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NEW CONCEPT

# Pharmacotherapy in Conjunction with a Diet and Exercise Program for the Treatment of Weight Recidivism or Weight Loss Plateau Post-bariatric Surgery: a Retrospective Review

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**Abstract**
*Background* Bariatric surgery is an effective therapeutic option for management of obesity. However, weight recidivism (WR) and weight loss plateau (WLP) are common problems. We present our experience with the use of two pharmacotherapies in conjunction with our standard diet and exercise program in those patients who experienced WR or WLP.
*Methods* From June 2010 to April 2014, bariatric surgery patients who experienced WR or WLP after undergoing Roux-en-Y gastric bypass (RYGB) or laparoscopic adjustable gastric banding (LAGB), and who were treated with phentermine (Ph) or phentermine–topiramate (PhT), were reviewed retrospectively. Generalized estimating equations were used to compare patient weights through 90 days between initial surgery type and medication type. Patient weights, medication side effect, and co-morbidities were collected during the first 90 days of therapy.
*Results* Fifty-two patients received Ph while 13 patients received PhT. Overall, patients in both groups lost weight. Among those whose weights were recorded at 90 days, patients on Ph lost 6.35 kg (12.8 % excess weight loss (EWL); 95 % confidence interval (CI) 4.25, 8.44) and those prescribed PhT lost 3.81 kg (12.9 % EWL; CI 1.08, 6.54). Adjusting for baseline weight, time since surgery, and visit through 90 days, patients treated with Ph weighed significantly less than those on PhT throughout the course of this study (1.35 kg lighter; 95 % CI 0.17, 2.53; $p$=0.025). There were no serious side effects reported.
*Conclusions* Phentermine and phentermine–topiramate in addition to diet and exercise appear to be viable options for weight loss in post-RYGB and LAGB patients who experience WR or WLP.

**Keywords** Phentermine · Phentermine–topiramate · Weight recidivism · Weight loss plateau · Bariatric surgery

## Introduction

Obesity is a global epidemic with over 500 million obese adults worldwide, and a projected estimate of 1.12 billion people by 2030 [1, 2]. Bariatric surgery remains the most effective method of sustainable weight loss. However, an estimated 10–30 % of patients regain their weight post-operatively starting as early as 18 months and as far out as 20 years [3, 4].

Current therapeutic interventions for weight regain after bariatric surgery include lifestyle modification, endoscopic therapies, and revisional surgery. Lifestyle modification in obese patients who have not undergone bariatric surgery can be effective and shows a monthly weight loss of 0.1–2.3 kg, which increased to 1.7–7.5 kg with the addition of a weight loss medication [5]. However, weight regain after surgery is difficult to manage with lifestyle alone as demonstrated by Sjostrom et al., who analyzed over 600 patients and found a 7.3 % weight regain from 2 to 10 years post-operatively as a result of nutritional non-compliance and physical inactivity. Endoscopic therapies, including StomaphyX (17 % excess weight loss (EWL)), sclerotherapy (9 % EWL), and endoscopic suturing devices (27.7 % EWL at 12 months), result in weight loss at 6 months, but no long-term data exists [6–9].

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Finally, revisional surgery is an effective approach to weight regain, with some studies reporting >30 % EWL [10]. However, revisional surgery has a high morbidity rate ranging from 12.1 to 33 % for Roux-en-Y gastric bypass [11].

Pharmacotherapy has been used for treatment of weight loss since the 1960s. Historically, only a small number of medications were approved by the Food and Drug Administration (FDA), including phentermine, until 2012, when two new medications, phentermine–topiramate ER and lorcaserin, were introduced to the market. Studies on pre-surgical and non-surgical patients have demonstrated a 5–10 % EWL when pharmacotherapy is used in conjunction with diet and exercise [12]. Additionally, only one study, conducted in 1996 by Jester et al., demonstrated an 8–65 % excess body weight loss over 12 weeks after weight regain post-Roux-en-Y gastric bypass [13]. Therefore, our aim was to summarize observed weight loss for patients on two different pharmacotherapies after weight recidivism or weight loss plateau following bariatric surgery. We hypothesized that pharmacologic therapy can assist with weight loss, in addition to diet and exercise, following weight recidivism or weight loss plateau after bariatric surgery.

## Methods

### Patient Selection

After receiving Institutional Review Board approval, which included waiver of informed consent, we performed a retrospective review of all post-bariatric surgery patients who were treated with pharmacotherapy from June 2010 to April 2014 at The Ohio State University. This subset of patients had presented to clinic interested in additional weight loss options, including pharmacotherapy, which is a standard of care option in our bariatric clinic. Patients included those who underwent either Roux-en-Y gastric bypass (RYGB) or laparoscopic adjustable gastric banding (LAGB). Patients who underwent laparoscopic sleeve gastrectomy were excluded due to small sample size and gastric plication patients were excluded as this procedure is investigational. Patients prescribed either phentermine (Ph) or phentermine–topiramate ER (PhT) were included in the final cohort as these were the most commonly prescribed medications. Patients who were taking other weight loss medications were excluded because of small sample sizes.

### Medication Prescribing Algorithm

To qualify for medications as part of standard of care, patients had to have a BMI of 27–29.9 kg/m$^2$ with at least one co-morbid condition, including diabetes mellitus (DM), medication-controlled hypertension (blood pressures consistently <140/80), hypercholesterolemia, and/or obstructive sleep apnea; or a BMI>30 kg/m$^2$ without co-morbidities. Additionally, patients with uncontrolled hypertension (systolic >150 or diastolic >100) or active cardiac conditions were excluded due to the effects of phentermine on the cardiovascular system (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/085128s065lbl.pdf).

Medications were prescribed according to FDA guidelines and the state of Ohio pharmacy law. Phentermine, approved for short-term use, was prescribed at 37.5 mg daily, for a total of 12 consecutive weeks, with clinic follow-up every 30 days while on the medication. The FDA guidelines for PhT, a medication intended for chronic use, entailed an initial oral daily dose of phentermine 3.75 mg/topiramate 23 mg for 14 days followed by a daily maintenance dose of phentermine 7.5 mg/topiramate 46 mg.

### Diet and Exercise Counseling

In conjunction with pharmacotherapy, patients received dietary counseling by a registered dietician, which included a recommended 1200 calories per day, in addition to exercise counseling provided by a nurse practitioner. This is the standard treatment, along with offering pharmacotherapy, for WR or WLP in our bariatric program, and compliance can be variable.

### Data Collection

Patient data was collected at baseline including comorbidities and associated prescribed medications, surgical history and weight at time of initial surgery, lowest weight since surgery, and weight just prior to start of pharmacotherapy. Additionally, patient weight and continuation or resolution of medication for two co-morbidities (DM and hypertension) were followed through 90 days post-prescription of Ph or PhT. For the purpose of this study, presence of DM and/or hypertension was defined as taking one or more medication for the diagnosis. Resolution of DM and/or hypertension was defined as off all medication for the diagnosis.

### Statistical Analysis

Patient demographics and baseline characteristics were summarized both overall and by medication cohort. Generalized estimating equations were used to fit a model with patient weight as the outcome and surgery type and prescription type as predictors. In addition, we adjusted for patient weight at baseline (i.e., at time of prescription), visits, and time since surgery by including them as covariates in the model. All available patient data up to day 90 were included in the analysis. An exchangeable correlation structure was used to account for repeated patient measures. In addition, point estimates and corresponding 95 % confidence intervals were

estimated for the mean patient weight loss at day 90 (from baseline) per group for those with 90 day weight measurements. All analyses were performed in SAS software (Version 9.3 of the SAS System for Windows, SAS Institute Inc., Cary, NC, USA).

## Results

### Patient Characteristics

From June 2010 to April 2014, a total of 108 patients were treated with pharmacotherapy post-bariatric surgery. Of these, 65 patients met our inclusion criteria with 57, 47, and 30 having follow-up measurements at 30, 60, and 90 days, respectively. Among these, 52 (80 %) were prescribed phentermine (Ph), while 13 (20%) were prescribed phentermine–topiramate ER (PhT). Fifty-one patients (78 %) previously underwent Roux-en-Y gastric bypass and 14 (22 %) had a laparoscopic adjustable gastric band. Overall, the mean age was 47.3 years (SD=10.8), and 89 % were female. Patient demographics were similar between the Ph and PhT groups; the average patient age at baseline was 46.8 years (SD=10.8) and 48.9 years (SD=10.9) for the Ph and PhT cohorts, respectively. The study included predominately female patients with 47 (90.4 %) in the Ph group and 11 (84.6 %) in the PhT group. Only one patient, in the Ph group, smoked during this study while no patients in the PhT cohort report smoking.

Preoperative average BMI for patients prescribed Ph and PhT was 50.4 kg/m$^2$ (SD=8.8) and 46.4 kg/m$^2$ (SD=4.3), respectively. Average BMI at nadir weights post-surgery was 34.4 kg/m$^2$ (SD=7.8; 58.2 % EWL) and 32.1 kg/m$^2$ (SD=6.3; 60.2 % EWL) for the Ph and PhT groups, respectively. The length of time from surgery to start of pharmacotherapy varied greatly from patient to patient. The median time to reach minimum weight from initial surgery for the Ph cohort was 14.5 and 11.9 months for the PhT group, and the median time from minimum weight to start of pharmacotherapy was 35.3 months within the Ph cohort and 36.3 months in the PhT cohort. At the time of first prescription, patients had regained an average of 15.5 kg (SD=8.3) and 14.7 kg (SD=10.2) in the Ph group and PhT group, respectively (Table 1).

### Comparison of Weight Loss Across Type of Pharmacotherapy

Weight loss over time was observed for all patients on pharmacotherapy. A total of 30 patients had observed weights at 90 days: 24 prescribed Ph and 6 prescribed PhT. In the Ph group, patients lost on average 6.3 kg (12.8 % EWL; 95 % confidence interval (CI) 4.25, 8.44) at 90 days, while those prescribed PhT lost on average 3.8 kg (12.9 % EWL; 95 % CI 1.08, 6.54). Statistically significant differences in patients' weights were observed throughout 90 days between the two cohorts of patients. After adjusting for patient weight at baseline, follow-up time, and time since surgery, those on Ph weighed, on average, 1.35 kg less than those on PhT ($p$=0.025; 95 % CI 0.17, 2.53). Note that type of surgery was also included in the model and no significant differences in weight were observed between the two types of surgery ($p$= 0.345).

### Co-morbidities

As a surrogate for a change in medical co-morbidities, the number of diabetic and anti-hypertensive medications was documented and followed throughout the course of the study. As previously noted, the presence of medications was used to define presence of DM and/or hypertension. Those whose DM and hypertension had not resolved by the start of pharmacotherapy did not see resolution of DM and/or hypertension 90 days post-pharmacotherapy.

### Complications

No patients required cessation of medical therapy due to hypertension, cardiac arrhythmias, or insomnia. One patient stopped Ph due to headaches and one patient due to nausea.

## Discussion

As the prevalence of obesity increases globally, so too will the number of bariatric procedures. Albeit surgery is the only proven method for sustainable weight loss in patients considered obese (i.e., BMI >30 kg/m$^2$), there continues to be a subset of bariatric patients who fail to maintain weight loss and/or who fail to achieve optimal weight loss after bariatric surgery. The options for patients with weight recidivism and/or weight loss plateau include lifestyle modification, endoscopic treatments, and revisional surgery. Each of these options provides suboptimal weight loss and increased morbidity proportional to their degree of invasiveness.

From the literature, we know that diet and exercise have a poor compliance rate in the obese population. Carvajal et al. report that an analysis of randomized clinical trials comparing PCP-driven weight loss intervention (behavior modification, including diet and exercise) versus standard of care saw only 1–3-kg weight loss in patients randomized to the interventional study arms [5]. In the post-bariatric surgery population, the StomaphyX randomized clinical trial included dietary counseling for both the treatment and sham arms; average weight loss in the sham arm by 3 months was 8.4 kg [7]. Finally, a randomized control study of a high-volume exercise program

**Table 1** Demographics and pre-intervention characteristics

| Variable | Level | Prescription | | Total ($n$=65) |
|---|---|---|---|---|
| | | Phentermine ($n$=52) | Phentermine–Topiramate ER ($n$=13) | |
| Surgical procedure | Band | 11 (21.2 %) | 3 (23.1 %) | 14 |
| | RNY | 41 (78.9 %) | 10 (76.9 %) | 51 |
| Age at Rx (in years) | #Missing | 0 | 0 | 0 |
| | Mean (SD) | 46.8 (10.8) | 48.9 (10.9) | 47.3 (10.8) |
| | (min, max) | (21.0, 70.0) | (33.0, 63.0) | (21.0, 70.0) |
| Gender | Female | 47 (90.4 %) | 11 (84.6 %) | 58 |
| | Male | 5 (9.6 %) | 2 (15.4 %) | 7 |
| Ethnicity | African American | 7 (13.5 %) | 2 (15.4 %) | 9 |
| | Caucasian | 44 (84.6 %) | 10 (76.9 %) | 54 |
| | Other/Unknown | 1 (1.9 %) | 1 (7.7 %) | 2 |
| Smoker | Unknown | 1 (1.9 %) | 1 (7.7 %) | 2 |
| | No | 50 (96.2 %) | 12 (92.3 %) | 62 |
| | Yes | 1 (1.9 %) | 0 (0.0 %) | 1 |
| Current medication use | | | | |
| Number of diabetes medications | None | 46 (88.5 %) | 12 (92.3 %) | 58 |
| | One | 4 (7.7 %) | 1 (7.7 %) | 5 |
| | Two or more | 2 (3.9 %) | 0 (0.0 %) | 2 |
| Number of hypertension medications | None | 38 (73.1 %) | 9 (69.2 %) | 47 |
| | One | 12 (23.1 %) | 2 (15.4 %) | 14 |
| | Two or more | 2 (3.8 %) | 2 (15.4 %) | 4 |
| Number of cholesterol medications | None | 44 (84.6 %) | 11 (84.6 %) | 55 |
| | One | 6 (11.5 %) | 2 (15.4 %) | 8 |
| | Two or more | 2 (3.9 %) | 0 (0.0 %) | 2 |
| Number of triglyceride medications | None | 44 (84.6 %) | 11 (84.6 %) | 55 |
| | One | 8 (15.4 %) | 2 (15.4 %) | 10 |
| | Two or more | 0 (0.0 %) | 0 (0.0 %) | 0 |
| Weight history | | | | |
| BMI at surgery | #Missing | 0 | 0 | 0 |
| | mean (SD) | 50.4 (8.8) | 46.4 (4.3) | 49.6 (8.2) |
| | (min, max) | (39.2, 83.6) | (38.6, 54.0) | (38.6, 83.6) |
| BMI at minimum weight | #Missing | 0 | 1 | 1 |
| | mean (SD) | 34.4 (7.8) | 32.1 (6.3) | 34.0 (7.5) |
| | (min, max) | (24.5, 62.5) | (26.0, 45.9) | (24.5, 62.5) |
| Weight loss (lbs) at minimum weight (from surgery) | #Missing | 0 | 1 | 1 |
| | Mean (SD) | 97.7 (42.6) | 89.4 (42.1) | 96.1 (42.3) |
| | (min, max) | (21.3, 212.2) | (12.0, 154.0) | (12.0, 212.2) |
| BMI at first prescription | #Missing | 0 | 0 | 0 |
| | mean (SD) | 39.7 (8.0) | 37.9 (6.6) | 39.3 (7.7) |
| | (min, max) | (29.0, 66.2) | (31.0, 53.5) | (29.0, 66.2) |
| Weight (lbs) at first prescription | #Missing | 0 | 0 | 0 |
| | mean (SD) | 245.0 (55.9) | 233.3 (50.3) | 242.6 (54.6) |
| | (min, max) | (163.8, 397.0) | (177.0, 341.6) | (163.8, 397.0) |
| Weight difference at first Rx (from minimum weight) | #Missing | 0 | 1 | 1 |
| | Mean (SD) | 32.4 (22.5) | 34.1 (18.3) | 32.7 (21.7) |
| | (min, max) | (−0.4, 124.0) | (5.0, 71.0) | (−0.4, 124.0) |

*Rx* prescription, *BMI* body mass index in $kg/m^2$, *lbs* pounds

versus control in RYGB and gastric banding patients at least 3 months post-surgery with a BMI of at least 35 reported a 12-week total weight loss of approximately 4.5 kg in both groups [14].

Weight loss medications have found some success in the preoperative bariatric population or in those who are not candidates for surgery. In particular, phentermine has been in use since 1959 and remains the most prescribed weight loss medication in the USA. Studies demonstrate a 5–10 % EWL with treatment of this medication in the short term (<6 months) [15]. Phentermine–topiramate ER was approved for long-term use in 2012, and studies have shown that at 1 year, weight loss nears 10 %, which is maintained at 2 years if the medication is continued [16, 17]. Both Ph and PhT have demonstrated a low complication rate and good safety profile in previous studies. However, known complications of these two medications include hypertension, cardiac arrhythmias, and insomnia (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/085128s065lbl.pdf) [12, 13].

Our aim was to compare observed weight loss for patients on two different pharmacotherapies for weight recidivism or weight loss plateau after bariatric surgery. The only published study on weight loss medication among patients in the post-bariatric setting was conducted and published in 1996 by Jester et al., who prospectively evaluated the use of phentermine and/or fenfluramine on patients who regained weight at least 18 months after RYGB or biliopancratic diversion (BPD). The authors followed patients every 4 weeks and demonstrated that at 12 weeks, 20 of 34 patients remained in the study, and the average weight loss was 11.8 and 11.4 kg for RYGB and BPD, respectively. Additionally, the combined percent EWL at 12 weeks was 34 % (range 8–65 %) [13].

Aside from this study, our results can only be compared to pharmacotherapy induced weight loss achieved in non-surgery patients. Specifically, a meta-analysis of randomized, placebo-controlled trials, with short-term follow-up, demonstrated that patients treated with phentermine showed a 3-kg greater weight loss than the placebo group [18, 19]. Additionally, multiple randomized controlled trials evaluating the effectiveness of phentermine–topiramate ER, including the CONQUER, EQUIP, and SEQUEL trials, have all demonstrated an average of 8–10-kg weight loss (5–10 % of baseline body weight), which was statistically significant compared to placebo over a 1–2-year period [16–20].

Our results demonstrate that at 90 days, patients in both the phentermine (6.35 kg, 12.8 % EWL) and phentermine–topiramate ER (3.81 kg, 12.9 % EWL) groups lost weight on pharmacotherapy. These results are consistent with weight loss achieved with pharmacotherapy in both surgery and non-surgery patients [12, 13]. Additionally, patients who received Ph demonstrated more weight loss throughout the course of the study than those receiving PhT. There was no large observed change in the number of medications that these patients were taking for diabetes and hypertension within either group after starting pharmacotherapy, potentially suggesting no improvement in the co-morbid conditions. However, the lack of objective data, such as hemoglobin A1C, and lack of information regarding medication dosage changes are a limitation in fully evaluating improvement of co-morbidities. Additionally, a major limitation of this study is the 90-day duration. This likely was too short a time frame to capture the potential improvements in co-morbidities.

Longer-term follow-up for post-bariatric surgery patients utilizing pharmacotherapy is needed to evaluate whether these therapies are associated with improved co-morbid conditions and provide sustainable weight loss. Follow-up through 90 days was selected for a number of reasons, including available patient follow-up. The vast majority of patients were lost to follow-up after 5 months. Only nine patients (13.8 %) had documented monthly follow-up at 120 days and three patients (0.5 %) at 150 days following the initiation of pharmacotherapy. The relatively short length of follow-up may have influenced the results of this retrospective review, as PhT is approved for chronic use and dose titration can take up to 3 months. Patient attrition for follow-up every 30 days is likely multifactorial. State law requiring follow-up every 30 days for patients on Ph and every 3 months for those on PhT may have contributed to patients not continuing on pharmacotherapy. Further, multiple patients used a combination of pharmacotherapy, in particular, transitioning from Ph to a chronic weight loss medication, including PhT, topimax, or wellbutrin, at the end of the 90-day therapy. Maintenance on an alternate pharmacotherapy in conjunction with patient attrition makes analysis of maintenance of weight loss and long-term effects of Ph or PhT unreliable in this study.

As with any study, this work is not without its limitations; this was a retrospective review and therefore includes limitations associated with all retrospective studies, including missing patient data observed throughout the 90-day time frame. Consequently, interpretations of patient weights over time should be made cautiously given different individuals have missing values at different time points. Additionally, this study does not include a control group of patients, who did not take pharmacotherapy but did initiate a diet and exercise program for weight loss, and therefore, no conclusion on the effectiveness of the medications, independent of diet and exercise, can be drawn, especially since all patients were placed on a diet and exercise plan at the start of pharmacotherapy. Further, adherence to the diet and exercise program could not be ensured, as there is no method to monitor patients' compliance in our program. Additionally, there is inherent

selection bias as patients were selected based on those who wanted to pursue weight loss options beyond diet and exercise and therefore were written prescriptions for pharmacotherapy. Thus, we were unable to capture patients who came to clinic for weight loss management but did not receive a prescription. Further, in this study, we are unable to comment on the maintenance of percent EWL after completion of 90 days of therapy due to the variability in follow-up of this patient population after the treatment course. Due to the prescribing limitations of Ph, many patients used a combination of therapies after completion of 90 days of phentermine. Therefore, drawing any conclusions from this data could be misleading. Finally, the 90-day time point for analysis does not take into account that phentermine–topiramate ER is approved for chronic use and therefore may show additional weight loss benefits with longer follow-up.

Further prospective trials are needed to evaluate larger cohorts of patients to determine if pharmacotherapy is a viable option as an alternative to lifestyle modification, endoscopic therapy, and revisional surgery for weight recidivism or weight loss plateau following bariatric surgery. Studies that evaluate potential improvement of co-morbid conditions in addition to weight loss are needed to determine if the benefits of pharmacotherapy outweigh the costs of the medication and follow-up. Our study provided evidence to suggest a statistically significant difference in weight loss between the Ph and PhT groups but more rigorous studies comparing the safety and efficacy of these two medications would be useful. If pharmacotherapy can be shown to be an effective means of sustainable weight loss, with associated improvements in co-morbid conditions, patients may have an effective alternative for weight loss with minimal morbidity.

## Conclusion

We observed weight loss in patients who underwent treatment with both Ph and PhT for weight recidivism post-bariatric surgery. We also observed significantly more weight loss in patients who took Ph when compared to PhT. Pharmacotherapy may be a viable option to add to our arsenal of treatments for weight recidivism or weight loss plateau following bariatric surgery; Ph may be more effective than PhT in promoting weight loss. Prospective trials with long-term outcomes are required to evaluate weight loss maintenance with medications, and potential complications from their utilization.

**Compliance with Ethical Standards** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Conflict of Interest** Dr. Mikami is a consultant for WL Gore, on the Advisor Board at CareFusion, and a consultant for Covidien. Allison Wehr, MS and Kathy Foreman, CNP have no relevant disclosures. Drs. Schwartz, Needleman, and Noria have no conflicts of interest or financial ties to disclose.

**Informed Consent** For this type of study, formal consent is not required.

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