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Weight regain after total meal replacement very low-calorie diet program with and with-out anti-obesity medications

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Abstract

Background: Very low-calorie diets (VLCDs) employing total meal replacement (TMR) offer substantial short-term weight loss. Concurrently, anti-obesity medications (AOMs) have shown promise as adjunctive treatments when combined with VLCDs.

Aims: This study aimed to investigate the impact of adjuvant AOMs on weight loss and weight regain within a comprehensive lifestyle program.

Methods: This is a retrospective study of patients with obesity enrolled in VLCD/TMR programs, specifically the OPTIFAST program.

Results: Data from 206 patients (68% women, mean age 52.39 ± 13.05 years, BMI 41.71 ± 7.04 kg/m^2) were analyzed. Of these, 139 received no AOM (AOM-), while 67 received AOMs (AOM+). Total body weight loss percentages (TWL%) at 6 and 18 months were −17.87% ± 7.02 and −12.10% ± 11.56, respectively. There was no significant difference in 6-month weight loss between the AOM groups. However, the AOM + group exhibited lower weight regain (3.29 kg ± 10.19 vs. 7.61 kg ± 11.96; $p = 0.006$) and weight regain percentage (WR%) (31.5% ± 68.7 vs. 52.16% ± 64.4; $p = 0.04$) compared with the AOM- group.

Conclusion: The findings highlighted the potential of AOMs and VLCD/TMR as effective strategies for long-term weight management in individuals with obesity.

KEYWORDS
obesity, pharmacotherapy, total meal replacement

1 | INTRODUCTION

Meal replacements, including those utilized in very low-calorie diets (VLCDs) and total meal replacement (TMR) programs, have demonstrated their effectiveness as powerful tools for short-term weight loss. Studies such as Egger et al. underscored the safety and efficacy of partial meal replacements when incorporated into low-energy diets.[1] Furthermore, previous studies have consistently found that meal replacements are on par with conventional structured weight-loss diets in terms of achieving short-term weight loss.[2–4] These findings align with the short-term effectiveness of meal replacements compared to other weight loss strategies, as highlighted by Astbury et al., who conducted a systematic review and meta-analysis revealing greater one-year weight loss in programs incorporating meal replacements.[5] Heymsfield et al. further supported this notion in a systematic review of randomized clinical trials utilizing meal replacement plans, demonstrating that these interventions can safely and effectively improve weight-related risk factors of disease.[6] This

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body of evidence emphasizes the significance of exploring their role in comprehensive weight management programs.

While the short-term effectiveness of meal replacements is well-documented, their long-term efficacy remains a subject of debate and ongoing investigation. Barrón et al. reported inconclusive evidence regarding the sustained benefits of meal replacements for long-term weight loss.[7] Keogh et al. echoed this uncertainty in their review, leaving the question of long-term effectiveness unanswered.[8] Nonetheless, to navigate the debate surrounding long-term efficacy, it is crucial to acknowledge the potential benefits of integrating meal replacements into a comprehensive weight management strategy. Ashley et al. observed that traditional weight loss interventions incorporating meal replacements were effective in various settings.[9] Notably, Lowe et al. found that a nutrition-focused approach involving meal replacements yielded modestly greater long-term weight loss than behavior therapy alone. These insights suggest that meal replacements could play a role in sustained weight management when integrated into a comprehensive strategy.[10] One compelling example of a TMR medically supervised weight-loss intervention is the OPTIFAST program, which has been studied at 800 kcal/day in a randomized controlled trial against a higher kcal food diet. These studies showed significantly greater weight loss at 6 and 12 months.[11] This specific case highlights both the potential and challenges of utilizing meal replacements for long-term weight management.

Anti-obesity medications (AOM) refer to medications demonstrating significant additional weight loss (>5%) often in conjunction with moderate intensity lifestyle interventions involving monthly visits aiming for a 500 kcal/day deficit. Previous studies have shown that the combination of VLCD and AOM such as orlistat, sibutramine, or topiramate plus phentermine can result in a clinically significant weight loss of 6.1 kg after 1 year.[12] Real-world studies have also confirmed the efficacy and safety of newly FDA-approved anti-obesity medications (e.g., orlistat, lorcaserin, bupropion/naltrexone-SR, phentermine/topiramate-ER, liraglutide, and semaglutide) for long-term usage.[13,14] Moreover, these medications have been employed as adjuvants in endoscopic bariatric procedures and metabolic surgery.[15,16]

In this study, the aim was to investigate the impact of adjuvant AOM use on weight loss and weight regain during and after a comprehensive lifestyle program encompassing the VLCD/TMR phase. To achieve this, a retrospective analysis of 6-month and 18-month weight loss outcomes was conducted, calculating the percentage of lost weight regained at 18 months, among individuals with obesity enrolled at institution's VLCD/TMR program (OPTIFAST). Subsequently, a comparison was made between the results of individuals receiving AOM and those not receiving AOM.

2 | METHODS

2.1 | Study design and population

This retrospective study was conducted at UPMC in Pittsburgh, PA between December 2014 and February 2019. Participants included patients with obesity enrolled in the OPTIFAST weight loss program. Inclusion criteria comprised men and women over 21 years old with a BMI $\geq$30 kg/m^2, enrolled in the OPTIFAST program, and who completed the initial 6-month program with additional 12-month follow-up weight data. Exclusions included patients on the program for less than 6 months, pregnant patients during or within the next 12 months, and patients undergoing bariatric surgery within the program or the subsequent 12 months. Data were collected from electronic medical records (EMR).

2.2 | Weight management program

The OPTIFAST program at UPMC is a medically supervised program utilizing Nestle's very low-calorie diet products. The program focused on nutrition and lifestyle counseling, transitioning to a low glycemic load partial meal replacement and whole food diet to sustain the glycemic benefits of weight loss. The program involved twice monthly visits with a registered dietitian (RD) for 6 months, covering diet and lifestyle topics. Participants followed a 600–900 kcal/day diet for the initial 3 months, consisting of OPTIFAST meal replacement products and raw non-starchy vegetables. Over the next 3 months, plant-based food groups were gradually incorporated, followed by animal protein. Monthly visits with an endocrinologist or a supervised Physician Assistant or Nurse Practitioner were conducted for medical adjustments and management of anti-obesity medications. This was followed by a weight maintenance program consisting of monthly RD visits for 1 year, and focusing on sustainable behaviors to prevent weight regain.

2.3 | Data collection

Demographic information, diabetes history, psychiatric medication usage, and data on FDA-approved anti-obesity medications (i.e., phentermine; phentermine-topiramate; liraglutide; bupropion-naltrexone; lorcaserin) were extracted from the EMR through manual chart review. Liraglutide at doses of 1.8 mg or lower, as well as 2.4 and 3 mg doses, were included. Only semaglutide at doses of 1.0 mg or lower were included as higher doses were neither approved nor available for the treatment of type 2 diabetes mellitus (T2DM) or obesity. If patients were on medication, the time of initiation was established as follows: before starting the program, during the first 6 months of the program, and after 6 months of the program. Weight measurements were recorded at the first visit, after 3 months, 6 months, and 18 months ($\pm$45 days). Weight was measured in kilograms at in-person visits without shoes using an electronic scale.

2.4 | Study endpoints

The primary endpoint was the weight loss regained in percentage (WR%) after 18 months from the weight loss achieved at 6-months

between patients taking AOMs versus no AOM. The outcome was calculated using the following formula:

$$\text{WR}\% = \frac{\text{Weight loss at 6 months} - \text{Weight loss at 18 months}}{\text{Weight loss at 6 months}} \times 100$$

Secondary endpoints included the total body weight loss percentage (TWL%) at 3, 6, and 18 months of follow-up as well as differences in TWL% and WR% among participants in the AOM group based on the AOM used.

2.5 | Statistical analysis

Baseline characteristics were summarized using mean and standard deviation (SD) for continuous variables, and frequency and percentages for categorical variables. Between-group comparisons for baseline variables were performed using Pearson χ^2 test for categorical variables and student *t*-test for continuous variables. Matched pair *t*-tests were used to calculate the mean difference in weight from baseline. The Wilcoxon test was used to compare between patients taking AOM and those not taking AOM. ANOVA was used to compare Statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Patient characteristics

Between December 2014 and February 2019, a total of 315 patients were initially enrolled in the weight management clinic and started the OPTIFAST program. After applying the inclusion criteria, 109 patients were excluded, resulting in a study cohort of 206 patients. Among these patients, 68% were women, with a mean (SD) age of 52.39 (13.05) years, body weight of 117.95 (24.06) kg, and a BMI of 41.71 (7.04) kg/m^2. At baseline, 49% of patients had diabetes. Of the study cohort, 139 patients did not take any anti-obesity medications (AOM-), while 67 patients were prescribed AOM (AOM+) at some point during the program. The only notable difference in baseline characteristics was a higher prevalence of diabetes in the AOM + group [44 (66%) versus 58 (40%); $p = 0.001$] (Table 1). The most commonly used medications were GLP-1 analogs, including liraglutide and semaglutide, accounting for 41% of the medication usage in this cohort. Detailed information on the medications used by this cohort is presented in Table 2.

3.2 | Weight loss and weight regain outcomes of the OPTIFAST program

Among the 206 patients, a total body weight loss percentage (TWL%) of −14.22% (4.57) after 3 months, −17.87% (7.02) after 6 months, and −12.10% (11.56) after 18 months was observed. This corresponded to a mean difference from baseline of −16.91 kg (95% CI −15.96 to −17.85; $p < 0.001$) at 3 months, −21.40 kg (95% CI −19.99 to −22.81; $p < 0.001$) at 6 months, and −14.95 kg (95% CI −12.53 to −17.36; $p < 0.001$) at 18 months. Consequently, a WR of 6.32 kg (95% CI 4.57 to 8.07; $p < 0.001$) and a WR% of 40.4% (95% CI 30.22 to 50.61) were observed, with no significant differences between males and females (Table 3).

When comparing TWL% between the AOM+ and AOM- groups, no statistically significant difference was found at 3, 6, or 18 months. Although not statistically significant, the mean weight loss was greater at 6 months in the AOM- group, but greater at 18 months in the AOM + group (Figure 1A). In terms of weight regain, patients in the AOM + group regained less weight compared to the AOM group

TABLE 2 Anti-obesity medications used by patients.

Medication	*N*	%
Liraglutide or semaglutide	28	41%
Phentermine	15	22%
Phentermine/Topiramate	9	13%
Liraglutide or semaglutide and phentermine +/−topiramate	7	10%
Liraglutide and bupropion/naltrexone	4	6%
Bupropion/naltrexone	3	4%
Lorcaserin	1	1%

TABLE 1 Baseline characteristics of patients.

	All patients *N* = 206	No AOMs *N* = 139 (67%)	AOMs *N* = 67 (33%)	*p*-value
Age, years	52.39 (13.05)	52.81 (13.34)	51.86 (12.73)	0.60
Sex, females	139 (67.96%)	97 (69%)	43 (65%)	0.51
BMI, kg/m2	41.71 (7.04)	41.77 (6.88)	41.64 (7.27)	0.90
Baseline weight, kg	117.95 (24.06)	119.13 (24.94)	117.37 (23.69)	0.64
Diabetes, yes	102 (49%)	58 (41%)	44 (66%)	0.001
Behavioral diagnosis at baseline, yes	87 (42.23%)	57 (40%)	30 (45.5%)	0.47

Note: Data are shown as mean (standard deviation) or number (percentage).
Abbreviations: AOM, anti-obesity medications; BMI, Body Mass Index.

TABLE 3 Weight loss outcomes of patients in the OPTIFAST program with and without anti-obesity medications.

	All patients	No AOMs N = 139 (67%)	AOMs N-67 (33%)	*p*-value
Total body weight loss at 3 months, %	−14.22 (4.57)	−14.59 (4.39)	−13.74 (4.78)	0.37
Total body weight loss at 6 months, %	−17.87 (7.02)	−18.74 (6.78)	−16.77 (7.21)	0.17
Total body weight loss at 18 months, %	−12.10 (11.56)	−11.66 (11.73)	−13.13 (11.18)	0.37
Weight regain, kg	+5.42 (11.26)	+7.61 (11.96)	+3.29 (10.19)	0.006
Total body weight regain, %	+55.69 (11.14)	+52.16 (64.4)	+31.57 (68.4)	0.04

Note: Data are shown as mean (standard deviation) or number (percentage).
**p*-value calculated with Wilcoxon Test.

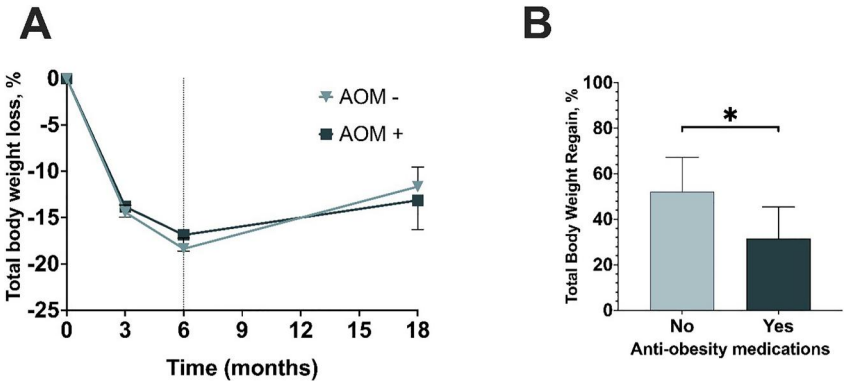

FIGURE 1 (A) Weight loss outcomes at 3, 6 and 18 months in patients taking AOM (AOM+) at some point during the program compared with patients not taking AOM (AOM-). (B) Total body weight regains at 18 months from maximum weight lost between patients taking AOM (AOM+) and patients not taking AOM (AOM-).

[WR%: 31.5% (68.7) versus 52.16% (64.4); $p = 0.04$] (Table 3) (Figure 1B). After 18 months, 26% of patients in the AOM + group achieved more than 20% weight loss, compared to only 18% of patients in the AOM- group ($p = 0.03$) (Figure 2).

Weight loss outcomes based on the specific AOM administered to participants were also reported in this study (Table 4). Notably, those taking Liraglutide or Semaglutide achieved substantial weight loss of −14.49% (3 months) and −18.42% (6 months) but showed a 4.6 kg regain at 18 months to −14.29%. Phentermine users reached −13.82% (3 months), −17.7% (6 months), and regained 2.83 kg to −13.19% (18 months). The Phentermine/Topiramate group experienced a significant weight regain (+4.48 kg) at 18 months. Combining Liraglutide/Semaglutide with Phentermine ± Topiramate showed improved weight maintenance. Conversely, the Liraglutide and Bupropion/Naltrexone group exhibited the highest weight loss (−15 kg) while Bupropion/Naltrexone alone users experienced modest regain (+7.27 kg). When comparing the differences between groups, none of these results were significantly different.

4 | DISCUSSION

In the study, an analysis of 206 participants in the OPTIFAST program revealed that after 3 months, the cohort exhibited a significant TWL% of −14.22% (4.57), which further improved to −17.87% (7.02) at 6 months, which is highly consistent with prior studies. However, a slight rebound effect was observed at 18 months, resulting in a TWL% of −12.10% (11.56). These findings were consistent with statistically significant mean differences from the baseline, indicating substantial weight loss at 3, 6, and 18 months. Interestingly, there were no significant differences in weight loss percentages between AOM+ and AOM- groups. However, AOM + patients exhibited better weight maintenance and significantly less weight regain. These findings suggest a potential role for anti-obesity medications in long-term weight management within the OPTIFAST program, warranting further investigation.

Weight loss with very low-calorie diets (VLCDs) typically averages 1.5 kg per week, resulting in a total loss of around 20 kg after 12–16 weeks.[17] However, without follow-up treatment, individuals often experience weight regain of 40%–50% within 1–2 years.[18,19] Transitioning individuals from a pro-obesogenic lifestyle to a healthy one is crucial in obesity management as it involves modifying the habits and environment that contributed to the severity of obesity in the first place. Studies have indicated that combining VLCD therapy with intensive lifestyle changes leads to longer-term weight reduction, which is more successful than VLCD therapy alone.

Food intake is regulated by internal physiological information and external environmental cues,[20] and obesity disrupts several of these signaling pathways. Medications may be necessary to optimize the weight reduction by influencing these pathways and helping patients avoid or manage cravings for high-carbohydrate, high-fat, and rapidly processed meals. They may also potentially impact the "set-point" weight that physiological systems aim to attain during weight recovery. Previous studies have shown that adjunct

pharmacotherapy with dexfenfluramine or sibutramine can minimize weight regain after VLCD treatment.[21] Although these drugs have been withdrawn from the market due to adverse effects, the concept of combination therapy remains valuable. In the study, it was demonstrated that this trend also holds true for newer FDA-approved anti-obesity medications.

This study comprehensively examined various FDA-approved AOMs, including phentermine, phentermine-topiramate, liraglutide, bupropion-naltrexone, and lorcaserin. Of particular note, the study incorporated liraglutide at varying doses, encompassing 1.8 mg or lower, 2.4 mg, and 3 mg. During the study period, we solely considered semaglutide at doses of 1.0 mg or lower for treating type 2 diabetes mellitus (T2DM) or obesity, as higher doses were neither sanctioned nor accessible.

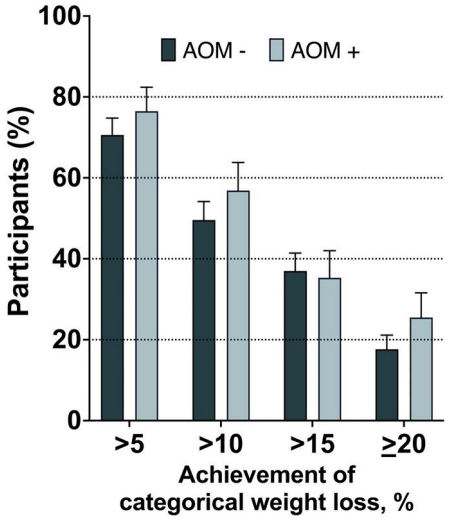

FIGURE 2 Proportion of patients taking AOM (AOM+) at some point during the program compared with patients not taking AOM (AOM-) achieving a categorical weight loss of 5-, 10-, 15-, or 20%.

Individuals with diabetes tend to lose less weight compared to those without diabetes in lifestyle interventions, AOM trials, and metabolic surgery.[13,22] Insulin resistance plays a significant role in the trajectory of weight loss. In this cohort, a difference in weight loss results between individuals with and without diabetes who were not taking AOM was not observed. This may be attributed to the use and effectiveness of type 2 diabetes medications that have weight loss and weight maintenance effects but are not approved as AOMs (such as other GLP-1 agonists, SGLT2 inhibitors, and metformin). A prospective, well-controlled study that excludes these medications in patients with diabetes would be necessary to determine whether VLCD/TMR programs yield similar weight loss results in both diabetic and non-diabetic populations. In this study, men were more likely to have diabetes, indicating potential differences in selection based on the motivation of referring physicians and male patients. The focus may lean more toward targeted comorbidity reduction rather than social pressure or the desire to appear thinner.

In light of the extensive background of VLCD/TMR, this study adds valuable insights into the role of AOM in combination with meal replacements for weight loss. Examining the impact of AOM on weight loss and weight regained during and after a comprehensive lifestyle program encompassing VLCD/TMR phases has contributed to the ongoing discussion regarding effective weight management strategies. These findings indicate that while meal replacements and unsustainably low kcal intake may serve as potent tools for short-term weight loss, the addition of AOM offers the potential for enhanced weight maintenance and reduced weight regained, especially in the long term. These results underscored the complexity of obesity management and the potential benefits of combining various interventions to address both short-term and long-term weight

TABLE 4 Weight loss outcomes by medication administration.

	Liraglutide or semaglutide	Phentermine	Phentermine/ topiramate	Liraglutide or Semaglutide + Phentermine +/−topiramate	Liraglutide and Bupropion/ Naltrexone	Bupropion/ Naltrexone	*p*-value
Number	28	15	9	7	4	3	
Total body weight loss AT 3 months, %	−14.49 (5.56)	−13.82 (5.01)	−12.59 (3.14)	−13.18 (3.28)	−14.92 (5.71)	−11.44 (1.15)	0.89
Total body weight loss at 6 months, %	−18.42 (7.5)	−17.7 (6.69)	−13.87 (9.78)	−14.38 (5.03)	−15.38 (4.67)	−14.61 (1.4)	0.62
Total body weight loss at 18 months, %	−14.29 (10.32)	−13.19 (6.43)	−10.4 (16.52)	−11.01 (11.17)	−22.71 (27.65)	−9.03 (6.24)	0.75
Weight regain, kg	+4.6 (5.98)	+2.83 (3.23)	+4.48 (15.55)	+1.95 (11.99)	−15 (32.14)	+7.27 (9.97)	0.18
Total body weight regain, %	+4.54 (6.01)	+2.86 (3.18)	+2.78 (14.86)	+2.7 (11.73)	−16.39 (32.99)	+5.78 (7.73)	0.13

Note: Data are shown as mean (standard deviation) or number (percentage).

*p-value calculated with ANOVA test.

control challenges. Further research is warranted to elucidate the intricate interplay of meal replacements, AOM, and lifestyle modifications in achieving lasting weight loss success.

The current study had several limitations. First, it is a retrospective analysis conducted at a single institution. However, these findings are consistent with previous studies, further supporting the notion that AOM can be used in conjunction with other weight loss approaches. One notable limitation pertains to the methodology used for calculating weight regained. In this study, 6 months was selected as the reference point for assessing weight regain, which may not capture individual variations in weight trajectories. The authors recognize that some participants may have started to regain weight before this time frame, while others might have continued to lose weight. To address this concern, future research could explore alternative methods for calculating weight regained that consider individual weight trends. Furthermore, to underscore the need for a prospective randomized controlled trial that specifically examines obesity-associated pharmacotherapy during very low-calorie diet/total meal replacement (VLCD/TMR) programs is essential. Such a trial should ensure consistent initiation of AOM at the same phase of the lifestyle program, while control patients receive the same overall care without AOM. Additionally, larger sample sizes and longer-term follow-up are necessary to gain a more comprehensive understanding of the clinical outcomes observed in this study and to assess whether continued use of AOM maintains weight loss beyond 18 months or if further weight regain occurs. Furthermore, patients who withdrew from the OPTIFAST program early or lacked follow-up data around the 18-month mark were excluded from this analysis. Therefore, the magnitude of weight loss should not be compared to studies that employed an intention-to-treat analysis, and the results do not reflect the mean outcomes of all patients who initiate similar programs in a real-world setting.

5 | CONCLUSION

This study demonstrates that using approved anti-obesity medications in conjunction with a very low-calorie diet and total meal replacement program is associated with significantly less weight regain at 18 months, highlighting the benefits of combination therapy in obesity management. Despite the medication group having a greater frequency of diabetes, no significant baseline differences or predictors of weight recovery were found. These findings emphasize the need to treat both physiological and lifestyle variables in obesity therapy, stressing medication's potential in enhancing weight loss and assisting patients in managing cravings and adjusting physiological set-points. More studies are needed to evaluate long-term efficacy beyond 18 months and determine the best time to start medications throughout the weight reduction program to avoid side effects.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare in relation to this publication.

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