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Medications for Obesity
A Review

Kimberly A. Gudzune, MD, MPH; Robert F. Kushner, MD, MS

IMPORTANCE Obesity affects approximately 19% of women and 14% of men worldwide and is associated with increased morbidity. Antiobesity medications (AOMs) modify biological processes that affect appetite and significantly improve outcomes, such as type 2 diabetes, hypertension, and dyslipidemia.

OBSERVATIONS AOMs should be administered in combination with lifestyle interventions and can be classified according to their mechanisms of action. Orlistat modifies digestive tract absorption and causes gastrointestinal adverse effects, such as oily fecal spotting and urgency, in more than 25% of patients. Centrally acting drugs, such as phentermine-topiramate and naltrexone-bupropion, regulate appetite in the brain and are associated with constipation in approximately 20% of patients, although the incidence of other adverse effects (eg, paresthesia, nausea) varies by medication. Nutrient-stimulated hormone-based medications, such as liraglutide, semaglutide, and tirzepatide, mimic the actions of enteropancreatic hormones that modify central appetite regulation and provide multiple cardiometabolic weight-loss benefits. Adverse effects of these drugs include nausea (28%-44%), diarrhea (21%-30%), and constipation (11%-24%). The relative potency of adult obesity medications has been studied in meta-analyses. Compared with placebo, orlistat was associated with 3.1% greater weight loss (52 randomized clinical trials [RCTs]; 16 964 participants), phentermine-topiramate was associated with 8.0% greater weight loss (5 RCTs; 3407 participants), naltrexone-bupropion was associated with 4.1% greater weight loss (6 RCTs; 9949 participants), liraglutide was associated with 4.7% greater weight loss (18 RCTs; 6321 participants), semaglutide was associated with 11.4% greater weight loss (5 RCTs; 4421 participants), and tirzepatide 15 mg was associated with 12.4% greater weight loss (6 RCTs; 1972 participants).

CONCLUSION AND RELEVANCE Obesity is associated with increased morbidity. Antiobesity medications are effective adjunctive therapy to lifestyle changes for improved weight loss and health outcomes.

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Supplemental content

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Author Affiliations: Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland (Gudzune); Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Gudzune); Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Kushner); Department of Medical Education, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Kushner).

Corresponding Author: Robert F. Kushner, MD, MS, 645 N Michigan Ave, Ste 530, Chicago, IL 60611 (rkushner@northwestern.edu).

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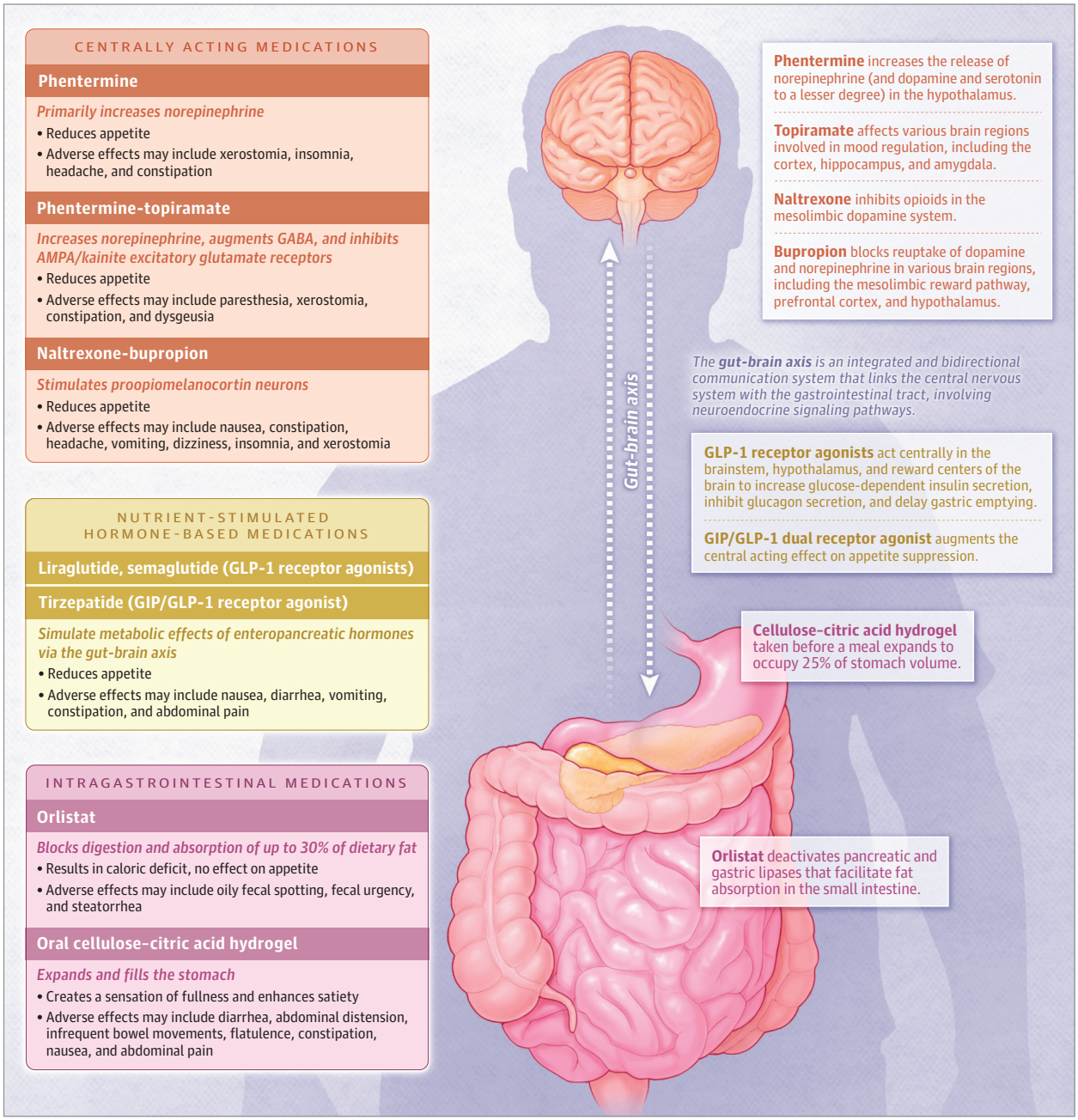
Obesity is a global public health problem associated with an increased prevalence of multiple chronic conditions compared with individuals without obesity.[1] Since 1999, the prevalence of obesity among adults, defined as a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 30 or greater, has risen from 30% to 42% in the US and is projected to affect nearly 1 in 2 adults by 2030.[2] Worldwide, obesity now affects 19% of women and 14% of men.[3] Lifestyle management is important for obesity treatment, but is often associated with weight regain due to counterregulatory physiologic changes that impair metabolism and increase appetite.[4] Antiobesity medications (AOMs) affect appetite dysregulation associated with obesity, thereby achieving and sustaining greater weight loss.[5] Multiple obesity treatment guidelines recommend pharmacotherapy in conjunction with lifestyle modification.[6-10] The US Food and Drug Administration (FDA) has approved multiple AOMs, which are indicated for adults with a BMI of 30 or greater or for adults with a BMI of 27 or greater with weight-related comorbidities, such as type 2 diabetes, hypertension, or dyslipidemia.[6-9] AOMs are also indicated for adolescents (aged ≥12 years) with BMI at or above the 95th percentile for age and sex.[10] Insufficient evidence exists for AOM use in children younger than 12 years.[10] Because adults of Asian and Southeast Asian ancestry experience obesity-related complications at lower BMIs, lower thresholds may be considered for AOM initiation in this population (BMI ≥27 or BMI ≥25 with weight-related comorbidities).[11] This review summarizes the efficacy and safety of AOMs. Currently available AOMs are presented in 3 groups based on their mechanisms of action: intragastrointestinal medications (orlistat), centrally acting medications (phentermine, phentermine-topiramate, naltrexone-bupropion), and nutrient-stimulated hormone-based medications (liraglutide, semaglutide, tirzepatide) (**Figure 1**).

Figure 1. Mechanisms of Action and Common Adverse Effects of 3 Classes of Antiobesity Medication



AMPA indicates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, γ-aminobutyric acid; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1.

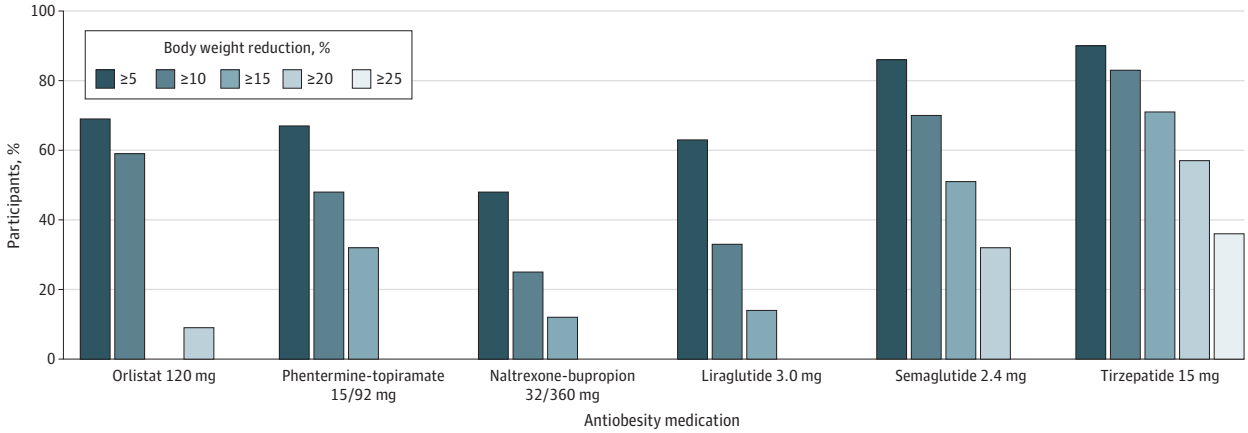
Methods

A literature search of PubMed was conducted between January 1, 2015, and February 27, 2024, using the following search terms: *antiobesity agents*, *obesity drug therapy*, and *obesity pharmacotherapy*. The search was limited to randomized clinical trials (RCTs), systematic reviews, and practice guidelines. A total of 744 articles were identified and 88 were included, consisting of 6 clinical practice guidelines, 5 systematic reviews, 4 meta-analyses, 43 RCTs, 9 observational studies, 17 reviews, 2 study designs/baseline trial data, 2 secondary analyses of trial data, 1 consensus statement, and 3 perspectives (the systematic reviews and meta-analyses were not mutually exclusive).

Intragastrointestinal Medications

Currently, only 1 FDA-approved AOM, orlistat, works by blocking fat absorption in the gastrointestinal (GI) tract. In the lumen of the stomach and small intestine, orlistat forms a covalent bond with the active site of intestinal lipases, blocking digestion and absorption of

Figure 2. Percentage of Adults With Obesity Without Diabetes Achieving Specific Weight-Loss Targets by Antiobesity Medication



Observed percentages of adult participants with overweight/obesity and without diabetes from randomized clinical trials who achieved categorical body weight reductions of at least 5%, 10%, 15%, 20%, and 25% from baseline while taking the study drug. Results from 1 trial for the following antiobesity medications are presented: orlistat 120 mg 3 times daily (52 weeks),[16] phentermine-topiramate 15/92 mg daily (56 weeks),[17] naltrexone-bupropion 32/360 mg total daily dose (56 weeks),[18] liraglutide 3.0 mg daily (56 weeks),[19] semaglutide 2.4 mg weekly (68 weeks),[20] and tirzepatide 15 mg weekly (72 weeks).[21] No long-term clinical trials are available for phentermine. No data were reported for ≥15% or ≥25% weight reduction for orlistat; ≥20% or ≥25% weight reduction for phentermine-topiramate, naltrexone-bupropion, and liraglutide; or ≥25% weight reduction for semaglutide.

approximately 30% of dietary fat, leading to a caloric deficit.[12] A separate treatment, cellulose–citric acid hydrogel, is administered like an oral medication and after ingestion, expands to occupy 25% of the stomach's volume, promoting a sensation of fullness and increased satiety.[13] This hydrogel was FDA-cleared as a device (manufacturers pursue clearance if the device is similar to other legally marketed devices, which differs from approval).[14]

Orlistat

Orlistat has been approved for adults since 1999 and for adolescents since 2003. Although most guidelines support its use in treating obesity in adults or adolescents,[6-8,10] the American Gastroenterological Association (AGA) guidelines recommended against orlistat due to its small effect on weight loss and adverse GI effects.[9] A meta-analysis of 52 RCTs that included 16 964 participants reported that orlistat was associated with 3.1% greater weight reduction than placebo (95% CI, 2.7%-3.5%) among adults with obesity.[15] Nearly 70% of orlistat participants achieved 5% or greater weight loss (**Figure 2**),[16-21] and adolescents had significant decreases in BMI (eTable 1 in the Supplement).[22]

Orlistat reduced waist circumference by approximately 10 cm, systolic blood pressure (SBP) by approximately 6 mm Hg, and low-density lipoprotein cholesterol (LDL-C) by approximately 9% among adults with obesity (**Table 1**).[16,23-29] Among patients with hypertension, a meta-analysis of 4 RCTs that included 2058 participants reported that orlistat was associated with 2.6 mm Hg greater decrease in SBP compared with placebo (95% CI, 1.4-3.8).[30] In a 4-year RCT, orlistat was associated with a 37.3% lower risk of incident type 2 diabetes compared with placebo (absolute 4-year incidence of type 2 diabetes: orlistat, 6.2%; placebo, 9.0%).[23] In a meta-analysis of 7 RCTs that included 1363 patients with type 2 diabetes, orlistat was associated with 2.0 kg greater weight loss (95% CI, 1.3-2.8) and 0.5% greater hemoglobin A_{1c} reduction (95% CI, 0.3%-0.6%) than placebo.[31] An RCT to test the effects of orlistat on cardiovascular events has not been completed.

Despite its modest effects on weight loss, orlistat typically has cardiometabolic benefits, including lowering SBP, hemoglobin A_{1c}, and LDL-C. Orlistat is also associated with prevention of type 2 diabetes. Orlistat may be most appropriate for patients who would benefit from the cardiometabolic effects of orlistat but do not tolerate or have contraindications to other AOMs (**Table 2**).[12,25-29,32-38] However, adherence to orlistat has been poor. In a large US health system, no patients prescribed orlistat continued to take the drug after 12 months.[39] Reasons for orlistat discontinuation were not reported.[39]

GI adverse effects, including oily fecal spotting (27%), fecal urgency (22%), and steatorrhea (20%), are common in the first year of orlistat use, but typically resolve within 4 weeks[12] and can be reduced by adhering to a low-calorie diet with less than 30% of calories from fat (**Table 3**).[12,40] Because of its mechanism of action, orlistat should be administered with meals containing some fat (10%-30% of calories) to be effective and limit adverse effects.

Cellulose–Citric Acid Hydrogel

Cellulose–citric acid hydrogel was FDA-cleared for adults in 2019.[13] AGA guidelines stated that there was insufficient evidence to recommend its use.[9] In a 24-week RCT, compared with placebo, the hydrogel achieved 2.1% greater mean weight loss and GI adverse effects were common (43%).[41] Product availability is unclear because the manufacturer filed for bankruptcy in October 2023.

Centrally Acting Medications

FDA-approved AOMs that act on the central nervous system include phentermine, phentermine-topiramate, and naltrexone-bupropion. These medications have various mechanisms of action in the brain. Combination regimens, such as phentermine-topiramate and naltrexone-bupropion, were developed to provide

Table 1. Weight and Cardiovascular Risk Factor Outcomes[a] of Antiobesity Medications in Adults With Obesity and Without Diabetes by Mechanism of Action

Mechanism of action group	Antiobesity medication	Time point, mo	Mean weight change, %	Mean systolic blood pressure change, mm Hg	Mean LDL-C change, %	Mean waist circumference change, cm	Common adverse effects	Mechanism of action
Intragastrointestinal medications	Orlistat[12,16,23]	12	−10.2	−6	−9.4	−9.6	Oily fecal spotting (27%), flatus with discharge (24%), fecal urgency (22%), steatorrhea (20%), oily discharge (12%), increased defecation (11%)	Intestinal lipase inhibitor
Centrally acting medications	Phentermine[24]	6	−6.1[b]	−6.4[b]	Not reported	−6.6[b]	Xerostomia (12%), insomnia (11%), headache (10%)	Sympathomimetic amine
	Phentermine-topiramate[17,25]	12	−10.9	−2.9	−8.4	−10.9	Paresthesia (20%), xerostomia (19%), constipation (16%), headache (11%)	Sympathomimetic amine combined with GABA augmentation
	Naltrexone-bupropion[18,26]	12	−6.1	−0.1[c]	−2.0[d]	−6.2	Nausea (33%), constipation (19%), headache (18%), vomiting (11%), dizziness (10%)	POMC neuron stimulation
Nutrient-stimulated hormone-based medications	Liraglutide[19,27]	12	−8.0	−4.2	−3.0	−8.2	Nausea (39%), diarrhea (21%), constipation (19%), vomiting (16%), injection site reaction (14%), headache (14%), dyspepsia (10%)	GLP-1 receptor agonist
	Semaglutide[20,28]	16	−14.9	−6.2	Not reported[e]	−13.5	Nausea (44%), diarrhea (30%), vomiting (24%), constipation (24%), abdominal pain (20%), headache (14%), fatigue (10%)	GLP-1 receptor agonist
	Tirzepatide[21,29]	17	−20.9	−7.6	−8.6	−18.5	Nausea (28%), diarrhea (23%), vomiting (13%), constipation (11%), abdominal pain (10%), dyspepsia (10%)	GIP/GLP-1 receptor agonist

Abbreviations: GABA, gamma-aminobutyric acid; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; LDL-C, low-density lipoprotein cholesterol; POMC, proopiomelanocortin.

[a] Outcomes reported for the following doses of each medication combined with lifestyle modifications: orlistat, 120 mg 3 times daily; phentermine, 15 mg daily; phentermine-topiramate, 15/92 mg daily; naltrexone-bupropion, 32/360 mg total daily dose; liraglutide, 3.0 mg daily; semaglutide, 2.4 mg weekly; and tirzepatide, 15 mg weekly. Information presented represents absolute changes and all outcomes represent statistically significant differences from control group, unless otherwise indicated.

[b] Statistical testing comparing phentermine 15 mg and placebo groups was not conducted.

[c] Statistically significant difference between naltrexone-bupropion and placebo groups, which favored the placebo group.

[d] Reported change was not statistically significant from control.

[e] Mean (%) change in LDL-C was not reported (results reported as ratio of LDL-C between baseline and 16 months [0.97]).

complementary effects to enhance weight loss. Phentermine is a sympathomimetic amine that primarily increases norepinephrine in the hypothalamus with lesser effects on dopamine and serotonin.[42] Although other sympathomimetic adrenergic agents are available (eg, diethylpropion), this review focuses only on phentermine because it is the most commonly used AOM in this category of drugs.[43,44] Information about phentermine may not apply to other sympathomimetics, such as diethylpropion or benzphetamine.[45]

Table 2. Individualizing Selection of Antiobesity Medications Among Specific Populations With Obesity Common in Primary Care Settings[a]

Medication	Depression/anxiety	CAD	HTN	Type 2 diabetes	Moderate kidney impairment[b]	Mild-moderate hepatic impairment[c]	Older adults (>65 y)[d]
Orlistat[12]	Use	Use	Use (lower BP)[30]	Use (lower A_{1c})[31]	Use	Use with caution; monitor cholelithiasis	Limited data
Phentermine[32,33]	Use with caution; limited data	No	Use with caution; baseline BP controlled; limited data	Unknown	Unknown	Unknown	Unknown
Phentermine-topiramate[25]	Use with caution; avoid maximum dose (15/92 mg) to decrease risk of adverse mood effects	Use with caution; monitor HR	Use (lower BP)[30]	Use (lower A_{1c})[34]	Limit dose to 7.5/46 mg daily	Limit dose to 7.5/46 mg daily	Limited data
Naltrexone-bupropion[26]	Unknown; avoid in young adults	Use with caution; monitor BP/HR	Use with caution; baseline BP controlled; monitor BP/HR	Use (lower A_{1c})[35]	Limit dose to 8/90 mg daily	Limit dose to 8/90 mg daily	Limited data
Liraglutide[27]	Use; monitor mood	Use; monitor HR	Use (lower BP)[19]	Use (lower A_{1c})[36]	Use	Use with caution; limited data	Limited data
Semaglutide[28]	Use; monitor mood	Use; monitor HR	Use (lower BP)[20]	Use (lower A_{1c})[37]	Use	Use; monitor cholelithiasis	Limited data
Tirzepatide[29]	Use; monitor mood	Unknown	Use (lower BP)[21]	Use (lower A_{1c})[38]	Use	Use; monitor cholelithiasis	Limited data

Abbreviations: BP, blood pressure; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; HR, heart rate; HTN, hypertension.

[a] Guidelines from the American Association of Clinical Endocrinologists/American College of Endocrinology and Obesity Canada suggest preferred antiobesity medications to use in certain patient populations,[7,8] which have been adapted for use in this table, along with information from package inserts and recent clinical trials. Specific medications are suggested for use in certain patient populations based on mechanisms of action, organ clearance, weight loss efficacy, adverse effects, warnings and contraindications, and available data for use of the medication within each population. Suggested use should not be interpreted to indicate FDA approval to treat the condition (eg, orlistat is not approved to treat HTN).

[b] Suggestions applicable to patients with moderate kidney impairment (eGFR 30-49 mL/min). For patients with severe kidney impairment (eGFR <30 mL/min), caution and close monitoring should occur if orlistat, liraglutide, semaglutide, or tirzepatide is used. Phentermine-topiramate and naltrexone-bupropion should be avoided in patients with severe kidney impairment.[7]

[c] Suggestions applicable to patients with mild to moderate hepatic impairment (Child-Pugh score of 5-9). For patients with severe hepatic impairment (Child-Pugh score of >9), antiobesity medications should generally be avoided in the primary care setting.[7]

[d] Only a small percentage of participants in randomized controlled trials of listed medications were older adults and subgroup analyses with this population have not been published. Therefore, there are limited data within this population. Guidelines recommend that antiobesity medications be used with extra caution in older adults.[7]

Phentermine has relatively low potential for abuse (Schedule IV), and signs of phentermine misuse or physical dependence have not been reported.[42] Topiramate augments γ-aminobutyrate activity and inhibits α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainite excitatory glutamate receptors[6]; therefore, phentermine-topiramate works through several central mechanisms to reduce appetite and increase satiety. Naltrexone and bupropion reduce appetite and food cravings through different mechanisms that stimulate proopiomelanocortin neurons.[6]

Phentermine

Phentermine was approved in the US for short-term use (3 months or fewer) in 1959, and therefore, its long-term use is considered off-label.[32,33,42] The Endocrine Society and AGA guidelines recommend long-term phentermine use to treat obesity in adults without cardiovascular disease.[6,9] Few RCTs have tested the efficacy and safety of phentermine for more than 3 months[45] and long-term trials are needed for the FDA to consider extending the approved duration of use. One 6-month RCT reported that phentermine 7.5 mg was associated with 5.5% weight loss and phentermine 15 mg was associated with 6.1% weight loss, which were significantly greater than 2.3% weight loss with placebo.[24] More than 40% of participants achieved 5% or greater weight loss with either dose of phentermine at 6 months.[24] Another RCT reported that phentermine 15 mg reduced weight by 4.1% compared with 0.6% for placebo at 6-month follow-up.[46]

There is little evidence regarding cardiometabolic outcomes with phentermine. A large observational study reported that phentermine use for more than 3 months was associated with greater weight reduction without increased risk of adverse cardiovascular events at 3-year follow-up.[47] No elevations in blood pressure were reported with phentermine use for 6 months and SBP decreased with its use (Table 1).[24,46,47]

Phentermine is the most inexpensive AOM for patients without insurance coverage for AOMs (Table 3). Clinicians should check that local regulations permit long-term prescribing of phentermine (eg, state medical and pharmacy boards) and should counsel patients about the off-label use, limited clinical trial data supporting long-term use, and unknown cardiovascular risks.

Few or no serious adverse events occurred in studies with a duration of 6 months or longer.[24,46,47] Common adverse effects are xerostomia (7%-12%), insomnia (6%-11%), headache (10%-12%), and constipation (4%-8%),[24,32,33,46] which may improve with dose reduction (Table 3). Phentermine may be unavailable in some countries outside the US where regulators have concerns about an

Table 3. Practical Considerations in Prescribing and Managing Antiobesity Medications, Listed by Currently Approved Medication

Medication, US approved population, and cost[a]	Administration and titration	Drug interactions	Patient populations with obesity			Strategies to improve safety and tolerability related to common adverse effects
			Consider use	Use with caution	Avoid use[b]	
Orlistat[12] ≥12 y $675/mo Discounts/coupons available online to reduce to approximately $200/mo; generic formulations may be available in some countries	Oral tablet taken with fat-containing meals 3 times a day (120 mg) Manufacturer-recommended titration: none	Levothyroxine Warfarin Amiodarone Cyclosporine AEDs Antiretroviral drugs	Adults with: type 2 diabetes to lower A_{1c} HTN to lower BP HLD to lower LDL type 2 diabetes prevention Weight-loss maintenance Adolescents	History of: Frequent diarrhea Oxalate nephrolithiasis Following a high-fat diet (eg, low-CHO, ketogenic) as increased GI side effects	History of: Malabsorption Cholestasis	Counsel on: Balanced, low-calorie diet with <30% of calories from fat to reduce GI adverse effects GI adverse effects typically subside within 4 weeks Take MVI-containing fat-soluble vitamins (A, E, D, K, beta-carotene) at bedtime to avoid deficiencies
Phentermine[32,33] ≥16 y $40-$95/mo Discounts/coupons available online to reduce to approximately $8/mo; generic formulations may be available in some countries	Oral tablet or capsule taken daily in the morning (15 mg, 30 mg, or 37.5 mg)[c] Oral tablet taken up to 3 times a day (8 mg)[c] Manufacturer-recommended titration: none	Alcohol MAOIs	Adults with: No AOM coverage for lowest out-of-pocket costs	History of: Insomnia Insufficient sleep Frequent constipation	History of: CVD Substance use disorder Agitated states Glaucoma Hyperthyroidism Uncontrolled HTN	Counsel on: Water and dietary fiber intake to reduce dry mouth and constipation Monitor and adjust: HR and BP for increasing with initiation and titration; lower dose Begin on low dose (8 mg or 15 mg daily); titrate slowly to balance weight loss and adverse effects; not all patients need maximum dose
Phentermine-topiramate[25] ≥12 y $250/mo Discounts/coupons available online to reduce to approximately $100/mo	Oral capsule taken daily in the morning[c] Manufacturer-recommended titration: Week 1-2: 3.75/23 mg Week 3-13: 7.5/46 mg Week 14 (3 mo): if 3% reduction in weight (adult) or BMI (adolescent) met: Week 14 and beyond: 7.5/46 mg If 3% reduction not achieved: Week 14-15: 11.25/69 mg Week 16 and beyond: 15/92 mg	Alcohol OCPs Amitriptyline Nonpotassium-sparing diuretics AEDs Carbonic anhydrase inhibitors MAOIs	Adults with: type 2 diabetes to lower A_{1c} HTN to lower BP Central adiposity to lower WC Lack AOM coverage as lower out-of-pocket costs	History of: Insomnia Insufficient sleep Frequent constipation Nephrolithiasis MDD Occupation requiring mental acuity	History of: Narrow-angle glaucoma Hyperthyroidism People with pregnancy potential who do not use effective contraception as risk of birth defects (oral clefts)	Counsel on: Water and dietary fiber intake to reduce dry mouth and constipation Irregular bleeding may occur for patients taking OCPs; no change in risk of pregnancy Monitor and adjust: Slowing titration may reduce adverse effects and increase tolerability Lower dose if paresthesia, mood, or cognitive difficulties ("brain fog") impair daily activities Electrolytes before and during treatment to increase Cr and lower HCO_3; lower dose if needed
Naltrexone-bupropion[26] ≥18 y $740/mo Discounts/coupons available online to reduce to approximately $100/mo	Oral tablet taken up to twice a day (8/90 mg) Manufacturer-recommended titration: Week 1: 1 tablet daily Week 2: 1 tablet twice a day Week 3: 2 tablets every morning and 1 tablet every evening Week 4 and beyond: 2 tablets twice a day	Opioids SSRIs or TCAs Antipsychotics β-Blockers Type 1C antiarrhythmics Digoxin Ticlopidine or clopidogrel Levodopa or amantadine AEDs Antiretroviral drugs MAOIs	Adults with: Type 2 diabetes to lower A_{1c} Central adiposity to lower WC Lack AOM coverage as lower out-of-pocket costs with discounts	History of: MDD SMI Liver disease Following a high-fat diet (eg, low-CHO, ketogenic) as increased adverse effects	History of: Substance use disorder Narrow-angle glaucoma Seizure disorder Anorexia or bulimia Uncontrolled HTN Chronic opioid use	Counsel on: Administering evening dose ≥3 h before bedtime to reduce sleep disturbance Water and dietary fiber intake to reduce dry mouth and constipation Lower portion size to manage nausea Interaction with opioids; provide medication management strategy if short-term opioids needed Monitor and adjust: Slowing titration may reduce adverse effects and increase tolerability; not all patients need maximum dose HR and BP increased with initiation and titration; lower dose Headache; lower dose Mood and SI; lower dose or discontinue with SI

(continued)

Table 3. Practical Considerations in Prescribing and Managing Antiobesity Medications, Listed by Currently Approved Medication (continued)

Medication, US approved population, and cost[a]	Administration and titration	Drug interactions	Patient populations with obesity			Strategies to improve safety and tolerability related to common adverse effects
			Consider use	Use with caution	Avoid use[b]	
Liraglutide[27] ≥12 y $1600/mo Discounts/coupons available online to reduce to approximately $1300/mo	Subcutaneous injection administered daily with multidose pen Manufacturer-recommended titration: Week 1: 0.6 mg Week 2: 1.2 mg Week 3: 1.8 mg Week 4: 2.4 mg Week 5 and beyond: 3.0 mg Of note, prescription for pen needles must be provided (dispensed medication does not include needles for administration)	GLP-1 receptor agonists Insulin Sulfonylureas Meglitinides	Adults with: Type 2 diabetes to lower A_{1c} HTN to lower BP Central adiposity to lower WC Adolescents	History of: Frequent nausea Frequent constipation Frequent diarrhea Cholelithiasis Pancreatitis	History of: Severe gastrointestinal disease Suicide attempts[d] Personal or family history of medullary thyroid carcinoma	Counsel on: Rotating injection site location to reduce pain; may use thigh, upper arm, or abdomen Water and dietary fiber intake to reduce constipation Lower portion size to manage nausea Last meal ≥2 h before bedtime to reduce heartburn Refrigerate multi-dose pens (may be kept at room temperature for 30 d) Monitor and adjust: Slowing titration may reduce side effects and increase tolerability; not all patients need maximum dose Hypoglycemia in patients on insulin or sulfonylureas; consider lowering doses of these medications with liraglutide initiation to reduce risk HR increase, particularly among patients with CVD; lower dose or discontinue if needed Mood and SI[d]; lower dose or discontinue with SI
Semaglutide[28] ≥12 y $1600/mo Discounts/coupons available online to reduce to approximately $1100/mo	Subcutaneous injection administered weekly with single-dose pen Manufacturer-recommended titration: Week 1-4: 0.25 mg Week 5-8: 0.5 mg Week 9-12: 1.0 mg Week 13-16: 1.7 mg Week 17 and beyond: 2.4 mg Of note, 1.7 mg may be a maintenance dose for adults	GLP-1 receptor agonists Insulin Sulfonylureas Meglitinides	Adults with: Type 2 diabetes to lower A_{1c} HTN to lower BP Central adiposity to lower WC CVD to lower major adverse cardiac events HFpEF to lower heart failure symptoms	History of: Frequent nausea Frequent constipation Frequent diarrhea Cholelithiasis Pancreatitis Diabetes-related eye disease	History of: Severe gastrointestinal disease Suicide attempts[d] Personal or family history of medullary thyroid carcinoma	Counsel on: Rotating injection site location to reduce pain; may use thigh, upper arm, or abdomen Water and dietary fiber intake to reduce constipation Lower dietary fat and portion size to manage nausea Last meal ≥2 h before bedtime to reduce heartburn Take MVI daily to avoid micronutrient deficiencies Refrigerate single-dose pens (may be kept at room temperature for 28 d) Monitor and adjust: Slowing titration may reduce adverse effects and increase tolerability; not all patients need to reach maintenance dose(s) Hypoglycemia in patients on insulin or sulfonylureas; consider lowering doses of these medications with semaglutide initiation to reduce risk HR increase, particularly among patients with known CVD; lower dose or discontinue if needed Mood and SI[d]; lower dose or discontinue with SI

(continued)

unfavorable risk-benefit profile, particularly given the lack of long-term cardiovascular outcomes.[42,48]

Phentermine-Topiramate

Phentermine-topiramate has been approved for long-term use in the US for adults since 2012 and was approved for adolescents (aged ≥12 years) in 2022.[25] A meta-analysis of 5 RCTs that included 3407 participants reported that phentermine-topiramate was associated with 8.0% greater weight loss than placebo (95% CI, 6.7%-9.3%) among adults with obesity.[15] At 12 months, mean weight loss was 7.8% with phentermine-topiramate 7.5/46 mg and 9.8% with phentermine-topiramate 15/92 mg.[49] A follow-up study reported that these weight reductions persisted at 2 years with continued medication use.[50] More than two-thirds of phentermine-topiramate 15/92 mg users achieved 5% or greater weight loss (Figure 2).[17] Adolescents had a significant 10.4% reduction in BMI with phentermine-topiramate 15/92 mg compared with placebo. The safety profile was similar to the safety profile in adults (eTable 2 in the Supplement).[51]

Phentermine-topiramate reduced waist circumference by approximately 11 cm, decreased SBP by approximately 3 mm Hg, and reduced LDL-C by approximately 6% among adults with obesity (Table 1).[17] Among 1030 patients with hypertension, phentermine-topiramate 15/92 mg statistically significantly reduced SBP 4.2 mm Hg (95% CI, 2.55-5.85) more than placebo.[30] At 2-year follow-up,

Table 3. Practical Considerations in Prescribing and Managing Antiobesity Medications, Listed by Currently Approved Medication (continued)

Medication, US approved population, and cost[a]	Administration and titration	Drug interactions	Patient populations with obesity			Strategies to improve safety and tolerability related to common adverse effects
			Consider use	Use with caution	Avoid use[b]	
Tirzepatide[29] ≥18 y $1275/mo Discounts/coupons available online to reduce to approximately $700/mo	Subcutaneous injection administered weekly with single-dose pen Manufacturer-recommended titration: Week 1-4: 2.5 mg Week 5-8: 5.0 mg Week 9-12: 7.5 mg Week 13-16: 10.0 mg Week 17-20: 12.5 mg Week 21 and beyond: 15.0 mg Of note, 5 mg, 10 mg, or 15 mg may be a maintenance dose for adults	GLP-1 receptor agonists Insulin Sulfonylureas Meglitinides	Adults with: Type 2 diabetes to lower A_{1c} HTN to lower BP HLD to lower LDL Central adiposity to lower WC	History of: Frequent nausea Frequent constipation Frequent diarrhea Cholelithiasis Pancreatitis Diabetes-related eye disease	History of: Severe gastrointestinal disease Suicide attempts[d] Personal or family history of medullary thyroid carcinoma	Counsel on: Rotating injection site location to reduce pain; may use thigh, upper arm, or abdomen Water and dietary fiber intake to reduce constipation Lower dietary fat and portion size to manage nausea Last meal ≥2 h before bedtime to reduce heartburn Take MVI daily to avoid micronutrient deficiencies Refrigerate single-dose pens (may be kept at room temperature for 21 d) Monitor and adjust: Slowing titration may reduce adverse effects and increase tolerability; 3 different maintenance doses available Hypoglycemia in patients on insulin or sulfonylureas; consider lowering doses of these medications with tirzepatide initiation to reduce risk Mood and SI[d]; lower dose or discontinue with SI

Abbreviations: AED, antiepileptic drugs; AOM, antiobesity medication; BP, blood pressure; CHO, carbohydrate; Cr, creatinine; CVD, cardiovascular disease; GI, gastrointestinal; HCO_3, bicarbonate; HFpEF, heart failure with preserved ejection fraction; HLD, hyperlipidemia; HR, heart rate; HTN, hypertension; LDL, low-density lipoprotein; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; MVI, multivitamin; OCP, oral contraceptives; SI, suicidal ideation; SMI, serious mental illness; WC, waist circumference.

[a] Given that many patients lack insurance coverage for AOMs, costs provided reflect US retail prices identified in early March 2024 on GoodRx.com. Below the retail price, an estimated price is provided if online discounts or coupons are used that are available online through pharmaceutical manufacturers or websites like GoodRx. Discounts from pharmaceutical manufacturers have certain eligibility criteria and are not available to all patients (eg, Medicare beneficiaries are ineligible). Patients with insurance coverage for a medication may have lower out-of-pocket costs than those listed in this table.

[b] List of patient populations where use should be avoided highlights common populations that may be encountered in the primary care setting and this list should therefore not be considered exhaustive of all contraindications. Clinicians should review all information available in the package insert for each medication prior to prescribing to be aware of all contraindications. In general, antiobesity medications are contraindicated among pregnant persons and individuals with known hypersensitivity to medication ingredients and are used cautiously in patients who are lactating.

[c] Medication is approved by the US Food and Drug Administration as Schedule IV controlled substance; therefore, prescribers need to adhere to federal and state regulations for prescribing and dispensing these types of medications.

[d] As of March 2024, package inserts for liraglutide, semaglutide, and tirzepatide include a warning about the risk of SI; however, no increased risk of suicide has been identified in monitoring studies,[40] which was acknowledged by the US Food and Drug Administration in January 2024.

phentermine-topiramate 15/92 mg reduced progression to type 2 diabetes compared with placebo.[50] Patients with type 2 diabetes achieved mean weight loss of 9.4% and hemoglobin A_{1c} reduction of 1.6% at 12 months with phentermine-topiramate 15/92 mg compared with placebo.[34] A cardiovascular outcomes trial has not been conducted for phentermine-topiramate. An observational study of the FDA Adverse Event Reporting System found no association between this medication and increased rates of cardiovascular events.[52]

As long-term phentermine-topiramate can achieve and sustain a 10% weight reduction, this AOM may be useful for patients who need to meet this goal, particularly to reduce blood pressure or manage diabetes (Table 2). In clinical practice, medication adherence declined over time (36% at 3 months; 13% at 12 months).[39] Reasons for phentermine-topiramate discontinuation were not reported.[39] Regular follow-up may be important for monitoring adherence. Phentermine-topiramate may be an affordable option for patients without insurance coverage (Table 3). Prescribing phentermine and topiramate separately may further reduce costs. However, clinicians and patients should be aware that this approach is an off-label use and limited clinical trial data support the approach.

Common adverse events associated with phentermine-topiramate include paresthesia (14%-20%), dry mouth (14%-19%), constipation (15%-16%), and dysgeusia (7%-9%),[25] which may improve with dose reduction (Table 3). Because of an increased risk of congenital fetal oral-cleft malformation from topiramate, individuals of childbearing age should have a negative pregnancy test result before treatment and should be monitored with monthly pregnancy testing as long as they take this drug. Individuals of childbearing age should also be counseled to use effective contraception consistently. Maximum dose is limited to phentermine-topiramate 7.5/46 mg daily in patients with moderate kidney and mild-to-moderate hepatic impairment and the highest dose should be avoided in patients with depression/anxiety (Table 2). Phentermine-topiramate may be unavailable in other countries where regulators cite the need for long-term data regarding cardiovascular, psychiatric, and cognitive outcomes to consider approval.[48]

Naltrexone-Bupropion

Naltrexone-bupropion was approved for long-term use in adults in 2014[26]; it has not been studied in adolescents. A meta-analysis of

6 RCTs that included 9949 adults with obesity reported that naltrexone-bupropion was associated with 4.1% greater weight loss than placebo (95% CI, 3.0%-5.2%).[15] Combining naltrexone-bupropion with intensive behavioral therapy was associated with 9.3% weight loss at 12 months, compared with 5.1% weight loss for placebo combined with intensive behavioral therapy.[53] Nearly half of naltrexone-bupropion participants achieved 5% or greater weight loss in another 56-week RCT (Figure 2).[18]

Compared with other AOMs, naltrexone-bupropion has fewer effects on cardiovascular risk factors (Table 1; eTable 3 in the Supplement).[18,35,53,54] Among patients with hypertension, naltrexone-bupropion had no significant effect on blood pressure compared with placebo.[30] Bupropion is known to increase blood pressure.[55] In contrast, other AOMs, such as orlistat and phentermine-topiramate, have lowered blood pressure among patients with hypertension.[30] Patients with type 2 diabetes achieved mean weight loss of 5.0% and hemoglobin A_{1c} reduction of 0.6% at 12 months with naltrexone-bupropion compared with placebo.[35] An RCT that included 8910 people reported no significant effects of naltrexone-bupropion on major adverse cardiovascular events (MACE) compared with placebo.[56]

Weight reduction is greater when naltrexone-bupropion is combined with intensive behavioral therapy. Therefore, it may be best suited for patients participating in intensive behavioral programs, in which monitoring of blood pressure during initiation and dose escalation can more easily occur. Naltrexone-bupropion is less expensive than other AOMs for patients who lack insurance coverage (Table 3). Prescribing naltrexone and bupropion separately may further reduce costs. However, this approach is an off-label use and limited trial data support the approach. In clinical practice, medication adherence is relatively low (34% at 3 months; 10% at 12 months).[39] Reasons for naltrexone-bupropion discontinuation were not reported.[39]

Common adverse effects of naltrexone-bupropion include nausea (33%), constipation (19%), headache (18%), vomiting (11%), dizziness (10%), insomnia (9%), and xerostomia (8%)[26] and dose adjustment may be needed to address tolerability (Table 3). The maximum dose is limited to naltrexone-bupropion 8/90 mg daily in patients with moderate kidney and mild to moderate hepatic impairment, and naltrexone-bupropion should be avoided in young adults with depression/anxiety (Table 2).

Nutrient-Stimulated Hormone-Based Medications

The discovery of the role of the gut-brain axis in controlling appetite has provided new biological targets for drug development, nutrient-stimulated hormone-based medications, which simulate the metabolic effects of naturally occurring entero-pancreatic hormones,[57] including glucagon-like peptide-1 (GLP-1),[58] glucose-dependent insulinotropic polypeptide (GIP),[59] glucagon,[60] and amylin.[61] GLP-1 receptor agonists (RAs) have been the most studied given their incretin effect (ie, amplified insulin secretion after oral vs intravenous glucose administration) and other pleiotropic cardiometabolic actions (eg, decreased blood pressure and inflammation) that are mediated by the widespread distribution of GLP-1 receptors throughout the body.[62] GLP-1 RAs were initially introduced for type 2 diabetes treatment and more recently for obesity treatment. Entero-pancreatic hormones, such as GLP-1, GIP, and glucagon, can have complementary or distinct biological activity that supports development of combination medications. For example, in addition to enhancing appetite suppression, GIP receptors exist in adipose tissue to promote lipoprotein lipase activation.[63] Glucagon enhances hepatic lipolysis and may increase energy expenditure,[64] whereas amylin enhances leptin sensitization and has direct brain activation to promote meal-ending satiety.[61] Nutrient-stimulated hormone-based medications represent a paradigm shift in the pharmacological treatment of obesity given their weight-loss efficacy, safety, and indirect beneficial effects on cardiometabolic and kidney disease risk factors.[65]

The FDA has approved 3 nutrient-stimulated hormone-based AOMs: liraglutide, semaglutide, and tirzepatide. As the half-life of native GLP-1 is only 2 to 3 minutes due to rapid degradation by dipeptidyl peptidase IV (DPP-4), these AOMs have modified structure to resist DPP-4 proteolysis and prolong half-life.[65] Liraglutide is a GLP-1 RA with 97% homology to human GLP-1 with reduced susceptibility to DPP-4 that increases half-life to 11 to 15 hours with daily subcutaneous administration.[27,66] Semaglutide is another GLP-1 RA that is designed for weekly subcutaneous administration, with a 183-hour half-life.[28,67] Tirzepatide is a dual GIP/GLP-1 RA with a 117-hour half-life with weekly subcutaneous administration.[29,68] GIP appears to act synergistically with GLP-1 in the brain to promote a greater magnitude of weight loss compared with GLP-1 alone.

Liraglutide

Liraglutide was approved for obesity treatment in 2014 for adults and in 2020 for adolescents (aged ≥12 years) (maximum dose, 3.0 mg daily).[27] A meta-analysis of 18 RCTs that included 6321 participants reported that, compared with placebo, liraglutide was associated with a 4.7% weight reduction (95% CI, 4.1%-5.3%) among adults with obesity. The meta-analysis included RCTs for both type 2 diabetes and obesity treatment.[15] Specifically targeting obesity, liraglutide has been studied in 5 RCTs (Satiety and Clinical Adiposity – Liraglutide Evidence [SCALE] trials) involving more than 5000 adults to evaluate its efficacy and safety (eTable 4 in the Supplement).[19,36,69-71] More than 60% of participants treated with liraglutide achieved 5% or greater weight loss (Figure 2).[19] The SCALE trials' intention-to-treat 1-year weight loss ranged from 3.4% to 6.1% compared with placebo. In a trial of adolescents with obesity, liraglutide attained a mean BMI reduction of 5% compared with placebo.[72]

Liraglutide reduced waist circumference by approximately 8 cm, decreased SBP by approximately 4 mm Hg, and reduced LDL-C by approximately 8% among adults with obesity (Table 1).[19] Among patients with type 2 diabetes, a higher dose of liraglutide for obesity (ie, 3.0 mg/d) did not attain greater reductions in hemoglobin A_{1c} relative to a lower dose (ie, 1.8 mg/d) for treatment of type 2 diabetes (eTable 4 in the Supplement).[36] Liraglutide 3.0 mg resulted in mean weight loss of 6.0% and mean hemoglobin A_{1c} decrease of 1.6% among adults with type 2 diabetes and obesity.[36] An RCT of 9340 participants with type 2 diabetes reported liraglutide reduced MACE compared with placebo.[73] A similar clinical trial has not been conducted in patients with obesity and without type 2 diabetes.[74]

Liraglutide may be a reasonable option for patients with coexisting type 2 diabetes (Table 2) when other nutrient-stimulated hormone-based AOMs are not covered by insurance or for patients who prefer to use a medication from this class, which has been on the market longest. In real-world settings, medication adherence declined over time (52% at 3 months; 17% at 12 months).[39] Reasons for liraglutide discontinuation were not reported.[39] Regular follow-up may be important to maximize adherence long-term.

The most common adverse effects associated with liraglutide are nausea (39%), diarrhea (21%), and constipation (19%), which are mild to moderate and occur primarily during the dose escalation phase.[27] Table 3 includes additional practical considerations in prescribing and managing liraglutide.

Semaglutide

Semaglutide was approved for chronic weight management in 2021 for adults and in 2022 for adolescents (aged ≥12 years) (maximum dose, 2.4 mg weekly).[28] Semaglutide 2.4 mg was also approved to reduce the risk of MACE in adults with established cardiovascular disease and either obesity or overweight in 2024. A meta-analysis of 5 RCTs that included 4421 participants reported an 11.4% greater weight loss than placebo (95% CI, 10.3%-12.5%) among adults treated for obesity.[15] The Semaglutide Treatment Effect in People with Obesity Program (STEP) included multiple RCTs comparing semaglutide 2.4 mg and placebo on weight loss, safety, and tolerability in adults (eTable 5 in the Supplement).[20,37,75-80] Compared with placebo, weight loss ranged from 6.2% to 14.8% at 68-week follow-up in STEP 1-4[20,37,76,77] and 12.6% at 2 years in STEP 5.[78] More than 85% of participants taking semaglutide attained 5% or greater weight loss (Figure 2).[20] When directly compared, weight loss was 15.8% for semaglutide and 6.4% for liraglutide.[80] In an RCT of adolescents with obesity, semaglutide attained a 16.1% BMI reduction compared with a 0.6% BMI increase for placebo.[81]

Semaglutide reduced waist circumference by approximately 14 cm and SBP by approximately 6 mm Hg (Table 1).[20,76] Semaglutide 2.4 mg resulted in mean weight loss of 9.6% and mean hemoglobin A_{1c} decrease of 1.6% among adults with type 2 diabetes and obesity.[37] In the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial, semaglutide 2.4 mg reduced MACE by 20% compared with placebo (absolute rates of MACE: semaglutide, 6.5%; placebo, 8.0%) in 17 604 adults with BMI of 27 or greater and preexisting cardiovascular disease without type 2 diabetes.[82] In an RCT of 529 participants with obesity and heart failure with preserved ejection fraction, semaglutide 2.4 mg reduced heart failure symptoms and body weight as well as increased 6-minute walk distance and reduced C-reactive protein levels compared with placebo.[83]

Because semaglutide achieves and sustains greater than 10% weight reduction while therapy is continued, this AOM may be most appropriate for patients who need to meet this goal, particularly among patients with multiple weight-related conditions (Table 2). In contrast with other AOMs, medication adherence with semaglutide remained relatively high over time in real-world settings (63% at 3 months; 40% at 12 months).[39]

Common adverse effects of semaglutide include nausea (44%), diarrhea (30%), vomiting (24%), constipation (24%), and abdominal pain (20%),[28] which are mild to moderate and mostly occur during dose escalation.[84] Nausea, diarrhea, and vomiting typically subside within a week; however, constipation may last approximately 45 days.[84] Counseling patients at initiation on key dietary modifications, such as decreased portion sizes, reduced fat, and increased dietary fiber intake, may help mitigate these GI effects (Table 3).

Tirzepatide

Tirzepatide was approved to treat obesity in adults in 2023.[29] A meta-analysis of 6 RCTs that included 1972 participants reported that tirzepatide 15 mg was associated with 12.4% greater weight loss than placebo (95% CI, 7.5%-17.2%) among adults with obesity, which included RCTs for both type 2 diabetes and obesity treatment.[85] In multiple RCTs in the SURMOUNT program,[86] weight loss ranged from 11.6% to 21.4% with tirzepatide 15 mg, compared with placebo, among adults with obesity (eTable 6 in the Supplement).[21,38,87,88] More than 90% of participants treated with tirzepatide 15 mg achieved 5% or greater weight loss (Figure 2).[21]

Dose-dependent improvements were seen with tirzepatide for multiple cardiometabolic outcomes (eTable 6 in the Supplement).[21,38,87,88] For example, tirzepatide 15 mg reduced waist circumference by approximately 19 cm, decreased SBP by approximately 8 mm Hg, and reduced LDL-C by 9% (Table 1).[21] Tirzepatide 15 mg resulted in mean weight loss of 14.7% and mean hemoglobin A_{1c} decrease of 2.1% among adults with type 2 diabetes and obesity.[38] A randomized clinical trial testing the effects of tirzepatide on cardiovascular outcomes among adults with obesity is ongoing.[89]

Similar to semaglutide, tirzepatide should be prescribed to adults needing to achieve greater weight reductions, particularly patients with greater weight-related morbidity (Table 2). Although there are no direct comparisons, tirzepatide 10 mg and 15 mg showed greater weight loss than semaglutide 2.4 mg.[90]

Adverse effects of tirzepatide are dose-dependent, and commonly include nausea (25%-29%), diarrhea (19%-23%), constipation (11%-17%), and vomiting (8%-13%).[29] These adverse effects typically occur during the dose escalation period and are primarily mild to moderate in severity (Table 3).

AOMs in Development

Combinations of nutrient-stimulated hormone-based medications (dual- and tri-agonists) are currently undergoing study among adults with obesity.[91] In a phase 1b study of 96 participants (mean BMI, 32.1), semaglutide 2.4 mg combined with cagrilintide 2.4 mg, a long-acting amylin analogue, resulted in mean weight loss of 17.1% at 20-week follow-up, compared with 9.5% for semaglutide alone.[92] In a phase 2 trial of 387 participants, a dual glucagon/GLP-1 RA, survodutide, attained weight loss of 14.9% at the 4.8-mg dose, compared with 2.8% for placebo at 46 weeks.[93] In a phase 2 trial of 338 participants, a tri-agonist RA for GIP/GLP-1/glucagon, retatrutide, attained a mean weight loss of 24.2% for the 12-mg dose at 24-week follow-up, compared with 2.1% for placebo.[94]

Orally administered nutrient-stimulated hormone-based AOMs are being studied in adults with obesity.[91] In a clinical trial of 667 participants, oral semaglutide 50 mg daily attained weight loss of 12.7% (95% CI, −14.2% to −11.3%), compared with placebo.[95] In a phase 2 trial of 272 participants, an oral nonpeptide GLP-1 RA, orforglipron, attained weight reduction of 14.7%, compared with 2.3% for placebo, at 36-week follow-up.[96]

New therapies with mechanisms of action that differ from nutrient-stimulated hormone-based therapeutics are in development. For example, an antibody that blocks activin type II receptors, bimagrumab, caused significant fat mass loss and gain in muscle mass.[97] A multicenter RCT to determine the efficacy and safety of 24-month phentermine use is ongoing.[98]

Lifestyle Change and AOMs

All AOMs are approved as adjunctive therapy to a reduced-calorie diet and increased physical activity. Clinicians should counsel patients

on these lifestyle modifications at the time of AOM initiation and recommend a strategy for patients to engage monthly with a lifestyle program or trained health care professional (eg, dietitian, health coach). Important nutritional recommendations exist for specific AOMs, such as avoiding a high-fat diet with orlistat or naltrexone-bupropion (Table 3).

Outcomes improve when AOMs, particularly naltrexone-bupropion, are combined with intensive behavioral therapy[53] (12-26 multicomponent sessions over 12 months).[53] The US Preventive Services Task Force recommends intensive behavioral therapy,[99] which is covered by Medicare and Medicaid programs in many states. Intensive behavioral therapy may be less important in conjunction with semaglutide or tirzepatide,[76,87] as their appetite suppression efficacy make it easier for patients to reduce food intake without feeling deprived. With semaglutide and tirzepatide, clinicians may focus counseling on healthy eating patterns and food quality,[100] prioritizing lean proteins and increasing consumption of fruits, vegetables, and complex carbohydrates.

Safety of AOMs

Clinicians should discuss the adverse effect profiles of AOMs with patients. Since 2012, FDA regulations require that AOMs be evaluated for cardiovascular safety,[101] and postmarketing surveillance studies are ongoing to update adverse effects profiles based on use in clinical practice. Clinicians should review up-to-date prescribing information on manufacturer websites. Given their varying mechanisms, clinicians should examine the risk-benefit profile of each AOM individually.[102]

One particular concern is maintaining lean body mass (muscle mass) during weight loss that is important for mobility and physical function, particularly among older adults who have a lower lean body mass due to aging. AOMs should be used in adults aged 65 years or older with caution.[7] Clinicians' physical activity counseling should integrate resistance training (eg, weight lifting, resistance bands) to decrease lean body mass loss and enhance functional strength and mobility.[103] Aerobic activity alone is typically insufficient to preserve lean body mass. Physical activity is also important for maintaining weight loss.[104]

AOMs are typically contraindicated among pregnant persons and should be avoided in patients who are lactating.[6] Use of reliable contraception among persons with pregnancy potential is recommended. Preconception planning is important because AOMs have different recommended durations of discontinuation before conception. For example, semaglutide should be discontinued at least 2 months before pregnancy is attempted.

Duration of AOM Use

In primary care settings, AOM use increases the proportion of patients achieving 5% or greater weight loss.[105] However, real-world studies have found poor medication adherence in clinical practice.[106] Due to the counter-regulatory metabolic changes that occur with weight reduction, such as reduced metabolic rate and increased appetite, weight gain is common when AOMs are discontinued.[77,88,107] Clinicians should use shared decision-making to determine medication duration, such as continuing an AOM long-term on the lowest effective dose, using intermittent therapy, or stopping medication followed by close weight monitoring (**Box**).

Box. Common Questions

1. Who is eligible for treatment with an antiobesity medication (AOM)?
AOMs are approved as adjunctive therapy to lifestyle change in adults with an initial body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 30 or greater (obesity) or 27 or greater (overweight) in the presence of at least 1 weight-related comorbid condition. Adolescents (aged 12 years or older) with BMI ≥95th percentile for age and sex may be considered for some AOMs (orlistat, phentermine-topiramate, liraglutide, and semaglutide).

2. How long can one continue receiving AOMs?
AOMs are approved for chronic weight management and are often needed to maintain weight reduction long-term. Patients should be continuously monitored for drug effectiveness, tolerability, adverse effects, and the need for dose modification (escalation or de-escalation). Clinicians should engage patients in shared decision-making to determine AOM duration.

3. How can the adverse gastrointestinal effects of glucagon-like peptide 1 (GLP-1) receptor agonists be reduced?
Clinicians may consider a slow dose escalation as well as counseling on lifestyle strategies (eg, diet changes) to mitigate adverse effects from GLP-1 receptor agonists. Dietary counseling, including decreased portion size, reduced fat, and increased dietary fiber intake, is particularly important to help manage the gastrointestinal adverse effects of GLP-1 receptor agonists.

Insurance Coverage and Affordability

Many people in the US lack insurance coverage for AOMs. Medicare does not cover AOMs to treat obesity alone—it may cover an AOM that is FDA-approved and used for obesity combined with another condition (ie, semaglutide was recently approved for cardiovascular risk reduction among those with overweight or obesity and preexisting cardiovascular disease). Medicare may cover nutrient-stimulated hormone-based medications to treat type 2 diabetes. AOMs are covered by Medicaid in only a few states.[108] Employer-sponsored health insurance often excludes coverage for AOMs as well.[109,110] Consequently, many patients must pay out of pocket for AOMs. Table 3 provides estimated retail costs and possible price reductions with online discounts and coupons. Medicare beneficiaries are ineligible for manufacturer discounts. Financial considerations are important for patients' ability to initiate and adhere to ongoing treatment. Medical practices may need to allocate staff time for prior authorizations commonly required to determine AOM coverage.

Limitations

This review has several limitations. First, effects of AOMs on physical function and quality of life were not reviewed. Second, quality of included studies was not systematically evaluated. Third, some relevant articles may have been missed. Fourth, lisdexamfetamine, approved for binge eating disorder, and setmelanotide, approved for monogenetic and syndromic obesity, were not discussed.

Conclusions

Obesity is associated with multiple comorbidities. AOMs are effective adjunctive therapies to lifestyle changes for improved weight loss and health outcomes.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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