Received: 1 July 2024 | Revised: 20 September 2024 | Accepted: 25 September 2024

DOI: 10.1002/oby.24177

ORIGINAL ARTICLE

Clinical Trials and Investigations

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

Weight maintenance on cost-effective antiobesity medications after 1 year of GLP-1 receptor agonist therapy: a real-world study

Nina U. Paddu[1,2] | Brianna Lawrence[2] | Sydnee Wong[1] | Sabrina J. Poon[3] | Gitanjali Srivastava[1,2,4,5]

[1]Department of Medicine, Division of Diabetes, Endocrinology & Metabolism, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[2]Vanderbilt Weight Loss Center, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[3]Department of Population Health, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[4]Department of Surgery, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[5]Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

Correspondence
Gitanjali Srivastava, Division of Diabetes, Endocrinology & Metabolism, Department of Medicine, Vanderbilt University School of Medicine, 719 Thompson Lane, Suite 22200, Vanderbilt Weight Loss Center, Nashville, TN 37204, USA
Email: gitanjali.srivastava@vumc.org

Abstract

Objective: The high cost of novel glucagon-like peptide-1 receptor agonist (GLP-1 RA) class agents often limits access and creates barriers to care. This real-world study evaluated the efficacy of older-generation generic antiobesity medications (AOMs) for weight maintenance after 1 year of GLP-1 RA therapy in patients who had achieved successful weight loss.

Methods: We prospectively followed patients ($N = 105$) who had completed 12 months of therapy and were part of a "medical weight loss bundle," which included 12 months of GLP-1 RA therapy followed by 6 months of transition care. The baseline mean BMI was 36.4 kg/m^2. Body weight outcomes were measured at 6, 12, 18, and 24 months.

Results: After the medical weight loss bundle, 40 patients transitioned to generic AOMs. At 12 months, this cohort lost an average of 18.3%, 95% CI [13.0%, 23.6%] body weight from baseline, with a mean BMI of 27.9 kg/m^2. At 18 months, they maintained the weight loss, with a mean BMI of 27.9 kg/m^2. Subsequent follow-up visits (average 1.5 months later) without GLP-1 RAs showed further reduction, resulting in a total average weight loss of 25.5%, 95% CI [23.1%, 27.9%] compared to the initial visit.

Conclusions: Patients successfully treated with GLP-1 RAs can maintain their weight loss using generic older-generation AOMs, suggesting potential cost savings for insurers and implications for policy regarding AOM coverage.

INTRODUCTION

Obesity has become a global epidemic over the past 20 years. It affects nearly every organ system, increasing morbidity and mortality and reducing quality of life. This complex chronic condition results from a variety of influences, including genetic variants, endocrine abnormalities, poor dietary choices, sedentary behavior, increased stress, inadequate sleep, medications, and disruptions in circadian rhythms. Almost half of Americans are projected to have obesity by 2030, highlighting the need for effective treatments. As several studies have shown, lifestyle changes alone are not sufficient to sustain long-term weight loss when severe obesity is present; often

there is weight regain due to an increase in appetite and a decrease in energy expenditure and satiety. Escalation in therapy, such as pharmacotherapy and/or bariatric surgery, is required to overcome metabolic adaptation. With the advent of novel therapeutics, namely glucagon-like peptide-1 receptor agonists (GLP-1 RAs), more patients are now able to achieve body mass index (BMI) of less than 30 kg/m^2. Furthermore, these agents result in sustained weight reduction for up to 4 years, an increase compared to lifestyle changes alone [1].

In addition, these medications have demonstrated improvement in weight-related comorbidities, such as type 2 diabetes, fatty liver, hyperlipidemia, hypertension, sleep apnea, cardiovascular disease, and joint pain. However, due to the high cost of these agents, many individuals cannot continue them long term. Medicare has restricted use of GLP-1 RAs to those with type 2 diabetes or established cardiovascular disease [2] based on data from the SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity) trial, which showed a 20% risk reduction in major adverse cardiac events with semaglutide 2.4 mg/week for 39.8 months [3]. This prompted Medicare to limit coverage of semaglutide 2.4 mg to patients with known heart disease or stroke history plus the presence of obesity, but it excluded those patients with obesity without these particular complications. Other insurance plans limit the use of GLP-1 RAs to only a short period of time (e.g., 12 months) and/or require individuals to lose a certain percentage of body weight (e.g., 5%) to permit the renewal of coverage [4]. As a result, many individuals are not able to access these novel and effective treatments. Additionally, due to medication back orders from the manufacturer, many doses of GLP-1 RAs are not consistently available.

Furthermore, the literature has demonstrated that those who start using GLP-1 RAs can see weight regain when they discontinue the medications; this occurs because these medications reduce body weight set point through hormonal changes that promote satiety and diminish appetite. In the SURMOUNT-4 study (a study of tirzepatide in participants with obesity and overweight for the maintenance of weight loss), individuals who discontinued tirzepatide therapy after 36 weeks and switched to placebo experienced a 14% weight regain after 52 weeks compared to baseline; conversely, those who continued tirzepatide therapy experienced a 23.5% weight loss from baseline [5]. Similarly, in the STEP-4 trial (effect of continued weekly subcutaneous semaglutide vs. placebo on weight loss maintenance in adults with overweight or obesity), individuals who stopped semaglutide treatment and started placebo regained 6.9% body weight, on average, after 48 weeks [6].

In response to pressing health challenges, our institution implemented a comprehensive weight management program initiated on January 1, 2022, as detailed by Srivastava et al. [7]. Briefly, we created a direct-to-employer bundled payment program that incentivizes high-quality care while minimizing unnecessary medical expenditures. The bundle lasts 18 months, has zero out-of-pocket costs for patients, and includes Food and Drug Administration (FDA)-approved and off-label antiobesity medications (AOMs), including several GLP-1 RA medications. In addition to AOM coverage, the bundle includes all consultations and related services at our multidisciplinary academic tertiary care obesity center (Vanderbilt University Medical Center, Nashville, Tennessee), which accommodates over 10,000 new patient visits annually. Following this period, patients could continue GLP-1 RA therapy if covered by their standard insurance or through self-funding; alternatively, some opted for more affordable second-generation AOMs to sustain their weight loss or chose solely lifestyle modifications for ongoing weight management.

This shift underscores the importance of an in-depth analysis of the posttreatment phase to refine a predictive value-based model that accurately reflects sustained weight loss results. Given the recent FDA approval of novel GLP-1 RAs and the consequent scarcity of long-term efficacy data, we initiated a prospective real-world cohort study among our program participants. The study aimed to evaluate

Study Importance

What is already known?

- Glucagon-like peptide-1 (GLP-1) receptor agonist (RA) medications have demonstrated effectiveness in weight reduction. However, discontinuation often leads to weight regain.
- Long-term access to GLP-1 RA medications faces several barriers, including insurance coverage gaps, cost considerations, and supply issues from manufacturers.

What does this study add?

- Older-generation antiobesity medications (AOMs) can mitigate weight regain commonly observed after discontinuing GLP-1 RA therapy.
- In a real-world study, individuals maintained their weight loss for up to 24 months by transitioning from 12-month GLP-1 RA therapy to generic AOMs.
- The most frequently used AOMs for weight maintenance after GLP-1 RA therapy were metformin (used by 80% of patients), topiramate (used by 32.5% of patients), and bupropion (used by 32.5% of patients).

How might these results change the direction of research or the focus of clinical practice?

- Given challenges with long-term GLP-1 RA access, second-generation AOM therapy could offer an effective and affordable solution to prevent weight regain.
- Patients who respond well to GLP-1 RA therapy within the first year may be suitable candidates for transitioning to generic AOMs after 12 months.
- Future research should explore the long-term efficacy of older-generation AOMs following initial GLP-1 RA treatment across a broader and more diverse patient population to validate these findings.

enduring weight maintenance in individuals who achieved BMI < 30 kg/m^2 after 1 year on GLP-1 RAs (semaglutide, dulaglutide, and/or tirzepatide) before transitioning to more cost-effective, older-generation, FDA-approved and/or off-label AOMs (metformin, topiramate, phentermine, bupropion, and/or naltrexone) as single or combination treatments. Primary outcomes included percentage changes in weight and BMI at intervals of 6 months up to 2 years.

METHODS

This study was exempt as determined by the institution's institutional review board (November 2020; renewal November 2023). All patients in the study were part of a "medical weight loss bundle" (MWLB), an 18-month program (12 months of treatment plus 6 months to transition care) designed by our institution [7]. Patients had to have a starting BMI >35 kg/m^2 to enroll in the MWLB and qualify for comprehensive weight management services under our center. At the time of the study, three large employers and/or institutions were participating in the MWLB, and therefore patients were located within the inner city or regionally. Pharmacy benefits as part of the MWLB also included unrestricted access to GLP-1 RA therapy for 12 months. Patients were AOM naïve prior to the initial medical obesity assessment visit. MWLB patients were transitioned to a "weight maintenance phase" if they had achieved a target clinical goal of <30 kg/m^2 with documented stability of weight without regain over 3 to 6 months. The transition plan included a referral back to the primary care physician and generic AOM prescriptions. Thus, we sought to study the highly selected cohort of patients in the MWLB weight maintenance phase. Patients who were not part of the MWLB were excluded from the study.

Electronic health records of MWLB patients who had achieved BMI ≤30 after 12 months of being on a GLP-1 RA class agent (either in combination with another AOM or as monotherapy) between 2022 and 2023 were extracted through informatics ($n = 105$). This time period was chosen because it coincided with activation of 12 months of obesity pharmacotherapy benefits (including GLP-1 RA therapy) for patients enrolled in the MWLB at our institution, and weight measurements beyond 12 months would likely be assessable for these patients. The records were deidentified and analyzed. Data were manually reviewed ($n = 2$ reviewers) and extracted to ensure accuracy. Data were collected retrospectively.

Initial anthropometrics were defined by the measured weight and height entered into the electronic health record at the first visit with the MWLB provider. End anthropometrics were defined by the 6-, 12-, 18-, and 24-month visit ±45 days and the most recent visit in the system. Patient demographics, weight-related medical complications, percentage weight reduction from the initial visit, percentage BMI reduction, and AOM utilization data were collected.

Antiobesity pharmacotherapy included FDA-approved agents (phentermine, phentermine/topiramate, naltrexone/bupropion, semaglutide, and tirzepatide) or off-label therapies (semaglutide and tirzepatide injections approved for type 2 diabetes, oral semaglutide, topiramate, bupropion, and metformin). Orlistat was not prescribed to any of the patients due to lack of clinical efficacy and significant side-effect profile.

The following were completed as part of routine initial new patient clinical assessments at the center: anthropometrics and body composition (Tanita bioelectrical impedance analysis) for weight and percentage body fat measurements. BMI was calculated at the initial and subsequent visits. Patients who completed at least two visits in 12 months were considered "completers" of the program, and those who participated in only one were "noncompleters" for this study. Medical comorbidities, such as depression/anxiety, type 2 diabetes, prediabetes, hypertension, hyperlipidemia, vitamin D deficiency, fatty liver, osteoarthritis, joint pain, and obstructive sleep apnea, were derived from the patient medical history.

Statistical significance was set at the 95% confidence interval (CI). A two-sided $p < 0.05$ was considered statistically significant. Data for numerical values were reported as the mean ± 95% CI. Statistical significance for weights over time was determined using repeated-measures design. Differences among continuous variables between the weight-responsive groups were determined using independent t tests, and χ^2 tests were used for assessment of statistical differences between categorical variables. Statistical analysis was done using SPSS software (IBM Corp.).

RESULTS

Informatics identified a total of 105 patients who achieved BMI <30 kg/m^2 after 12 months on treatment with AOMs during the MWLB. These patients were included in the initial analysis. Baseline characteristics of this cohort are presented in Table 1. Patients, on average, were 45.2 years old with a mean BMI of 36.4 kg/m^2 at the initial visit. Of these patients, 92.1% were female, and 80.6% were White. Four individuals had history of Roux-en-Y gastric bypass, and three had history of vertical sleeve gastrectomy. The prevalence of any obesity-related medical condition was 75.2% (depression/anxiety 40%, type 2 diabetes 8.5%, prediabetes 11.4%, hypertension 26.6%, hyperlipidemia 20%, vitamin D deficiency 7.6%, fatty liver 7.6%, osteoarthritis 3.8%, joint pain 28.6%, obstructive sleep apnea 12.4%; 76.1% had other comorbidities, such as gastroesophageal reflux disease, polycystic ovarian syndrome, tachycardia, attention-deficit/hyperactivity disorder, chronic back pain, or heart failure).

Of these 105 patients, 7 did not desire treatment with GLP-1 RAs due to adverse effects or other reasons, and 4 individuals left the MWLB early due to change in employment or desire to pursue a pregnancy instead. Of the 105 patients, 25 had not yet completed the entire 18-month MWLB program ($n = 36$ total, pre–weight maintenance phase; Table 2). A total of 69 patients finished 12 months of GLP-1 RA therapy and the 6-month transition period. After the 18-month MWLB program (weight maintenance phase), some individuals

TABLE 1 Demographics of medical weight management patients upon first obesity encounter who were able to achieve BMI <30 kg/m^2 upon completion of program at 12 mo ($N = 105$)

Demograhics including medical complications	Results	Confidence interval where applicable	Range and/or % where applicable
Age (y)	45.2	95% CI ± 1.9	Range: 23–60
Gender	94 F; 10 M; 3 missing data		92.1% F
Race and ethnicity	83 White; 14 Black; 5 Hispanic; 2 unknown (80.6% White)		
Initial weight (lb)	221.4	95% CI ± 4.60	
Initial BMI (kg/m^2)	36.4	95% CI ± 0.48	Range: 34.6–41.6
Initial body fat (%)	45.9	95% CI ± 0.96	
RYGB (Roux-en-Y gastric bypass)	4		
VSG (vertical sleeve gastrectomy)	3		
Abdominal banding	0		
Any comorbidity	79 (75.2%)		
Depression and/or anxiety	42 (40%)		
Type 2 diabetes	9 (8.5%)		
Prediabetes	12 (11.4%)		
Hypertension	28 (26.6%)		
Hyperlipidemia	21 (20%)		
Vitamin D deficiency	8 (7.6%)		
Fatty liver	8 (7.6%)		
Osteoarthritis	4 (3.8%)		
Joint pain	30 (28.6%)		
Obstructive sleep apnea	13 (12.4%)		
Other comorbidities (gastroesophageal reflux disease, polycsystic ovarian syndrome, hypothyroidism, tachycardia, attention-deficit/hyperactivity disorder, back pain, congestive heart failure, etc.)	80 (76.1%)		

either (1) remained on GLP-1 RAs ($n = 12$; of whom 9 individuals had type 2 diabetes and thus were able to continue the GLP-1 RA class agent through standard insurance and 3 individuals chose cash-pay option for GLP-1 RA coverage) or (2) did not receive any AOM therapy ($n = 17$) due to desire to maintain weight loss with lifestyle changes alone or due to being lost to follow-up in clinic (Table 2). A total of 40 individuals were given therapy with GLP-1 RAs for 12 months and then were transitioned to older-generation generic therapy (phentermine, generic phentermine/topiramate, topiramate, metformin, bupropion, and/or naltrexone) to assist with weight loss maintenance after the MWLB ended.

As shown in Table 3, 69 of 105 patients received GLP-1 RA therapy specifically during the MWLB for 12 months. Of these patients, 71% were treated with semaglutide 2.0 mg/week, 49% were treated with semaglutide 2.4 mg/week, 14.5% received oral semaglutide, 13% received dulaglutide, and 7% received tirzepatide (Table 3). The utilization of GLP-1 RAs was greater than 100% as more than one GLP-1 RA was used for an individual patient; this was done due to medication shortages, decreased efficacy, or side effects.

Of these 69 patients, 40 patients were transitioned to generic second-generation AOMs after the MWLB ended (Table 3). Of the 69 patients, 80% were given metformin extended release, 20% were given phentermine, 32.5% were given topiramate, 32.5% were given bupropion, and 2.5% were given naltrexone to help maintain weight loss. However, upon transition to primary care, for weight maintenance, phentermine was avoided due to its controlled substance designation. On average, most patients required more than one generic AOM to help maintain weight loss after discontinuing GLP-1 RA therapy, which is why utilization was greater than 100%.

In total, 105 patients enrolled in the MWLB achieved an average weight loss of 22.2% ± 3.3% at 12 months compared to baseline (Table 4). Of note, this includes all patients who received 12 months of AOM therapy, regardless of treatment completion or type (novel GLP-1 RA therapy and/or older generic options). At 18 months, 27 patients had extractable body weight data from the obesity clinic within 45 days of the 18-month window and maintained their weight, with an average BMI of 29.0 ± 0.8 kg/m^2. At an average of 576 ± 20.2 days after the initial visit, weight loss was maintained at a mean

TABLE 2 Excluded patients in analysis ($N = 65$).

Reason for exclusion	*n*
Pre–weight maintenance phase/treatment	
Generic second-generation AOMs in MWLB only (no GLP-1 RA use)	7
MWLB (with GLP-1 RA use) ended early	4
MWLB (with GLP-1 RA use) not completed yet	25
Subgroup 1 total	36
Weight maintenance phase	
GLP-1 RA use in MWLB, then continued GLP-1 RA therapy ($n = 9$ T2DM; $n = 3$ cash-pay option)	12
GLP-1 RA use in MWLB, but no generic AOMs prescribed	17
Subgroup 2 total	29
Total subgroup 1 + subgroup 2	65

Note: 105 patients in MWLB who achieved BMI <30 kg/m^2 at 12 mo after enrollment were identified. Only patients who completed 12 mo of therapy and transitioned to older-generation generic AOMs were included in the data analysis in this study ($n = 40$). These patients were placed on oral metformin, topiramate, bupropion, naltrexone monotherapy, or combination; phentermine was avoided in many cases due to its controlled substance designation upon transition to primary care.
Abbreviations: AOM, antiobesity medication; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MWLB, medical weight loss bundle; T2DM, type 2 diabetes mellitus.

TABLE 3 AOMs prescribed during first 12 mo of program ($N = 69$)

	n	%
Branded or more expensive, $$–$$$ ($N = 69$)		
Phentermine/topiramate ER	0	0
Naltrexone/bupropion ER	0	0
Semaglutide 2.0 mg	49	71
Semaglutide 2.4 mg	34	49
Liraglutide 3.0 mg	0	0
Liraglutide 1.8 mg	0	0
Dulaglutide	9	13
Semaglutide oral	10	14.5
Tirzepatide	5	7
GLP-1 RA class	107	>100% utilization[a]
Generics or less expensive, $ ($N = 40$)[b]		
Metformin	32	80
Phentermine 37.5 mg	5	12.5
Phentermine 15 mg	1	2.5
Phentermine 8 mg	2	5
Topiramate	13	32.5
Bupropion	13	32.5
Naltrexone	1	2.5
Hydrogel capsule	0	0
Zonisamide	0	0
Empaglifozin	0	0
Dapagliflozin	0	0
Total no. of AOMs prescribed per patient after MWLB ended	Mean: 1.7	

Abbreviations: AOM, antiobesity medication; ER, extended-release; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MWLB, medical weight loss bundle; $, <~$20, exceptions: empagliflozin and dapagliflozin need diagnosis of type 2 diabetes; $$, ~$50-100, phentermine/topiramate ER, naltrexone/bupropion ER; $$$, >~$900, GLP-1RA class agents.
[a]GLP utilization >100% as some patients may have switched GLP-1 RA due to side effects on generics or switched between GLP-1 RA classes.
[b]Generic AOMs: Only 40 patients transitioned to generic second-generation AOMs; the other 29 patients either continued GLP-1 RA therapy, chose to maintain weight loss with lifestyle changes, or did not follow up after MWLB ended.

of 25.2% ± 2.2% compared to baseline ($n = 77$ with extractable weight data available in electronic health record from primary care or specialist visits). At 24 months, patients maintained a mean weight loss of 16.1% ± 1.6% ($n = 5$ with extractable weight data available). Although some weight regain was observed by 24 months, the difference in weight reduction between 18 months and 24 months was not statistically significant. Notably, 25.7% ($n = 27$) of patients followed up with a specialist obesity medicine provider at 18 months, whereas 73.3% ($n = 77$) of patients followed up with their primary care physician and/or another provider at the 576-day time frame and had extractable weight data in the electronic health record, likely due to end of bundle enrollment coverage and discharge from the obesity clinic with a referral back to primary care. However, compliance and adherence dropped significantly at the 24-month mark, with only 4.7% of the patients following up with either an obesity provider or a primary care physician. This suggests that the 18- to 24-month weight maintenance phase may be a critical time to educate primary care providers on the importance of continued and more frequent medical visits to prevent weight regain until stability is achieved.

Table 5 shows this subgroup of patients who completed GLP-1 RA therapy in the MWLB and then transitioned to second-generation AOM therapy for weight maintenance. At the initial visit, this group had a mean BMI of 36.5 ± 0.7 kg/m^2. At 12 months, patients had lost an average of 18.3% ± 5.3% body weight from baseline, obtaining an average BMI of 27.9 ± 0.8 kg/m^2, which was a statistically significant difference ($p < 0.05$). There was also a decrease of 12% in body fat percentage at 12 months versus baseline as measured by the Tanita bioelectrical impedance analysis (47.2% ± 1.2% at baseline vs. 35.5% ± 2.8% at 12 months). Afterward, at 18 months, this cohort maintained weight loss (mean BMI was still 27.9 ± 0.9 kg/m^2). These patients ($n = 40$) then had a follow-up visit at Vanderbilt University Medical Center with another specialist or their primary care provider, on average 1.5 months later (593 ± 25.7 days after initial visit), and their average BMI remained at 27.2 ± 0.9 kg/m^2, representing a mean total weight reduction of 25.5% ± 2.4% compared to the initial visit. The mean BMI was not statistically significantly different between the visits at 12 months, 18 months, and 593 days and the 24-month follow-up ($p > 0.05$). At this follow-up visit, individuals were not taking GLP-1 RAs. This suggests that these patients were able to maintain weight loss on generic second-generation AOMs.

TABLE 4 Weight loss maintenance outcomes of successful medical weight loss bundle patients (defined as BMI <30 kg/m^2 at 12 mo)

	Initial visit	6 mo ± 45 d	12 mo* ± 45 d	18 mo** ± 45 d	24 mo** ± 45 d	576 d** ± 20.2 d (most recent encounter in health record)
Weight (lb)	221.4 ± 4.6	188.8 ± 3.9	169.58 ± 3.9	172.9 ± 4.6	187.9 ± 4.9	168 ± 4.5
BMI (kg/m^2)	36.4 ± 0.5	30.43 ± 0.9	27.6 ± 0.8	29.0 ± 0.8	34.2 ± 1.1	27.7 ± 0.6
Weight loss (%) from initial obesity encounter	0	−14.8 ± 1.5	−22.2 ± 3.3	−22.8 ± 1.6	−16.1 ± 1.6	−25.2 ± 2.2
N	105	93	85	27	5	77
Body fat (%), $p < 0.05$	45.9 ± 0.9		35.8 ± 1.6			

Note: Data at 6, 12, 18, and 24 mo derived from medical weight management encounters; data at 576 d derived from most recent encounter note either with specialist or primary care. Patients were transitioned off glucagon-like peptide-1 receptor agonist class of agents at 12 mo and transitioned to oral generics (metformin, topiramate, bupropion, naltrexone monotherapy, or combination; phentermine was avoided in most cases due to its controlled substance designation upon transition to primary care). Data are mean ± 95% CI unless otherwise indicated.
*$p < 0.05$, 6 mo vs. 12 mo.
**$p > 0.05$, 12 mo vs. 18 mo, 576 d, 24 mo; 18 mo vs. 24 mo.

TABLE 5 Subgroup analyses of patients who had a GLP-1 RA class agent prescription for weight loss during first 12 mo and then transitioned to generic AOMs ($N = 40$)

	Weight (lb)	BMI (kg/m^2)	Weight loss (%) from initial visit	Body fat (%)
Initial visit ($N = 40$)	219.5 ± 5.2	36.5 ± 0.7		47.1 ± 1.2
6 mo ± 45 d ($n = 34$)	187.6 ± 4.8	31.2 ± 0.7	−13.8 ± 1.6	
12 mo ± 45 d ($n = 33$)	168.4 ± 5.9	27.9 ± 0.8	−18.3 ± 5.3	35.5 ± 2.8
18 mo ± 45 d ($n = 15$)	167.9 ± 6.4	27.9 ± 0.9	−25.1 ± 2.6	
593 d ± 25.7 d ($n = 40$)	163.5 ± 6.4	27.2 ± 0.9	−25.5 ± 2.4	
24 mo ± 45 d ($n = 2$)	180.1 ± 11.9	31.0 ± 1.3	−20.6 ± 3.2	

Note: Data are mean ± 95% CI. Average of 4.1 provider visits within the first 12 mo (range: 3–6). $P < 0.05$ initial vs. 6, 12, 12+, or 18 mo.
Abbreviation: GLP-1 RA, glucagon-like peptide-1 receptor agonist.

Additionally, from the last visit at our obesity center (around 14 months) and the most recent follow-up appointment at another provider's office within the health system (when the patients were not on GLP-1 RAs), there was still a mean 1.46 lb decrease in weight noted using older-generation generic AOMs. This follow-up appointment was, on average, 166 days (5.5 months) after the most recent visit in the bundle program when the patients were on GLP-1 RAs.

DISCUSSION

This prospective real-world study demonstrates that patients treated with GLP-1 RA therapy for 12 months who achieved BMI <30 kg/m^2 and then transitioned to cost-effective alternative AOMs were able to lose 25.1% ± 2.6% of their body weight, on average, and maintain the weight reduction up to 24 months. Furthermore, fat percentage (based on a bioelectrical impedance analysis) decreased by 10% after 12 months. Among this cohort, those who transitioned to generic AOMs (such as metformin, topiramate, phentermine, and bupropion) after the MWLB pharmacy coverage ended at 12 months were able to maintain their weight loss up to 24 months. This demonstrates that alternative and inexpensive medications can be used for weight maintenance if GLP-1 RA therapy cannot be continued. These generic medications can offset the weight regain expected with GLP-1 RA discontinuation. These results are noteworthy as many patients lose insurance coverage for GLP-1 RAs and are concerned about weight regain off the medications. Since these older-generation AOMs also target appetite, insulin resistance, cravings, and satiety, they are suitable and cost-effective alternatives for the treatment of obesity and overweight at the appropriate doses.

Furthermore, this subgroup of patients who transitioned from GLP-1 RA therapy to generic AOMs experienced significant weight loss (Table 5), with an average reduction from 219.5 lb to 163.5 lb over approximately 593 days. Notably, there was a reduction in BMI from 36.5 to 27.2 over the study period, and weight loss of 20.6% was maintained over 24 months. These data indicate significant weight loss during the initial 12 months of GLP-1 RA therapy, with continued weight loss after transitioning to AOM therapy. This

suggests that the combination of these therapies can be effective for long-term weight management and sustained weight loss. Moreover, body fat percentage decreased from 47.1% to 35.5% at 12 months, highlighting the effectiveness of the therapies in reducing fat mass (which is crucial for metabolic health), reducing obesity-related risks, and providing overall improvement in health outcomes, including depression and anxiety (75.2% prevalence of any obesity-related medical condition; 40% depression/anxiety in study cohort). The slight increase in weight and BMI at the 24-month mark (though not found to be statistically significant) suggests a potential challenge in maintaining weight loss over the long term, indicating the need for ongoing support and possibly additional interventions for weight regain. In addition, the average of 4.1 provider visits within the first 12 months underscores the importance of regular follow-up and monitoring to achieve and maintain weight loss goals. Overall, these findings support the use of GLP-1 RAs followed by AOM therapy as a viable strategy for significant and sustained weight loss.

The most common medications prescribed were metformin, topiramate, bupropion, and phentermine. Metformin has been shown to helpful in weight loss by improving insulin resistance and promoting appetite suppression through increased secretion of GLP-1 [8] and peptide YY and increased hypothalamic leptin sensitivity [9, 10]. Furthermore, it can alter the gut microbiome and can induce expression and secretion of growth-differentiating factor 15, which reduces food intake, body mass, fasting insulin, and glucose intolerance [11, 12]. Phentermine is a sympathomimetic agent, which primarily increases norepinephrine and epinephrine levels to suppress appetite and increase energy expenditure. It stimulates the central nervous system. Topiramate is an anticonvulsant that lowers the seizure threshold and serves as a GABA-A RA (γ-aminobutyric acid-A receptor agonist). It is also a weak carbonic anhydrase inhibitor and antagonizes the glutamate receptor. Through these mechanisms, it enhances appetite suppression and satiety [13]. Bupropion was also prescribed to help with weight loss maintenance as it helps decrease emotional eating and cravings by working as a dopamine and norepinephrine reuptake inhibitor and decreasing the reward associated with food intake [14]. Naltrexone works synergistically with bupropion to induce satiety by inhibiting β-endorphin activity at the μ-opioid receptor and blocking autoinhibition of pro-opiomelanocortin neuron [15].

As demonstrated in Table 4, the average BMI decreased significantly at 12 months compared to the initial visit, remained about the same at 18 months, and again remained about the same at an average of 576 ± 20.2 days (after initial visit) at the patient's follow-up visit, indicating that the severity of obesity had decreased. A decreased obesity severity represents a decrease in adiposity; this corresponds to a decrease in treatment intensity.

Studies have shown that obesity directly mediates systemic inflammation, which contributes to insulin resistance and makes sustained weight loss difficult to achieve [16]. Specifically, obesity has been shown to involve high rates of plasma fatty acid mobilization and uptake, which play a central role in development of insulin resistance [17]. However, with significant weight loss, particularly a combination of healthy dietary modifications, GLP-1 RA therapy, and an increase in physical activity, there is a reduction in fatty acid mobilization and uptake, which is a key process in reducing insulin resistance. Phentermine/topiramate, metformin, bupropion, and naltrexone can also improve insulin sensitivity by facilitating calorie restriction by decreasing hunger, thereby promoting weight loss over time. As a result, a patient who is now in the overweight category is more likely to respond to these older-generation AOMs, as there is less inflammation and insulin resistance, even though (on average) these generic medications are weaker in efficacy compared to GLP-1 RAs.

While the study provides valuable insights into the efficacy of older-generation AOMs for weight maintenance, several limitations warrant consideration. First, the patient group analyzed was predominantly White and female. Consequently, the findings may not fully represent the diverse population affected by obesity. Our study focused on patients with severe obesity (BMI >35 at initial visit) who were self-selected as high responders to treatment (all achieving BMI <30) at 12 months. Existing research indicates that early responders to treatment tend to achieve long-term success [18]. In addition, the study cohort included predominantly female patients, though the MWLB was offered to both men and women. Our study was not powered to elucidate gender differences. However, it is noteworthy that 66% of the patients currently presenting to the comprehensive medical obesity center at our institution are female. Despite potential selection bias in our study, it suggests a specific patient profile: Those who respond well to treatment within 12 months may be able to transition from expensive GLP-1 RA therapy to more affordable oral generic AOMs. Future research should include a broader range of ethnicity, race, and gender to ensure generalizability. Similarly, clinicians should consider individual patient characteristics, including ethnicity, race, and gender, when tailoring obesity treatment plans. Recognizing that responses to AOMs may vary across different patient groups can guide personalized treatment decisions. Additionally, the exact timing of patients discontinuing GLP-1 RA medications after the 12-month period remains unknown. It is plausible that some patients continued taking them beyond 12 months, potentially confounding the weight maintenance data.

It is important to note that genetic obesity testing was not conducted in this study. Incorporating genetic information into obesity management can significantly enhance treatment plans and improve long-term outcomes for patients transitioning from GLP-1 RA to AOM therapy. Genetic variations can influence how patients metabolize and respond to medications, with certain genetic variants predisposing individuals to obesity and affecting their response to weight loss therapies. Personalized medicine approaches, which tailor treatments based on these genetic differences, hold great promise. Further research is needed to explicate the role of obesity pharmacogenomics during the weight maintenance phase.

Another limitation of this study is that it did not capture lifestyle modifications, including the patients' nutritional intake, exercise, sleep quality, emotional state, or stress level experienced in the weight maintenance phase, which could have also confounded the results. Some patients reported drinking socially, though there were no reports of alcoholism or marijuana use. Furthermore, the 24-month

follow-up data are incomplete, which affects the reliability of the results. Specifically, only five individuals shown in Table 4 and two in Table 5 had weight data available at the 24-month mark after starting treatment, resulting in a small cohort that makes it challenging to generalize findings. Although some patients did have medical visits around the 2-year period, these visits occurred either before or after the defined 24-month time frame in the study and were therefore excluded from the results. Variations in weight measurement may arise because follow-up weights were recorded at different provider offices using different scales. Consistent use of the same weighing scale during follow-up visits can improve accuracy. Lastly, among patients transitioning from GLP-1 RAs to generic AOMs, those who underwent bariatric surgery (gastric sleeve or Roux-en-Y gastric bypass) introduce additional metabolic complexities that could confound treatment effects.

CLINICAL IMPLICATIONS AND CONCLUSIONS

This study provides valuable insights into the potential of older-generation AOMs as a cost-effective strategy for maintaining weight loss achieved through GLP-1 RA-based pharmacotherapy. The findings suggest that, after significant weight reduction, the body's decreased inflammation and insulin resistance may enhance its responsiveness to therapies such as metformin, topiramate, phentermine/topiramate, or bupropion. Given the current challenges of medication scarcity and insurance barriers, transitioning patients to economical AOMs emerges as a prudent alternative for long-term weight management in addition to maintaining a healthy lifestyle. Patients who respond well to GLP-1 RA therapy within the first year may be suitable candidates for transitioning to generic AOMs. Clinicians should discuss the benefits, risks, and cost-effectiveness of transitioning from expensive GLP-1 RA medications to oral generics. Patients who have undergone bariatric surgery (e.g. gastric sleeve or Roux-en-Y gastric bypass) may experience metabolic changes affecting weight maintenance. Clinicians should account for these surgical effects when evaluating treatment outcomes. Moreover, regular follow-up visits are crucial to assess weight maintenance and treatment efficacy. Clinicians and researchers should track patients' progress beyond the initial 18- to 77-month period to understand real-world long-term outcomes. Insurers and employers should recognize the potential cost savings associated with transitioning patients to generic AOMs. State plans aiming to expand AOM coverage should consider evidence from studies like this. In conclusion, the results of this study underscore the importance of personalized, adaptable treatment strategies in obesity management. The study highlights the potential of older-generation generic AOMs in maintaining weight loss and the need for future research to validate these findings across diverse patient groups.O

CONFLICT OF INTEREST STATEMENT

Gitanjali Srivastava reports receiving advisory fees from Novo Nordisk, Eli Lilly and Company, and Rhythm Pharmaceuticals; being on the speaker's bureau for Novo Nordisk and Eli Lilly; and receiving research grant support from Eli Lilly and Company. The other authors declared no conflict of interest.

ORCID

Gitanjali Srivastava https://orcid.org/0000-0002-8326-3089

REFERENCES

1. Ryan DH, Lingvay I, Deanfield J, et al. Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial. *Nat Med*. 2024;30:2049-2057. doi:10.1038/s41591-024-02996-7
2. Hernandez I, Wright DR, Guo J, Shrank WH. Medicare part D coverage of anti-obesity medications: a call for forward-looking policy reform. *J Gen Intern Med*. 2024;39(2):306-308. doi:10.1007/s11606-023-08416-9
3. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563
4. Murphy T. Supply problems and insurance issues make popular weight-loss drugs hard to get. Associated Press. September 16, 2023. Accessed June 28, 2024. https://apnews.com/article/wegovy-ozempic-mounjaro-shortage-insurance-64014bc2887a518b33c597b2bf936e37
5. Aronne LJ, Sattar N, Horn DB, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. *JAMA*. 2024;331(1):38-48. doi:10.1001/jama.2023.24945
6. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA*. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224
7. Srivastava G, Paris C, Johnson J, et al. Specialized medical weight management intervention for high-risk obesity. *J Health Econ Outcomes Res*. 2021;8(2):1-5. doi:10.36469/001c.24896
8. Duca FA, Côté CD, Rasmussen BA, et al. Metformin activates a duodenal Ampk–dependent pathway to lower hepatic glucose production in rats. *Nat Med*. 2015;21(5):506-511. doi:10.1038/nm.3787
9. DeFronzo RA, Buse JB, Kim T, et al. Once-daily delayed-release metformin lowers plasma glucose and enhances fasting and postprandial GLP-1 and PYY: results from two randomised trials. *Diabetologia*. 2016;59(8):1645-1654. doi:10.1007/s00125-016-3992-6
10. Yerevanian A, Soukas AA. Metformin: mechanisms in human obesity and weight loss. *Curr Obes Rep*. 2019;8(2):156-164. doi:10.1007/s13679-019-00335-3
11. Day EA, Ford RJ, Smith BK, et al. Metformin-induced increases in GDF15 are important for suppressing appetite and promoting weight loss. *Nat Metab*. 2019;1(12):1202-1208. doi:10.1038/s42255-019-0146-4
12. Rodriguez P, Pantalone KM, Griebeler ML, Burguera B. Should I consider metformin therapy for weight loss in patients with obesity but without diabetes? *Cleve Clin J Med*. 2023;90(9):545-548. doi:10.3949/ccjm.90a.22096
13. Donavon B, Johnson JQ. Topiramate and phentermine. StatPearls. StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK482165/
14. Huecker MR, Smiley A, Saadabadi A. Bupropion. StatPearls. StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK470212/
15. Kulak-Bejda A, Bejda G, Waszkiewicz N. Safety and efficacy of naltrexone for weight loss in adult patients - a systematic review. *Arch Med Sci*. 2021;17(4):940-953. doi:10.5114/aoms.2020.96908
16. Schleh MW, Caslin HL, Garcia JN, et al. Metaflammation in obesity and its therapeutic targeting. *Sci Transl Med*. 2023;15(723):eadf9382. doi:10.1126/scitranslmed.adf9382

17. Schenk S, Harber MP, Shrivastava CR, Burant CF, Horowitz JF. Improved insulin sensitivity after weight loss and exercise training is mediated by a reduction in plasma fatty acid mobilization, not enhanced oxidative capacity. *J Physiol*. 2009;587(Pt 20):4949-4961. doi:10.1113/jphysiol.2009.175489
18. Srivastava G, Buffington C. Early weight loss outcomes from a newly established hospital-affiliated specialized obesity care delivery model in Central Florida. *Int J Obes (Lond)*. 2019;43(1):132-138. doi:10.1038/s41366-018-0092-3

How to cite this article: Paddu NU, Lawrence B, Wong S, Poon SJ, Srivastava G. Weight maintenance on cost-effective antiobesity medications after 1 year of GLP-1 receptor agonist therapy: a real-world study. *Obesity (Silver Spring)*. 2024; 32(12):2255-2263. doi:10.1002/oby.24177