Real World Use of Anti-Obesity Medications and Weight Change in Veterans

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ABSTRACT

BACKGROUND: Anti-obesity medications (AOMs) can be initiated in conjunction with participation in the VA national behavioral weight management program, MOVE!, to help achieve clinically meaningful weight loss.

OBJECTIVE: To compare weight change between Veterans who used AOM + MOVE! versus MOVE! alone and examine AOM use, duration, and characteristics associated with longer duration of use.

DESIGN: Retrospective cohort study using VA electronic health records.

PARTICIPANTS: Veterans with overweight or obesity who participated in MOVE! from 2008–2017.

MAIN MEASURES: Weight change from baseline was estimated using marginal structural models up to 24 months after MOVE! initiation. The probability of longer duration of AOM use (≥ 180 days) was estimated via a generalized linear mixed model.

RESULTS: Among MOVE! participants, 8,517 (1.6%) used an AOM within 24 months after MOVE! initiation with a median of 90 days of cumulative supply. AOM + MOVE! users achieved greater weight loss than MOVE! alone users at 6 (3.2% vs. 1.6%, $p < 0.001$), 12 (3.4% vs. 1.4%, $p < 0.001$), and 24 months (2.7% vs. 1.5%, $p < 0.001$), and had a greater probability of achieving ≥ 5% weight loss at 6 (38.8% vs. 26.0%, $p < 0.001$), 12 (43.1% vs. 28.4%, $p < 0.001$), and 24 months (40.4% vs. 33.3%, $p < 0.001$). Veterans were more likely to have ≥ 180 days of supply if they were older, exempt from medication copays, used other medications with significant weight-gain, significant weight-loss, or modest weight-loss side effects, or resided in the West North Central or Pacific regions. Veterans were less likely to have ≥ 180 days of AOM supply if they had diabetes or initiated MOVE! later in the study period.

CONCLUSIONS: AOM use following MOVE! initiation was uncommon, and exposure was time-limited. AOM + MOVE! was associated with a higher probability of achieving clinically significant weight loss than MOVE! alone.

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INTRODUCTION

The combined prevalence of overweight (37%) and obesity (41%) in Veterans receiving care in the Veterans Health Administration (VA) is greater than the prevalence in the general US population (72%).[1, 2] To help Veterans manage their weight, the VA implemented the MOVE! Weight Management Program for Veterans (MOVE!), a system-wide comprehensive lifestyle intervention, with adjunctive treatment (e.g., anti-obesity medications (AOMs) and bariatric surgery) in some instances.[3] Prior studies have found that 25% of MOVE! participants achieve clinically meaningful (i.e., ≥ 5%) weight loss at one year.[4, 5] Veterans with more intensive participation achieve greater weight loss, with studies citing up to 30% achieving clinically meaningful weight loss at one year.[4]

Since behavioral weight management is associated with modest weight loss and bariatric surgery is provided to only 1% of eligible patients each year, AOMs are an important population management strategy.[6] Randomized trials have shown when adhered to, AOMs induce 6–11% reductions in baseline weight.[7] Several studies show compared to behavioral intervention alone, AOMs combined with behavioral intervention increase the likelihood of achieving ≥ 5% weight loss.[8–11] Whether Veterans receiving VA care achieve clinically meaningful weight loss with AOMs has received little study.

Despite the potential utility of AOMs, only 1–2% of the general population initiate an AOM.[12] This is due to a variety of barriers, including insurance coverage restrictions and provider-facing issues related to safety, AOM knowledge, and weight bias.[13] Rates of AOM initiation are similarly low in VA.[3, 14] One potential barrier to initiation for Veterans was the VA policy requiring 90 days of MOVE! participation to become eligible for an AOM; since July 2016, this is no longer required.[9]

It is important to understand the impact of AOM use in combination with MOVE! as VA has facilitated greater access to AOMs, and interest in AOMs is increasing with approval of semaglutide for weight loss.[15] A recent study of MOVE! participants in 2010–2020 foundAOM users lost more weight and had lower blood sugar, blood pressure, and cholesterol than non-users.[11] However, this study was limited to a subgroup who initiated AOM within one month of MOVE! initiation, despite the prior requirement of 90 days of MOVE! participation before eligibility for AOM use.[11] We build upon prior literature by examining the larger group of all AOM users and comparing weight change between AOM + MOVE! users and MOVE! users to describe the real-world effectiveness of AOMs and predictors of AOM use following MOVE! participation. Based on a prior call to understand duration of AOM use and who may be more likely to benefit,[14] we also describe the use and duration of exposure to AOMs and identify factors associated with duration of exposure. These results will inform an important evidence gap in real-world AOM exposure and impacts.

METHODS

Study Population and Data

This retrospective cohort study used VA electronic health record data and included Veterans with overweight or obesity who initiated MOVE! in FY2008-2017. MOVE! participants were included if they had ≥ 1 body mass index (BMI) value of ≥ 25 in the two years before their initial MOVE! visit, which served as their index date; resided in the US; and had a valid ZIP code (Supplemental Fig. 1). MOVE! participants were excluded if they had a recorded death before or on index date, were institutionalized (hospital or nursing home) at time of index, had a cancer diagnosis within 5 years before index, had an amputation before index, or received an AOM in the 2 years before index. The duration analysis sample included 8,517 MOVE! participants who initiated AOMs and 534,581 MOVE! participants who did not initiate AOMs. For the weight-change analysis, Veterans without ≥ 1 weight measurement within 24 months after their index MOVE! visit were dropped, resulting in an analytic sample of 523,971.

Exposure, Outcomes, and Covariates

AOM use was identified based on ≥ 1 fill of one of eight AOMs (orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion, liraglutide, phentermine, diethylpropion, sibutramine). For the weight-change analysis, AOM use was operationalized as a binary time-varying variable that was positive if a Veteran had ≥ 1 AOM fill, since the objective was to compare AOM + MOVE! to MOVE! alone. Thus, taking an intention-to-treat approach to compare AOM + MOVE! to MOVE! alone, Veterans were considered "exposed" even if they discontinued AOM during the 24-month interval.

For the comparison of AOM + MOVE! users and MOVE! users, the primary clinical outcome was percentage weight loss from baseline (i.e., MOVE! initiation), which was examined at 6-, 12-, 18-, and 24-months following MOVE! initiation. We also examined the proportion of Veterans who achieved ≥ 5% weight loss at the same time points. Unadjusted percentage weight loss from baseline was also reported for each AOM.

Medication outcomes of interest included number of prescription fills and total days supply of AOM in the 24 months after MOVE! initiation. For AOM users, a binary outcome was constructed of total AOM days supply for ≥ 180 days in the 24 months following MOVE! initiation to represent longer duration of use, identified as the 75th percentile.

We constructed several baseline patient characteristics associated with weight change identified in prior research, including demographics, clinical factors, and prior healthcare use.[16] Demographic factors included age, sex, race, Hispanic/Latino ethnicity, marital status, enrollment priority group, Medicare eligibility, Medicaid eligibility, census division, and distance to closest VA. Clinical factors included the VA comorbidity summary score called Nosos[17] and 17 conditions diagnosed in the year before index date. Other clinical factors included closest BMI and weight before or on MOVE! initiation date, fiscal year of MOVE! initiation and use of medications (e.g., antihyperglycemics, antidepressants) in the prior six months that had potential for significant weight-gain (≥ 3 kg [kg][18]), significant weight-loss (≥ 3 kg), modest weight-gain (< 3 kg), or modest weight-loss (< 3 kg) side effects. These medication lists were put together after literature review by study team members.[18–24] Healthcare use factors included hospitalization, inflation-adjusted VA costs, and the number of primary care, specialty care, and mental health visits in the fiscal year before the fiscal year of MOVE! initiation.

Analysis

Characteristics of AOM users and non-users and the medication use outcomes (fills, days supply) were evaluated descriptively for each AOM. Characteristics associated with the binary

outcome of total AOM supply ≥ 180 days in the 24 months after MOVE! initiation were examined in a generalized linear mixed model with logit link and binomial error distribution, adjusting for clustering by VA facility.

To compare weight change in the 24 months following MOVE! initiation of AOM users and non-users, we used marginal structural modeling (MSM).[25] This approach generates inverse probability of treatment weights (IPTWs) to handle time-varying treatments (e.g., AOM) and time-varying confounders (e.g., number of MOVE! visits) that could influence both the timing of AOM initiation and subsequent weight change. Time-varying IPTWs for the probability of AOM initiation at each healthcare visit were generated using random survival forest (RSF)[26] with 100 trees, as this produces less biased estimates than standard and semi-parametric and techniques[27] and impose no assumptions on the survival function, such as proportional hazards.

To generate stabilized IPTW, we modeled time until initiating AOM in two models: a numerator model and a denominator model.[28] The numerator model included only baseline variables as predictors, specifically age, gender, marital status, race, ethnicity, enrollment priority, census division, distance to nearest VA, four indicators for use of medication with significant (≥ 3 kg) or modest (< 3 kg) weight-gain or weight-loss, indicators for 17 prior-year comorbidities, and year of index date. The denominator model included the same predictors as well as two time-varying predictors of AOM initiation: percent weight change and number of MOVE! visits from baseline up to the beginning of the present interval.

The ensuing structural modeling of percent weight change from baseline during the 24-months post-MOVE! initiation was conducted using weighted generalized additive mixed models (GAMM). Percent weight change from baseline was modeled via a linear model, and probability of ≥ 5% decrease in baseline weight was modeled in a second logistic GAMM. Linear contrasts within the context of the model were examined at 6-, 12-, 18-, and 24-month time points to quantify the effect of AOM. After truncating the IPTW at 0.1% and 99.9%, the IPTW ranged from 0.21 to 10.56, with a mean of 1.04.

Descriptive analyses and logistic models were conducted using SAS Enterprise Guide 8.3. Marginal structural modeling was conducted using R (version 4.2.0). The 'LTRCforests' package[26] was used to conduct random survival forest analyses, and the 'gamm4' package (version 0.2–6) was used to analyze GAMM models. This study was approved by Durham VA Health Care System Institutional Review Board.

RESULTS

Patient Characteristics and AOM Use

Among 543,098 Veterans who used MOVE! between 2008 and 2017, 8,517 (1.6%) had one or more AOM prescriptions in VA within 24 months after MOVE! initiation. Compared to non-users (Table 1), AOM users were younger (mean age = 51.6 vs. 55.6, standardized mean difference [SMD] = 0.34) and had a higher baseline BMI (mean = 39.3 kg/m^2 vs. 35.4 kg/m^2, SMD = 0.58). AOM users were more likely to be classified as Black (28.1% vs. 23.8%, SMD = 0.11), but less likely to be male (71.6% vs. 86.5%, SMD = 0.37) or enrolled in Medicare (29.7% vs. 37.9%, SMD = 0.18).

AOM Exposure

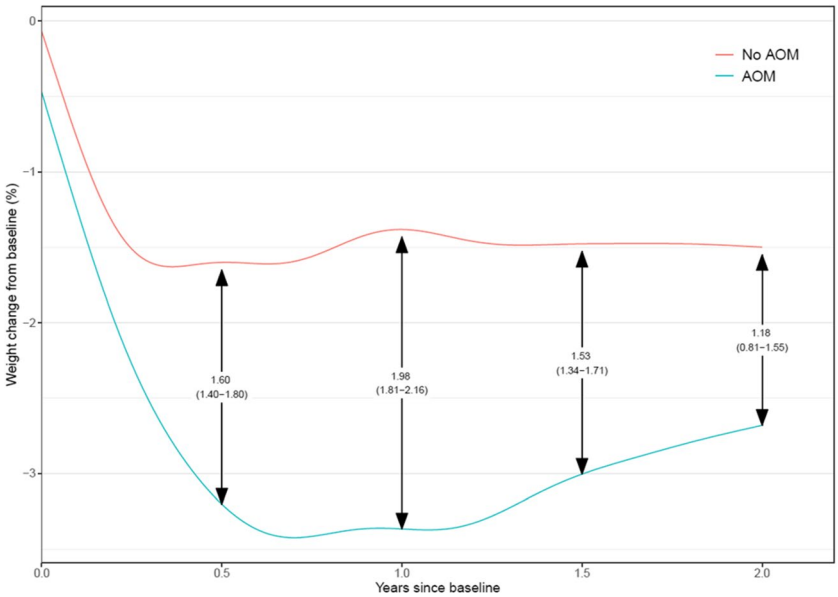
Across the study period, the most used AOM was orlistat (83%), followed by phentermine-topiramate (6%) and naltrexone-bupropion (5%). Between 2008 and 2013, almost all AOM use was orlistat, which declined to 42% by 2017 (Supplemental Fig. 2) as more AOMs became available. In the two years after MOVE! initiation (Table 2), AOM users on average used one AOM, with a mean of 3.8 AOM prescription fills (median = 3 fills) and a mean of 135 days of supply (median = 90 days). Phentermine-topiramate and liraglutide users had a higher mean (157 and 183 days, respectively) and median day supply (106 and 150 days, respectively).

Among AOM initiators (Table 3), Veterans were more likely to have ≥ 180 days of cumulative supply if they were older (adjusted odds ratio [aOR] = 1.02, 95% confidence interval [CI]: 1.01–1.02); exempt from medication copays (aOR = 1.16, 95% CI: 1.03–1.29); used medications with potential significant weight-gain (aOR = 1.22, 95% CI: 1.09–1.37), weight-loss (aOR = 1.19, 95% CI: 1.04–1.37), or modest weight-loss (aOR = 1.17, 95% CI: 1.04–1.32) side effects; or resided in the West North Central (aOR = 1.53, 95% CI: 1.13–2.09) or Pacific census divisions (aOR = 1.57, 95% CI: 1.11–2.21). Veterans were less likely to have ≥ 180 days of AOM supply if they had diabetes (aOR = 0.80, 95% CI: 0.70–0.91) or MOVE! initiation later in the study period (all aORs except 2016 and 2017 significantly < 1.00 for years after 2009 vs. 2008).

Differences in Weight Change for AOM + MOVE! versus MOVE! alone

In adjusted analysis (Fig. 1), AOM + MOVE! was associated with significantly greater weight loss than MOVE! at 6 months after MOVE! initiation (3.2% of index body weight for AOM vs. 1.6% for no AOM), resulting in a 1.6% point difference [95% CI: 1.40–1.80]. Significantly greater loss among AOM initiators persisted at 12 months (3.4% vs. 1.4%, 1.98% point difference [95% CI: 1.81–2.16]), 18 months (3.0% vs. 1.5%, 1.53% point difference [95% CI: 1.34–1.71), and 24 months after MOVE! initiation (2.7% vs. 1.5%, 1.18% point difference [95% CI: 0.81–1.55]).

In the logistic model, AOM + MOVE! was associated with significantly greater odds of ≥ 5% weight reduction at 6 months (aOR = 1.80, 95% CI: 1.73–1.88), 12 months



Note. Estimates derived from weighted generalized additive mixed models of percent weight change from baseline.
AOM = anti-obesity medication
Index date represents MOVE! initiation

Figure 1 Estimated Mean Weight Loss at 6, 12, 18, and 24 months for AOM + MOVE! versus MOVE! alone

(aOR = 1.91, 95% CI: 1.85–1.98), 18 months (aOR = 1.51, 95% CI: 1.46–1.57), and 24 months (aOR = 1.36, 95% CI: 1.27–1.45). The corresponding modeled probabilities of a given patient achieving ≥ 5% reduction are depicted in Figure 2. According to these, the probability of ≥ 5% reduction in baseline weight was 38.8% (95% CI: 37.7%-39.8%) for AOM + MOVE! vs. 26.0% (95% CI: 25.6%-26.3%) for MOVE! alone at 6 months; 43.1% (95% CI: 42.2%-44.0%) vs. 28.4% (95% CI: 28.0%-28.7%) at 12 months; 41.3% vs. 31.7% (95% CI: 31.3%-32.1%) at 18 months, and 40.4% (95% CI: 38.7%-42.1%) vs. 33.3% (95% CI: 32.9%-33.7%) at 24 months. Supplemental Fig. 3 shows unadjusted percentage weight loss from baseline stratified by AOM used.

DISCUSSION

This real-world study of a national cohort of Veterans who initiated MOVE! from 2008 to 2017 found AOM + MOVE! led to greater mean weight loss in the two years after MOVE! initiation than MOVE! alone (2.7% vs. 1.5% at 2 years). Most (83%) of the AOM + MOVE! cohort were taking orlistat, so these results generalize primarily to orlistat users. The 3.4% loss of baseline weight for Veterans taking AOMs at 12 months is comparable to the 3.1% loss reported in a meta-analysis of 57 orlistat trials that provided AOMs with lifestyle intervention,[7] suggesting real-world weight loss associated with AOM + MOVE! approximates that from AOM use alone. On average, MOVE! is associated with modest weight loss effects (0.13–3.3 kg at 12 months),[4, 29] suggesting the greater weight loss seen in the AOM + MOVE! cohort may have been associated with AOM use. More intensive MOVE! participation is associated with more weight loss,[4, 29] so the combined weight-loss effects of AOM use with increased MOVE! participation could be larger.

We also found a higher estimated proportion of AOM + MOVE! users achieved ≥ 5% weight loss than users of MOVE! alone, which is consistent with a prior VA study using 2012–2016 data in which the unadjusted proportion achieving ≥ 5% weight loss at 5 months was 26% for MOVE! participants but 40% in the phentermine-topiramate + MOVE! group.[30] A more recent study of 3,732 MOVE! participants in 2010–2020 found 39% of AOM users lost ≥ 5% weight at 12 months compared to 21% of matched nonusers.[11] This suggests a substantial portion of AOM users lose ≥ 5% weight even if mean weight loss among all AOM users is < 5%.

Similar to a prior VA study, we also saw greater weight loss in the phentermine-topiramate + MOVE! group compared to the orlistat + MOVE! or lorcaserin + MOVE! groups.[30] Compared to these latter two groups, our study also showed greater weight loss in the liraglutide + MOVE! and phentermine + MOVE! groups, however, these were descriptive analyses., A future comparative effectiveness trial comparing AOMs could help to determine which AOMs lead to greater weight loss.

Despite greater weight loss through 24 months after MOVE! initiation in the AOM + MOVE! cohort, we found AOM users had short duration of exposure (median = 90 days). A prior non-VA cohort study also

Table 1 Patient Characteristics

	Users of AOM ($n = 8,517$)	Non-users of AOM ($n = 534,581$)	SMD
Age, mean (SD)	51.6 (11.5)	55.6 (11.9)	0.336
[median (25^{th},75^{th} percentile]	[53.0 (44.0, 61.0)]	[58.0 (48.0, 64.0)]	
Male, n (%)	6,102 (71.6%)	462,126 (86.4%)	0.370
Race, n (%)			0.110
Black	2,393 (28.1%)	127,007 (23.8%)	
White	5,610 (65.9%)	378,354 (70.8%)	
Other[1]	390 (4.6%)	20,812 (3.9%)	
Unknown	124 (1.5%)	8,408 (1.6%)	
Ethnicity, n (%)			0.063
Hispanic/Latino	547 (6.4%)	37,766 (7.1%)	
Not Hispanic/Latino	7,892 (92.7%)	488,551 (91.4%)	
Unknown	78 (0.9%)	8,264 (1.5%)	
Marital status, n (%)			0.010
Married	4,532 (53.2%)	283,801 (53.1%)	
Not married	3.951 (46.4%)	248,304 (46.4%)	
Unknown	34 (0.4%)	2,476 (0.5%)	
VA enrollment group, n (%)			0.235
Priority level 1	3,555 (41.7%)	168,922 (31.6%)	
Priority levels 2–4	1,921 (22.6%)	121,460 (22.7%)	
Priority levels 5–6	2,231 (26.2%)	171,548 (32.1%)	
Priority levels 7–8	–	72,170 (13.5%)	
Unknown	-	481 (0.1%)	
Medicare[2], n (%)	2,527 (29.7%)	202,685 (37.9%)	0.175
Medicaid, n (%)	681 (8.0%)	39,939 (7.5%)	0.020
Census division, n (%)			0.446
New England	129 (1.5%)	17,816 (3.3%)	
Middle Atlantic	344 (4.0%)	45,712 (8.6%)	
East North Central	603 (7.1%)	87,779 (16.4%)	
West North Central	998 (11.7%)	37,252 (7.0%)	
South Atlantic	1,959 (23.0%)	115,910 (21.7%)	
East South Central	601 (7.1%)	32,732 (6.1%)	
West South Central	1,902 (22.3%)	73,280 (13.7%)	
Mountain	841 (9.9%)	57,935 (10.8%)	
Pacific	1,140 (13.4%)	66,165 (12.4%)	
Distance to nearest VA facility in miles, mean (SD) [median (25^{th},75^{th} percentile]	12.5 (11.7) [8.1 (3.9, 18.0)]	10.8 (11.9) [7.3 (3.6, 14.0)]	0.142
Nosos risk score[3], mean (SD)	1.4 (1.0)	1.2 (0.9)	0.146
[median (25^{th},75^{th} percentile]	[1.1 (0.7, 1.7)]	[0.9 (0.6, 1.5)]	
Inflation-adjusted costs in prior fiscal year in 2020 USD, mean (SD) [median (25^{th},75^{th} percentile]	11,013 (19,568) [5,460 (1,764, 12,666)]	9,620 (20,213) [3,886 (1,043, 10,111)]	0.070
Had VA inpatient stay in prior fiscal year	916 (10.8%)	50,477 (9.4%)	0.044
Number of VA visits in prior fiscal year, mean (SD) [median (25^{th},75^{th} percentile]			
Primary care	3.5 (3.7) [3.0 (1.0, 5.0)]	3.0 (3.5) [2.0 (1.0, 4.0)]	0.135
Specialty care	1.6 (3.3) [0.0 (0.0, 2.0)]	1.4 (3.3) [0.0 (0.0, 1.0)]	0.082
Mental health	5.4 (13.6) [0.0 (0.0, 4.0)]	4.8 (14.7) [0.0 (0.0, 3.0)]	0.042
Comorbidity[3], n (%)			
Alcohol use disorder	539 (6.3%)	33,262 (6.2%)	0.004
Apnea	1,916 (22.5%)	77,610 (14.5%)	0.207
Asthma	456 (5.4%)	20,400 (3.8%)	0.074
Coronary artery disease	693 (8.1%)	53,019 (9.9%)	0.062
Cannabis use disorder	120 (1.4%)	8,096 (1.5%)	0.009
Chronic kidney disease	231 (2.7%)	15,507 (2.9%)	0.011
Depression	2,647 (31.1%)	130,239 (24.4%)	0.150
Diabetes	2,504 (29.4%)	159,528 (29.8%)	0.010
GERD	1,071 (12.6%)	56,002 (10.5%)	0.066
Hypertension	3,927 (46.1%)	246,020 (46.0%)	0.002
Hyperlipidemia	3,213 (37.7%)	205,870 (38.5%)	0.016
NAFLD	51 (0.6%)	2,484 (0.5%)	0.018
Opioid use disorder	78 (0.9%)	5,334 (1.0%)	0.008
Osteoporosis	1,265 (14.9%)	58,160 (10.9%)	0.119
Peripheral artery disease	85 (1.0%)	7,383 (1.4%)	0.035
PTSD	1,742 (20.5%)	88,900 (16.6%)	0.098
Substance use disorder	381 (4.5%)	21,754 (4.1%)	0.020

Table 1 (continued)

	Users of AOM ($n = 8,517$)	**Non-users of AOM ($n = 534,581$)**	**SMD**
Used medication associated with…[4]			
Weight gain < 3 kg	2,539 (29.8%)	134,523 (25.2%)	0.104
Weight gain ≥ 3 kg	3,162 (37.1%)	165,567 (31.0%)	0.116
Weight loss < 3 kg	3,800 (44.6%)	207,897 (38.9%)	0.130
Weight loss ≥ 3 kg	1,328 (15.6%)	61,840 (11.6%)	0.118
BMI[5] in kg/m^2, mean (SD)	39.3 (7.0)	35.4 (6.2)	0.580
[median (25th,75th percentile]	[38.2 (34.2, 43.0)]	[34.4 (31.0, 38.8)]	
Weight[5] in pounds, mean (SD)	265.4 (57.6)	242.4 (49.0)	0.429
[median (25th,75th percentile]	[258.6 (224.5, 299.0)]	[236.0 (208.0, 269.5)]	
FY of start of MOVE!, n (%)			0.371
2008	1,166 (13.7%)	35,685 (6.7%)	
2009	1,183 (13.9%)	63,315 (11.8%)	
2010	1,093 (12.8%)	60,758 (11.4%)	
2011	911 (10.7%)	57,344 (10.7%)	
2012	742 (8.7%)	58,638 (11.0%)	
2013	562 (6.6%)	58,356 (10.9%)	
2014	550 (6.5%)	57,960 (10.8%)	
2015	596 (7.0%)	53,302 (10.0%)	
2016	668 (7.8%)	47,154 (8.8%)	
2017	1046 (12.3%)	42,069 (7.9%)	
AOM Used[6]			
Orlistat	7,091 (83.3%)	n/a	n/a
Lorcaserin	249 (2.9%)	n/a	n/a
Phentermine-topiramate	487 (5.7%)	n/a	n/a
Naltrexone-bupropion	430 (5.0%)	n/a	n/a
Liraglutide	229 (2.7%)	n/a	n/a
Phentermine[7]	206 (2.4%)	n/a	n/a
Diethylpropion[7]	0 (0.0%)	n/a	n/a
Sibutramine[7]	266 (3.1%)	n/a	n/a
Number of unique AOM used, mean (SD)	1.1 (0.2)	n/a	n/a
[median (25th,75th percentile]	[1.00 (1.00, 1.00)]		
Days from MOVE! initiation to start of first AOM, mean (SD) [median (25th,75th percentile)]			
Any medication (n = 8,517)	177.8 (151.3) [135 (60, 265)]	n/a	n/a
Orlistat (n = 7,091)	165.3 (144.3) [125 (55, 240)]	n/a	n/a
Lorcaserin[8] (n = 249)	208.9 (153.6) [175 (92, 296)]	n/a	n/a
Phentermine-topiramate (n = 487)	227.8 (157.5) [206 (97, 333)]	n/a	n/a
Naltrexone-bupropion (n = 430)	268.5 (185.6) [262 (98, 407)]	n/a	n/a
Liraglutide (n = 229)	238.2 (166.2) [230 (82, 370)]	n/a	n/a
Phentermine[7] (n = 206)	186.8 (146.9) [160 (65, 280)]	n/a	n/a
Sibutramine[7,8] (n = 266)	167.5 (127.4) [141 (78, 233]	n/a	n/a

n/a not applicable; *AOM* anti-obesity medication; *BMI* body mass index; *FY* fiscal year; *GERD* gastroesophageal reflux disease; *NAFLD* Non-alcoholic fatty liver disease; *PTSD* post-traumatic stress disorder; *SMD* standardized mean difference; *USD* U.S. dollar;

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[1] Other race includes Asian, Pacific Islander, American Indian, Alaskan Native, Native Hawaiian, or those with multiple races selected

[2] Eligible in at least one month in the twelve months prior to index, where index date = MOVE! initiation date

[3] Assessed in the 1 year prior to and including index date. Required at least 1 inpatient or 2 outpatient diagnoses

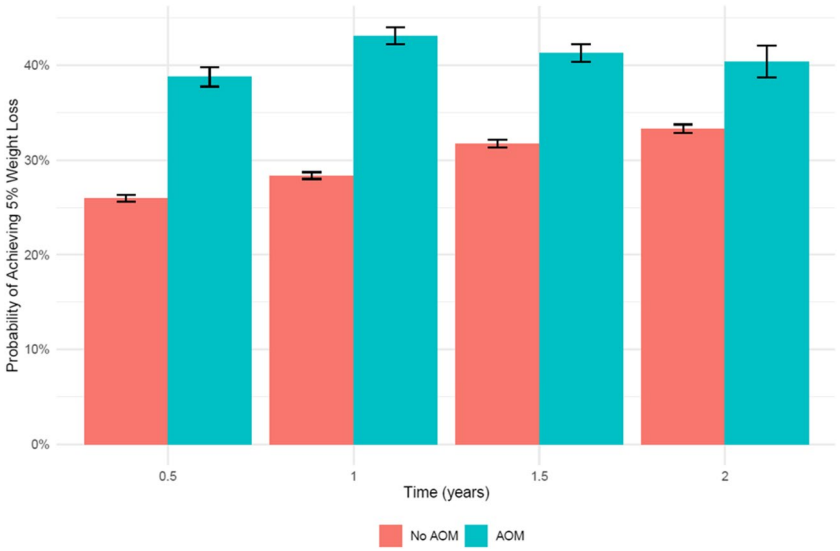
[4] Medications are assessed in the 6 months prior to index date and require ≥ 2 fills of the same medication type with a supply of 30 days or more within the 6 month timeframe

[5] From measurement closest prior to including index

[6] Percentages sum to > 100% because patients could have used more than 1 AOM

[7] FDA-approved for short-term (up to 12 weeks) weight loss, whereas other five medications are approved for long-term weight loss

[8] No longer on the market



Note. Estimates derived from weighted generalized additive mixed models of percent weight change from baseline.
AOM = anti-obesity medication

Figure 2 Estimated Probability of Achieving ≥ 5% Weight Loss at 6, 12, 18, and 24 Months for Anti-Obesity Medication Users versus Non-Users

Table 2 Unadjusted Utilization of Anti-Obesity Medications over 24 Months After MOVE! Initiation

	Number of Fills		Total Days Supply	
	Mean (SD)	Median (25^{th},75^{th} percentile)	Mean (SD)	Median (25^{th},75^{th} percentile)
Any medication (n = 8,517)	3.8 (3.5)	3 (1, 5)	134.6 (118.1)	90 (60, 180)
Orlistat (n = 7,091)	3.5 (3.2)	3 (1, 4)	125.4 (109.5)	90 (60, 180)
Lorcaserin[b] (n = 249)	3.7 (3.3)	3 (1, 5)	113.6 (98.6)	90 (56, 140)
Phentermine-topiramate (n = 487)	5.2 (4.4)	4 (2, 7)	156.8 (135.8)	106 (60, 224)
Naltrexone-bupropion (n = 430)	3.5 (3.7)	2 (1, 4)	131.7 (128.5)	90 (40, 180)
Liraglutide (n = 229)	5.4 (4.4)	4 (2, 8)	182.8 (141.5)	150 (60, 240)
Phentermine[a] (n = 206)	3.4 (3.3)	2 (1, 4)	103.4 (101.4)	60 (30, 120)
Sibutramine[a,b] (n = 266)	4.0 (3.3)	3 (1, 5)	123.9 (105.5)	90 (30, 150)

[a] FDA-approved for short-term (up to 12 weeks) weight loss, whereas the other five medications are approved for long-term weight loss

[b] No longer on the market

found median duration of use of approximately 4 months[12] and a prior meta-analysis of longer-term AOM clinical trials found high attrition rates (30–45% in all trials) and that users of longer-term AOMs were more likely to discontinue them compared to placebo due to an adverse event.[31] Even among the AOMs indicated for longer-term use (i.e., orlistat, phentermine/topiramate, buprenorphine/naltrexone, liraglutide, and lorcaserin before market withdrawal), duration was generally short (3–5 months). It was unclear whether short duration of use was due to reasons related to side effects versus effectiveness. Manufacturer-provided prescribing information recommends patients discontinue these AOMs if they are unable to achieve ≥ 4% or 5% weight loss at 12–16 weeks. A better understanding of the adverse events experienced from real-world use of AOMs, as well as potential mental health and quality of life benefits, should be explored in future research.

We also found several patient characteristics were associated with longer duration of use (i.e., ≥ 180 days), including older age, being exempt from medication copays, not having diagnosed diabetes, and use of medications with potential for significant weight-gain or weight-loss side effects. Clinicians with patients initiating AOMs may want to consider tracking concurrent antidepressants, diabetes medications, or other medications with the potential for weight gain, since 30–40% of AOM users were taking such medications in the months leading up to MOVE! initiation. VA clinical practice guidelines recommend eliminating or reducing medications that induce weight-gain, suggesting there is room to discontinue and substitute with medications that are weight-neutral or even have weight-loss side effects.[32] Given the

Table 3 Characteristics Associated with Longer Duration of Medication Use (at Least Cumulative 180-day Supply) Among Veterans who Received Anti-Obesity Medications

	Adjusted Odds Ratio (95% CI)
Age	**1.02 (1.01–1.02)**
Male	0.96 (0.84–1.1)
Race (ref: White)	
Black	0.95 (0.83–1.08)
Other[1] or Unknown	0.91 (0.73–1.13)
Ethnicity (ref: Not Hispanic/Latino)	
Hispanic/Latino	1.10 (0.89–1.35)
Unknown	1.25 (0.76–2.07)
Marital status (ref: Not Married)	
Married	1.01 (0.91–1.12)
Unknown	1.35 (0.64–2.88)
Rx copay exempt	**1.16 (1.03–1.29)**
Medicare[2]	1.01 (0.89–1.14)
Medicaid[2]	1.15 (0.95–1.38)
Census division (ref: West South Central)	
New England	1.44 (0.86–2.41)
Middle Atlantic	1.09 (0.74–1.6)
East North Central	1.31 (0.95–1.81)
West North Central	**1.53 (1.13–2.09)**
South Atlantic	1.44 (0.86–2.41)
East South Central	1.29 (0.87–1.91)
Mountain	1.12 (0.76–1.63)
Pacific	**1.57 (1.11–2.21)**
Distance to nearest facility in 10-mile increments	1.03 (0.99–1.08)
Comorbidity[3]	
Alcohol use disorder	0.90 (0.69–1.17)
Apnea	1.06 (0.94–1.2)
Asthma	0.98 (0.78–1.22)
Coronary artery disease	1.00 (0.83–1.21)
Cannabis use disorder	1.37 (0.88–2.13)
Chronic kidney disease	1.04 (0.77–1.41)
Depression	0.93 (0.82–1.04)
Diabetes	**0.80 (0.70–0.91)**
GERD	1.02 (0.88–1.19)
Hypertension	0.89 (0.79–1.01)
Hyperlipidemia	1.05 (0.94–1.18)
NAFLD	0.79 (0.42–1.5)
Opioid use disorder	1.15 (0.69–1.91)
Osteoporosis	1.09 (0.95–1.25)
Peripheral artery disease	0.77 (0.46–1.27)
PTSD	0.93 (0.81–1.06)
Substance use disorder	0.87 (0.63–1.19)
Used medication associated with…	
Weight gain < 3 kg	1.06 (0.94–1.19)
Weight gain ≥ 3 kg	**1.22 (1.09–1.37)**
Weight loss < 3 kg	**1.17 (1.04–1.32)**
Weight loss ≥ 3 kg	**1.19 (1.04–1.37)**
Obesity class (ref: Overweight [BMI 25 to < 30])	
Obesity class 1 (BMI 30 to < 35)	0.95 (0.74–1.23)
Obesity class 2 (BMI 35 to < 40)	1.11 (0.86–1.42)
Obesity class 3 (BMI 40 +)	1.07 (0.83–1.38)
FY of MOVE! initiation (ref: 2008)	
2009	0.92 (0.77–1.1)
2010	**0.80 (0.66–0.97)**
2011	**0.65 (0.53–0.8)**
2012	**0.75 (0.60–0.93)**
2013	**0.57 (0.44–0.73)**
2014	**0.69 (0.54–0.88)**
2015	**0.72 (0.57–0.92)**
2016	0.80 (0.64–1.01)
2017	1.01 (0.83–1.24)

Table 3 (continued)

CI confidence interval; *Rx* prescription medication; *GERD* gastroesophageal reflux disease; *NAFLD* Non-alcoholic fatty liver disease; *PTSD* post-traumatic stress disorder; *kg* kilograms; *BMI* body mass index; *FY* fiscal year

*Some patients began AOM use more than 1.5 years after MOVE! initiation, meaning that they could not have had ≥ 180 days of duration within the two-year follow-up period; however, this proportion was very small (2.6%)

[1] Other race includes Asian, Pacific Islander, American Indian, Alaskan Native, Native Hawaiian, or those with multiple races selected

[2] Eligible in at least one month in the twelve months prior to index

[3] Assessed in the 1 year prior to and including index date (MOVE! initiation date). Required at least 1 inpatient or 2 outpatient diagnoses

Bold means it is statistically signficant

short duration of AOM real-world use, identifying alternatives to weight gain-inducing medications may be a more sustainable, as well as complementary, approach to addressing obesity.

Barriers to AOM access need to be addressed for AOMs to become more integrated in population weight management. Unlike non-VA settings that often restrict AOM coverage, VA includes three of five FDA-approved AOMs in the national formulary. Yet our study and others find that AOM use in VA is very low.[3, 33] Until 2016, VA required ≥ 90 days' participation in MOVE! before receipt of AOM.[30] Now, VA only requires conjunctive participation in a comprehensive lifestyle intervention, which may expand access.[8, 30] There may also be provider-level barriers including concerns about safety, time constraints of routine visits, lack of confidence in providing weight loss treatments, weight bias, or insufficient knowledge about current AOMs.[34] Providers lack of clarity about the available AOMs and their tradeoffs may be compounded by changes in available AOMs between 2010 and 2015 (sibutramine withdrawn in 2010, lorcaserin approved in 2012, phentermine-topiramate approved in 2012, and bupropion-naltrexone approved in 2014). With the availability of newer, more effective AOMs, future work should examine provider attitudes and preferences about AOMs and the effectiveness of these newer AOMs in real-world use among Veterans.

Several limitations must be acknowledged. Most AOM use (83%) in this study consisted of orlistat, so weight differences between AOM users and non-users may not generalize to patients taking more recently approved AOMs. As the use of newer AOMs increases, assessment of weight change from these AOMs will be needed. This study also included AOMs available during the study period but were at some point removed from the market (sibutramine in 2010, lorcaserin in 2020), although this may not bias results significantly since their combined prevalence was low (6%).Despite applying MSMs to increase comparability between the two cohorts, there may be unobserved confounding such as patients' lifestyle behaviors, psychological characteristics, or weight loss expectations at MOVE! initiation. Additionally, when identifying combination AOMs, such as buprenorphine/naltrexone and phentermine/topiramate, we included single-agent

prescriptions if filled within 30 days of one another similar to a prior study.[3] It is possible that we missed some AOM use if single-agent prescriptions were not filled within 30 days of one another. However, some single agents (i.e., buprenorphine, naltrexone, and topiramate) have other common uses (e.g., depression, seizures). Finally, AOMs that were obtained outside of VA and not paid for by VA were not captured.

CONCLUSION

This nationwide VA study found that AOM use following MOVE! initiation was uncommon and exposure was time-limited but that AOM+MOVE! was associated with a higher probability of achieving clinically significant weight loss than MOVE! alone.

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Declarations:

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