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Clinical Trials and Investigations

Early- and later-stage persistence with antiobesity medications: A retrospective cohort study

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Abstract

Objective: The study's objective was to examine the percentage of patients with an initial antiobesity medication (AOM) fill who were persistent with AOM at 3, 6, and 12 months and to characterize factors associated with persistence at 12 months.

Methods: This retrospective cohort study used electronic health records from January 2015 to July 2023 in a large health system in Ohio and Florida and included adults with BMI ≥30 kg/m^2 who had an initial AOM prescription filled between 2015 and 2022.

Results: The authors identified 1911 patients with a median baseline BMI of 38 (IQR, 34–44). Over time, 44% were persistent with AOM at 3 months, 33% at 6 months, and 19% at 12 months. Across categories of AOM, the highest 1-year persistence was in patients receiving semaglutide (40%). Semaglutide (adjusted odds ratio [AOR] = 4.26, 95% CI: 3.04–6.05) was associated with higher odds of 1-year persistence, and naltrexone-bupropion (AOR = 0.68, 95% CI: 0.46–1.00) was associated with lower odds, compared with phentermine-topiramate. Among patients who were persistent at 6 months, a 1% increase in weight loss at 6 months was associated with 6% increased odds of persistence at year 1 (AOR = 1.06, 95% CI: 1.03–1.09).

Conclusions: Later-stage persistence with AOM varies considerably based on the drug and the weight loss at 6 months.

INTRODUCTION

Obesity is a global public health challenge. It increases the risk of cardiovascular disease, type 2 diabetes, cancer, osteoarthritis, obstructive sleep apnea, and asthma, among other major health complications [1]. The past decade has witnessed major progress in the development of new and effective, but expensive, antiobesity medications (AOMs) [2, 3]. Newer AOMs have greater efficacy than those previously approved by the Food and Drug Administration (FDA) [4]. For example, in a randomized trial setting, semaglutide (a glucagon-like peptide-1 receptor agonist [GLP-1 RA]) allowed patients to lose an average of 15% of their body weight at 68 weeks [5].

However, as in other chronic disease management, AOM discontinuation has been linked to weight regain and reduction of the achieved health benefits [6, 7]. In the STEP 1 trial extension study, 1 year after discontinuation of treatment with semaglutide and lifestyle intervention, participants on average regained two thirds of their lost weight and experienced reversal of cardiometabolic improvements [6].

It is critical to understand persistence with AOM (defined by evidence of at least primary adherence [i.e., initial prescription fill] and refills over a specific time period, indicating medication availability) [8, 9], as short-term AOM use represents low-value health care, but little is known about patients' persistence with AOM and the factors associated with nonpersistence. Such understanding could help in projecting costs associated with AOM coverage by third-party payers, as well as addressing the barriers to continued use of AOM.

This study aimed to examine (a) 3-, 6-, and 12-month persistence with AOM and (b) factors associated with 12-month persistence. We hypothesized that individuals receiving novel AOM agents and experiencing greater 6-month weight loss would be more likely to persist with their AOM treatment at 1 year. We also hypothesized that there would be significant variation in AOM persistence by insurance type.

Study Importance

What is already known?

- Nonpersistence with antiobesity medications (AOM) is increasingly becoming a concern and might inform decisions regarding AOM coverage.

What does this study add?

- This retrospective cohort study of 1911 patients from Ohio and Florida who filled an initial AOM prescription between 2015 and 2022 found that 44% were persistent with AOM at 3 months, 33% at 6 months, and only 19% at 1 year.
- Patients who received semaglutide were most likely to be persistent (40% persistent at 1 year). Persistence at 1 year also varied based on the achieved weight loss at 6 months and the insurance carrier among privately insured individuals.

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

- Our findings indicate that although later-stage persistence with AOM remains low, patients receiving more effective AOMs and those experiencing greater medium-term weight loss have higher odds of later-stage persistence.
- Future studies should examine the role of specific insurance design features in continuous access to AOM as well as interventions to help increase persistence.

METHODS

Study design and setting

This retrospective cohort study was approved by the Cleveland Clinic Institutional Review Board. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. Data were obtained from the Cleveland Clinic electronic health records (EHR) in Ohio and Florida locations, including Surescripts dispensed prescription records from January 1, 2015, to July 28, 2023.

Study participants

We identified adult (age ≥ 18 years) patients who filled an initial prescription for AOM from July 1, 2015, to June 30, 2022, and had body mass index (BMI) ≥ 30 kg/m^2, recorded on the date of AOM treatment initiation (index date) or during the latest available primary care visit before the index date. To assure that these were new AOM prescriptions, we excluded patients prescribed AOM between January 1, 2015, and June 30, 2015. Individuals were required to have at least 3, 6, and 12 months of follow-up (outpatient visit or prescription fill) to be included in 3-, 6-, and 12-month persistence analyses, respectively. Patients who had pregnancy or cancer diagnoses during the study period or underwent bariatric surgery within 3 years of their initial AOM fill were also not eligible for inclusion (Figure S1).

We captured AOM fills with dosage forms approved by the FDA for chronic weight management, including phentermine-topiramate, naltrexone-bupropion, orlistat, semaglutide injection 2.4 mg (including its starting doses), and liraglutide injection 3 mg (including its starting doses). We also included injectable forms of semaglutide and liraglutide approved by the FDA for diabetes management in patients who did not have a diagnosis code for diabetes during the study period, indicating their off-label use as an AOM [10]. Patients who switched from brand name AOM to generic combinations of phentermine and topiramate or naltrexone and bupropion were classified as receiving phentermine-topiramate or naltrexone-bupropion, respectively, to account for that common clinical practice.

Study variables

The primary outcomes of this study were (1) 3-month persistence with AOM, defined as a cumulative gap of less than 15 days within 3 months after the initial prescription fill, (2) 6-month persistence, defined as a cumulative gap of less than 45 days within 6 months after initial prescription fill, and (3) 12-month persistence, defined as a cumulative gap of less than 90 days within the first year after initial prescription fill. Patients who switched between AOMs but had a cumulative gap of <15, <45, and <90 days were considered persistent at 3, 6, and 12 months, respectively. We also captured the total number of days covered by AOM during the study follow-up.

AOM was classified based on the last prescription fill data within the first year given that precertification by third-party payers for some

of these medications requires step therapy, that is, trying one or more of the cheaper drugs before coverage for a more expensive alternative is preauthorized. For example, if a patient received naltrexone-bupropion initially and then switched to semaglutide injection within the first year, they would be classified in the semaglutide group in this study. Nevertheless, only a small fraction of patients (17%) had a different AOM in their last versus first fill within the first year.

Sociodemographic variables, including patients' age, sex, race/ethnicity, payer type, health insurance carrier, and area deprivation index (ADI) based on Census Block Group neighborhood-level data [11] were captured using EHR data at the patient's primary care visit closest to the index date. We grouped patients' self-reported race/ethnicity into White, Black, Hispanic, and Other categories. ADI percentiles are structured by ranking the ADI from low to high within the nation, where an ADI with a ranking of 1 indicates the lowest level of "disadvantage" and 100 indicates the highest level of "disadvantage" [11]. We grouped the ADI rankings into quartiles. Payer types were classified into private, Medicare, Medicaid, self-pay, and other categories. Among privately insured patients, we also captured the insurance carrier, including Aetna, Blue Cross Blue Shield, Cigna, Cleveland Clinic's employee health plan (CCF EHP), Medical Mutual Ohio, United Healthcare, and other commercial carriers.

We also captured from the EHR patients' BMI at baseline and percentage weight loss at 6 and 12 months since the first AOM fill; whether they had a diagnosis code for diabetes during the study period (based on the International Classification of Disease codes, ninth and tenth revisions); and the age-adjusted Charlson comorbidity index [12]. Baseline BMI was calculated using the available weight data at the time of the first AOM prescription or fill. Weight at each follow-up time point was determined by interpolating the two closest weight measurements on either side of the time point. If a weight measure after a set time point was not available, weight measures captured <1 month before the 6-month follow-up and <3 months before the 1-year follow-up times were carried forward; otherwise, the weight measure at that point was considered missing. We calculated percentage weight loss at 6 and 12 months using the following formula: percentage weight loss = 100 × ([weight at baseline − weight at follow-up]/weight at baseline). Manual chart reviews of randomly selected samples were conducted throughout the study for data validation purposes.

Statistical analysis

We used Pearson χ^2 test, Fisher exact test, and Wilcoxon rank sum test for standard group comparisons. A multivariable logistic regression model was used to examine the association between sociodemographic characteristics, AOM agent, and the odds of 1-year persistence, controlling for the age-adjusted Charlson comorbidity index. To examine the association of percentage weight loss at 6 months and the odds of 1-year persistence, we used an additional logistic regression model where the study population was limited to individuals who were persistent and had weight measurement at 6 months, controlling for the previously listed variables.

In the multivariable models, complete data were available for patient age, sex, AOM, and age-adjusted Charlson comorbidity index. In the primary model, 5.2% of patients had missing data on race/ethnicity, payer type, or ADI. Given the relatively small amount of missing data and similar distribution across comparator groups, such cases were subject to list wise deletion in the multivariable regression models. All statistical testing was 2-tailed with an α of 0.05 used to determine statistical significance. All analysis was conducted in R, Version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

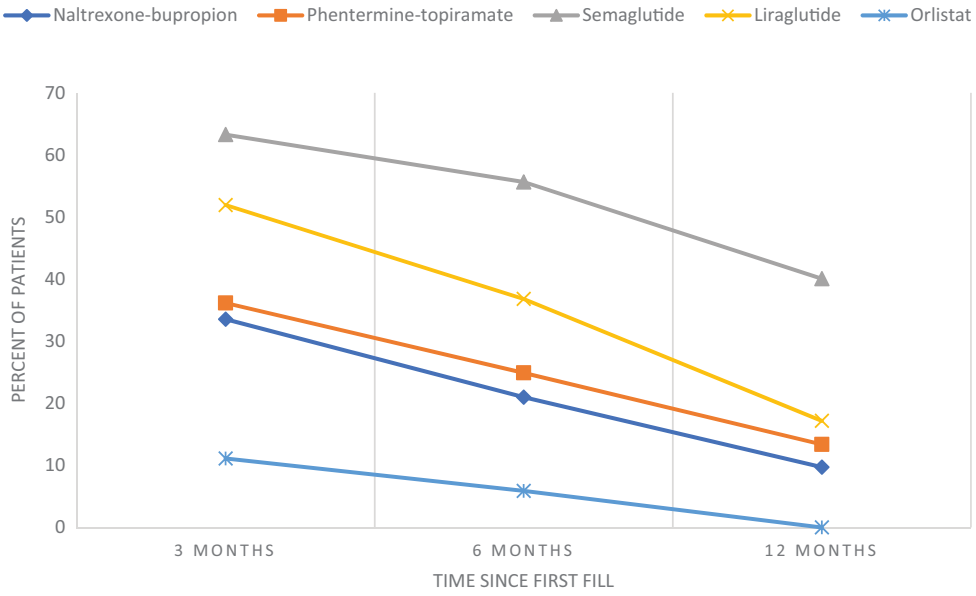
We identified 1911 patients who filled an initial prescription for AOM from July 1, 2015, to June 30, 2022, with a mean age of 44 (SD, 12) and median baseline BMI of 38 kg/m^2 (interquartile range [IQR], 34–44); 75% were female, 76% White, 16% Black, and 4.5% Hispanic. Most patients were privately insured (84%). The median follow-up time was 2.4 years (IQR, 1.4–4.9). Overall, 25% of the cohort filled a prescription for semaglutide, 34% for naltrexone-bupropion, 26% for phentermine-topiramate, 14% for liraglutide, and 0.9% for orlistat.

At 3 months, 44% ($n = 840$) of the patients were persistent with AOM, 33% ($n = 615$) were persistent at 6 months, and 19% ($n = 325$) were persistent at 1 year. The percentages varied considerably across drugs, with 1-year persistence ranging from 10% in patients taking naltrexone-bupropion to 40% in patients receiving semaglutide. Semaglutide and liraglutide had the highest persistence rates at 3 months (63% and 52%) and 6 months (56% and 37%, respectively) as well (Figure 1). The median total number of days covered by AOM during the study follow-up was 504 days (IQR, 394–672) among patients who were persistent at 1 year and 120 days (IQR, 56–240) among those who were not, $p < 0.001$. Individuals who were persistent at 1 year had greater weight loss at 12 months (mean 10%; SD, 8%) compared with individuals who were not, (mean 2%; SD, 8%; $p < 0.001$).

Persistence at 3 months was associated with AOM agent, race/ethnicity, payer type, ADI quartile, year of first AOM fill, and diabetes status (Table 1). The persistence rate at 3 months was 63% for semaglutide, 52% for liraglutide, 36% for phentermine-topiramate, 34% for naltrexone-bupropion, and 11% for orlistat, $p < 0.001$ (Figure 1).

Individuals who were persistent with AOM at 1 year differed from those who were not persistent based on the medication, insurance carrier (for those who were privately insured), percentage weight loss at 6 months, and the year of first AOM fill (Table 1). Persistence rates at 1 year were 40% for semaglutide, 17% for liraglutide, 13% for phentermine-topiramate, and 10% for naltrexone-bupropion, $p < 0.001$. There were no patients taking orlistat at 12 months (Figure 1).

In the multivariable analyses of persistence at 1 year, semaglutide (adjusted odds ratio [AOR] = 4.26, 95% confidence interval [CI],



Number of persistent patients/those with available follow-up at 3, 6, and 12 months			
	≥3 months	≥6 months	≥12 months
Semaglutide	303/479	262/471	161/402
Naltrexone-bupropion	220/656	137/653	61/628
Phentermine-topiramate	180/498	123/494	63/471
Liraglutide	135/260	92/250	40/233
Orlistat	2/18	1/17	0/17

FIGURE 1 Percentage of patients who were persistent with antiobesity medication (AOM) at early stage, medium term, and long term, by AOM agent. [Color figure can be viewed at wileyonlinelibrary.com]

3.04–6.05) was associated with higher odds of persistence and naltrexone-bupropion (AOR = 0.68, 95% CI, 0.46–1.00) was associated with lower odds, compared with phentermine-topiramate, whereas other AOM agents did not have significantly different odds (Table 2). Age, race/ethnicity, sex, ADI quartile, payer type, and age-adjusted Charlson comorbidity index were not significantly associated with persistence at 1 year. Within the subset of patients who were persistent at 6 months ($n = 524$), a 1% increase in total body weight loss at 6 months was associated with a 6% increase in the odds of persistence (AOR = 1.06, 95% CI, 1.03–1.09) at year 1 (Table S1). The odds of persistence at 1 year also varied based on the insurance carrier among those who were privately insured (Table S2).

DISCUSSION

In this large sample of patients with obesity who filled at least one prescription for AOM during 2015 to 2022, 44% were persistent with AOM at 3 months, 33% at 6 months, and only 19% at 1 year. Later-stage persistence with AOM varied significantly by AOM agent, from 10% in patients taking naltrexone-bupropion to 40% among those receiving semaglutide. Persistence at 1 year also depended on the percentage weight loss at 6 months and the insurance carrier (among privately insured patients). Receipt of the novel and more effective agent semaglutide and greater weight loss at 6 months were both associated with persistence at 1 year.

Although we did not observe significant differences in later-stage persistence based on payer type and ADI, a prior study from our group among adults with obesity who attended at least one weight-management program or received an initial prescription for AOM/GLP-1 RA medications (including semaglutide or liraglutide) showed that having Medicaid, Medicare, Medicare Advantage, or other insurance types, as well as living in areas with higher neighborhood ADI, was associated with lower odds of receiving a prescription for AOM/GLP-1 RA [13]. AOMs are expensive [2, 14], with monthly costs ranging from $200 (for phentermine-topiramate) to $1300 (for liraglutide 3.0 mg and semaglutide 2.4 mg). Most state Medicaid programs, as well as Medicare Part D prescription drug plans, do not cover AOMs [15]. Among privately insured individuals, AOM coverage varies by insurance carrier, and even if included, its coverage is subject to stringent preauthorization criteria [2]. The present study's participants were predominantly privately insured (84%) and likely had either insurance coverage for AOM or the means to fill at least 1 prescription.

TABLE 1 Patient characteristics of those who were persistent with antiobesity medication at 3 and 12 months versus those who were not

Characteristic	Not persistent at 3 months[a] ($n = 1071$)	Persistent at 3 months[a] ($n = 840$)	p value[b]	Not persistent at 12 months[a] ($n = 1426$)	Persistent at 12 months[a] ($n = 325$)	p value[b]
Age	44 (12)	45 (12)	0.2	44 (12)	45 (12)	0.1
Sex						
Female	814 (76%)	626 (75%)	0.5	1085 (76%)	247 (76%)	0.9
Male	257 (24%)	214 (25%)		341 (24%)	78 (24%)	
Race/ethnicity						
White	779 (73%)	671 (80%)	<0.001	1084 (76%)	248 (76%)	0.2
Black	207 (19%)	100 (12%)		230 (16%)	45 (14%)	
Hispanic	47 (4.4%)	39 (4.6%)		58 (4.1%)	22 (6.8%)	
Other	34 (3.2%)	28 (3.3%)		48 (3.4%)	10 (3.1%)	
Not reported	4 (0.4%)	2 (0.2%)		6 (0.4%)	0 (0%)	
Payer type						
Private	893 (83%)	703 (84%)	0.02	1197 (84%)	273 (84%)	0.1
Medicare	61 (5.7%)	67 (8.0%)		84 (5.9%)	31 (9.5%)	
Medicaid	94 (8.8%)	49 (5.8%)		109 (7.6%)	18 (5.5%)	
Other	7 (0.7%)	12 (1.4%)		16 (1.1%)	1 (0.3%)	
Self-pay	13 (1.2%)	6 (0.7%)		16 (1.1%)	2 (0.6%)	
Unknown	3 (0.3%)	3 (0.4%)		4 (0.3%)	0 (0%)	
Private insurance carrier[c]						
Aetna	63 (7.1%)	68 (9.7%)	0.5	86 (7.2%)	32 (12%)	0.002
Blue Cross Blue Shield	223 (25%)	183 (26%)		300 (25%)	70 (26%)	
Cigna	49 (5.5%)	33 (4.7%)		59 (4.9%)	16 (5.9%)	
CCF EHP	124 (14%)	88 (13%)		185 (15%)	20 (7.3%)	
Medical Mutual Ohio	225 (25%)	182 (26%)		297 (25%)	78 (29%)	
United Healthcare	105 (12%)	76 (11%)		128 (11%)	34 (12%)	
Other commercial carriers	104 (12%)	73 (10%)		142 (12%)	23 (8.4%)	
ADI quartile						
1st quartile: 1–25	141 (13%)	142 (17%)	0.02	202 (14%)	56 (17%)	0.6
2nd quartile: 26–50	295 (28%)	261 (31%)		413 (29%)	95 (29%)	
3rd quartile: 51–75	358 (33%)	243 (29%)		459 (32%)	94 (29%)	
4th quartile: 76–100	227 (21%)	152 (18%)		285 (20%)	66 (20%)	
Unknown	50 (4.7%)	42 (5.0%)		67 (4.7%)	14 (4.3%)	
Charlson comorbidity index	1 (0–2)	1 (0–2)	0.5	1 (0–2)	1 (0–2)	0.9
Diabetes diagnosis	200 (19%)	112 (13%)	0.002	257 (18%)	44 (14%)	0.05
Baseline BMI	38 (35–43)	38 (34–44)	0.5	38 (34–43)	38 (34–43)	0.9
% weight loss at 6 months	N/A	N/A		2 (7)	9 (8)	<0.001
Medication						
Phentermine-topiramate	318 (30%)	180 (21%)	<0.001	408 (29%)	63 (19%)	<0.001
Naltrexone-bupropion	436 (41%)	220 (26%)		567 (40%)	61 (19%)	
Semaglutide	176 (16%)	303 (36%)		241 (17%)	161 (50%)	
Liraglutide	125 (12%)	135 (16%)		193 (14%)	40 (12%)	
Orlistat	16 (1.5%)	2 (0.2%)		17 (1.2%)	0 (0%)	
Year of first medication fill[d]						
2015	43 (4.0%)	28 (3.3%)	<0.001	62 (4.3%)	9 (2.8%)	<0.001
2016	105 (9.8%)	56 (6.7%)		138 (9.7%)	20 (6.2%)	
2017	163 (15%)	110 (13%)		234 (16%)	34 (10%)	

(Continues)

TABLE 1 (Continued)

Characteristic	Not persistent at 3 months[a] ($n = 1071$)	Persistent at 3 months[a] ($n = 840$)	p value[b]	Not persistent at 12 months[a] ($n = 1426$)	Persistent at 12 months[a] ($n = 325$)	p value[b]
2018	152 (14%)	82 (9.8%)		210 (15%)	19 (5.8%)	
2019	120 (11%)	68 (8.1%)		156 (11%)	22 (6.8%)	
2020	91 (8.5%)	67 (8.0%)		122 (8.6%)	24 (7.4%)	
2021	229 (21%)	199 (24%)		306 (21%)	88 (27%)	
2022	168 (16%)	230 (27%)		198 (14%)	109 (34%)	

Abbreviations: ADI, Area Deprivation Index; CCF EHP, Cleveland Clinic's employee health plan.
[a]*n* (% within the column); mean (SD); median (IQR).
[b]Based on Fisher exact test, Pearson χ^2 test, or Wilcoxon rank sum test.
[c]The denominator for the private insurance carrier variable only included privately insured individuals in each group.
[d]Our sample included individuals who were prescribed antiobesity medication from July 1, 2015, to June 30, 2022.

TABLE 2 Factors associated with persistence with antiobesity medication at 1 year, $n = 1660$

Variable	Adjusted odds ratio	95% CI	p value
Age[a]	1.01	0.99–1.02	0.3
Sex			
Female	Reference		
Male	0.91	0.66–1.23	0.5
Race/ethnicity			
White	Reference		
Black	0.84	0.56–1.23	0.4
Hispanic	1.30	0.73–2.24	0.4
Other	0.62	0.26–1.32	0.2
Payer type			
Private	Reference		
Medicare	1.37	0.79–2.35	0.3
Medicaid	1.03	0.58–1.75	0.9
Other	0.39	0.02–2.01	0.4
Area deprivation index quartile			
1st quartile: 1–25	Reference		
2nd quartile: 26–50	0.92	0.62–1.37	0.7
3rd quartile: 51–75	0.86	0.58–1.29	0.5
4th quartile: 76–100	0.93	0.60–1.46	0.8
Charlson comorbidity index	0.93	0.83–1.05	0.2
Medication type			
Phentermine-topiramate	Reference		
Naltrexone-bupropion	0.68	0.46–1.00	0.049
Semaglutide	4.26	3.04–6.05	<0.001
Liraglutide	1.40	0.90–2.16	0.13
Orlistat	N/A		

[a]Reported for 1 year increase in age.

Our findings add to the literature on the later-stage persistence with AOM. In a Canadian study of 355 adult patients who initiated treatment with liraglutide 3.0 mg during 2015 to 2016, half were persistent ≥6 months [16]. In our sample, only 37% of patients receiving liraglutide were persistent that long. A United States-based study, which also included phentermine (approved only for short-term use as an AOM) and used claims data from commercial health insurers from 2004 to 2018, found that time on AOM treatment averaged 81 days [17]. Access barriers specific to the US health care system likely impact persistence with AOM [2, 18]. For comparison, the long-term discontinuation rates at ~1 year in the main phase 3 trials were 31% to 36% for phentermine plus topiramate (CONQUER trial) [19]; 49% to 51% for naltrexone plus bupropion (COR-I trial) [20]; 28% for 3.0 mg of liraglutide (Weight Management trial) [21]; and 17% for 2.4 mg semaglutide injection (STEP 3 trial) [22].

There is anecdotal evidence that US employers have considered restricting insurance coverage for AOM, often citing the unsustainable cost burden of the GLP-1 RAs as well as the rapid weight gain after discontinuation of treatment [2, 23]. The earlier assumption is often based on how many covered lives could qualify for the more expensive AOMs [23]. Nevertheless, population-based studies continue to show that only a small fraction of individuals qualifying for pharmacological or surgical management of obesity and its clinically severe forms undergo such treatment each year, for a variety of reasons [2, 3, 24]. The present study showed that the vast majority of patients discontinued their fills within 3 months. Furthermore, those who achieved greater weight loss at 6 months, had higher odds of persistence at 1 year. These findings, along with future qualitative and population-based studies on determinants of nonpersistence with AOM could offer opportunities for more nuanced insurance benefit design, incorporating evidence-based usage management tools, rather than limiting or eliminating AOM coverage altogether. Finally, although third-party payers cite weight regain due to nonpersistence as a reason for limiting AOM coverage, limitations in coverage and certain precertification criteria such as step therapy may contribute to nonpersistence.

This study used data from EHR, including Surescripts dispensed prescription data, and included adult patients in Ohio and Florida in a single large integrated health system. Coverage for AOM by Medicaid and marketplace health insurance plans vary by state [15, 18], and other sociodemographic factors vary across the United States, which may limit the generalizability of our findings. Furthermore, during

the study period shortages of certain AOM, particularly semaglutide were reported, which could have limited the ability of patients to continuously access these medications. Nevertheless, we somewhat mitigated this issue by capturing injectable forms of semaglutide and liraglutide that were off-label used as AOM, capturing generic combinations of brand name AOMs, and considering patients who switched between AOMs but had continued coverage as persistent. Finally, patient-provider-related factors not captured in our data set (e.g., discontinuation of AOM due to inadequate weight loss at 3 months) could not be examined in this study. The strengths of our study were its large sample comprising multiple years of data, as well as our ability to capture documented prescription fills using Surescripts (including those paid for via insurance benefits, cash, coupons, or other method) and integrate prescription fills data with clinical information. As of 2017, Surescripts prescription data service covered nearly 240 million patients in the United States, including nearly all major pharmacies and pharmacy benefit managers [25, 26].

CONCLUSION

Although later-stage persistence with AOM remains low, patients receiving the newer, more effective forms of AOM and those experiencing greater medium-term weight loss are more likely to persist. Among privately insured individuals, there is also significant variation in AOM persistence based on insurance carrier. Future studies should examine determinants of nonpersistence with AOM, ways to help increase persistence, and the role of specific insurance design features in continuous access to AOM.O

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CONFLICT OF INTEREST STATEMENT

Michael B. Rothberg has a consulting relationship with the Blue Cross Blue Shield Association. The other authors declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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