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SSAT QUICK SHOT PRESENTATION

Patterns of Weight Loss Medication Utilization and Outcomes Following Bariatric Surgery

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Abstract

Background Bariatric surgery is the most effective treatment for obesity; however, some patients experience significant weight regain. Weight loss medications (WLM) are being increasingly used in surgery patients with limited evidence. We examine weight loss outcomes in patients using WLM after bariatric surgery.

Methods In a retrospective study, 197 bariatric surgery patients who started WLM between 2016 and 2019 at a single center were analyzed. Patients were categorized into 3 groups based on outcomes of the initial surgery: (1) Weight regainers (WR) = achieved goal weight loss after surgery (15% total body weight loss (TBWL) for sleeve gastrectomy (SG) and 25% TBWL for Roux-en-Y gastric bypass (RYGB)) with subsequent regain of > 20% of weight lost; (2) Adequate weight loss (AWL) = achieved goal weight loss without > 20% weight regain; (3) Non-responders (NR) = never achieved goal weight loss. Weight loss and medication use patterns were analyzed.

Results Among the three categories, there was no significant difference in duration of medical therapy or %TBWL with medications. RYGB patients lost more weight than SG patients using WLM ($p = 0.03$). Of the medications used, patients treated with phentermine + topiramate had the highest likelihood of achieving 5%, 10%, and 15% weight loss. Compared to other 2 groups, AWL group initiated WLM earlier and experienced more weight loss when compared to their pre-operative weight or post-operative nadir.

Conclusions RYGB patients respond better to WLM than SG patients. Those who had started WLM before regaining weight (AWL) experienced greater overall weight loss, suggesting that proactive medical therapy at the time of weight plateau can help with greater total weight loss. Phentermine + topiramate is the most effective WLM in post-bariatric surgery patients.

Keywords Bariatric surgery, Weight recidivism, Weight loss medication

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Introduction

Obesity and its related metabolic disorders are a well-recognized national and international epidemic. By the year 2030, it is estimated that 1 in 4 Americans will suffer from severe obesity with a BMI > 35, and that the prevalence of obesity will be greater than 50% in 29 states.[1] Bariatric surgery has been shown to be the most effective and durable treatment of weight loss, as well as associated metabolic syndrome co-morbidities compared to medical therapy or lifestyle changes.[2–4] Some weight regain after patients reach their nadir weight is common and an expected part of the post-operative process. Weight nadir has been found to be around 2 years with weight regain occurring after this time.[5–7] Some patients, however, experience pathological weight regain following surgery which can have deleterious effects on comorbidity management, mental health scores, and quality of life.[8, 9]

Studies have shown that 15–35% of patients regain > 15% of the weight lost after surgery[10–12] with an average weight regain for RYGB patients of the weight lost after surgery between 23.4 and 30%.[6, 13] Given these outcomes, there has been significant interest in developing strategies to minimize weight regain after surgery.

Weight recidivism after bariatric surgery is multifactorial, with behavioral factors (dietary non-compliance, physical inactivity), anatomic changes (enlarged pouches, gastrogastric fistulae), psychiatric influences, and metabolic causes all playing a role.[13–16] Treatment approaches for weight regain or inadequate weight loss after surgery include diet and lifestyle modifications, and use of weight loss medications, as well as revisional endoscopic and surgical interventions. Pharmacotherapy for weight loss has been used as a relatively safe, non-surgical option for decades, with phentermine, one of the most commonly prescribed WLM, first approved for this indication in 1959. The observed weight loss with approved medication beyond diet and lifestyle changes ranges from 3 to 9% at 1 year,[17, 18] but outcomes in the post-bariatric surgery cohort is less well studied.

In order to develop better interventions for management of poor weight loss response to bariatric surgery, it is important to acknowledge that this group represents a heterogenous patient cohort and helpful to carefully categorize patients based on their post-surgery weight loss profiles to non-responders, weight regainers, and those who achieve expected weight loss but remain unsatisfied. As there are multiple etiologies for weight regain, there may be different treatment options which could have variable outcomes in each such patient population.

There is currently limited evidence guiding the practice of WLM in post-bariatric surgery patients. Most studies reviewing this practice are small retrospective reviews.[19–25] The two largest series demonstrate between 37 and 56% of patients achieving at least 5% weight loss on medications following surgery.[23, 24] In this study, we perform a retrospective analysis of weight loss outcomes in bariatric surgery patients initiated on WLM.

Materials and Methods

Inclusion/Exclusion Criteria

After obtaining approval from the Brigham and Women's Hospital Institutional Review Board, a retrospective chart review was performed in a two-practitioner weight management clinic. The majority of the patients were seen by a single practitioner. Eligibility criteria included adult patients > 18 years of age, prior bariatric surgery (primary sleeve gastrectomy (SG), primary Roux-en-Y gastric bypass (RYGB), conversion procedure to SG, or conversion procedure to RYGB), initiation of WLM post-operatively, and follow-up appointment at least 2 months after initiation of WLM. Exclusion criteria were patients lost to follow-up after initiation of medications, inconsistent compliance with medication as determined by clinic notes, previous history of WLM after bariatric surgery prior to initiating care with our clinic, endoscopic revisions after bariatric surgery, bariatric surgeries not included above, or limb distalization of RYGB. Surgeries could have been performed at another institution as long as pre-operative and post-operative nadir weight data were available. Given our status as a tertiary referral center and higher percent of revision surgeries, conversions to either SG or RYGB were included to improve the power of our analysis. In these cases, pre-operative weight was established to be prior to the index surgery, and nadir weight was following the revision surgery. The time from surgery to medication initiation referenced the revision surgery. This was done to best reflect the baseline weight status of the patient prior to bariatric surgery, as well as the physiologic response to the patient's anatomic configuration during their medical therapy. Patients were evaluated in our weight management clinic where decisions were made regarding which medication to initiate, at what dose, and when to change medications at follow-up appointments. These decisions were made based off of medical comorbidities, anticipated and observed side effects, observed weight loss, drug interactions, cost and insurance coverage, and patient preference for injectable vs. oral medications. The following medication regimens were used: phentermine, topiramate, bupropion, metformin, phentermine + topiramate, bupropion + naloxone, bupropion + topiramate, topiramate + metformin, and GLP-1 agonists including liraglutide and dulaglutide.

Data Collection

Using the electronic health record (Epic), 450 patients were identified as having been seen in our weight management practice for further weight loss after bariatric surgery between April 2016 and November 2019. One hundred and ninety-seven of these patients met inclusion criteria. Demographic information was obtained including age, gender, history of hypertension and/or diabetes, and BMI. Data regarding surgical intervention was obtained including date of initial bariatric surgery, pre-operative weight and BMI, post-operative nadir weight, and time from surgery to medication initiation. Exact surgery date was unavailable for 4.5% of patients whose data was excluded in calculating the time from surgery to medication initiation, but included for all weight response analysis. Data regarding medication utilization was also obtained including pre-medication weight, type of medication initiated, whether medications were changed during course of treatment, weight trends after medication initiation, time from medication initiation to weight nadir, and total duration of medical therapy. From this, the nadir weight and time to nadir

after medication initiation were determined. Due to the retrospective nature of this study and inclusion of patients in the weight management clinic who did not have their index operation at our institution, it was not possible to determine the indication for revision surgery such as conversion from SG to RYGB. Because of the multifactorial causes for medication termination or changes, the exact reason for every change could not be determined from the medical record. For example, while some were documented provider driven decisions due to side effects, other patient-specific reasons such as simple non-compliance, prohibitive cost, or being lost to follow-up made it difficult to track these data in a clinically meaningful way. As such, a binary method of whether or not patients had any medication changes was used to approximate this variable.

Data Analysis

Weight loss goals following surgery were determined to be > 15% total body weight loss (TBWL) for SG and > 25% TBWL for RYGB from the time of surgery to weight loss nadir after surgery. Because the time period over which maximum weight loss occurs following bariatric surgery is consistently between 12 and 24 months, the best way to determine weight loss goals is to measure the difference of pre-surgery and post-operative nadir weight as a percent of total body weight without a pre-specified time cutoff, as has become standard practice**.** Patients were organized into three categories based on their pattern of post-operative weight loss using these criteria: (1) Weight regainers (WR): achieved goal weight loss after surgery with subsequent regain of > 20% of the weight lost at post-operative nadir; (2) Adequate weight loss (AWL): achieved the goal weight loss and did not regain > 20% of their weight lost but were not satisfied with the outcome and desired additional weight loss medication; and (3) Non-responders (NR): did not achieve goal weight loss. All patients were then analyzed solely in terms of their final surgical anatomy (SG vs. RYGB), including a subgroup analysis of primary procedures only, as well as identifying patients with and without medication changes during their course of treatment. In those without medication changes, a subgroup analysis was performed comparing the different medication used.

For statistical analysis, unpaired 2 tailed student's *t* test was used to compare averages of continuous variables and chi-squared analysis was performed for categorical variables. Analysis of variance was used to compare means of greater than two groups of continuous variables. An unadjusted logistic regression analysis was performed for patients achieving weight loss goals of 5%, 10%, and 15% after starting medication. All hypothesis testing was performed at 5% level of significance. A p value less than 0.05 was used for assessing statistical significance. All confidence interval reporting was at a 95% level. Statistical analysis was performed using R software, version 6.3.1.

Results

Weight Loss Category

Of the 197 patients that met inclusion criteria, 90.3% were female with an average age at the time of index surgery of 43.2 years, and pre-operative BMI of 46. Baseline demographics were similar between the three categories of patients (Table 1). Weight loss outcomes and medication use patterns are shown in in Table 2. Revision surgeries made up 19% of WR, 13.9% of AWL, and 31.6% of NR patients, which was significantly different between NR and the other two groups. There was a higher percent of SG patients (86.1%) in the AWL category compared to WR (58.5%, $p < 0.01$) and NR (57.9%, $p = 0.02$). The average %TBWL from the time of medication initiation to weight nadir for all patients was 7.5% (± 5.9). There was no difference in %TBWL on WLM between the three categories. Time from surgery to medication initiation was significantly shorter in the AWL group compared to both WR and NR groups ($p < 0.01$ and $p = 0.03$ respectively). There was no difference between groups in the duration of therapy or the time that it took to achieve nadir weight on WLM. The AWL experienced a statistically significantly greater %TBWL from post-operative nadir to nadir on medication compared to WR patients (− 16.5 vs. 4.0, $p < 0.01$) and NR patients (− 2.3 vs. 4.0, $p = 0.04$). The AWL group was the only one to experience a net loss in weight from the time of post-operative nadir to nadir on WLM. Despite this, 20% of patients in the WR category and 53% of NR patients still achieved weight loss on WLM to within 2 kg of their post-operative nadir weight (compared to 69% of AWL patients). The AWL group also had statistically significant greater weight loss from pre-operative weight to nadir on medications than both the WR and NR groups ($p < 0.01$) There was no significant association between weight loss category and the odds of achieving 5%, 10%, and 15% weight loss on WLM (Table 4).

Type of Surgery

Table 3 shows weight loss outcomes and medication use patterns for all patients stratified by surgery type and medication changes. SG was performed in 125 (63.5%) patients and RYGB in 72 (36.5%). This included primary and revision cases with end anatomy as described. The BMI at the time of medication initiation for RYGB patients was higher than SG (39.2 vs. 37.3 kg/m^2, $p = 0.02$). The %TBWL on medication was significantly higher for patients with RYGB anatomy than SG (9.12% vs. 6.46%, $p < 0.01$). There was a longer time

Table 1 Patient demographics. *WR* weight regain, *AWL* adequate weight loss, *NR* non-responders. Continuous variables listed as mean (± standard deviation). Categorical variables listed as number (%)

	All patients $n = 197$	WR	AWL	NR	*p* values		
		$n = 142$ (72.4)	$n = 36$ (18.1)	$n = 19$ (9.5)	WR vs. AWL	WR vs. NR	AWL vs. NR
Age at surgery	43.2 (± 11.3)	42 (± 10.7)	44.3 (± 12.8)	48.4 (± 11.1)	0.27	*0.02*	0.25
Female	178 (90.3%)	131 (92.3%)	32 (86.5%)	16 (84.2%)	0.60	0.45	0.88
Pre-operative weight (kg)	122.1 (± 26.0)	121.1 (± 23.8)	128.7 (± 35.5)	117.7 (± 20.9)	0.15	0.57	0.24
Pre-operative BMI (kg/m^2)	46.0 (± 8.0)	45.6 (± 7.4)	48.4 (± 10.4)	44.3 (± 6.2)	0.07	0.45	0.12
History of hypertension	79 (40.1%)	59 (41.5%)	14 (38.9%)	6 (27.8%)	0.73	*0.05*	0.14
History of diabetes mellitus	38 (19.3%)	27 (19%)	4 (11%)	7 (38.9%)	0.12	*< 0.01*	*< 0.01*

Significant *p* values = < 0.05 italicized

from surgery to medication initiation in the RYGB group ($p < 0.01$). RYGB patients achieved their nadir weight on WLM later than SG patients and had a longer duration of therapy on WLM. A subgroup analysis was performed in primary only patients by surgery type. Patients who underwent primary RYGB also had significantly greater weight loss compared to primary SG (8.61 vs. 6.34 %TBWL, $p = 0.01$). SG patients were less likely to achieve 5%, 10%, and 15% weight loss on WLM compared to RYGB (odd ratio (OR) = 0.702, CI 0.38–1.28; OR = 0.647, CI 0.35–1.22; and OR = 0.297, CI 0.11–0.77 respectively), noting that only the 15% weight loss distinction achieving statistical significance ($p = 0.015$) (Table 4).

Medication Changes

When patients changed medications, it was often done more than once and for a variable period of time. In order to simplify this analysis, patients were identified to either have changed medication at some point during their treatment ($n = 95$, 48%) or remained on the same medication throughout their treatment ($n = 102$, 52%). Among the patients who changed medication, the following number of patients initiated each medication: phentermine ($n = 38$), phentermine + topiramate ($n = 20$), GLP-1 agonists ($n = 20$), and 17 on "other" medications [lorcaserin ($n = 3$), metformin + phentermine ($n = 1$), metformin ($n = 2$), metformin + topiramate ($n = 3$), topiramate ($n = 4$), liraglutide + topiramate ($n = 2$), naltrexone + bupropion ($n = 2$)]. The following number of patients did not change medication: phentermine + topiramate ($n = 43$), phentermine ($n = 21$), GLP-1 agonist ($n = 29$), and 10 designated as "other" [topiramate ($n = 2$), metformin ($n = 2$), bupropion + naloxone ($n = 2$), bupropion + topiramate ($n = 1$), topiramate + metformin ($n = 2$), bupropion ($n = 1$)].

There was no difference in the %TBWL on WLM between patients having medication changes and no medication changes. In patients who changed medication, there was a longer time to nadir weight on medications and duration of treatment ($p < 0.01$) (Table 3). There was no difference in the odds of achieving 5%, 10%, or 15% weight loss whether or not patients changed medications during their treatment period on WLM. In the group of patients that did not change medication, those on phentermine + topiramate had the highest odds of achieving 5%, 10%, and 15% weight loss (OR 4.38, CI 1.81–11.57; OR 3.53, CI 1.47–8.81; and OR 2.14, CI 0.64–7.72 respectively). The group that was least likely to achieve these weight loss goals was the phentermine monotherapy group with an OR of 0.27 (CI 0.096–0.72) to achieve 5% weight loss, 0.09 (CI 0.005–0.47) for 10% weight loss, and no patients achieving 15% weight loss. The average %TBWL on each of the medication subtypes was 9.8 (± 5.6) for phentermine + topiramate, 4.5 (± 3.7) for phentermine monotherapy, 7.7 (± 6.0) for GLP-1 agonists, and 6.2 (± 4.8) for "other." An analysis of variance demonstrated a statistically significant difference in these means ($p < 0.01$) with individual group comparisons using students *t* test showing a statistically significant difference between phentermine + topiramate and phentermine ($p < 0.001$), and GLP-1 agonists and phentermine ($p = 0.03$) (Table 4).

Discussion

We found an average %TBWL of 7.5 (± 5.9) from the time of initiating WLM after bariatric surgery to weight nadir on medication therapy. This degree of weight loss is clinically significant as many health benefits including the reduction in cardiovascular morbidity, hepatic steatosis, and obstructive sleep apnea are seen around 5–10% TBWL.[18, 26, 27] Glycemic control, lipid profiles, depression, quality of life, urinary incontinence, and infertility associated with polycystic ovarian syndrome have been shown to improve with even more modest weight loss.[28] We also found no statistically significant difference in %TBWL on WLM between the three categories of

Table 2 Weight loss outcomes and medication use patterns among the three categories of patients. *WR* weight regain, *AWL* adequate weight loss, *NR* non-responders, *SD* standard deviation, *IQR* first interquartile range. Continuous variables listed as mean (±SD)

	All patients	WR	AWL	NR	*p* values		
					WR vs. AWL	WR vs. NR	AWL vs. NR
Weight at start of medication (kg)	101.5 (± 19.4)	101.7 (± 18.8)	97.2 (± 23.5)	107.9 (± 14.4)	0.25	0.18	0.09
BMI at start of medication (kg/m^2)	38.0 (± 5.8)	38.0 (± 5.9)	36.6 (± 5.9)	40.2 (± 4.3)	0.18	0.12	*0.02*
%TBWL at post-op nadir	29.4 (± 10.5)	32.1 (± 10.1)	25.1 (± 7.1)	17.1 (± 7.0)	*< 0.01*	*< 0.01*	*< 0.01*
%TBWL on meds from initiation	7.5 (± 5.9)	7.7 (± 5.9)	6.7 (± 5.9)	7.6 (± 6.7)	0.34	0.91	0.50
%TBWL on meds from post-op nadir	− 11.3 (± 23.3)	− 16.5 (± 24.7)	4.0 (± 10.7)	− 2.3 (± 10.7)	*< 0.01*	*0.02*	*0.04*
%TBWL on meds from pre-op weight	22.9 (± 10.0)	22.5 (± 9.3)	28.1 (± 10.4)	15.4 (± 9.1)	*< 0.01*	*< 0.01*	*< 0.01*
Time (months) from surgery to medications							
Mean (±SD)	65.6 (± 106.5)	67.3 (± 51.7)	32.6 (± 22.1)	47.2 (± 33.8)	*< 0.01*	0.17	*0.03*
Median (IQR)	44.0 (26.4)	47.8 (31.0)	25.9 (17.5)	42.8 (24.8)			
Time (months) on medication							
Mean (±SD)	11.2 (± 8.4)	11.0 (± 8.7)	11.4 (± 7.1)	12.2 (± 7.5)	0.82	0.47	0.57
Median (IQR)	9.0 (4.0)	8.5 (4.0)	9.0 (6.0)	12.0 (6.5)			
Time (months) to weight nadir on medication							
Mean (±SD)	7.6 (± 5.7)	7.3 (± 7.0)	6.9 (± 4.6)	9.3 (± 4.7)	0.77	0.21	0.07
Median (IQR)	6.0 (3.0)	6.0 (3.0)	6.0 (3.0)	8.5 (6.1)			
Percent revisions	38 (19.3%)	27 (19%)	5 (13.9%)	6 (31.6%)	0.32	*0.01*	*< 0.01*
Percent sleeve	125 (63.5%)	83 (58.5%)	31 (86.1%)	11 (57.9%)	*< 0.01*	0.95	*0.02*
Percent RYGB	72 (36.5%)	59 (41.5%)	5 (13.9%)	8 (42.1%)			
%TBWL on medication (sleeve)	6.46 (± 4.9)	6.8 (± 4.6)	6.3 (± 6.2)	6.3 (± 3.2)	0.66	0.77	0.98
%TBWL on medication (RYGB)	9.12 (± 7.1)	9.0 (± 7.1)	9.0 (± 4.2)	9.4 (± 10.3)	0.98	0.91	0.93
p value: sleeve vs. RYGB	*0.01*	*0.02*	0.36	0.34			

Significant *p* values = < 0.05 italicized

patients defined: medications prescribed after significant weight regain (WR), at weight loss nadir (AWL), or in patients who did not achieve goal weight loss (NR). Other studies have shown no difference in weight loss between patients who were started on WLM at the time of weight loss nadir or after weight regain.[19–21, 23, 29] In our study, patients in the AWL group who did not experience weight regain of > 20% were initiated on medications sooner after surgery than the NR and WR groups (average weight regain prior to medication in the AWL was 7.5%). By initiating medication sooner, this group was the only group that achieved a net weight loss using WLM compared to the post-operative nadir weight, as well as statistically significant greater weight loss from pre-operative weight. A review by Stanford et al. found greater weight loss on WLM from pre-operative weight in the group starting medications at weight loss nadir compared to those initiating medication after weight regain, but to our knowledge our data are the first to show statistical significance for this distinction.[23] This demonstrates that more proactive medical therapy at the time of weight loss nadir or plateau decreases weight regain and leads to more significant total weight loss following bariatric surgery. It is important to note that there is inherent selection bias in a retrospective review considering that this group may have also represented more motivated patients who sought medication sooner and engaged in other healthy lifestyle choices to mitigate weight regain. The exact date of weight nadir was often not available in clinic notes, so we were unable to more precisely determine the time from post-surgery nadir to medication initiation. However, the AWL group demonstrated a median time of 25.9 months from surgery to WLM initiation, which is consistent with well described patterns of maximum weight loss occurring between 12 and 24 months following bariatric surgery.

We also demonstrate that RYGB patients experienced greater weight loss using WLM than SG patients. This finding is supported by other studies.[23–25, 29] There was also a longer interval between surgery and medication initiation in the RYGB group compared to SG, which reflects the recent increase in SG as percent of total bariatric surgeries performed.

Patients who did not change medication achieved weight loss nadir earlier than those who changed medication at least

Table 3 Weight loss outcomes and medication use patterns for all patients shown by procedure type and if medications were changed throughout duration of therapy. Primary sleeve and Roux-en-Y gastric bypass (RYGB) included. *SD* standard deviation, *IQR* first interquartile range. Continuous variables listed as mean (±SD)

	Sleeve ($n = 125$)	RYGB ($n = 72$)		Medication changes		
			p values	No ($n = 102$)	Yes ($n = 95$)	*p* values
Weight at start of medication (kg)	99.5 (± 20.3)	104.9 (± 17.6)	0.08	103.9 (± 20.4)	98.7 (± 18.1)	0.08
BMI at start of medication (kg/m^2)	37.3 (± 5.9)	39.2 (± 5.3)	*0.02*	39.0 (± 6.0)	36.9 (± 5.4)	*0.01*
%TBWL on medication	6.5 (± 4.9)	9.1 (± 7.1)	*< 0.01*	7.8 (± 5.7)	7.2 (± 6.2)	0.49
Time (months) from surgery to medication						
Mean (±SD)	36.6 (± 19.2)	97.6 (± 59.1)	*< 0.01*	64.6 (± 51.6)	50.9 (± 41.8)	0.05
Median (IQR)	32.0 (24.0)	83.2 (51.4)		47.0 (30.1)	39.1 (41.9)	
Time (months) to nadir on medication						
Mean (±SD)	7.0 (± 6.4)	8.8 (± 6.2)	*0.03*	6.6 (± 5.4)	8.7 (± 5.8)	*< 0.01*
Median (IQR)	6 (3)	8 (4)		4 (3)	7.3 (4)	
Time (months) on medication						
Mean (±SD)	10.1 (± 7.3)	13.0 (± 9.4)	*0.02*	8.1 (± 6.3)	14.6 (± 9.0)	*< 0.01*
Median (IQR)	9 (4)	14 (4.8)	–	6 (3)	14 (6)	
Changed medication	58 (46.4%)	37 (51.4%)	0.60			
Primary procedures only						
Weight at start of medication (kg)	98.8 (± 21.0)	105.7 (± 18.0)	*0.04*			
BMI at start of medication (kg/m^2)	37.1 (± 5.5)	39.2 (± 5.5)	*0.01*			
%TBWL on medication	6.3 (± 4.3)	8.6 (± 6.6)	*0.01*			
Time (months) from surgery to medications						
Mean (±SD)	36.6 (± 19.5)	102.7 (± 59.6)	*< 0.01*			
Median (IQR)	31.9 (24)	87.3 (57.2)				
Time (months) to nadir on medication						
Mean (±SD)	6.8 (± 5.0)	8.6 (± 6.4)	0.05			
Median (IQR)	5 (3)	6.2 (4)				
Time (months) on medication						
Mean (±SD)	9.7 (± 7.1)	12.5 (± 9.7)	*0.03*			
Median (IQR)	6 (3)	10 (4)				

Significant *p* values = < 0.05 italicized

once. There are number of factors that contribute to the clinical decision to change mediation such as side effects, insurance coverage, and other patient-specific factors. This likely explains the observation that this group reaches nadir weight later as it will take longer to identify their suitable medication regimen. Importantly, weight loss at 3 to 4 months on WLM predicts weight loss at 1 year, so medications will often be changed if expected weight loss is not observed during this initial interval.[30]

In the subgroup analysis of patients who did not change medication, we found that phentermine + topiramate combination therapy was the only regimen that resulted in a statistically significant increased odds of achieving 5% and 10% weight loss (OR 4.38, CI 1.81–11.57; OR 3.53, CI 1.47–8.81, respectively). The average %TBWL was significantly lower using Phentermine compared to both phentermine + topiramate and GLP-1 agonists. These results are consistent with other short-term studies in non-surgery patients showing greater weight loss with phentermine + topiramate rather than either monotherapy.[31] Although there is a lack of long-term studies of phentermine monotherapy, phentermine + topiramate has been shown to have increased weight loss compared to placebo with a dose/response relationship over 2 years of follow-up.[24–26] Phentermine + topiramate has also been shown to achieve better weight loss than GLP-1 agonists, naltrexone/bupropion, lorcaserin, and orlistat.[32] Liraglutide, a GLP-1 agonist, has been the only medication other than phentermine + topiramate shown to meet the FDA's primary efficacy criteria of > 5% weight loss, and has been shown to be effective in achieving meaningful weight loss and treating recurrent type 2 diabetes mellitus following bariatric surgery.[33–36] A retrospective review in post-bariatric surgery patients found similar % weight loss in patients on phentermine and phentermine + topiramate at 90 days, but when

Table 4 Logistic regression with predictors shown by % weight loss goal achieved during medical therapy

		5%				10%				15%			
		% of patients	OR	*p* value	95% CI	%	OR	*p* value	95% CI	%	OR	*p* value	95% CI
All patients		61.4	–	–	–	28.9	–	–	–	9.6	–	–	–
Categories													
WR		61.3	0.98	0.94	(0.51, 1.84)	29.6	1.12	0.75	(0.57, 2.29)	10.6	1.52	0.49	(0.51, 5.48)
AWL		63.9	1.14	0.74	(0.54, 2.46)	30.6	1.1	0.81	(0.49, 2.37)	5.6	0.50	0.36	(0.08, 1.85)
NR		57.9	0.85	0.74	(0.33, 2.29)	21.1	0.63	0.43	(0.17, 1.83)	10.5	1.11	0.89	(0.17, 4.36)
Surgery													
RYGB (ref)		66.7	–	–	–	34.7	–	–	–	16.7	–	–	–
Sleeve		58.4	0.70	0.25	(0.38, 1.28)	25.6	0.65	0.18	(0.35, 1.22)	5.6	0.30	*0.02*	(0.11, 0.77)
Medication changes													
No (ref)		63.3	–	–	–	28.0	–	–	–	12.7	–	–	–
Yes		59.8	0.89	0.69	(0.50, 1.58)	26.9	0.95	0.88	(0.51, 1.77)	6.3	0.60	0.30	(0.21, 1.55)
Single medication	%TBWL												
Ph + T*	9.8 (± 5.6)	81.4	4.38	*< 0.01*	(1.81, 11.57)	44.2	3.53	*< 0.01*	(1.47, 8.81)	16.3	2.14	0.22	(0.64, 7.72)
Ph	4.5 (± 3.7)	38.1	0.27	*0.01*	(0.10, 0.72)	4.8	0.09	*0.02*	(0.01, 0.47)	0	*NA*	*NA*	*NA*
GLP-1**	7.7 (± 6.0)	58.6	0.77	0.555	(0.32, 1.87)	31	1.14	0.79	(0.43, 2.85)	13.8	1.32	0.67	(0.33, 4.59)
Other	6.2 (± 4.8)	50	0.55	0.371	(0.14, 2.11)	10	0.25	0.19	(0.01, 1.40)	10	0.83	0.86	(0.04, 5.08)

Significant *p* values = < 0.05 italicized

WR weight regain, *AWL* adequate weight loss, *NR* non-responders. *Ph + T* phentermine + topiramate, *Ph* phentermine, *GLP-1* GLP-1 agonists. %TBWL listed as mean (± standard deviation)

*$p < 0.001$ compared to phentermine

**$p = 0.03$ compared to phentermine

adjusting for baseline weight and time since surgery found a significantly greater weight loss of only 1.35 kg in the phentermine monotherapy group. It is possible that this outcome was limited by the short follow-up compared to other studies including our own that demonstrate longer time to weight loss nadir.[21] A recent study by Istfan et al. demonstrated mitigation of post-operative weight regain in patients on phentermine and topiramate used either in combination or as a monotherapy.[37] However, their patients were prophylactically initiated on WLM earlier in the post-operative course, and they found post-operative nadir weight in WLM users was lower than surgery patients not on medication. This suggests that the optimal time to initiate WLM may be after maximal weight loss from surgery has been experienced. Other studies in surgery patients have either not examined response to individual medications, or did not include combination phentermine + topiramate or GLP-1 agonists.[23, 24] As such, our study may be the largest series to demonstrate the improved weight loss outcomes in post-bariatric surgery patients using combination phentermine +topiramate. It should be noted that medication doses were not incorporated into our analysis due to changes for side effects or other reasons, and specific recommendations for prescribing practices cannot be generated from these data.

Differences in weight loss and regain definitions have led to variability in published outcomes.[38] We defined adequate weight loss as 15% TBWL for SG and 25% TBWL for RYGB. While average or expected weight loss has been found to be higher, this is within an acceptable range and we felt this was an appropriate cutoff below which would be considered treatment failure to designate patients as non-responders. Setting this cutoff higher, as some may argue, would have led to an even greater discrepancy in size between the NR and other two groups. We defined weight regain as > 20% of the weight lost at post-operative nadir weight for both procedures. While other studies have used > 15% as the cutoff to define weight regain,[6, 10, 11, 23] 72.4% of our patients experienced weight regain of > 20%, and using a less strict cutoff would have again led to an even greater discrepancy for analysis. These criteria for weight loss goals and weight regain were irrelevant to the analysis comparing total RYGB and SG patients.

There are several limitations of this study. As a retrospective review, the heterogeneity in prescribing patterns based off patient compliance and side effect profiles could not be controlled for**.** Not being able to more closely track and describe indications for medication changes has important clinical implications related to medication tachyphylaxis and their

overall safety profile. Future prospective studies are needed to establish this as a primary outcome. Patient follow-up was also variable, so the interval of weight recordings was inconsistent. It was for this reason that a nadir weight on WLM was used rather than a set time following medication initiation, because it would have limited the percent of patients who had follow-up at that exact time point. Using a nadir weight could have introduced bias favoring those who had been on medication for a longer period of time, but this likely represents the true efficacy of a therapy. Because patients were not prospectively followed, the only way in which we were able to estimate length of follow-up was by total duration of therapy as presented in Table 2. It does not differentiate between those who had discontinued therapy, and those who may have still been actively taking medication at the time of data collection, and therefore allowed the possibility of underreporting eventual weight loss. However, there was no significant difference in duration of therapy between WR, AWL, and NR groups. Of note, the RYGB group had more substantial weight loss, but had a longer period of time to weight loss nadir and were on medication for a longer period of time compared to SG. However, the mean and median time duration of therapy in the SG group was longer than the time to nadir weight on therapy in the RYGB group, suggesting that SG patients were given adequate time to demonstrate equivalent weight loss of the RYGB cohort. Some may also argue with including revisional cases. While this introduces heterogeneity in our patient population, we felt that the final anatomy following the revision case would dictate post-surgery weight loss and provide a reliable baseline from which to measure the response to WLM. Accepting this to be the case, using the almost 20% of cases that were revisions increased the power of our study and allowed the three categories of patients to have sufficient numbers for meaningful analysis. There was a statistically significant higher percentage of revision cases in the NR group which is likely attributed to the smaller number of patients in this group as it only contained 6 revision patients. Finally, we are unable to interpret these results in the context of a larger surgery cohort, because this was a retrospective analysis performed in patients who initiated therapy in our medical weight management program between April 2016 and November 2019, which may introduce selection bias. This interval was chosen due to increase in clinical volume during that time. Patients were included who may have had their index surgery outside of our institution, starting with the earliest patient in 1996. There was one other patient whose index surgery was in 1999 and the remainder were all after 2000, with the majority (82%) occurring after 2010. While this increases the sample size to augment the power of the study, it introduces data heterogeneity. As such, this analysis is only able to be interpreted in the context of the selected cohort, not to determine the percentage of patients who seek WLM following bariatric surgery. Furthermore, due to inadequate documentation of the primary reason for initiation of medication at the time of initial clinic visit, we estimate the indication for referral to our clinic by using weight loss and regain patterns after surgery to classify them as "weight regainers," "adequate weight loss," and "non-responders." We believe that doing so is a more objective and sensitive method for differentiating these unique cohorts of patients.

Conclusion

WLM following bariatric surgery is effective in combating weight recidivism, with the greatest benefit seen in RYGB patients. Starting medication at weight loss nadir leads to greater total weight loss from pre-operative weight and should be pursued. Phentermine + topiramate combination therapy demonstrates superior weight loss outcomes compared to other therapies. Future prospective randomized studies are needed to be able to control for variability in prescribing habits and patient compliance.

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Compliance with Ethical Standards

Conflict of Interest Dr. Colston Edgerton, Dr. Meetal Mehta, Dr. Danny Mou, Tanujit Dey, and Dr. Lalita Khaodhiar have no relevant conflicts of interest or financial ties to disclose. Dr. Ali Tavakkoli is a cofounder and consultant for AltrixBio.

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