

# Long-term weight loss maintenance with obesity pharmacotherapy: A retrospective cohort study

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## Abstract

**Objective:** To determine the association of anti-obesity medications (AOMs) with weight loss maintenance over 2 years.

**Methods:** This is a retrospective observational cohort study of adults treated for obesity between 1 April 2014 and 1 April 2016 at a tertiary academic weight management center and who completed 2 years of follow-up. Main outcome measures were mean percent weight loss, percent of individuals who achieved clinically significant long-term weight loss ( $\geq 5\%$  weight loss over 2 years), and long-term weight loss maintenance (achievement of  $\geq 5\%$  weight loss at 1 year and maintenance of the  $\geq 5\%$  reduction for the second year).

**Results:** Of the 1566 new patients, 421 completed 1- and 2-year follow-up appointments. Patients were mostly female and on average 51 years old; they weighed 100.1 kg and had a BMI of 35.8 kg/m<sup>2</sup> at initial visit. Mean weight losses at 1 and 2 years were 10.1% and 10.2%, respectively. The proportion of patients who experienced  $\geq 5\%$  weight loss was 75.5% at 1 year and 72.9% at 2 years. Long-term weight loss maintenance was achieved by 65.3% of patients. Almost all (96.2%) were on  $\geq 1$  AOM at 2 years, with metformin, phentermine, and topiramate among the most prescribed. AOM usage and older age demonstrated trends toward predicting weight loss maintenance over 2 years.

**Conclusions:** Long-term weight loss maintenance was observed among adults with medically managed obesity who completed 2 years of follow-up.

## KEYWORDS

anti-obesity, weight control, weight loss, weight maintenance, weight management

## 1 | INTRODUCTION

The efficacy of anti-obesity medications (AOMs) for weight management is well established in randomized clinical trials (RCTs) for both weight loss and weight loss maintenance.<sup>1-6</sup> However, the

effectiveness of AOMs for weight loss maintenance in real-world clinical practices has been poorly reported due to the lack of a standardized definition of weight loss maintenance.<sup>7</sup> The National Heart, Lung and Blood Institute defined weight loss maintenance as “a regain of weight that is less than 6.6 pounds (3 kg) in 2 years and a

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sustained reduction in waist circumference of at least 1.6 inches (4 cm)<sup>8</sup>. However, RCTs utilizing AOMs have defined weight loss maintenance as  $\geq 5\%$  weight-reduced from baseline after 4 weeks to 1 year of active weight loss.<sup>3,6,9</sup> The duration that defines maintenance also varies, ranging from 12 to 24 months in RCTs.<sup>3,6,10,11</sup> Meanwhile, the largest prospective study of long-term weight loss maintenance, the National Weight Control Registry, enrolled individuals who “maintained at least a 30-pound weight loss for 1 year or longer”.<sup>12</sup>

Obesity is a chronic, relapsing condition and thus weight loss maintenance is both challenging and elusive. In a meta-analysis of 29 studies, more than half of the weight lost was regained within 2 years and 80% was regained by 5 years.<sup>13</sup> Weight loss leads to a counterregulatory response manifesting as a reduction in energy expenditure<sup>14</sup> and central and peripheral hormonal changes that lead to increased hunger, decreased satiety and increased energy intake.<sup>15</sup> AOMs that target these neurohormonal adaptations may potentially blunt weight regain and facilitate weight loss maintenance.<sup>3,6</sup> For example, liraglutide has been associated with an attenuated reduction in leptin and increased postprandial peptide YY in the setting of weight loss.<sup>16</sup>

Retrospective cohort studies that have examined the long-term use of AOMs for weight loss maintenance have been limited to specific FDA-approved AOMs<sup>17,18</sup> or specific populations.<sup>19</sup> A retrospective chart review of 103 patients treated at the Austin Health Weight Control Clinic in Australia evaluated weight loss outcomes associated with just one AOM, phentermine-topiramate<sup>20</sup>; while 61 patients discontinued therapy after a mean duration of 10 months, 30 patients remained on phentermine-topiramate for a mean duration of 22 months and lost on average 6.7 kg (standard deviation (SD) not reported). More on-label AOMs (orlistat, phentermine, lorcaserin, and phentermine-topiramate) were examined for weight loss efficacy in a retrospective observational cohort study of 6988 men at the Veterans Administration (VA) as compared to a historical control group ( $n = 59,047$ ) who were enrolled in a lifestyle modification program (MOVE!).<sup>18</sup> The primary outcome was defined as percent weight change from baseline to  $\geq 20$  weeks (“6 months”), and a secondary outcome was percent weight change at 36 weeks. Average weight loss at 6 months was 3.6% (11.5), 4.1% (12.6), 2.1% (12.7), 3.6% (11.9), and 1.6% (12.8) in the lorcaserin, phentermine-topiramate, orlistat, phentermine, and MOVE! groups, respectively, and weight loss at 36 weeks was 4.6% (11.8), 4.3% (14.1), 2.8% (14.5), 2.5% (14.4), and 1.9% (15.0), respectively. Adherence was reported as a medication possession ratio (MPR) calculated as the total days' supply of medication provided over 180 days divided by 180 days, and MPR ranged from 0.5 (orlistat) to 0.65 (phentermine-topiramate). Long-term data on real-world use of off-label AOMs is limited to one study of 51 adults (age  $\geq 60$ ) in Brazil who were managed with monotherapy or combination therapy of sibutramine, orlistat, fluoxetine, sertraline, topiramate, fenproporex, mazindol or amfepramone.<sup>21</sup> After a mean follow-up of  $39.3 \pm 26.4$  months, mean weight loss was 6.7 kg. At 24 months, mean weight loss was 7.8 kg, with 69.7% of patients achieving  $\geq 5\%$  weight loss. Standard

deviations were not reported. Maximum duration of AOM therapy ranged from 1.4 years (orlistat) to 7.2 years (fluoxetine). The study's small size, specific population, and use of AOMs not available in the United States precludes its applicability to a broader population. Long-term weight loss maintenance associated with on-label AOMs naltrexone-bupropion or liraglutide 3.0 mg have not been evaluated in a real-world setting. Due to limited information on the real-world use of on- and off-label AOMs, this study aimed to explore the association of on- and off-label AOMs for maintaining clinically significant weight loss over 2 years in a real-world practice setting.

## 2 | METHODS

This is a retrospective observational analysis of 2-year weight loss maintenance outcomes in patients who established care at the Weill Cornell Medicine Comprehensive Weight Control Center between 1 April 2014 and 1 April 2016. The primary objective was to determine the association of AOMs with weight loss maintenance over 2 years. AOMs were defined as medications used on- or off-label for weight management. Weight loss maintenance was defined as having achieved  $\geq 5\%$  weight loss at 1 year and maintaining the  $\geq 5\%$  reduction for the second year.<sup>3,9</sup> Other secondary outcomes included mean percent weight loss at 2 years, percent of patients who achieved  $\geq 5\%$  or  $\geq 10\%$  weight loss at 2 years, number of AOMs, and AOMs used.

All patients ages 18–75 years who established care between 1 April 2014 and 1 April 2016 for weight management and who completed 1- and 2-year follow-up appointments were eligible for analysis. One-year outcomes were extracted from  $12 \pm 3$ -month follow-up appointments. Two-year outcomes were extracted from  $24 \pm 6$ -month follow-up appointments. For individuals who had multiple visits within this 18- to 30-month window, the visit closest to 24 months was used. Patients were excluded for the following: missed their 1- or 2-year follow-up appointments, established care for a non-obesity-related concern, were participants in an active research study involving weight loss, were managed with lifestyle modifications only (i.e., no AOM prescribed at initial visit), became pregnant during study period, or underwent a surgical or non-surgical bariatric procedure during the study period. Study period was defined as the 2-year of follow-up from initial visit.

Patients were identified by electronic medical record query, and data was extracted by three independent reviewers. Information abstracted included demographics, weight, BMI, medical history, use of on-label and off-label AOMs, number of AOMs prescribed, and number of visits with a registered dietitian (RD), nurse practitioner (NP), or physician (MD). Type 2 diabetes (T2D) medications used to treat obesity were counted as AOMs. Off-label medications were coded as AOMs as long as they were prescribed by the obesity medicine practitioner (e.g., bupropion was considered an antidepressant if prescribed by a non-obesity medicine practitioner). Combination brand-name medications (i.e., Qsymia, Contrave) were counted as two medications whether they were prescribed as the brand name or as generic components.

The Comprehensive Weight Control Center is an academic tertiary weight management center comprised of physicians, nurse practitioners, and registered dietitians. Lifestyle recommendations followed expert guidelines<sup>22</sup> and included reducing caloric intake (via low glycemic diet, calorie counting, or meal replacements) and increasing physical activity. Use and choice of AOMs were not protocolized and were determined by prescriber and patient.

## 2.1 | Statistical analysis

This study used a convenience sample of all new patients ( $n = 1775$ ) with evaluable data seen at the Comprehensive Weight Control Center between 4 January 2014 and 4 January 2016. After excluding patients who did not meet the inclusion criteria, the study had a total of 421 patients. A subgroup analysis of 69 patients with T2D was included to explore glycemic outcomes. Descriptive statistics were calculated to report the demographic and clinical variables of interest using  $N$  (%) for categorical variables and mean, median, and range for continuous variables where appropriate.

Multivariable logistic regression analysis was used to evaluate the independent effects of age, T2D status, baseline BMI, gender, number of visits, and number of AOMs on the primary endpoint of interest (i.e., proportion of patients who maintain  $\geq 5\%$  weight loss at 2 years) after controlling for demographic and clinical variables of interest. Collinearity between predictors in the model were evaluated prior to the formulation of the final multivariable model. All  $p$ -values were two-sided with statistical significance evaluated at the  $\alpha = 0.05$  level. Ninety-five percent confidence intervals for all parameters were calculated to assess the precision of the obtained estimates. All analyses were performed in R Version 3.1.3.

The study was approved by the Weill Cornell Medical College Institutional Review Board (IRB protocol # 1603017065).

## 3 | RESULTS

Electronic medical query identified 1775 patients who were seen between 4 January 2014 and 4 January 2016 of which 209 were not new to the practice (Figure 1). Of the 1566 new patients, 1145 were excluded due to lack of follow-up, non-obesity chief complaint, non-medically managed obesity, research participation, age  $<18$  or  $>75$  years, pregnancy, or bariatric procedure within the study period. A total of 689 completed 1-year follow-up, and 421 patients completed 1- and 2-year follow-up.

### 3.1 | Baseline characteristics

At baseline, patients were mostly female (74%) and on average 51 years old, weighed 98.6 kg and had a BMI of 35.3 (Table 1). About one-third of patients had class I obesity, one-fourth had class II obesity, and one-fifth had class III obesity; 4% had a BMI  $\geq 50$ . Most declined to provide their race or ethnicity. Patients had a median of 1 [0, 2] comorbidity. The most common comorbidity was prediabetes (26%), followed by hypertension (25%) and hyperlipidemia (21%), and a minority had T2D (16%).

### 3.2 | Weight loss outcomes

In this cohort of completers, mean weight change was  $-10.1\%$  (7.7) over year 1 and  $-0.2\%$  (6.0) over year 2. Overall, weight decreased by 10.2% (8.7) over 2 years (Figure 2). Clinically significant weight loss of  $\geq 5\%$  of baseline weight was achieved by 318 (75.5%) patients at 1 year and 307 (72.9%) patients at 2 years (Table 2). The proportion of patients who experienced  $\geq 10\%$  weight loss was 46.3% at 1 year and 47.0% at 2 years; and 24.2% and 27.1% lost  $\geq 15\%$  of their weight after 1 and 2 years, respectively. Clinically significant weight loss was maintained by

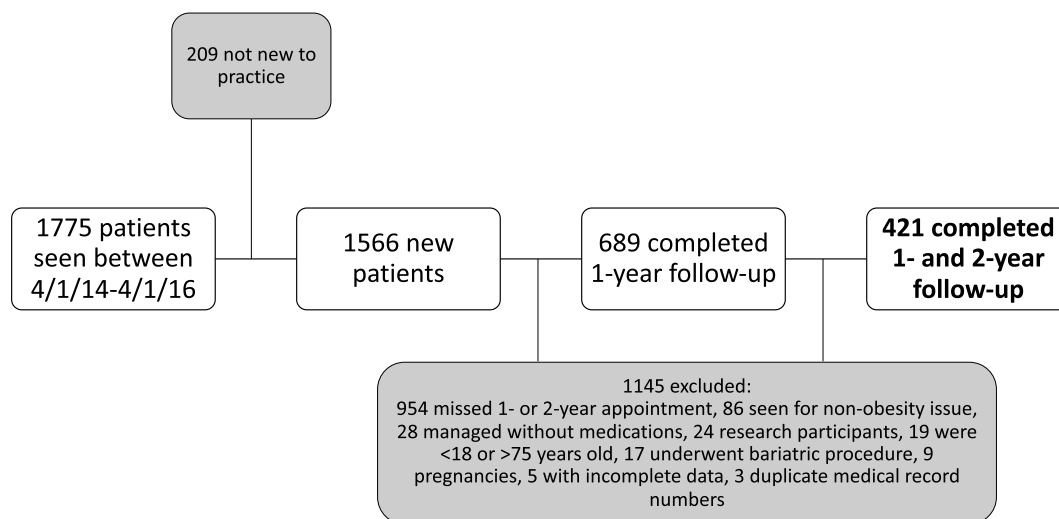


FIGURE 1 Flow chart of patients

TABLE 1 Baseline characteristics

	Completers (N = 421)
Age (years)	51 (13.8)
Female	310 (74)
Weight (kg)	98.6 (22.3)
BMI (kg/m <sup>2</sup> )	35.3 (6.8)
Class I	143 (34)
Class II	104 (25)
Class III	84 (20)
BMI ≥50	16 (4)
Race	
American Indian or Alaskan Native	1 (0.2)
Asian	4 (1)
Black or African American	16 (4)
White	144 (34)
Other	18 (4)
Declined	238 (57)
Ethnicity	
Hispanic/Latino	14 (3)
Non-Hispanic/Latino	141 (34)
Declined	266 (63)
Number of comorbidities	1 [0, 2]
Type 2 diabetes	69 (16)
HbA1c (%) <sup>a</sup>	7.4 (1.6)
Prediabetes	109 (26)
Hypertension	104 (25)
Systolic blood pressure (mmHg)	137 (18)
Diastolic blood pressure (mmHg)	81 (9)
Hyperlipidemia	87 (21)
Cardiovascular disease	16 (4)
Non-alcoholic fatty liver disease	15 (4)
Obstructive sleep apnea	60 (14)

Note: Data presented as mean (standard deviation), median [interquartile range], or *n*(%) where applicable.

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c.

<sup>a</sup>In patients with T2D.

275 of 318 patients between year 1 and 2, resulting in a long-term weight loss maintenance rate of 65.3%. Of the 195 patients who lost ≥10% after 1 year, 150 (76.9%) maintained this loss through the second year. Weight changes over 2 years demonstrated significant interindividual variability across the study population, ranging from weight loss of 38.8% to weight gain of 12.5% (Figure 3). Almost all (96.2%) were on ≥1 AOM at 2 years,

with 10% on 4 or more. The most prescribed AOMs were metformin (79%), phentermine (26%), and topiramate (22%) (Figure 4). The top three most common combinations were metformin plus phentermine/topiramate (Qsymia), metformin plus phentermine, and metformin plus liraglutide.

### 3.3 | Type 2 diabetes subgroup

In patients with T2D at initial visit (*n* = 69), mean age was 60 years and 55% were female (Table S1). Baseline mean weight was 101.9 kg, BMI was 35.9 kg/m<sup>2</sup>, and HbA1c was 7.4%. Most patients did not report their race or ethnicity. The most common comorbidity was hypertension (51%) followed by hyperlipidemia (17%).

Mean weight losses after 1 and 2 years were 8.2% and 8.4%, respectively (Table S2). The proportion of patients who experienced ≥5% and ≥10% weight loss was 66.7% and 36.2% at year 1 and 63.8% and 39.1% at year 2, respectively. About one-fifth lost at least 15% of their baseline weight: 18.8% at year 1 and 23.2% at year 2. Of the 46 individuals who achieved clinically significant weight loss after 1 year, 40 (87.0%) maintained weight loss. HbA1c decreased by 0.7% after 1 year, which was maintained at 2 years. Of the 33 patients who started with an HbA1c ≥ 7.0, 13 (39.4%) achieved control with HbA1c < 7.0 at 2 years.

### 3.4 | Predictors of weight loss and weight loss maintenance

Clinically significant weight loss at 2 years was predicted by higher initial BMI and AOM usage (Table 3). Even though the median number of AOMs were similar in those who did or did not achieve clinically significant weight loss, the distribution (i.e., interquartile ranges) differed significantly. Individuals with T2D were less likely to achieve ≥5% weight loss at 2 years, but this did not reach statistical significance (OR 0.60 [0.35, 1.04], *p* = 0.085). Trends for older age (*p* = 0.058) and more AOMs (*p* = 0.067) were noted as predictors of weight loss maintenance (Table 4), albeit not statistically significant.

## 4 | DISCUSSION

This study is the first retrospective cohort study to report long-term weight loss maintenance associated with polypharmacotherapy with on- and off-label AOMs among patients compliant with 2 years of management. Of those who completed 1- and 2-year follow-up appointments, almost two-thirds of patients achieved long-term weight loss maintenance. Heterogeneity in response was notable, with weight changes ranging from −38.8% to +12.5% over 2 years and a trend for less weight loss in patients with T2D, consistent with data from other studies.<sup>18,23</sup>

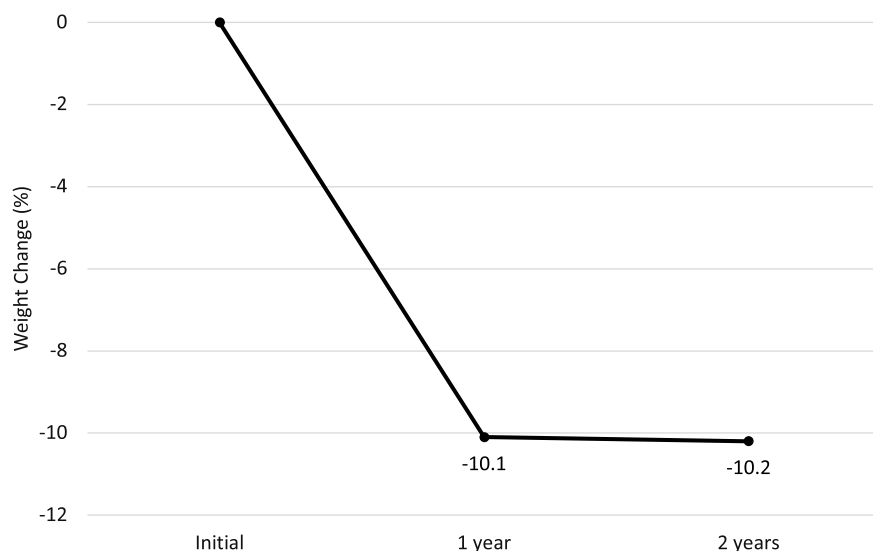


FIGURE 2 Mean weight changes over 2 years

TABLE 2 Weight changes over 2 years

Weight changes (%)	
Initial to 1 year	-10.1 (7.7)
1 year to 2 years	-0.2 (6.0)
Overall (initial to 2 years)	-10.2 (8.7)
BMI changes (kg/m <sup>2</sup> )	
Initial to 1 year	-3.7 (3.2)
1 to 2 years	-0.1 (2.4)
Overall (initial to 2 years)	-3.7 (3.4)
Categorical outcomes	
≥5% weight loss at 1 year	318 (75.5)
≥10% weight loss at 1 year	195 (46.3)
≥15% weight loss at 1 year	102 (24.2)
≥5% weight loss at 2 years	307 (72.9)
≥10% weight loss at 2 years	198 (47.0)
≥15% weight loss at 2 years	114 (27.1)
2-Year weight loss maintenance	275 (65.3)

Note: Data presented as mean (SD) or *n* (%) where applicable.

Abbreviation: BMI, body mass index.

As a completers' analysis, this study emphasizes that weight loss maintenance is attainable assuming compliance with the program. Patients do not typically remain on AOMs for 2 years; for example, in the VA study, only two in every five patients demonstrated at least 80% adherence to phentermine-topiramate over a 6-month period.<sup>18</sup> As such, this study represents outcomes in a population of "outliers" who are adherent to AOMs for extended periods. Adherence has been consistently demonstrated to result in better weight loss outcomes with various interventions, such as commercial weight loss programs,<sup>24</sup> AOMs,<sup>18</sup> or post-bariatric surgery follow-up.<sup>25</sup> A 10% increase in adherence was associated with a

BMI reduction of 2.6 kg/m<sup>2</sup> in a smartphone-based behavioral weight loss program.<sup>26</sup>

This study found that the use of more AOMs was associated with clinically significant long-term weight loss but not weight loss maintenance. With about one-third of patients on two or more AOMs, this data provides impetus for further examination of combination regimens.

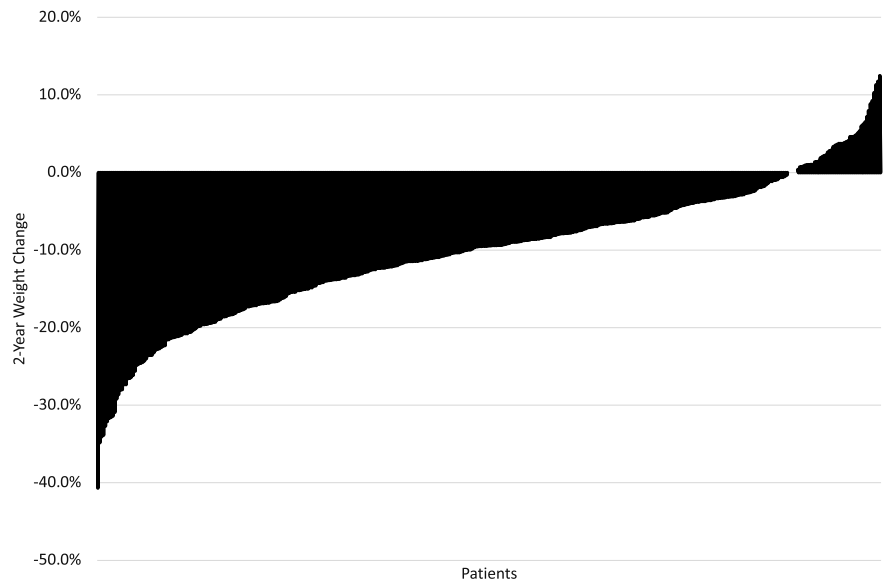
The Obesity Society guidelines recommend monthly or more frequent contact when providing lifestyle interventions alone for successful long-term weight loss maintenance.<sup>22</sup> However, this study found that the number of visits with a physician, nurse practitioner, or registered dietitian over 2 years did not correlate with clinically significant weight loss or weight loss maintenance at 2 years. The number of visits significantly decreased over the second year (data not shown), which likely affected the power to detect differences.

The retrospective nature of this study assumes several important limitations: lack of granularity regarding specific lifestyle interventions (e.g., physical activity), comorbidities' statuses, and AOM dose regimens. The use of other diabetes medications (e.g., insulin, sulfonylureas, and SGLT2 inhibitors) not captured in this data abstraction may be confounders.

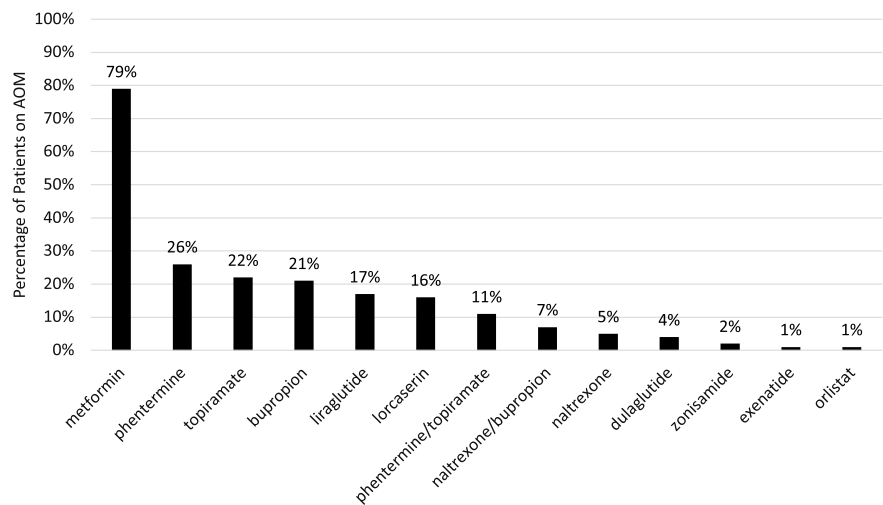
As a completers' analysis, this data are limited in its generalizability given the degree of incomplete data, which is comparable to similar studies of its kind.<sup>18,21</sup> This data are most applicable to individuals who remain on AOMs for extended periods, which may be driven by a variety of factors such as individual biological responses and practice management styles. Consistent predictors of attrition have been difficult to identify, though patterns have been observed in some studies of lifestyle or bariatric interventions<sup>27</sup>; for example, lower initial weight loss has predicted attrition and was likely a contributing factor to this study's observed weight loss outcomes.

This study is strengthened by its long-term assessment of 2 years, relatively large population compared to similar studies,<sup>19</sup> and inclusion of off-label AOMs rather than limitation to on-label AOMs

**FIGURE 3** Individual patients' weight changes at 2 years



**FIGURE 4** Anti-obesity medications used



**TABLE 3** Predictors of clinically significant weight loss at 2 years ( $\geq 5\%$  of baseline weight)

	<5% weight loss (n = 114)	$\geq 5\%$ weight loss (n = 307)	p-value
Age (years)	50.2 (14.2)	51.7 (13.6)	0.340
Female	83 (72.8)	227 (73.9)	0.912
Initial BMI ( $\text{kg}/\text{m}^2$ )	33.9 (6.4)	35.9 (6.9)	<b>0.006</b>
Type 2 diabetes	25 (21.9)	44 (14.3)	0.085
Total MD/NP/RD visits	11.0 (5.3)	11.7 (4.8)	0.208
MD/NP/RD visits between 1 and 2 years	4.9 (2.5)	5.1 (2.4)	0.474
Number of AOMs at 2 years	2 [1, 3]	2 [2, 3]	<b>&lt;0.001</b>

Note: Data presented as mean (SD), n(%), or median [interquartile range] where applicable. Bolding highlights significant p-values.

Abbreviations: AOMs, anti-obesity medications; BMI, body mass index; MD, physician; NP, nurse practitioner; RD, registered dietitian.

TABLE 4 Predictors of weight loss maintenance

	Weight regain (n = 97)	Weight loss maintenance (n = 221)	p-value
Age	49.2 (13.6)	52.4 (13.2)	0.058
Female	71 (73.2)	163 (73.8)	1.000
Initial BMI	36.0 (7.4)	35.9 (6.7)	0.922
Type 2 diabetes	10 (10.3)	36 (16.3)	0.221
Total MD/NP/RD visits	11.5 (5.1)	12.0 (4.8)	0.426
MD/NP/RD visits between 1 and 2 years	4.7 (2.7)	5.14 (2.3)	0.207
Number of AOMs at 2 years	2 [1, 3]	2 [2, 3]	0.067

Note: Data presented as mean (SD), median [interquartile range], or n(%) where applicable.

Abbreviations: AOMs, anti-obesity medications; BMI, body mass index; MD, physician; NP, nurse practitioner; RD, registered dietitian.

only.<sup>18</sup> The use of off-label AOMs is arguably necessary in real-world practice given the enormous need for effective obesity therapies<sup>28</sup> and the often prohibitive costs of on-label AOMs.<sup>29</sup> A majority of the study population were utilizing metformin as an off-label AOM, which has been previously reported to be associated with 7% weight loss over 1 year.<sup>30</sup> Metformin is a widely available, generic, and inexpensive medication with long-term safety data<sup>31</sup> and should be considered as an adjunct to lifestyle modifications in the treatment of obesity.<sup>32</sup> Obesity pharmacotherapy is an essential tool to address the treatment gap of obesity,<sup>33</sup> which is anticipated to narrow with the advent of more effective or diverse agents.<sup>34–36</sup> The interindividual variability in response to weight loss interventions has been a consistent observation<sup>37</sup> and reflects the heterogeneity of obesity as a disease. As the first to report observed weight loss maintenance outcomes associated with polypharmacotherapy utilizing on- and off-label AOMs among patients who complied with 2 years of management, this study highlights multiple areas for prospective exploration in determining effective strategies for long-term weight loss maintenance.

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Alpana P. Shukla and Louis J. Aronne were responsible for study concept and design. Data acquisition was performed by Beverly G. Tchang and Mohini Aras. Formal data analysis was performed by Alan Wu. All authors were involved in data interpretation. Manuscript draft was prepared by Beverly G. Tchang, Mohini Aras, Alan Wu, and Alpana P. Shukla. All authors participated in manuscript review and edits. Study was supervised by Alpana P. Shukla. Thank you to Lindsay Mandel, B.A., for help in data abstraction and development of the initial dataset. Alan Wu was supported by a grant (1-UL1-TR002384-01) to the Clinical and Translational Science Center at Weill Cornell Medicine.

#### CONFLICT OF INTERESTS

Louis J. Aronne reports receiving consulting fees from and serving on advisory boards for Jamieson Laboratories, Pfizer, Novo

Nordisk, Eisai, Erx Pharmaceuticals, Real Appeal, Janssen Pharmaceuticals, and Gelesis; receiving research funding from Aspire Bariatrics, Allurion, Eisai, AstraZeneca, Gelesis, Janssen Pharmaceuticals and Novo Nordisk; having equity interests in Intellihealth Corp, Allurion, Erx Pharmaceuticals, Zafgen, Gelesis, Myos Corp., and Jamieson Laboratories; and serving on a board of directors for Intellihealth Corp., Myos Corp., and Jamieson Laboratories. Beverly G. Tchang reports consulting and/or commission fees from Novo Nordisk, 2nd.MD, and Elsevier. All other authors have nothing to disclose.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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