

Chapter 3 outlines the proposed study methods, including the starting, target, and maximum dosages of topiramate to be used. Topiramate will be started at 25 mg per day before bed. Claudino et al. and McElroy et al. utilized a starting dose of 25 mg per day of topiramate in their studies, both of which assessed binge eating and weight as outcome measures\textsuperscript{23, 24}. Dr. Fatima Cody Stanford, in her article titled “Controversial Issues: A practical guide to the use of weight loss medications after bariatric surgery for weight regain or inadequate weight loss”, also advises a starting dose 25 mg per day of topiramate\textsuperscript{48}. Subsequently, the dose will be titrated up to a target dose of 200 mg per day, then to a maximum of 300 mg per day in patients who tolerated the target dose well. This titration schedule is modeled after Claudino et al., who set the target dose of topiramate at 200 mg per day with a maximum daily dose of 300 mg\textsuperscript{24}. McElroy et al. chose a target dose of 300 mg per day and a maximum daily dose of 400 mg\textsuperscript{23}. Due to the 29% discontinuation rate and three occurrences of serious adverse events in the latter study, a lower target and maximum dose will be used for this proposed study.

2.4.3 Choice of Study Length

The proposed study will include a 16-week treatment period and a six-month follow-up period. A treatment period of 16 weeks is modeled after several studies that assessed the effects of topiramate on weight loss and eating pathologies which varied in length from 12 to 16 weeks\textsuperscript{14, 21, 23, 28}. This treatment length was sufficient to produce
significant differences in outcome measures. A follow-up period of six months will be
used to determine if the effects of topiramate on LOC eating and weight are enduring.

2.4.4 Choice of Control Group

The control group in this proposed study will receive placebo pills that are
identical to the topiramate pills administered to the treatment group. All subjects enrolled
in the study will be instructed at enrollment to follow-up with their bariatric surgery team
and abide by the recommendations put forth by the American Association of Clinical
Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric
Surgery49, which includes recommendations regarding diet and exercise.

2.4.5 Study Participants and Inclusion and Exclusion Criteria

Eligible participants in this study will be adults with both obesity and regular
LOC eating who have undergone successful completion of bariatric surgery at the Yale
Bariatric/Gastrointestinal Surgery Program approximately six to twelve months prior to
study enrollment. Obesity will be defined as a BMI ≥ 30 kg/m², which coincides with the
Centers for Disease Control and Prevention definition of obesity50.

The presence of LOC eating will be confirmed using the Eating Disorder
Examination Questionnaire (EDE-Q) (see Appendix C), a self-report tool used to assess
eating disorder attitudes and behaviors using a seven-point (0-6) rating scale for four
subscale categories including dietary restraint, eating concern, shape concern, and weight
concern51. Scores ≥4 are deemed clinically significant. A global score is calculated as the
average of the four subscale scores. The EDE-Q is a helpful instrument to assess relevant
eating disorder psychopathology for the proposed study because it accounts for both
objective bulimic episodes (OBE) and subjective binge eating episodes (SBE). OBE are
instances where there is a subjective sense of LOC while consuming abnormally large amounts of food, while SBE are defined as a subjective sense of LOC that accompanies consumption of small or normal amounts of food\(^1\). Inclusion of both OBE and SBE is instrumental in accurately capturing the eating disorder pathology that exists in the post-bariatric surgery population due to the resulting physical restraints on food consumption\(^2\).

Regular LOC eating will be defined as one or more OBE or SBE per week over the past 28 days, the same definition used in other studies to assess LOC eating\(^1, 2, 52, 53\).

Age between 18 and 65 years will be an inclusion criterion. McElroy and colleagues included the same age range in their 2007 placebo-controlled study that evaluated topiramate for the treatment of BED\(^23\). Other studies that evaluated the effect of topiramate on weight loss have limited participants to those between 18 and 60 years of age\(^21, 24\) or 18 and 75 years of age\(^17\), so an upper age limit of age 65 will be used as a middle-ground value. Additionally, adults over the age of 65 will not be eligible due to risk of cognitive impairment and risk of falling\(^54\). Several studies have reported cognitive impairment\(^17, 21, 23, 24, 55\) and somnolence\(^14, 17, 21, 23, 24\) as adverse effects of topiramate.

Exclusion criteria will remain as minimal as possible to increase generalizability of the proposed study results while still protecting participant safety. Exclusion criteria will include any exposure that may impact weight and eating disorder outcomes during the trial. Individuals will be excluded if they meet one or more of the following:

- Any current or past DSM-5\(^11\) defined psychiatric illness (including substance abuse) that may interfere with study protocol or adherence
- Clinically significant suicidality or previous suicide attempt
- Pregnancy or lactation
• Not using an accepted means of birth control for patients of childbearing potential
• History of metabolic acidosis, nephrolithiasis, renal impairment, seizures, glaucoma, cardiovascular events, arrhythmias, or cardiomyopathy
• Need for medication that might interact with topiramate or obscure its effects (stimulants, antidepressants, or carbonic anhydrase inhibitors)
• Contraindication/allergy to topiramate, or previous treatment with topiramate
• Clinically unstable medical illness
• Use of drugs or psychotherapies within the three months of random assignment that are known to affect weight or eating patterns
• Treatment with psychoactive medications (other than mood stabilizers) within two weeks of random assignment
• Exposure to an experimental drug within the past year
• Recent smoking cessation or intent to attempt cessation during the trial

Topiramate use in pregnancy can cause cleft lip or palate, and topiramate passes into breast milk so patients who are pregnant or lactating will not be eligible for the study. Hyperchloremic metabolic acidosis has been observed as an adverse effect of topiramate. Topiramate has been shown to disrupt acid-base balance by impairing normal reabsorption of HCO$_3^-$ in the kidney. Therefore, a history of metabolic acidosis or renal impairment are exclusion criteria. Nephrolithiasis and narrow-angle glaucoma are rare but serious side effects of topiramate, hence patients with a history of these conditions will not be eligible for this study. These criteria are adapted from those published in a 2007 study by Claudino et al. that evaluated the use of topiramate as an
adjunct to CBT in patients with BED, and those published in studies\textsuperscript{21, 23} by McElroy et al. that evaluated the use of topiramate for the treatment of BED associated with obesity.

\textbf{2.4.6 Primary and Secondary Outcome Measures}

The primary aim of this study is to investigate the effect of topiramate versus placebo on mean percentage weight change in adults with obesity and LOC eating after bariatric surgery. Percent weight change will be defined as change from baseline (enrollment) to the end of the 16-week intervention and change from baseline to a six month follow-up after treatment ends. Many studies that have evaluated the effect of topiramate in eating behavior associated with obesity have designated weight loss since baseline as the primary outcome. A 2016 RCT evaluating the effect of topiramate monotherapy, fluoxetine monotherapy, and combination therapy on eating behavior before bariatric surgery had a primary outcome of mean weight loss at six months after initiation of treatment\textsuperscript{25}. Zilberstein and colleagues assessed a primary outcome of mean increase in excess weight loss since baseline at three months in their 2004 case series that studied the use of topiramate in patients with binge eating and difficulty losing weight after AGB\textsuperscript{28}. Although a significant increase in mean excess weight loss was observed at three months, the proposed study will also assess mean percent weight loss since baseline at six months to investigate if the effects of topiramate on weight loss are more enduring. Stanford et al. studied relative change in weight as a primary outcome in their 2017 retrospective study that assessed the utility of weight loss medications after bariatric surgery in patients who either experienced weight regain or inadequate weight loss\textsuperscript{27}. Toth et al. had percent change in weight as the primary endpoint of their 2018 retrospective cohort study that evaluated weight loss medications, including topiramate,
in young adults after bariatric surgery\textsuperscript{26}. Finally, Bray and colleagues studied the use of topiramate for weight loss in obesity in a RCT published in 2003 that had a primary outcome of mean percent weight change from baseline at 24 weeks\textsuperscript{17}.

The secondary outcomes of this proposed study will include LOC eating frequency, which will be assessed using mean change in EDE-Q scores among treatment and control groups, and the proportion of patients who achieve abstinence from LOC eating, as defined by zero OBE or SBE during the past 28 days, at the post-intervention and the six-month follow-up assessment. White et al. published a 24-month follow-up study in 2010 that studied LOC eating in patients who had undergone bariatric surgery\textsuperscript{1}. They, too, used the EDE-Q to measure LOC eating pathology at 6 months, 12 months, and 24 months. Similarly, other studies have used the bariatric surgery version of the EDE (EDE-BS) to assess LOC eating as a primary or secondary outcome\textsuperscript{9, 52}. An additional secondary outcome will be the proportion of patients who achieve abstinence from LOC eating at the post-intervention and the six-month follow-up assessments. Abstinence from LOC eating or binge eating has been an endpoint in other studies\textsuperscript{24, 52}.

### 2.4.7 Monitoring of Side Effects and Adverse Events

The Systematic Assessment for Treatment Emergent Events - Specific Inquiry (SAFTEE-SI) will be used to monitor side effects and adverse events throughout this study. SAFTEE-SI is a detailed questionnaire that addresses 29 body systems, is rated on five levels of severity, and takes approximately 30-45 minutes to complete\textsuperscript{58}. The SAFTEE-SI provides clinicians with probing questions to elicit information from patients and covers all body systems. Importantly, the SAFTEE-SI provides information regarding onset, duration, and patients’ suspicions regarding the origin of adverse events.
and effects\textsuperscript{58}. The SAFTEE-SI will be administered at each office visit throughout the treatment period. Office visits will be scheduled approximately once every two weeks, as modeled after the study published by McElroy and colleagues\textsuperscript{21}. Important side effects to note in patients taking topiramate include paresthesias and changes in cognition\textsuperscript{48}. The SAFTEE-SI specifically elicits information regarding cognition and allows for assessment of study-specific event inquiries\textsuperscript{59}, such as paresthesias.

2.5 Identification of Possible Confounding Variables

This proposed study is a randomized, placebo-controlled trial, therefore allocation bias and confounding variables should be minimal. However, several studies have noted possible sources of confounding. A RCT published in 2021 by Grilo et al. assessed treatments for LOC eating following bariatric surgery and found that race was associated with post-treatment outcomes. Specifically, they found that a higher percentage of nonwhite participants achieved LOC eating abstinence compared to white participants (43.6\% vs 17.3\%), and a lower percentage of nonwhite participants achieved 5\% weight loss compared to white participants (11.3\% vs 26.7\%)\textsuperscript{52}. These findings are consistent with results reported in 2019 by Wood et al. in a study that showed that black patients achieved lower mean total body weight loss at one year post-surgery compared to white patients (32.0 kg vs 38.3 kg, \( p < 0.001 \))\textsuperscript{60}. Additionally, a retrospective review by Thomas and colleagues of patients who underwent RYGB at a multi-ethnic center between 2004 and 2015 found that African Americans and Hispanics experienced a significantly higher mean weight regain relative to mean weight loss (22.4 \( \pm 1.9\% \) and 17.2 \( \pm 2.6\% \), respectively) after surgery compared to Caucasians (13.5\%\( \pm 1.5\% \))\textsuperscript{61}. The same study also found that age and presurgical BMI significantly affect weight regain following surgery.
2.6 Conclusion

There are currently no studies that have evaluated the use of topiramate in adults with LOC eating and obesity after bariatric surgery. Because topiramate has proven to be effective at reducing weight and eating disorder psychopathology in other populations and contexts, its use in the proposed study population is warranted. Topiramate has also been shown to be tolerable and safe, and is approved by the FDA. The primary outcome of this proposed study will be mean percent weight change in adults with obesity and LOC eating after bariatric surgery. Percent weight change will be defined as change from baseline (enrollment) to the end of the 16-week intervention and change from baseline to a six month follow-up after treatment ends. Secondary outcomes will include LOC eating frequency and the proportion of patients who achieve abstinence from LOC eating at the post-intervention and the six-month follow-up assessments. Adverse events will be monitored throughout the study, especially cognitive changes and paresthesias. If topiramate proves to be superior to placebo with regard to study outcome measures, its use may be indicated in adults with LOC eating and obesity after bariatric surgery.
2.7 References


Chapter 3: Study Methods

3.1 Participant Recruitment and Evaluation

Patients will be recruited from the Yale Bariatric/Gastrointestinal Surgery Program. The Joint Data Analytics Team (JDAT), formed in October of 2014 to coordinate data reporting and analytics for researchers in a centralized location\(^1\), will send IRB-approved study recruitment letters through MyChart to individuals who have not opted out of research and who might be eligible based on the medical record. For instance, JDAT can identify adults 18-65 who had bariatric surgery at Yale during the past year. Simple random sampling will be used to sample Yale Bariatric/Gastrointestinal Surgery Program patients.

The inclusion criteria for participants in this study will be age between 18 and 65 years, obesity, confirmed LOC eating using EDE-Q, BMI $\geq 30$ kg/m\(^2\), and successful completion of bariatric surgery at the Yale Bariatric/Gastrointestinal Surgery Program approximately six to twelve months prior to study enrollment. Exclusion criteria for this study will include any current or past DSM-5\(^2\) defined psychiatric illness (including substance abuse) that may interfere with diagnostic assessment, treatment, or study adherence, clinically significant suicidality, previous suicide attempt, pregnancy, lactation, not using a medically accepted means of birth control for patients of childbearing potential, metabolic acidosis, renal impairment, contraindication or allergy to topiramate, use of drugs or psychotherapies within the previous three months that are known to affect weight or eating patterns, exposure to an experimental drug within the past year, previous treatment with topiramate, recent smoking cessation or intent to attempt cessation during the trial, a history of metabolic acidosis, nephrolithiasis,
seizures, glaucoma, cardiovascular events (myocardial infarction, stroke), arrhythmias, or cardiomyopathy, need for medication that might interact with topiramate or obscure its effects (stimulants, antidepressants, or carbonic anhydrase inhibitors), clinically unstable medical illness, or treatment with psychoactive medications (other than mood stabilizers) within two weeks of random assignment. Use of antidepressants will be permitted, as long as the patient has been stable on the drug for at least 3 months, in accordance with a previous study. Written consent will be obtained from all patients prior to enrollment (see Appendix F for a sample consent form).

3.2 Initial Assessment and Outcome Measures

Prior to enrollment, participants will be thoroughly screened by study technicians to determine satisfaction of study inclusion criteria and absence of exclusion criteria. Presence of obesity, as defined by a BMI of 30 kg/m$^2$ or greater, will be determined using self-reported height and weight measures. Presence of LOC eating will be ascertained using the EDE-Q, a self-reported questionnaire used to assess features of disordered eating. A urine pregnancy test will also be used to screen for pregnancy in participants with childbearing potential.

The primary outcome will be mean percent weight change in adults with obesity and LOC eating post-surgery. Percent weight change will be defined as change from baseline (enrollment) to the end of the 16-week intervention and change from baseline to six months follow-up after treatment ends. Secondary outcomes will include LOC eating frequency (assessed using EDE-Q) and the proportion of patients who achieve abstinence from LOC eating at the post-intervention and six-month follow-up assessments.
### 3.3 Study Design

This will be a 16-week, outpatient, double-blind, single-center, flexible-dose randomized control trial conducted at the Yale Bariatric/Gastrointestinal Surgery Program to compare the effect of treatment with a target daily dose of 200 mg per day of topiramate versus placebo on mean percentage weight change since baseline at the end of the 16-week intervention and change from baseline to six months follow-up after treatment ends. The study will be comprised of a 12-month recruitment period, followed by a two-week run-in period, a 16-week double-blind treatment period, and a 6-month follow-up period (see Appendix A). Patients who meet inclusion criteria after the two-week run-in period will be randomly assigned to receive either topiramate treatment or placebo. During the 2-week run-in period, patient height and weight will be measured and the EDE-Q will be completed and scored by trained clinicians to assess baseline LOC eating frequency. Subjects will be administered placebo during the run-in period.

During the treatment period patients will be seen by appointment every two weeks, beginning week one, to screen for adverse effects and titrate dosages. A urine pregnancy test will be performed for subjects with childbearing potential at the first appointment. Topiramate will be discontinued at the final appointment during the treatment period. Patients will be given contact information at the first visit to report any adverse effects, and will be instructed to seek emergency medical services prior to doing so in the case of severe symptoms.

Patients randomly assigned to receive topiramate will be initiated on a starting dosage of 25 mg once daily before bed for seven days. After day seven, the dosage will be increased by 25 mg/day per week for three weeks, reaching 100 mg/day by week four.
The dosage will then be increased to 150 mg per day by week five, to the target dosage of 200 mg per day by week six, and to a maximum dosage of 300 mg per day by week seven in patients who tolerated 200 mg per day. The titrated dose will be maintained until the end of the 16-week treatment period. Half of each daily dose will be administered in the morning and half at bedtime. Down-titration to the previously tolerated dosage will be permitted in patients who cannot tolerate their current dosage.

Following the 16-week treatment period, primary and secondary outcomes will be assessed. A six-month follow-up period will follow, during which patients will not be contacted. After six months they will be examined by designated clinicians to obtain data regarding primary and secondary outcomes, as well as adverse effects.

3.4 Randomization and Blind-Assessment Protocols

Computer-generated randomization will be used to randomize participants to receive either topiramate or placebo in a 1:1 ratio using permuted blocks, in accordance with other studies. Research clinicians and patients will be blind to treatment arm allocations. Identical appearing topiramate and placebo pills will be concealed in coded bottles to uphold double-blind protocol.

3.5 Assessment of Adherence

Medication adherence will be assessed using the number of returned pills at the end of the treatment period. This method of measuring medication adherence is adopted from McElroy et al, a placebo-controlled study that evaluated the effect of topiramate on binge eating frequency.
3.6 Monitoring of Adverse Events

Adverse effects and events will be elicited from patients at each appointment throughout the treatment period using the SAFTEE-SI. Prompt documentation will follow any patient report of adverse effects. Additionally, upon dropout or discontinuation of treatment, patients will be asked to share their reason for withdrawal, which will also be documented.

3.7 Data Collection

Patient weight will be measured at baseline (study enrollment), every two weeks during the treatment period, at completion of the treatment period, and after six months of follow-up using the same high-capacity digital scale. LOC eating frequency will be measured at baseline and after six months of follow-up using the EDE-Q.

3.8 Sample Size Calculation

The calculation of sample size was based on data from Stanford et al. and White et al. for the intervention group and control group, respectively.\textsuperscript{5,6} In a retrospective study evaluating the effect of 15 weight loss medications in patients experiencing inadequate weight loss or weight regain following bariatric surgery, Stanford and colleagues found that mean weight loss since baseline in patients receiving topiramate was 20.2 lb (SD = 24.5), while mean weight loss since baseline in patients not on topiramate was 13.99 lb (SD = 13.6). From these values, it was determined that patients on topiramate experienced a mean weight loss that was 44.4% higher than those not prescribed topiramate. The most significant limitation of this study is the lack of a control group for comparison. Patients who did not receive topiramate were prescribed one or more weight loss medications. It is likely that this will cause underestimation of the effect
size. Additionally, this study did not account for confounding factors such as how long patients received such medications, the presence of concurrent weight loss strategies such as diet and exercise, and comorbid conditions that could potentially lead to weight gain, such as obstructive sleep apnea. Variability was also quite high in this study, with a standard deviation of 24.5 lb.

In a prospective, 24-month follow-up study that evaluated the clinical significance of LOC eating in 361 post-bariatric surgery patients, White et al. found that mean weight loss since baseline at 12 months post-surgery among patients with LOC eating was approximately 34.4%, a value extrapolated from Figure 2 (see Appendix D) due to lack of provided numerical values. It should be noted that this study is limited by the fact that 86% of participants were female and mean BMI was 51.1 kg/m² (SD = 8.3), which could decrease external validity. Moreover, patients in this study underwent gastric bypass, so results may not generalize to those who undergo alternative weight loss procedures.

Based on the previously mentioned data, an absolute effect size was estimated to be 10% between intervention and control groups. This was calculated as the difference between mean percentage weight loss since baseline (44.4% - 34.4% = 10%). Sample size was calculated using Power and Precision software (Englewood, New Jersey) as a two-tailed test, powered at 80% with an alpha of 0.05. Based on these assumptions, a sample size of 192 was determined (see Appendix E).

Since the study conducted by Stanford et al. was a retrospective cohort study, we turn our attention to a study conducted in 2003 by McElroy and colleagues to estimate dropout rate⁷. The aforementioned study was a 14-week, randomized, placebo-controlled study that evaluated the effect of topiramate on binge-eating outcomes and weight in
adults with BED and obesity. The dropout rate for both the intervention and control group was 30%. Assuming a 30% dropout rate for this study, the final sample size of this study is 250 participants.

3.9 Statistical Methods

The statistical analyses implemented will be akin to those utilized in past pharmacotherapy BED and LOC eating trials. To assess baseline characteristics between groups, the student's t-test will be used for continuous variables and Chi-square test for dichotomous variables. ITT analysis will be followed to compare topiramate and placebo outcomes at post-treatment and at six months follow-up using mixed-models analysis so that all data is used for each participant and each individual can have varying numbers of observations.

The sole dependent variable of this study is use of topiramate at a target daily dose of 200 mg. The primary outcome of this study is mean percentage weight change from baseline (enrollment) to the end of the 16-week intervention and change from baseline to a six month follow-up after treatment ends. This outcome measure is a continuous variable and will therefore be analyzed using the student's t-test. Secondary outcomes include LOC eating frequency (assessed using mean percentage change in EDE-Q scores since baseline) and achievement of LOC eating remission, as defined by zero episodes of LOC eating in the past 28 days, at the end of treatment and at six months following completion of the intervention period. The mean percentage change in EDE-Q scores to determine LOC eating frequency is a continuous variable and will be analyzed using the student’s t-test. Achievement of LOC eating remission is a dichotomous
variable and will therefore be analyzed using the Chi-square test. All statistical analyses will be two-sided with a significance level of 0.05.

3.10 Timeline and Resources

This proposed clinical trial will require two years to complete. Approximately one year will be dedicated to recruitment and screening, followed by a two-week run-in period during the last two weeks of recruitment, followed by a 16-week treatment period, followed by six months of follow-up. This timeline allows for six unscheduled weeks, should additional time be needed for any portion of the study.

Those recruited during the first 12 months will enter a two-week run-in period in which additional screening will take place. Final assessment of patients will take place to determine if inclusion and exclusion criteria are satisfied. Subjects will be administered placebo during this time. Eligible patients will then begin the 16-week treatment period and receive either placebo pills or the starting 25 mg dose of topiramate, as well as education on healthy lifestyle practices.

Throughout the treatment period, participants will return for office visits every two weeks, during which time they will be weighed, administered the SAFTEE-SI to inquire about adverse effects and events, and counseled further on healthy lifestyle improvements. Drug dose titrations will occur during these visits. A urine pregnancy test will be performed during the first visit if appropriate. A six month follow-up appointment will be scheduled at the last appointment, and study drugs will be discontinued.

The follow-up period will begin immediately following the treatment period and will last six months, during which time patients will not be contacted, except for a reminder telephone call one week before their scheduled follow-up appointments. The
final visit will include measurement of the patient's weight and completion of the EDE-Q to assess LOC eating frequency, as well as completion of the SAFTEE-SI. A compensation of $200 will be distributed at the post-treatment assessment, and $250 will be distributed at the six-month follow-up assessment. Compensation will not be distributed if subjects miss more than one office visit throughout the study. Parking will be validated at each office visit.

The Yale Center for Clinical Investigation (YCCI) offers a facility to accommodate outpatient studies, the Church Street Research Unit (CSRU). CSRU is equipped with six exam rooms and staffed with a full-time nurse, nurse practitioners, and bilingual medical assistant. This outpatient facility can provide the necessary space to conduct office visits and is conveniently located in downtown New Haven, CT, close to public transportation.
3.11 References

Chapter 4: Conclusion

The presence of LOC eating after bariatric surgery is associated with less weight loss and decreased mental health-related quality of life\textsuperscript{1,2}. Individuals with LOC eating have been shown to experience similar levels of eating disorder and depressive symptoms compared to those with BED, despite differences in quantities of food consumed\textsuperscript{3}. However, no study has yet evaluated the use of pharmacotherapy in patients with obesity and LOC eating following bariatric surgery. Topiramate is an FDA approved anticonvulsant medication that has been shown to improve weight and binge eating outcomes among those with BED\textsuperscript{4-6}. Thus, a study evaluating the use of topiramate for weight loss and eating disorder symptomatology in LOC eating is justified. The objective of this proposed study is to identify whether topiramate improves weight loss and eating disorder psychopathology in patients with obesity and LOC eating after bariatric surgery compared to placebo. The results of this study will enhance our understanding of topiramate for weight loss in patients with LOC eating and obesity after bariatric surgery. If topiramate proves to be effective at increasing weight loss in adults with obesity after bariatric surgery, this trial may guide clinicians as they work to treat these patients.

4.1 Advantages

This proposed study is a randomized, placebo-controlled trial, therefore confounding variables and allocation bias should be minimal. Its double-blind nature is advantageous because it prevents purposeful manipulation of study results and information bias. Inclusion of adults between the ages of 18 and 65 increases external validity by incorporating a wide range of ages. Finally, a conservative dropout rate of 30\% was utilized, resulting in a final sample size calculation of 250 participants. Other
RCTs that have studied the use of topiramate in BED had much smaller sample sizes, numbered at less than 100 participants\textsuperscript{4, 5}.

4.2 Disadvantages

This study poses several limitations that require consideration. First, the intervention period is 16 weeks, which is relatively brief. Whether or not results would generalize to longer intervention periods is unknown. However, other studies that evaluated topiramate for BED utilized similar intervention periods\textsuperscript{5, 7}, so this is acceptable. A second limitation is exclusion of patients with clinically significant comorbid psychiatric conditions. Results may not generalize to this population, but we feel it is important exclude any comorbid conditions that may have an effect on weight and weight loss. This exclusion criterion was included in several other studies that looked at LOC eating after bariatric surgery\textsuperscript{3} and the use of topiramate in patients with BED\textsuperscript{4, 5, 7}. Finally, this study was limited to participants who had undergone bariatric surgery at the Yale Bariatric/Gastrointestinal Surgery Program, therefore results may not generalize to other populations or to individuals who had bariatric surgery at other centers or regions.

4.3 Clinical and Public Health Significance

Bariatric surgery is the most effective treatment for severe obesity and is associated with long-term reduction in overall mortality, diabetes, myocardial infarction, stroke, and cancer\textsuperscript{8}. The American Society for Metabolic and Bariatric Surgery reports that 252,000 people underwent bariatric surgery in 2018 in the United States alone. An estimated 6.4\% of patients meet BED criteria post-surgically\textsuperscript{9}. The physical restraints on food consumption imposed by bariatric surgery may preclude a BED diagnosis in those who would
otherwise meet all criteria for BED, except for consumption of large quantities of food. When this criterion is removed, an estimated 22.5% of patients meet criteria for BED\textsuperscript{1}. These modified criteria are referred to as LOC eating, which is associated with poorer weight-related and mental health outcomes up to seven years postoperatively\textsuperscript{1, 2, 10}. As many as 35% of patients do not reach their goal weight loss after surgery\textsuperscript{11}, resulting in suboptimal cardiovascular health benefits\textsuperscript{8}. This is of particular importance considering heart disease was the most common cause of death in the U.S. in 2020, surpassing both cancer and COVID-19\textsuperscript{12}. Beyond public health considerations, heart disease carries great economic burden, costing the US an estimated $363 billion each year\textsuperscript{13}.

Should topiramate prove to be an effective pharmacologic weight-loss agent in adults with LOC eating and obesity after bariatric surgery, it may have indications in clinical practice with potential to ameliorate both the physical and mental toll among patients struggling with LOC eating and obesity after surgery, as well as the economic burden of cardiovascular disease in the U.S.
4.4 References

Appendices

Appendix A: Timeline of proposed study, including recruitment, run-in, intervention, and follow-up periods.

![Study Course Timeline](image)
Appendix B: Medical subject headings used in literature search.

The following medical subject headings (MeSH) were used: *topiramate*, *Topamax*, *gastric bypass*, *bariatric surgery*, *sleeve gastrectomy*, *obesity*, *obese*, *overweight*, *body mass index*, *loss of control eating*, *loss-of-control eating*, *loss of control*, *loss-of-control*, *binge eating*, *binge-eating*, *binge eating disorder*, *binge-eating disorder*. 
Appendix C: Eating Disorder Examination Questionnaire (EDE-Q)


**EATING QUESTIONNAIRE**

Instructions: The following questions are concerned with the past four weeks (28 days) only. Please read each question carefully. Please answer all of the questions. Please only choose one answer for each question. Thank you.

Questions 1 to 12: Please circle the appropriate number on the right. Remember that the questions only refer to the past four weeks (28 days) only.

<table>
<thead>
<tr>
<th>On how many of the past 28 days ......</th>
<th>No days</th>
<th>1-5 days</th>
<th>6-12 days</th>
<th>13-15 days</th>
<th>16-22 days</th>
<th>23-27 days</th>
<th>Every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight (whether or not you have succeeded)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2 Have you gone for long periods of time (6 waking hours or more) without eating anything at all in order to influence your shape or weight?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>3 Have you tried to exclude from your diet any foods that you like in order to influence your shape or weight (whether or not you have succeeded)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>4 Have you tried to follow definite rules regarding your eating (for example, a calorie limit) in order to influence your shape or weight (whether or not you have succeeded)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>5 Have you had a definite desire to have an empty stomach with the aim of influencing your shape or weight?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6 Have you had a definite desire to have a totally flat stomach?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7 Has thinking about food, eating or calories made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>8 Has thinking about shape or weight made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9 Have you had a definite fear of losing control over eating?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>10 Have you had a definite fear that you might gain weight?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>11 Have you felt fat?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>12 Have you had a strong desire to lose weight?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
Questions 13-18: Please fill in the appropriate number in the boxes on the right. Remember that the questions only refer to the past four weeks (28 days).

Over the past four weeks (28 days)........

13 Over the past 28 days, how many times have you eaten what other people would regard as an unusually large amount of food (given the circumstances)? ..........................

14 ....On how many of those times did you have a sense of having lost control over your eating (at the time that you were eating)? ..........................

15 Over the past 28 days, on how many DAYS have such episodes of overeating occurred (i.e. you have eaten an unusually large amount of food and have had a sense of loss of control at the time)? ..........................

16 Over the past 28 days, how many times have you made yourself sick (vomit) as a means of controlling your shape or weight? ..........................

17 Over the past 28 days, how many times have you taken laxatives as a means of controlling your shape or weight? ..........................

18 Over the past 28 days, how many times have you exercised in a "driven" or "compulsive" way as a means of controlling your weight, shape or amount of fat or to burn off calories? ..........................

Questions 19-21: Please circle the appropriate number. Please note that for these questions the term "binge eating" means eating what others would regard as an unusually large amount of food for the circumstances, accompanied by a sense of having lost control over eating.

<table>
<thead>
<tr>
<th>Question</th>
<th>Description</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Over the past 28 days, on how many days have you eaten in secret (i.e. furtively)? Do not count episodes of binge eating</td>
<td>No days, 1-5 days, 6-12 days, 13-15 days, 16-22 days, 23-27 days, Every day</td>
</tr>
<tr>
<td>20</td>
<td>On what proportion of the times that you have eaten have you felt guilty (felt that you’ve done wrong) because of its effect on your shape or weight? Do not count episodes of binge eating</td>
<td>None of the times, A few of the times, Less than half, Half of the times, More than half, Most of the time, Every time</td>
</tr>
<tr>
<td>21</td>
<td>Over the past 28 days, how concerned have you been about other people seeing you eat? Do not count episodes of binge eating</td>
<td>Not at all, Slightly, Moderately, Markedly</td>
</tr>
</tbody>
</table>
Questions 22-28: Please circle the appropriate number on the right. Remember that the questions only refer to the past four weeks (28 days)

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Markedly</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 Has your <strong>weight</strong> influenced how you think about (judge) yourself as a person?</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 Has your <strong>shape</strong> influenced how you think about (judge) yourself as a person?</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 How much would it have upset you if you had been asked to weigh yourself once a week (no more, or less, often) for the next four weeks?</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 How dissatisfied have you been with your <strong>weight</strong>?</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 How dissatisfied have you been with your <strong>shape</strong>?</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 How uncomfortable have you felt seeing your body (for example, seeing your shape in the mirror, in a shop window reflection, while undressing or taking a bath or shower)?</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 How uncomfortable have you felt about others seeing your shape or figure (for example, in communal changing rooms, when swimming, or wearing tight clothes)?</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What is your weight at present? (Please give your best estimate). ..........................

What is your height? (Please give your best estimate). ..........................

If female: Over the past three-to-four months have you missed any menstrual periods? ...............  

    If so, how many? ..........................

    Have you been taking the "pill"? ..........................

THANK YOU
Appendix D: Figure 2 from White et al. (2010) for use in calculation of sample size.

Figure 2.
Mean weight loss (% loss from baseline) as a function of point-specific LOC
Appendix E: Sample size calculation.

Sample size was calculated using Power and Precision software (Englewood, New Jersey) as a two-tailed test, powered at 80% with an alpha of 0.05.
Appendix F: Sample consent form.

Created using the following template: “Compound authorization and consent for participation in a research project. 200 fr. 4 ( 2016-2).”

Compound Authorization and Consent for Participation in A Research Project
Yale University
Yale University School of Medicine, Physician Associate Program
Yale-New Haven Hospital:

Study Title: Topiramate for weight loss in adults with obesity and loss of control eating after bariatric surgery.
Principal Investigator: Valentina Ivezaj, PhD, Yale School of Medicine
Co-Principal Investigator: Amanda Faxon, PA-SII

Invitation to Participate and Description of Project

You are invited to take part in a research study designed to look at the role of topiramate, an anti-seizure medication, in the treatment of loss of control eating in adults with obesity after bariatric surgery. You have been asked to take part because you are between the ages of 18 and 65 and have recently undergone bariatric surgery at the Yale Bariatric/Gastrointestinal Surgery Center of Excellence. Approximately 250 participants will take part in this study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to take part in this study, you will be asked to participate in a 16-week treatment period of either topiramate or placebo (a pill with no therapeutic value), as well as a 6-month follow-up period. A computer will be used to randomly select participants to receive either topiramate or placebo. You will not know to which you are assigned. You will be asked to attend biweekly in-person office visits during the treatment period, beginning the first week. Each visit will last approximately 1 hour. A 6-month follow-up appointment will be scheduled at the last visit of the treatment period. Weight measurements will be taken at each visit and drug doses will be titrated. You will also be asked about drug side effects at each appointment. A urine pregnancy test will be
administered at the first appointment if appropriate. You will receive education on healthy lifestyle practices at the first appointment. After completion of the 16-week treatment period, you will not be contacted during the 6-month follow-up period, with the exception of a telephone call to remind you of the follow-up visit one week prior to when it is scheduled. At the final visit, your weight will be measured and you will be asked about adverse effects. You will also be administered a survey about eating behaviors.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

**Risks and Inconveniences**

There are some risks to participating in this study. You may be at risk for increased eye pressure, changes in vision, decreased sweating, increased body temperature, metabolic acidosis (changes in your body’s acid concentration), increased thoughts of suicide, confusion, difficulty concentrating, difficulty remembering, depressed mood, fatigue, and kidney stones.

Women who are pregnant will not be eligible for this study because topiramate may cause cleft lip and/or palate in fetuses. Additionally, breastfeeding women will not be eligible because topiramate passes into breast milk and it is unknown whether or not it is harmful to children.

Participation in this study may involve risks that are currently not known.

There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers, except those with fewer than 15 employees, to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

**Benefits**

You may lose weight during this study and experience less symptoms related to disordered eating.

**Economic Considerations**

You will be compensated for participating in this study. You will receive $200 at the post-intervention assessment and $250 at the six month follow-up assessment. You will
not be compensated if you miss more than one office visit during the study. Parking will be validated at each office visit.

According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income.

You will receive either topiramate or placebo at no cost to you.

**Treatment Alternatives**

Other treatment options are available to you as an alternative to taking part in this study. You can consult your doctor for treatment, take part in other clinical trials, or try lifestyle modifications. You may choose not to seek treatment if you do not wish to do so.

**Confidentiality and Privacy**

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name, date of birth, and address. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. Research materials will be stored in locked cabinets and data stored on a computer will be password-protected. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for, 1 year after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely. The information about your health that will be collected in this study includes:

- Research study records
- Medical/laboratory records of only those services provided in this study
- Records about phone calls made as part of this research
- Records about your study visits regarding reportable infectious diseases, physical exams, surveys and questionnaires, the diagnosis and treatment of a mental health condition, use of illegal drugs or the study of illegal behavior
- Records about any study drug you received
Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about the new drug product [or device] involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those providers who are participants in the Electronic Medical Record (EMR) system.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator, co-investigators, and research team members
- The study sponsor or manufacturer of study drug/device
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of this study

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.
You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. However, by deciding to take part in a single or double blinded treatment study and sign this permission form, you will not be allowed to look at or copy your study related information until after the research is completed.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

**In Case of Injury**

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

**Voluntary Participation and Withdrawal**

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

**Withdrawing from the Study**

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

The researchers may withdraw you from participating in the research if necessary. Conditions under which you might be withdrawn from the research include development of serious side effects or non-compliance with study protocol.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital. We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment.
Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff at any time. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form. By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject:________________________

Signature:___________________________________Date:_______

Signature of Principal Investigator

or

Signature of Person Obtaining Consent

Date

Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203/432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator at (xxx) xxx-xxxx. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.
Bibliography


