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ORIGINAL CONTRIBUTIONS

Utilization of Anti-obesity Medications After Bariatric Surgery: Analysis of a Large National Database

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Abstract

Purpose A significant proportion of patients experience insufficient weight loss or weight regain after bariatric surgery. There is a paucity of literature describing anti-obesity medication (AOM) use following bariatric surgery. We sought to identify prevalence and trends of AOM use following bariatric surgery.

Materials and Methods We utilized the IBM Explorys® database to identify all adults with prior bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy). Those prescribed AOMs (semaglutide, liraglutide, topiramate, phentermine/topiramate, naltrexone/bupropion, orlistat) within 5 years of surgery were further identified. Data was analyzed to characterize AOM utilization among different age, demographic, and comorbid populations.

Results A total of 59,160 adults with prior bariatric surgery were included. Among AOMs studies, prevalence of use was highest for topiramate (8%), followed by liraglutide (2.9%), phentermine/topiramate (1.03%), naltrexone/bupropion (0.95%) semaglutide (0.52%), and orlistat (0.17%). Age distribution varied, with the highest utilization among those age 35–39 years for topiramate, 40–44 years for phentermine/topiramate and naltrexone/bupropion, 45–49 years for semaglutide, and 65–69 years for liraglutide and orlistat. African American race was associated with higher utilization across all AOMs. Among comorbidities, hypertension, hyperlipidemia, and diabetes mellitus were most associated with AOM use.

Conclusion Despite a relatively high incidence of weight regain, AOMs are underutilized following bariatric surgery. It is imperative that barriers to their use be addressed and that AOMs be considered earlier and more frequently in patients with insufficient weight loss or weight regain after bariatric surgery.

Keywords Anti-obesity medication · Bariatric · Weight loss · Roux-en-Y gastric bypass · Sleeve gastrectomy

Key Points
- In this analysis, FDA-approved AOMs were only prescribed in 0.17–2.91% of patients within 5 years of bariatric surgery.
- Of the AOMs studied, topiramate was used with highest prevalence (8.0%) after bariatric surgery and is more likely to be used in younger patients.
- GLP-1 receptor agonists are more likely to be prescribed among patients with comorbid diabetes and cardiovascular risk factors.

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Abbreviations

USPSTF	United States Preventive Services Task Force
BMI	Body mass index
IWL	Insufficient weight loss
WR	Weight regain
RYGB	Roux-en-Y gastric bypass
AOM	Anti-obesity medication
GABA	Gamma aminobutyric acid
GLP-1	Glucagon-like peptide-1
FDA	Food and Drug Administration
SG	Sleeve gastrectomy
SNOMED-CT	Systematized Nomenclature of Medicine-Clinical Terms
HIPAA	Health Insurance Portability and Accountability Act
CVA	Cerebrovascular accident
MI	Myocardial infarction
OR	Odds ratio

CI	Confidence interval
EWL	Excess weight loss
TWL	Total weight loss

Introduction/Purpose

Obesity is a global pandemic affecting over 650 million adults worldwide [1]. In the USA alone, 41.9% of adults have obesity—a figure estimated to approach 50% by the year 2030 [2, 3]. The United States Preventive Services Task Force (USPSTF) recommends screening all adults for obesity and referring those with a body mass index (BMI) ≥ 30 kg/m^2 to intensive, multicomponent specialty resources [4]. Yet despite implementation of obesity screening and management strategies, obesity and obesity-related comorbidities continue to contribute significant social, economic, and healthcare burden.

Bariatric surgery is the most effective and durable weight loss solution, with nearly 200,000 procedures performed in 2020 in the USA [5, 6]. In addition to weight loss, bariatric surgery is associated with significant reduction in obesity-related comorbidities, malignancy, and overall mortality [7–9]. Despite its efficacy, a proportion of patients can experience insufficient weight loss (IWL) or weight regain (WR) following surgery. IWL is commonly defined as achieving <50% excess weight loss (EWL) and WR as 10% of nadir weight or 25% EWL from nadir, with a conservative estimate of 20–25% of patients experiencing significant WR after surgery [10, 11]. Furthermore, a re-emergence of previously resolved or "in remission" related metabolic diseases is seen with WR [12, 13]. Determinants of WR include increased time from surgery, dietary indiscretion, gastrojejunal stomal diameter, gastric sleeve volume, behavioral eating patterns (food urges, binge eating, disinhibition), dysphagia, and genetics; and can often be multi-factorial and complex [14–16].

Treatment options for IWL and WR after bariatric surgery are limited, as many patients qualified for primary weight loss surgery have already attempted and failed intensive dietary and lifestyle interventions. Various endoscopic and surgical revisional therapies may be considered; however, reoperation carries a higher risk of complications compared to the primary surgery [17]. As such, in the absence of any anatomic issue promoting weight regain, a pharmacologic approach with anti-obesity medications presents a potentially attractive alternative for this population.

Anti-obesity medications (AOMs) have been utilized since at least the 1960s. However, in response to the ballooning obesity crisis, there has also been expansion in the number of Food and Drug Administration (FDA)-approved AOMs [18]. As of this study's completion, five medications are approved by the US FDA for long-term use in treating obesity—semaglutide, liraglutide, phentermine-topiramate, naltrexone-bupropion, and orlistat. AOMs confer an additional 3–9% total body weight loss (TBWL) compared to placebo, with newer incretin-targeting AOM generations surpassing 15% TBWL, though limited data exist describing their use in the post-bariatric surgery population [19].

In a large, retrospective analysis of 319 patients with WR after bariatric surgery, Stanford et al. reported that 56% achieved clinically meaningful (≥ 5%) weight loss with AOM use. Yet, only topiramate was significantly associated with predicting weight loss [20]. Additional analyses are limited by small sample sizes and lack of inclusion of all currently-approved AOMs. To adequately treat this chronic, relapsing disease, it is imperative that the role of AOMs in the post-bariatric surgery patient with weight regain is more fully understood. As such, we present the largest study to date analyzing utilization of AOMs after bariatric surgery.

Materials and Methods

Study Design and Database

A population-based commercial database (IBM® Explorys® database, IBM, Armonk, NY) was utilized to identify all adult subjects who had undergone bariatric surgery (RYGB or sleeve gastrectomy [SG]) between October, 2009 and September, 2022. Explorys® aggregates de-identified, longitudinal healthcare data derived from over 64 million unique patients from over 400 acute care centers across all 50 states. Data regarding diagnoses, procedures and medications are arranged in the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) hierarchy and RxNorm. As data is de-identified and thus compliant with the Health Insurance Portability and Accountability Act (HIPAA), the study was exempt from approval by the Institutional Review Board.

Explorys® was queried using appropriate SNOMED-CT codes to define bariatric surgeries (Supplemental Table 1) and variables of interest. FDA-approved long-term AOMs—semaglutide (Ozempic), liraglutide (Saxenda, Victoza), phentermine-topiramate (Qsymia), naltrexone-bupropion (Contrave), and orlistat (Alli, Xenical)—with the exception of setmelanotide (IMCIVREE), as well as topiramate monotherapy were included for analysis (Fig. 1). Lorcaserin (Belviq) was not included due to its withdrawal from the US Market in 2020, and tirzepatide (Zepbound) was not yet approved for weight loss at the time of this analysis. Topiramate, although not FDA-approved for long-term use for weight loss, was included as it has previously demonstrated significant association with predicting weight loss in bariatric patients with WR [20]. Subjects with history of migraines, seizure disorders and phentermine use were

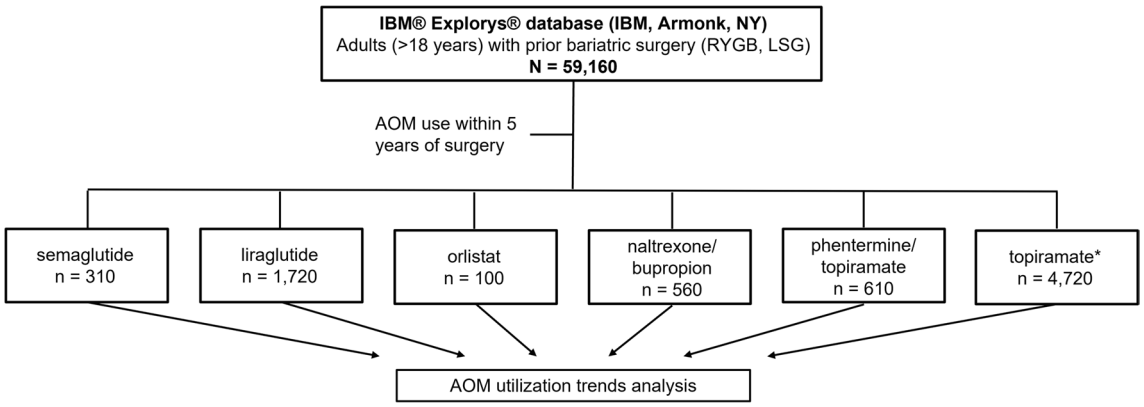

Fig. 1 Study flowchart. *Excluded from topiramate group: migraine, seizure disorder, phentermine use. RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; AOM: anti-obesity medication

excluded from the topiramate group. Only AOMs initiated within 5 years after surgery were included for analysis due to expected accumulation of unaccounted confounders with increased post-surgical time.

Demographic and Clinical Data

Subject characteristics included age, sex, race, BMI and comorbid conditions. The BMI correlating to obesity in the database is coded as BMI > 30 kg/m^2 and > 40 kg/m^2; thus, subjects were stratified and included as such according to the designation as of the time of inclusion (i.e. surgery). Age was further stratified for sub-analysis into 5-year age groups, from < 20 years to ≥ 90 years, which is the entire spectrum of age ranges available in Explorys®. Comorbidities investigated included smoking, alcohol use, diabetes mellitus, hyperlipidemia, cerebrovascular accident (CVA), and myocardial infarction (MI). The primary outcome of interest was prevalence of AOM use following bariatric surgery among various comorbid populations, with the aim of identifying characteristic trends of AOM use. The secondary outcome of interest was to identify predictors of AOM use within 5 years of bariatric surgery (RYGB or SG).

Statistical Analysis

Demographics data extracted from Explorys® were categorical and thus presented as counts and percentages. Prevalence of AOM use among various groups was calculated as a percentage of the whole cohort of bariatric surgery patients. Univariable analysis was performed to assess differences in prevalence of demographic and comorbid conditions for those prescribed AOMs vs controls by calculating odds ratios (OR) and 95% confidence interval (CI). OR, standard error and 95% CI were calculated according to Altman, 1991, using the MedCalc Statistical Software with a cohort study [21]. For all analyses, a 2-sided p-value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 59,160 adults with a history of RYGB or SG were included in the analysis (Table 1), 69.4% of which were SG. The median age range for eligible subjects was 50-54 years (n = 8080) and 77.42% of subjects were under 65 years of age. Similar to prior analyses, the majority of subjects were Caucasian (75.85%) and female (77.79%). Metabolic comorbidities were most commonly represented, with rates highest for hypertension (65.57%), followed by hyperlipidemia (53.85%) and diabetes mellitus (38.86%), while rates of CVA and MI were relatively low (0.69% and 4.75%, respectively). Most subjects had at least one recorded BMI > 40 mg/kg^2 (56.44%).

Prevalence of AOM Use After Bariatric Surgery

Among long-term FDA-approved AOMs started within 5 years of bariatric surgery, liraglutide displayed the highest prevalence at 2.91% (Fig. 2). Next was phentermine-topiramate (1.03%) followed by naltrexone-bupropion (0.95%), semaglutide (0.52%) and orlistat (0.17%). Topiramate monotherapy was the most frequently prescribed overall, with use seen in 8.0% of subjects following surgery. AOM use was more prevalent among subjects with metabolic comorbidities (hypertension, diabetes, hyperlipidemia) across all medications, with the highest prevalence seen for the GLP-1 agonists, semaglutide and liraglutide.

Table 1 Baseline characteristics of all adult subjects with history of bariatric surgery and AOM use within 5 years of surgery. Analysis of the IBM® Explorys® database

	Overall (*n* = 59,160)		Semaglutide (*n* = 310)		Liraglutide (*n* = 1720)		Topiramate (*n* = 4720)		Phentermine-topiramate (*n* = 610)		Naltrexone-bupropion (*n* = 560)		Orlistat (*n* = 100)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Subject characteristics														
Age (years)														
Adult (18–65)	45,640	77.15	240	77.42	1310	76.16	4190	88.77	530	86.89	480	85.71	70	70
Senior (>65)	13,590	22.97	70	22.58	410	23.84	540	11.44	80	13.11	80	14.29	30	30
Race														
Caucasian	44,870	75.85	210	67.74	1340	77.91	3610	76.48	450	73.77	420	75	70	70
African American	10,610	17.93	90	29.03	350	20.35	1060	22.46	160	26.23	130	23.21	30	30
Hispanic	750	1.27	0	0	30	1.74	50	1.06	0	0	0	0	0	0
Sex														
Female	46,020	77.79	230	74.19	1290	75	4170	88.35	520	85.25	470	83.93	80	80
Male	13,130	22.19	70	22.58	430	25	550	11.65	90	14.75	90	16.07	20	20
Comorbidities														
Smoking	9820	16.6	50	16.13	360	20.93	910	19.28	90	14.75	80	14.29	20	20
Alcohol	2590	4.38	0	0	70	4.07	260	5.51	10	1.64	10	1.79	0	0
Hypertension	38,790	65.57	270	87.10	1480	86.05	3250	68.86	400	65.57	420	75	90	90
Diabetes	22,990	38.86	270	87.10	1480	86.05	2010	42.58	220	36.07	220	39.29	60	60
Hyperlipidemia	31,860	53.85	260	83.87	1420	82.56	2850	60.38	380	62.3	350	62.50	80	80
CVA	410	0.69	0	0	20	1.16	40	0.85	0	0	0	0	0	0
MI	2810	4.75	30	9.68	140	8.14	210	4.45	20	3.28	20	3.57	0	0
BMI (kg/m^2)														
>30	18,340	31	170	54.84	790	45.93	2020	42.8	310	50.82	280	50	50	50
>40	33,390	56.44	230	74.19	1230	71.51	3250	68.86	430	70.49	400	71.43	60	60

AOM anti-obesity medication, *CVA* cerebrovascular accident, *MI* myocardial infarction, *BMI* body mass index

Only data for those patients started on the specified AOMs within 5 years of surgery date were included for analysis

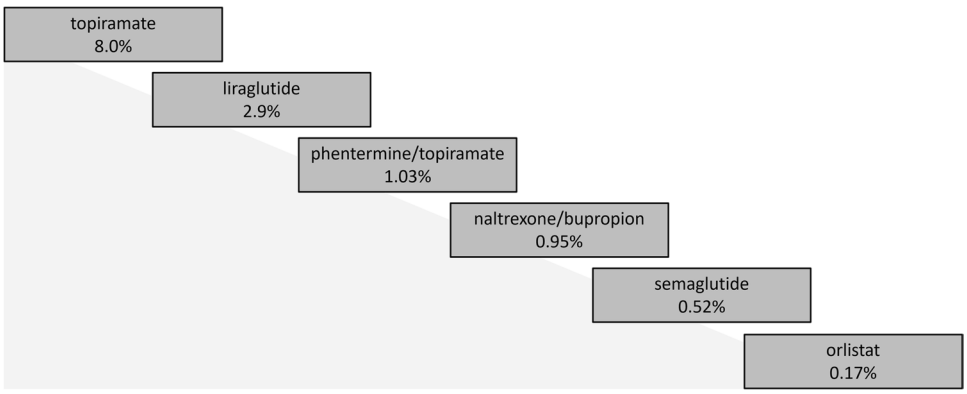

Fig. 2 Prevalence of AOM use within 5 years of surgery among patients with prior bariatric surgery. Analysis of the IBM® Explorys® database. AOM: anti-obesity medication

Univariable Analysis

Distribution of AOM use by age can be seen in Table 2 and Fig. 3. There was significant variability by age group at which different AOMs were most prescribed. Topiramate monotherapy was utilized most among younger patients, with those aged 35–39 years having the highest likelihood of topiramate use (OR 1.53, 95% CI 1.39–1.69). Meanwhile, increasing age was negatively correlated with topiramate use. AOMs most likely to be prescribed in the oldest age groups were liraglutide and orlistat, with highest OR among the 65–69-year age range (OR 1.55, 95% CI 1.35–1.78 and

Table 2 Age distribution of AOM use within 5 years of bariatric surgery

	Semaglutide		Liraglutide		Topiramate		Phentermine-Topiramate		Naltrexone-Bupropion		Orlistat	
Age (years)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Adult (18-65)	1.02 (0.78-1.33)	0.909	0.95 (0.84-1.06)	0.324	2.48 (2.26-2.72)	**<0.001**	1.97 (1.56-2.5)	**<0.001**	1.79 (1.41-2.26)	**<0.001**	0.69 (0.45-1.06)	0.09
Senior (>65)	0.98 (0.75-1.27)	0.87	1.05 (0.94-1.18)	0.387	0.41 (0.37-0.45)	**<0.001**	0.5 (0.4-0.64)	**<0.001**	0.56 (0.44-0.71)	**<0.001**	1.44 (0.94-2.21)	0.096
15-19	--	--	--	--	--	--	--	--	--	--	--	--
20-24	--	--	--	--	0.82 (0.05-1.3)	0.401	--	--	--	--	--	--
25-29	--	--	0.62 (0.4-0.97)	**0.035**	1.04 (0.84-1.29)	0.732	0.89 (0.47-1.66)	0.708	--	--	--	--
30-34	0.7 (0.37-1.31)	0.26	0.62 (0.47-0.82)	**<0.001**	1.3 (1.14-1.48)	**<0.001**	0.71 (0.45-1.1)	0.128	0.77 (0.49-1.21)	0.26	--	--
35-39	0.86 (0.54-1.35)	0.501	0.6 (0.48-0.75)	**<0.001**	1.53 (1.39-1.69)	**<0.001**	1.11 (0.83-1.49)	0.483	1.22 (0.91-1.63)	0.183	--	--
40-44	0.87 (0.59-1.26)	0.455	0.71 (0.6-0.85)	**<0.001**	1.4 (1.29-1.53)	**<0.001**	1.41 (1.12-1.76)	**0.003**	1.35 (1.07-1.72)	**0.013**	--	--
45-49	1.36 (1.01-1.85)	**0.045**	0.95 (0.82-1.1)	0.499	1.28 (1.18-1.39)	**<0.001**	1.19 (0.95-1.49)	0.135	1.32 (1.05-1.65)	**0.018**	0.76 (0.4-1.46)	0.821
50-54	1.22 (0.9-1.65)	0.205	1.13 (0.99-1.29)	0.074	1.28 (1.18-1.39)	**<0.001**	1.24 (1-1.54)	**0.048**	1.21 (0.97-1.52)	0.095	0.7 (0.37-1.35)	0.289
55-59	1.32 (0.97-1.79)	0.074	1.34 (1.18-1.53)	**<0.001**	1.02 (0.93-1.11)	0.701	1.19 (0.95-1.49)	0.135	0.82 (0.63-1.07)	0.248	1.71 (1.05-2.8)	**0.031**
60-64	1.14 (0.82-1.6)	0.43	1.26 (1.1-1.45)	**0.001**	0.86 (0.78-0.95)	**0.003**	0.8 (0.64-1.1)	0.202	1.1 (0.86-1.42)	0.446	1.93 (1.18-3.15)	**0.009**
65-69	1.33 (0.96-1.86)	0.091	1.55 (1.35-1.78)	**<0.001**	0.66 (0.58-0.74)	**<0.001**	0.8 (0.6-1.07)	0.132	0.69 (0.5-0.95)	**0.023**	2.25 (1.38-3.67)	**0.001**
70-74	1.29 (0.88-1.88)	0.189	1.07 (0.89-1.27)	0.479	0.54 (0.47-0.62)	**<0.001**	0.62 (0.43-0.89)	**0.011**	0.92 (0.67-1.27)	0.625	1.33 (0.69-2.57)	0.387
75-79	--	--	0.93 (0.73-1.18)	0.548	0.41 (0.33-0.51)	**<0.001**	--	--	0.4 (0.21-0.74)	**0.004**	--	--
80-84	--	--	0.65 (0.42-1.02)	0.059	0.22 (0.14-0.35)	**<0.001**	--	--	--	--	--	--

AOM anti-obesity medication, *OR* odds ratio, *CI* confidence interval. Bolded values indicate statistical significance. Italicized cells indicate age group most likely to be prescribed each medication. Dashed lines indicate not enough data was available for that group. No AOMs were prescribed in patients age ≥85 years; thus, these values were excluded from the table

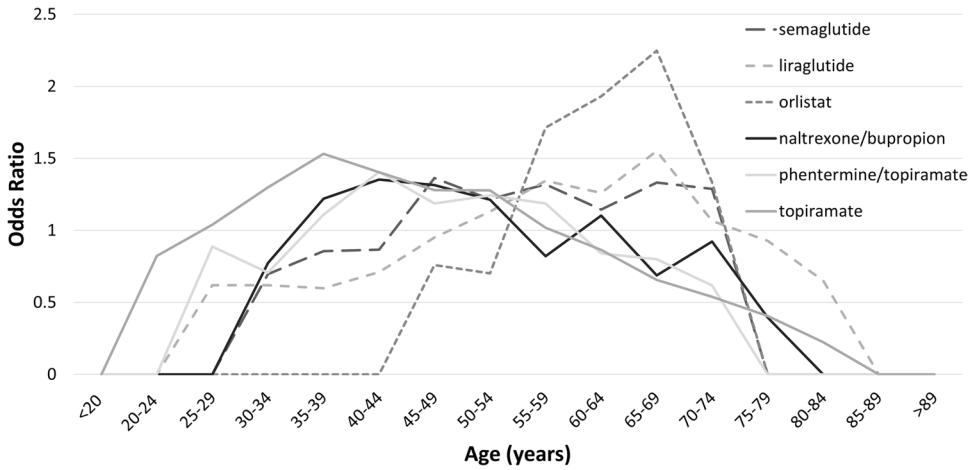

Fig. 3 Likelihood of various AOM use by age. Age with maximum odds ratio, 95% confidence interval for each AOM: topiramate: 35–39 years (1.53; 1.39–1.69); phentermine-topiramate: 40–44 years (1.41; 1.12–1.76); naltrexone-bupropion: 40–44 years (1.35; 1.07–1.72); semaglutide: 45–49 years (1.36; 1.01–1.85); liraglutide: 65–69 years (1.55; 1.35–1.78); orlistat: 65–69 years (2.25; 1.38–3.67)

OR 2.25, 95% CI 1.38–3.67, respectively). Combination phentermine-topiramate and naltrexone-bupropion were both most likely to be prescribed among subjects age 40–44 years (OR 1.41, 95% CI 1.12–1.76 and OR 1.35, 95% CI 1.07–1.72, respectively), while semaglutide was most utilized in patients aged 45–49 years (OR 1.36, 95% CI 1.01–1.85).

Analysis of AOM use among various demographic and comorbid populations is shown in Table 3. Despite AOMs more frequently being prescribed to Caucasian patients, African American race was a higher predictor of post-surgical AOM use across all medications. Similarly, female sex was more associated with use of topiramate (OR 2.28, 95% CI 2.08–2.5), phentermine-topiramate (OR 1.66, 95% CI 1.32–2.08), and naltrexone-bupropion (OR 1.5, 95% CI 1.19–1.88), while male sex was slightly more associated with liraglutide use (OR 1.17, 95% CI 1.05–1.31). No significant difference was seen in semaglutide or orlistat use among different sexes.

Significant correlation was seen between AOM use and metabolic comorbidities for nearly all medications. Both GLP-1 agonists (semaglutide, liraglutide) understandably showed high utilization among subjects with diabetes (OR 10.73 and 10.3, respectively), but also in subjects with

Table 3 Univariable analysis of AOM use after bariatric surgery among various populations

	Semaglutide		Liraglutide		Topiramate		Phentermine/topiramate		Naltrexone/bupropion		Orlistat	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Race												
Caucasian	0.67 (0.53–0.85)	**<0.001**	1.13 (1–1.27)	**0.043**	1.04 (0.97–1.11)	0.286	0.9 (0.75–1.07)	0.229	0.96 (0.79–1.16)	0.639	0.74 (0.48–1.14)	0.173
African American	1.88 (1.47–2.40)	**<0.001**	1.18 (1.04–1.32)	**0.008**	1.36 (1.27–1.46)	**<0.001**	1.64 (1.37–1.96)	**<0.001**	1.39 (1.14–1.69)	**0.001**	1.96 (1.28–3.01)	**0.002**
Hispanic	--	--	1.4 (0.97–2.2)	0.074	0.82 (0.62–1.1)	0.183	--	--	--	--	--	--
Sex												
Female	0.82 (0.64–1.06)	0.127	0.85 (0.76–0.95)	**0.005**	2.28 (2.08–2.5)	**<0.001**	1.66 (1.32–2.08)	**<0.001**	1.5 (1.19–1.88)	**<0.001**	1.14 (0.7–1.87)	0.595
Male	1.02 (0.78–1.34)	0.869	1.17 (1.05–1.31)	**0.005**	0.44 (0.4–0.48)	**<0.001**	0.6 (0.48–0.76)	**<0.001**	0.67 (0.53–0.84)	**<0.001**	0.88 (0.54–1.43)	0.598
Comorbidities												
Smoking	0.97 (0.71–1.31)	0.824	1.34 (1.19–1.51)	**<0.001**	1.22 (1.13–1.32)	**<0.001**	0.87 (0.69–1.09)	0.219	0.84 (0.66–1.06)	0.14	1.26 (0.77–2.05)	0.361
Alcohol use	--	-	0.93 (0.73–1.18)	0.526	1.3 (1.14–1.49)	**<0.001**	0.36 (0.19–0.68)	**0.002**	0.4 (0.21–0.74)	**0.004**	--	--
Hypertension	3.56 (2.56–4.97)	**<0.001**	3.33 (2.9–3.82)	**<0.001**	1.18 (1.1–1.25)	**<0.001**	1 (0.85–1.18)	0.998	1.58 (1.31–1.92)	**<0.001**	4.74 (2.46–9.1)	**<0.001**
Diabetes	10.73 (7.7–14.97)	**<0.001**	10.3 (8.98–11.82)	**<0.001**	1.18 (1.11–1.26)	**<0.001**	0.89 (0.75–1.05)	0.155	1.02 (0.86–1.21)	0.836	2.36 (1.58–3.53)	**<0.001**
Hyperlipidemia	4.48 (3.31–6.07)	**<0.001**	4.2 (3.7–4.76)	**<0.001**	1.34 (1.26–1.42)	**<0.001**	1.42 (1.21–1.68)	**<0.001**	1.43 (1.21–1.7)	**<0.001**	3.43 (2.1–5.61)	**<0.001**
CVA	--	--	1.72 (1.1–2.7)	**0.02**	1.25 (0.9–1.73)	0.183	--	--	--	--	--	--
MI	2.16 (1.48–3.16)	**<0.001**	1.82 (1.52–2.17)	**<0.001**	0.93 (0.8–1.07)	0.311	0.68 (0.43–1.06)	0.088	0.74 (0.47–1.16)	0.189	--	--
BMI (kg/m^2)												
>30	2.72 (2.17–3.4)	**<0.001**	1.93 (1.75–2.13)	**<0.001**	1.75 (1.65–1.86)	**<0.001**	2.32 (1.98–2.72)	**<0.001**	2.25 (1.9–2.65)	**<0.001**	2.23 (1.5–3.3)	**<0.001**
>40	2.23 (1.73–2.87)	**<0.001**	1.97 (1.78–2.19)	**<0.001**	1.78 (1.67–1.9)	**<0.001**	1.86 (1.56–2.21)	**<0.001**	1.94 (1.62–2.33)	**<0.001**	1.16 (0.78–1.73)	0.473

AOM anti-obesity medication, *OR* odds ratio, *CI* confidence interval, *CVA* cerebrovascular accident, *MI* myocardial infarction, *BMI* body mass index

Bolded values indicate statistical significance

hypertension (OR 3.56, 95% CI 2.56–4.97 and OR 3.33, 95% CI 2.9–3.82, respectively) and hyperlipidemia (OR 4.48, 95% CI 3.31–6.07 and OR 4.2, 95% CI 3.7–4.76, respectively). History of MI was also a positive predictor of GLP-1 agonist use. Metabolic comorbidities similarly predicted use of topiramate and orlistat while phentermine-topiramate and naltrexone-bupropion use were only positively correlated with presence of hyperlipidemia, and naltrexone-bupropion negatively correlated with diabetes. Interestingly, liraglutide and topiramate were more likely to be used among smokers (OR 1.34, 95% CI 1.19–1.51 and OR 1.22, 95% CI 1.13–1.32, respectively) as well as a higher utilization of topiramate among subjects with alcohol use (OR 1.3, 95% CI 1.14–1.49). Conversely, alcohol use was negatively associated with use of phentermine-topiramate (OR 0.36, 95% CI 0.19–0.68) and naltrexone-bupropion (OR 0.4, 95% CI 0.21–0.74). Finally, not surprisingly, both BMI >30 kg/m^2 and >40 kg/m^2 were significantly associated with post-surgical AOM use across the board, except for orlistat, which is likely due to smaller sample size.

Discussion/Conclusion

In this large, population-based analysis, considering an estimated 25% of patients following bariatric surgery experience significant WR with an additional percentage experiencing primary IWL, post-surgical AOM use within 5 years was exceedingly low [10, 11]. Prevalence of post-surgical AOMs is highest for topiramate (8.0%), followed by liraglutide (2.91%), phentermine-topiramate (1.03%), naltrexone-bupropion (0.95%), semaglutide (0.52%), and orlistat (0.17%). Substantial age variation exists at which different AOMs are utilized, with topiramate prescribed most commonly among younger patients (age 34–39 years) and liraglutide and orlistat used most among older patients (age 65–69 years). On our analysis, African American race was a predictor of AOM use across all medications, while female sex was associated with use of topiramate, phentermine-topiramate, and naltrexone-bupropion. Metabolic comorbidities (hypertension, diabetes, hyperlipidemia) were strong predictors of semaglutide, liraglutide, topiramate and orlistat use but less-so for phentermine-topiramate and naltrexone-bupropion. Cardiovascular disease (CVA, MI) was also associated with GLP-1 agonist use. In the largest analysis of AOM utilization after bariatric surgery to date, this study not only identifies prescribing trends but also highlights a gross underutilization of these effective medications.

Insufficient weight loss and WR are prominent considerations regarding the long-term durability of bariatric surgery. WR is a primary indication for revisional surgery and cause for significant deterioration of quality of life and increased medical costs; thus, mitigation and management of WR are vital [17, 22]. In the absence of anatomic causes of WR/IWL warranting endoscopic or surgical intervention (such as a gastrogastric fistula), AOMs should be strongly considered. Although data for post-operative AOM use for WR is limited, studies suggest that the majority of patients with weight regain will achieve at least 5% total weight loss (TWL), which is considered clinically significant in regards to improving health metrics and outcomes [4, 20, 23]. In a large, retrospective analysis, Stanford et al. found that 319 of 5110 (6.24%) of subjects were prescribed AOMs after RYGB or SG [20]. Many were tried on multiple AOMs, suggesting that different AOMs are more effective for different patient phenotypes. 56% of subjects experienced at least 5% of post-surgical TWL, with 30.1% losing at least 10% and 16% losing 15% of total weight. After adjusting for covariates, only topiramate was a significant predictor of weight loss (OR 1.9, $p = 0.018$ for at least 10% TWL). Furthermore, they report a higher cumulative weight loss when AOMs were initiated at weight plateau compared to awaiting WR.

Despite these data showing a high rate of clinically meaningful response, we found very low prevalence of post-operative AOM use. Of specific AOMs studied, topiramate was the most utilized, consistent with prior data reporting a preponderance for off-label AOM use [20, 24]. Despite documented weight-loss efficacy and high rates of weight regain, FDA-approved AOMs continue to be underutilized following bariatric surgery, with prevalence ranging from <1 to 3%. For semaglutide, this is likely related to its only-recent approval for weight loss in July 2021; however, this has been utilized for glycemic control with known benefits on weight for much longer. Among the FDA-approved non-GLP-1 AOMs, none was utilized in >1% of individuals post-operatively.

While AOMs have been shown to improve cardiometabolic risk factors, prior to the approval of GLP-1 agonists for weight loss, no AOM had shown reduction in cardiovascular morbidity or mortality [19]. However, several novel antiglycemic agents including GLP-1 agonists have since exhibited reductions in major adverse cardiovascular events, particularly in patients with documented atherosclerotic cardiovascular disease [25]. As such, these are now widely used among patients with cardiovascular disease and diabetes. In this study, GLP-1 agonist use showed an expected association with MI as well as multiple cardiovascular comorbidities. Temporal relationship between GLP-1 prescription and MI or onset of cardiovascular disease was outside the scope of this analysis however these findings confirm current multisocietal recommendations for GLP-1 agonist use in patients at high cardiovascular risk [26].

African American race was more predictive of post-operative AOM utilization as well. This is somewhat counterintuitive considering the majority of patients who undergo bariatric surgery are Caucasian. No studies have demonstrated

race to be a risk factor for IWL or WR; however, obesity does disproportionately affect African Americans [27, 28]. In particular, African American women have 20% higher rates of overweight and obesity compared to white women [27]. Additionally, diabetes and cardiovascular disease are more prominent among non-Hispanic black individuals compared to white individuals [29, 30]. While it is likely the higher rates of metabolic comorbidities account for some of the disparity among the GLP-1 medications, our findings that AOMs are more utilized among African Americans may also suggest either higher risk of IWL/WR or potentially more willingness to accept AOMs among this population.

There is also significant age variability at which different AOMs are utilized, likely related to increasing comorbidities, medication mechanism of action and potential side effects. For example, topiramate use is associated with younger age and negatively associated with increasing age. This may be related to known cognitive and central nervous system-depressing side effects of the medication increasing risk of adverse events in elderly patients. Conversely, GLP-1s are more utilized among older patients, which could be explained by higher rates of cardiovascular comorbidities and possibly diabetes along with relatively safe side effect profiles.

Several limitations must be addressed when interpreting this analysis. First there exist inherent limitations of the database, which utilizes SNOMED-CT nomenclature and thus limits the range of variables that may be studied. No code exists for RYGB performed specifically for obesity, which might overestimate the number of individuals for which AOMs would be indicated. Likewise, the database cannot distinguish primary from revisional surgeries and provides limited data regarding the severity of metabolic comorbidities (e.g., hemoglobin A1c) from which to gauge chronicity and refractoriness of the disease. Additionally, potential bias in data entry and classification may influence the true estimates of covariates. However, compared to ICD coding, SNOMED-CT allows for more concepts to be coded per clinical document, making it more accurate in documenting diagnoses and pertinent information [31–35].

Second, it is impossible to evaluate duration of medication use or compliance within the database, as well as their effect on weight loss. However, undocumented noncompliance would only further reduce true medication utilization. Third, although Explorys® was founded in 2009, newer medication use may be underestimated. We attempted to mitigate this effect by limiting analysis to AOMs prescribed within 5 years of surgery. Additionally, topiramate, liraglutide, and semaglutide have alternate indications for use and while the most common diagnoses for topiramate use (seizures, migraines) were excluded from analysis, this may reduce accuracy of prescribing trends for these medications. However, this again would only serve to further reduce the true prevalence of these medications used for post-operative weight loss from what is reported. Finally, while these data are overall generalizable, there is limited information regarding utilization in races other than white or African American. Despite these limitations, there is clinical utility in a study of this size highlighting underutilization of post-operative AOM use and identifying overlooked patient populations in which they should be considered.

In conclusion, despite high rates of WR/IWL following bariatric surgery and an increasing pool of literature confirming their efficacy in the post-bariatric surgery population, FDA-approved AOMs are only prescribed in a small fraction of post-bariatric surgery patients. Disparities in utilization exist across different age, race, and comorbid populations. Upon recognition of IWL or WR, a multidisciplinary strategy toward management is warranted, including behavioral and dietary counseling, medical and potentially surgical or endoscopic interventions [10]. However, with an ever-expanding armamentarium of effective and well-tolerated AOMs, these medications should be considered earlier and more frequently for IWL or WR as a long-term therapy to keep obesity and related metabolic diseases in remission.

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Declarations

Ethics Approval For this type of study, formal consent is not required.

Informed Consent Informed consent does not apply.

Conflict of Interest The authors declare no competing interests.

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