Management of obesity

Lourdes Cross, PharmD, BCACP, CDCES, Sullivan University College of Pharmacy and Health Sciences, Louisville, KY, USA

Purpose: This review summarizes the comprehensive management of obesity with a focus on the pharmacology, efficacy, and safety of anti-obesity medications.

Summary: Obesity is a highly prevalent chronic disease with significant health risks, requiring a multifaceted approach to treatment. While most approved weight loss medications have modest effects, newer medications such as semaglutide and tirzepatide have shown greater than 15% reduction in baseline weight. Optimal selection of therapy requires taking into consideration patient factors, such as comorbidities and goals, and medication-related factors, including weight loss efficacy, contraindications, and improvements in cardiovascular risk. As the availability of anti-obesity medications increases, multidisciplinary care teams will play an important role in selecting optimal strategies for long-term health benefits in individuals with obesity.

Conclusion: The expanding array of anti-obesity medications provides valuable treatment options alongside lifestyle interventions and surgical approaches for managing obesity and reducing weight-related health risks. As this therapeutic area continues to grow, selecting optimal agents and educating patients on administration, monitoring, and potential adverse effects will be critical for improving overall outcomes.

Keywords: endocrinology, new drug therapy, obesity, pharmacotherapy, weight loss

Am J Health-Syst Pharm. 2025;82:48-59

Obesity has become increasingly prevalent in the US over recent decades. In 1999 through 2000, the estimated prevalence of obesity among US adults was 33.6%, rising to 36.1% by 2009 through 2010.[1] The most recent surveys conducted by the Centers for Disease Control and Prevention and state health departments suggest a further increase, with an estimated 41.9% of US adults now classified as obese based on self-reported weight and height data.[2] However, the actual prevalence is likely even higher, as self-reported measurements tend to underestimate obesity rates.[3,4] The 2017-2020 National Health and Nutrition Examination Survey revealed that obesity prevalence remains relatively consistent across age groups, with 39.8% of adults aged 20-39, 44.3% of those aged 40-59, and 41.5% of those aged 60 and over classified as obese.[5] Notably, these data also highlighted significant racial and ethnic disparities. Obesity is most prevalent among non-Hispanic Black adults (49.9%), followed by Hispanic adults (45.6%), non-Hispanic White adults (41.4%), and non-Hispanic Asian adults (16.1%).[5]

The terms *overweight* and *obese* are commonly defined by a body mass index (BMI) of 25 to 29.9 kg/m^2 and 30 kg/m^2 or higher, respectively. Lower BMI criteria for identifying individuals who are overweight (23 to 27.4 kg/m^2) and obese (≥27.5 kg/m^2) have been suggested for Asian and Asian American populations by some organizations due to increased health risks at lower body weights.[6,7] While BMI is a common tool for assessing weight-related health risks, it has several limitations. One challenge is that its standard thresholds are primarily based on data from non-Hispanic White populations. Additionally, BMI does not reflect total

Address correspondence to Dr. Cross (LVCross@sullivan.edu).

https://doi.org/10.1093/ajhp/zxae273

body fat or fat mass in different body sites or account for the crucial distinction between "apple" and "pear" body shapes. The apple pattern, characterized by central obesity with fat accumulation around the abdomen, is associated with higher cardiometabolic risk compared to the pear pattern, where fat is predominantly distributed in the hips and thighs.[8] This difference in fat distribution can lead to misestimating health risks, as 2 individuals with the same BMI may have vastly different metabolic profiles based on their fat distribution patterns. Furthermore, body fat distribution differs by race and ethnicity.[9] There are limited data to establish race-specific BMI cutoffs that might address these disparities. Clinical judgment incorporating assessments of adipose distribution, such as waist circumference and waist-to-hip ratio, is recommended to estimate obesity-related health risks fully.[10-12] These additional measures can help differentiate between apple and pear body types, providing a more comprehensive assessment of an individual's metabolic health beyond BMI measurement.

Obesity carries significant health risks, including for type 2 diabetes (T2D), hypertension, dyslipidemia, cancer, infertility, kidney disease, nonalcoholic fatty liver disease, atherosclerotic cardiovascular disease, sleep apnea, and osteoarthritis.[13] These potential consequences underscore the importance of effective weight management. A comprehensive approach to obesity treatment is essential, encompassing lifestyle modifications, behavioral interventions, and, when appropriate, pharmacological and surgical options. The following sections discuss management strategies, providing evidence-based guidance for healthcare professionals in addressing this complex and chronic disease.

General approach to management of obesity

Nonpharmacological interventions should be considered the foundation of any weight loss program. These interventions include dietary modifications, increased physical activity, and behavioral changes. The 2013 guidelines from the American College of Cardiology, American Heart Association, and Obesity Society recommend at least 150 minutes per week of moderate-intensity physical activity and a reduced-calorie diet (deficit of 500-750 kcal/day).[14] The plate method is a simple yet effective tool for portion control and balanced eating, where half the plate is filled with nonstarchy vegetables, a quarter with lean protein, and a quarter with whole grains or starchy vegetables.[15,16] The plate model serves as a visual guide, making it easier for individuals to understand and implement balanced eating habits. Motivational interviewing, a patient-centered counseling approach, has also shown promise in promoting behavior change and adherence to lifestyle modifications.[17] Given the prevalence of obesity, pharmacists are uniquely positioned to provide education, reinforce healthy habits, and offer guidance on nonpharmacological strategies at every interaction.

KEY POINTS

- Combination therapy involving lifestyle modifications, pharmacological interventions, and/or bariatric surgery offers a comprehensive approach to long-term obesity management, potentially improving overall outcomes.
- Newer anti-obesity medications (AOMs) such as semaglutide and tirzepatide demonstrate significant weight loss potential, with reductions of at least 15%, surpassing historical standards.
- Insurance coverage remains a major barrier to AOM access, with many plans not covering these medications, highlighting the need for improved accessibility in obesity management.

Maintaining weight loss achieved through lifestyle interventions alone is notoriously challenging, highlighting the need for additional therapeutic approaches. Guidelines generally suggest considering an anti-obesity medication (AOM) in addition to lifestyle modification for individuals with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with a weight-related comorbidity.[7,14,18,19] The American Association of Clinical Endocrinologists advocates considering treatment for individuals with a BMI of 25 kg/m^2 or higher in the presence of obesity-associated health risks, such as cardiovascular and renal disease, gastroesophageal reflux disease, and prediabetes.[7,13] Current long-term AOMs approved by the Food and Drug Administration (FDA) for chronic weight management include orlistat, phentermine/topiramate extended-release (ER), naltrexone/bupropion ER, liraglutide, semaglutide, and tirzepatide. Medication choice should be guided by efficacy, safety profile, and patient-specific factors such as comorbidities and contraindications, as discussed in subsequent sections.

While pharmacotherapy offers valuable options for weight management, bariatric surgery remains a highly effective intervention, with recent guidelines expanding its recommended use. The 2022 American Society for Metabolic and Bariatric Surgery and International Federation for the Surgery of Obesity and Metabolic Disorders guidelines recommend metabolic and bariatric surgery (MBS) for individuals with a BMI of ≥35 kg/m^2, irrespective of comorbidities.[20] For the Asian population, the BMI threshold for MBS consideration is lowered to 27.5 kg/m^2 or higher. Furthermore, the guidelines suggest that MBS should be considered for individuals with a BMI of ≥30 kg/m^2 who have not achieved substantial or durable weight loss through nonsurgical methods, even in the absence of metabolic disease. Postoperatively, patients undergo significant dietary modifications, progressing from clear liquids to pureed foods and eventually to solid

foods over 4 to 8 weeks.[21] This necessitates medication adjustments, often requiring liquid or crushed formulations initially. Long-term vitamin and mineral supplementation, including of vitamin B_{12}, iron, and calcium, is important due to malabsorptive changes.[21,22] The rapid weight loss and metabolic improvements following bariatric procedures can dramatically alter medication requirements. For example, in patients with T2D, glycemic control often improves rapidly after bariatric surgery. This rapid improvement necessitates immediate reduction or discontinuation of insulin and oral hypoglycemics to prevent hypoglycemia.[22] Similarly, antihypertensive medications frequently require down-titration or cessation. Although bariatric surgery can lead to substantial and sustained weight loss, ongoing pharmacotherapy may still play a role in long-term weight maintenance.[23] Therefore, it is important to examine the role of pharmacotherapy in the comprehensive care of patients with obesity.

Phentermine

While lifestyle modifications and bariatric surgery are powerful tools for weight loss, pharmacotherapy continues to play a vital role in obesity management. Phentermine was one of the earliest AOMs approved by FDA. As a sympathomimetic agent, it acts centrally to stimulate hypothalamic norepinephrine release, thereby reducing appetite.[24] Phentermine is indicated for short-term use, with a maximum duration of 12 weeks. Typical dosing ranges from 15 to 37.5 mg once daily before breakfast or 1 to 2 hours after, although an 8-mg tablet dosed 3 times daily 30 minutes before meals can also be used (Table 1).[25,26]

Adverse effects include elevated blood pressure, palpitations, and potential ischemia.[26] Phentermine carries several contraindications, including cardiovascular disease, hyperthyroidism, glaucoma, substance abuse history, recent monoamine oxidase inhibitor (MAOI) use, and pregnancy. Given its mechanism as a stimulant, caution is required in patients with structural heart disease, arrhythmias, or uncontrolled hypertension. Its pharmacological similarity to amphetamines raises concerns about abuse potential and dependency with prolonged use.

Although phentermine is only indicated for short-term weight loss, there are some data evaluating its longer-term effects. An observational study using electronic health records classified 13,972 patients with a mean BMI of 37.8 kg/m^2 into short-term users with a treatment episode of ≤112 days and long-term continuous users with a single treatment episode lasting over 1 year.[34] Short-term users exhibited a pattern of initial weight loss followed by regain over time. The 2.68% weight reduction achieved at 6 months diminished to 1.38% by 12 months and 0.16% by 24 months. In contrast, long-term continuous users had lost 7.4% (95% confidence interval [CI], 5.8% to 9.0%) more weight than short-term users after 24 months. The composite outcome of cardiovascular disease or death was rare overall (0.3% incidence) and did not differ between the long-term and short-term groups over the 3 years of follow-up. Although no difference in cardiovascular risk was found with phentermine, caution is still warranted due to limited data regarding the potential risk/benefit ratio for longer durations of use.

Orlistat

While phentermine may be effective for short-term weight management, the chronic nature of obesity often calls for more sustained interventions. FDA approved orlistat in 1999 as one of the first medications for long-term weight management, marking a significant shift in the approach to pharmacological treatment of obesity. As a lipase inhibitor, it works by reversibly blocking the action of gastric and pancreatic lipases, thereby decreasing the absorption of dietary fat. Orlistat is administered orally at a dose of 120 mg 3 times daily during or up to 1 hour after each main meal containing fat.[27] For nonprescription use, the recommended dose is 60 mg 3 times daily, not exceeding 180 mg per day.[28] No specific renal or hepatic dosage adjustments are provided in the manufacturer's labeling, but dosage adjustment is most likely not necessary due to the low systemic absorption.

Common gastrointestinal adverse effects include abdominal discomfort, flatulence, urgent bowel movements, oily spotting, and steatorrhea.[27,35] These adverse events may worsen with high-fat meals. Thus, patients should adhere to a low-fat diet, distributing fat intake evenly across 3 main meals. Orlistat has also been shown to reduce the absorption of fat-soluble vitamins and β-carotene, necessitating separate vitamin supplementation. Orlistat administration should be separated from that for multivitamin supplements containing fat-soluble vitamins by at least 2 hours. Contraindications include chronic malabsorption syndromes, cholestasis, and pregnancy.

The 4-year, double-blind XENDOS trial randomized 3,305 patients with a BMI of ≥30 kg/m^2 to lifestyle changes plus orlistat 120 mg or placebo 3 times daily.[35] Mean weight loss was greater with orlistat (5.8 vs 3.0 kg with placebo; $P < 0.001$). Additionally, 72.8% of the orlistat group had achieved at least 5% weight loss at 1 year, compared to only 45.1% of those receiving placebo ($P < 0.001$). Gastrointestinal events were more common with orlistat, occurring in 91% vs 65% of participants in year 1, although the rates of such events decreased to 36% and 23% by year 4 for orlistat and placebo, respectively. The frequency of study discontinuation due to adverse events was 8% with orlistat and 4% with placebo, primarily driven by gastrointestinal issues. Beyond weight loss, orlistat demonstrated favorable cardiometabolic effects, with greater reductions in systolic blood pressure (SBP; 4.9 vs 3.4 mm Hg), diastolic blood pressure (DBP; 2.6 vs 1.9 mm Hg), low-density lipoprotein (LDL) cholesterol (12.8% vs 5.1%), and total cholesterol (7.9% vs 2.3%)

Table 1. Therapies for Adults with Obesity[a]

Medication (trade name)	Drug class	Dosing[b]	Adverse effects	Contraindications	Additional comments
Phentermine (Adipex-P, Lomaira)	Sympathomimetic	Orally: • Phentermine (excluding Lomaira): 15 to 37.5 mg daily in 1 or 2 divided doses • Lomaira: 8 mg 3 times daily	Increased HR/BP, insomnia, irritability, nervousness, dry mouth, taste disturbance, constipation	History of CVD, hyperthyroidism, glaucoma, history of drug abuse, use during or within 14 days following MAOI therapy, pregnancy	• Approved for short-term use (8-12 weeks) • Potential for abuse due to amphetamine-like effects; controlled substance (C-IV) • Dose adjustments recommended in patients with renal impairment
Orlistat (Alli [nonprescription], Xenical)	Lipase inhibitor	Orally: • Alli: 60 mg 3 times daily with each main meal containing fat • Xenical: 120 mg 3 times daily with each main meal containing fat	Intestinal cramps, flatulence, fecal incontinence, oily spotting/leakage	Chronic malabsorption syndrome (eg, chronic diarrhea, celiac disease, inflammatory bowel disease, bariatric surgery), cholestasis, pregnancy	• Administer during or up to 1 hour after each main meal containing fat; omit dose if a meal is missed or contains no fat • Patients should take a daily multivitamin containing fat-soluble vitamins; separate administration from orlistat by ≥2 hours
Phentermine/topiramate ER (Qsymia)	Sympathomimetic + GABA receptor modulator	Orally: • Initially phentermine 3.75 mg/topiramate 23 mg daily • Titrate gradually up to phentermine 15 mg/topiramate 92 mg daily if needed	Increased HR/BP, constipation, dry mouth, paresthesia, taste disturbance, depression, anxiety, cognitive impairment, insomnia; *rare*: metabolic acidosis, kidney stones	History of CVD, hyperthyroidism, glaucoma, history of drug abuse, use during or within 14 days following MAOI therapy, pregnancy	• Controlled substance (C-IV) • Teratogenic (topiramate): increased risk of oral cleft; negative pregnancy test recommended before initiation and monthly • Dose adjustments recommended in patients with hepatic or renal impairment
Naltrexone/bupropion ER (Contrave)	Opioid antagonist + dopamine/norepinephrine reuptake inhibitor	Orally (1 tablet = naltrexone 8 mg/bupropion 90 mg): • Week 1: 1 tablet every morning • Week 2: 1 tablet twice daily • Week 3: 2 tablets every morning and 1 tablet every evening • Week 4+: 2 tablets twice daily	Nausea, vomiting, constipation, headache, dizziness, insomnia, dry mouth, transient increase in BP (average of 1-2 mm Hg) and/or HR	Uncontrolled HTN, seizure disorder, eating disorder, use of other bupropion-containing products, short- or long-term opioid therapy, use during or within 14 days following MAOI therapy, pregnancy	• Boxed warning: suicidal thinking • Potential neuropsychiatric effects • Take early in the day (potential for insomnia) • Dose adjustments recommended in patients with hepatic or renal impairment
Liraglutide (Saxenda)	GLP-1 receptor agonist	Subcutaneously: • Week 1: 0.6 mg daily • Week 2: 1.2 mg daily • Week 3: 1.8 mg daily • Week 4: 2.4 mg daily • Week 5+: 3 mg daily	Nausea, vomiting, diarrhea, constipation, hypoglycemia (if used in conjunction with diabetes medications known to cause hypoglycemia), injection site reactions; *rare*: pancreatitis, gallbladder disease	Personal or family history of medullary thyroid carcinoma, personal history of multiple endocrine neoplasia syndrome type 2, pregnancy	• Monitor glucose and adjust co-administered sulfonylureas and insulin as needed to prevent potentially severe hypoglycemia • Should not be used with other GLP-1 receptor agonists or DPP4 inhibitors

Continued on next page

Continued from previous page

Table 1. Therapies for Adults with Obesitya

Medication (trade name)	Drug class	Dosing[b]	Adverse effects	Contraindications	Additional comments
Semaglutide (Wegovy)	GLP-1 receptor agonist	Subcutaneously: • Weeks 1-4: 0.25 mg weekly • Weeks 5-8: 0.5 mg weekly • Weeks 9-12: 1 mg weekly • Weeks 13-16: 1.7 mg weekly • Week 17+: 2.4 mg weekly	Nausea, vomiting, diarrhea, constipation, hypoglycemia (if used in conjunction with diabetes medications known to cause hypoglycemia), injection site reactions; *rare*: pancreatitis, gallbladder disease	Personal or family history of medullary thyroid carcinoma, personal history of multiple endocrine neoplasia syndrome type 2, pregnancy	• Monitor glucose and adjust co-administered sulfonylureas and insulin as needed to prevent potentially severe hypoglycemia • Semaglutide: monitor patients with diabetic retinopathy for eye complications • Should not be used with other GLP-1 receptor agonists or DPP4 inhibitors
Tirzepatide (Zepbound)	GIP/GLP-1 receptor agonist	Subcutaneously: • Weeks 1-4: 2.5 mg weekly • Weeks 5-8: 5 mg weekly • Week 9+: may increase in 2.5-mg increments every 4 weeks if needed • Max dose of 15 mg/week	Nausea, vomiting, diarrhea, constipation, hypoglycemia (if used in conjunction with diabetes medications known to cause hypoglycemia), injection site reactions	Personal or family history of medullary thyroid carcinoma, personal history of multiple endocrine neoplasia syndrome type 2, pregnancy	• Monitor glucose and adjust co-administered sulfonylureas and insulin as needed to prevent potentially severe hypoglycemia • Should not be used with other GLP-1 receptors agonists or DPP4 inhibitors

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; DPP4, dipeptidyl peptidase-4; ER, extended-release; GABA, γ-aminobutyric acid; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HR, heart rate; HTN, hypertension; MAOI, monoamine oxidase inhibitor.
[a]Information derived from package inserts.[25-33]
[b]Dosing is for adults with normal kidney and liver function unless otherwise noted in the comments.

compared to placebo ($P < 0.01$ vs placebo for all comparisons).

Phentermine/topiramate ER

Phentermine/topiramate ER is a combination therapy designed to provide a synergistic approach for weight loss management. It combines topiramate, an antiseizure agent, and phentermine, a sympathomimetic medication. It is thought that phentermine suppresses appetite by acting centrally to stimulate hypothalamic norepinephrine release and topiramate affects appetite and satiety through modulation of γ-aminobutyric acid (GABA) receptors.[36] The recommended dosing regimen starts with phentermine/topiramate ER 3.75 mg/23 mg once daily for 2 weeks, followed by escalation to phentermine/topiramate ER 7.5 mg/46 mg daily for 12 weeks to evaluate weight loss response.[29] If at least 3% weight loss is not achieved, the dose may be further increased based on tolerability up to the maximum of phentermine/topiramate ER 15 mg/92 mg daily. For patients with a creatinine clearance of less than 50 mL/min or moderate hepatic impairment, the maximum recommended dose is phentermine/topiramate ER 7.5 mg/46 mg daily. Phentermine/topiramate ER is not recommended for use in patients with end-stage kidney disease or severe hepatic impairment due to a lack of data from clinical studies.

Common adverse effects include increased heart rate, constipation, dry mouth, and insomnia (Table 1).[29,37] Risk of kidney stones may be elevated due to topiramate's inhibition of carbonic anhydrase. Additionally, topiramate is contraindicated in pregnancy, because it is a teratogen that increases the risk of embryo-fetal toxicity with congenital malformations, including oral cleft, in infants exposed in utero. A risk evaluation and mitigation strategy informs clinicians and patients of this potential risk. Similar to phentermine monotherapy, phentermine/topiramate ER should not be used in individuals with a history of cardiovascular disease and is contraindicated in those with a history of hyperthyroidism, glaucoma, or recent use of MAOIs. If discontinuing, gradual withdrawal is recommended to avoid increased seizure risk from

the topiramate component. Given the amphetamine-like properties of phentermine, there is a potential for abuse and dependence with prolonged use of phentermine/topiramate ER.

The CONQUER trial randomized 2,487 adults with a BMI of 27 to 45 kg/m^2 and at least 2 weight-related comorbidities to receive placebo, phentermine/topiramate ER 7.5 mg/46 mg, or phentermine/topiramate ER 15 mg/92 mg once daily for 56 weeks. At week 56, the mean weight change from baseline was –1.4 kg with placebo, –8.1 kg with the 7.5 mg/46 mg dose, and –10.2 kg with the 15 mg/92 mg dose ($P < 0.001$ vs placebo for all comparisons).[37] The proportion achieving at least 5% weight loss was 21% with placebo, compared to 62% with the 7.5 mg/46 mg dose and 70% with the 15 mg/92 mg dose. In the 52-week SEQUEL extension study, which included 676 participants from the CONQUER trial, the mean percentage weight change from baseline at 108 weeks was –1.8%, –9.3%, and –10.5% in the placebo, 7.5 mg/46 mg, and 15 mg/92 mg groups, respectively ($P < 0.0001$ vs placebo for all comparisons).[38] The corresponding absolute mean weight reductions were –2.1 kg, –9.6 kg, and –10.9 kg ($P < 0.0001$ vs placebo for all comparisons).

A systematic review and meta-analysis examined the effects of phentermine/topiramate ER on weight loss and adverse events in adults. Three doses of phentermine/topiramate ER given once daily were analyzed: 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg. Compared to placebo, phentermine/topiramate ER led to a higher average weight loss of 7.73 kg (95% CI, 6.60 to 8.85 kg), with the 15 mg/92 mg dose resulting in a weight loss of 8.25 kg (95% CI, 6.92 to 9.79 kg).[39] While associated with increased risks of adverse events such as dysgeusia, paresthesia, dry mouth, and constipation compared to placebo, the combination demonstrated favorable impacts on cardiovascular risk factors. Notably, phentermine/topiramate ER reduced SBP by an average of 2.92 mm Hg (95% CI, 2.09 to 3.75 mm Hg) and DBP by an average of 0.96 mm Hg (95% CI, 0.40 to 1.52 mm Hg) vs placebo. Beneficial effects were also seen for lipids, with total cholesterol decreasing by 2.30% (95% CI, 1.27% to 3.33%) and triglycerides reduced by 13.38% (95% CI, 10.39% to 16.37%) in the active treatment group relative to placebo. These findings suggest potential cardiovascular benefits accompanying the weight loss achieved with phentermine/topiramate ER combination therapy.

Naltrexone/bupropion ER

Naltrexone/bupropion ER is a combination of naltrexone, an opioid antagonist, and bupropion, a dopamine and norepinephrine reuptake inhibitor. Although its precise mechanisms are not fully understood, it is thought to modulate appetite and reward pathways in the brain.[40] Typical dosing starts at 1 tablet of naltrexone/bupropion ER (8 mg/90 mg) daily for 1 week, gradually increasing to a maximum of 2 tablets twice daily.[30] For patients with moderate or severe renal impairment or moderate hepatic impairment, the maximum recommended dose is 1 tablet twice daily. Naltrexone/bupropion ER is not recommended for use in patients with end-stage renal disease or severe hepatic impairment. Dose adjustments may be required when naltrexone/bupropion ER is used with medications that interact with cytochrome P450 enzymes.

The most common adverse effects include gastrointestinal disturbances and neurological symptoms, including headache and sleep disturbances (Table 1).[30] Minor increases in blood pressure and heart rate have also been noted in clinical trials.[41,42] Several contraindications exist for naltrexone/bupropion ER, including chronic opioid use, acute opioid withdrawal, uncontrolled hypertension, seizure disorders, eating disorders, concomitant use of MAOIs, and pregnancy. Naltrexone/bupropion ER should not be used in patients who are at risk for alcohol withdrawal, as the bupropion component can increase susceptibility to seizures by lowering the seizure threshold. Additionally, this therapy carries a boxed warning regarding an increased risk of suicidal thoughts and behaviors, particularly in patients under 24 years of age, as observed in clinical studies with antidepressants.

The COR-I study evaluated the efficacy and safety of naltrexone/bupropion ER for weight loss. This randomized trial enrolled 1,742 adults with a BMI of 30 to 45 kg/m^2 or 27 to 45 kg/m^2 with weight-related comorbidities.[41] Participants received naltrexone/bupropion ER 32 mg/360 mg (with naltrexone 8 mg and bupropion 90 mg in each tablet, 2 tablets taken twice a day), naltrexone/bupropion ER 16 mg/360 mg (with naltrexone 4 mg and bupropion 90 mg in each tablet, 2 tablets taken twice a day), or placebo for 56 weeks in addition to lifestyle modification. Compared to a mean weight change of –1.3% in the placebo group, the 32 mg/360 mg and 16 mg/360 mg groups achieved significantly greater weight reductions of –6.1% and –5.0%, respectively ($P < 0.0001$ vs placebo for all comparisons). Nearly half (48%) of participants in the highest-dose group lost at least 5% of their baseline weight, compared to only 16% of patients in the placebo arm ($P < 0.0001$). While there was an initial increase of approximately 1.5 mm Hg in SBP, levels returned to baseline by week 12 and were modestly decreased by approximately 1 mm Hg thereafter in the active treatment groups. A similar change was seen for DBP. Heart rate was 1.5 to 2.5 beats per minute higher in the treatment groups compared to the placebo group. Combination therapy was not associated with increased risk of depression or suicidality compared to placebo.

A systematic review and meta-analysis evaluating data from 4 randomized clinical trials examined the benefits and harms of naltrexone/bupropion ER for weight loss.[42] The analysis found that significantly more participants taking naltrexone/bupropion ER achieved an at least 5% reduction in body weight compared to placebo (risk ratio, 2.1; 95% CI,

1.35 to 3.28). This corresponded to an average greater weight loss from baseline of 2.53 kg (95% CI, 1.85 to 3.21 kg) with the active treatment vs placebo. Additionally, naltrexone/bupropion ER led to favorable changes in several cardiometabolic parameters compared to placebo, including reductions in LDL cholesterol (mean difference [MD], –2.92 mg/dL; 95% CI, –5.16 to –0.69 mg/dL) and blood glucose (MD, –1.19 mg/dL; 95% CI, –2.15 to –0.23 mg/dL). However, the combination was also associated with small but significant elevations in SBP (MD, 1.47 mm Hg; 95% CI, 0.48 to 2.47 mm Hg) and DBP (MD, 0.98 mm Hg; 95% CI, 0.50 to 1.45 mm Hg). While the combination showed beneficial effects on cardiovascular risk factors, the meta-analysis noted uncertainty around the precise effect sizes due to incomplete outcome reporting across the trials.

GLP-1 RAs

The discovery of the incretin hormone glucagon-like peptide-1 (GLP-1) and its effects on weight paved the way for a new class of therapies. GLP-1 receptor agonists (GLP-1 RAs) are a class of medications that mimic the actions of endogenous GLP-1. These agents improve glycemic control by binding to and activating GLP-1 receptors in the pancreas, promoting glucose-dependent insulin release and suppressing glucagon secretion. GLP-1 RAs also exert effects beyond pancreatic islet cells. In the central nervous system, GLP-1 RA activity impacts vagal afferent neurons and regions such as the brainstem and hypothalamus.[43] This results in increased satiety, delayed gastric emptying, and reduced appetite, ultimately leading to caloric restriction and weight loss. While the fundamental mechanisms underlying weight reduction are shared across GLP-1 RAs, the magnitude of effect varies for individual agents, as demonstrated in clinical trials (Table 2).

A common barrier to use of GLP-1 RAs is gastrointestinal adverse effects such as nausea, vomiting, and

Table 2. Outcomes of Select Trials Evaluating Weight Loss in Adults after 1 to 2 Years with FDA-Approved Medications[a]

Drug	Study	Duration, weeks	Study arms (No. participants)	Baseline weight,[b] kg	Baseline BMI,[b] kg/m²	≥5% weight loss, %	≥10% weight loss, %	Difference from placebo in weight reduction
Orlistat	XENDOS[35]	52	Placebo (1,295) vs orlistat 120 mg 3 times daily (1,487)	110.6 (16.5) vs 110.4 (16.3)	37.4 (4.5) vs 37.3 (4.2)	45 vs 73	21 vs 41	–4.4 kg ($P < 0.001$)
Phentermine/topiramate ER	CONQUER[37]	56	Placebo (994) vs phentermine/topiramate7.5 mg/46 mg (498) vs phentermine/topiramate15 mg/92 mg (995)	103.3 (18.1) vs 102.6 (18.2) vs 103.0 (17.6)	36.7 (4.6) vs 36.2 (4.4) vs 36.6 (4.5)	21 vs 62 vs 70	7 vs 37 vs 48	–6.6% (95% CI, –7.4 to –5.8) vs –8.6% (95% CI, –9.3 to –8.0)
Naltrexone/bupropion ER	COR-I[41]	56	Placebo (581) vs 4 mg/90 mg, 2 tablets twice daily (578) vs 8 mg/90 mg, 2 tablets twice daily (583)	99.5 (14.3) vs 99.5 (14.8) vs 99.7 (15.9)	36.2 (4.0) vs 36.2 (4.3) vs 36.1 (4.4)	16 vs 39 vs 48	7 vs 20 vs 25	–3.7% ($P < 0.0001$) vs –4.8% ($P < 0.0001$)
Liraglutide	SCALE Obesity and Prediabetes[44]	56	Placebo (1,244) vs liraglutide 3.0 mg daily (2,487)	106.2 (21.7) vs 106.2 (21.2)	38.3 (6.3) vs 38.3 (6.4)	27 vs 63	11 vs 33	–5.4% (95% CI, –5.8 to –5.0)
Semaglutide	STEP 1[45]	68	Placebo (655) vs semaglutide 2.4 mg weekly (1,306)	105.2 (21.5) vs 105.4 (22.1)	38.0 (6.5) vs 37.8 (6.7)	32 vs 86	12 vs 69	–12.4% (95% CI, –13.4 to –11.5)
Tirzepatide	SURMOUNT-1[46]	72	Placebo (643) vs tirzepatide 5 mg weekly (630) vs tirzepatide 10 mg weekly (636) vs tirzepatide 15 mg weekly (630)	104.8 (21.4) vs 102.9 (20.7) vs 105.8 (23.3) vs 105.6 (22.9)	38.2 (6.9) vs 37.4 (6.6) vs 38.2 (7.0) vs 38.1 (6.7)	35 vs 85 vs 89 vs 91	19 vs 69 vs 78 vs 84	–11.9% (95% CI, –13.4 to –10.4) vs –16.4% (95% CI, –17.9 to –14.8) vs –17.8% (95% CI, –19.3 to –16.3)

Abbreviations: CI, confidence interval; ER, extended-release; FDA, Food and Drug Administration.
[a]In addition to lifestyle modification, which typically involved calorie-restricted diets (deficit of 500-600 calories/day) plus at least 150 minutes of physical exercise every week.
[b]Data shown as mean (SD).

abdominal discomfort, which often exhibit a dose-dependent relationship.[31,32] Injection site reactions represent another potential adverse effect. When used as monotherapy, these agents seldom cause hypoglycemia. However, combining them with medications that increase hypoglycemic risk, such as sulfonylureas or insulin, requires close monitoring of blood glucose levels. Rare but serious adverse events include pancreatitis, gallbladder disease, thyroid C cell tumors, and biliary disorders. GLP-1 RAs are contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2. Additionally, GLP-1 RAs should not be used during pregnancy.

Liraglutide. Liraglutide was the first GLP-1 RA to receive FDA approval for chronic weight management in adults with obesity or overweight and at least one weight-related comorbidity. The recommended dosage for weight loss is 3 mg once daily, administered subcutaneously.[32] This dose is achieved through a gradual titration process, starting at 0.6 mg and increasing by 0.6 mg weekly until reaching 3 mg (Table 1). If dose escalation is not well tolerated, a delay of approximately 1 week before increasing the dose may be considered. Discontinuation of liraglutide is advised if the 3-mg dose cannot be tolerated.

The SCALE program included 4 major randomized controlled trials assessing liraglutide 3 mg once daily vs placebo for weight loss over 56 to 160 weeks in individuals with obesity, with or without intensive behavioral therapy.[44,47-49] In the SCALE Obesity and Prediabetes trial, 3,371 patients received once-daily subcutaneous injections of liraglutide 3 mg or placebo for 56 weeks in addition to lifestyle modification.[44] Liraglutide led to significantly greater mean weight loss than placebo (–8.4 vs –2.8 kg, respectively), a difference of –5.6 kg (95% CI, –6.0 to –5.1 kg). A total of 63.2% achieved at least 5% weight loss with liraglutide, compared to 27.1% of participants receiving placebo ($P < 0.001$). The 3-year extension study showed sustained weight loss benefit with liraglutide at week 160 (estimated difference [ED], –4.3%; 95% CI, –4.9% to –3.7%).[49] The SCALE Maintenance trial in participants who lost at least 5% weight during a low-calorie diet run-in period demonstrated 6.2% additional weight loss with liraglutide vs 0.2% with placebo over 56 weeks (ED, –6.1%; 95% CI, –7.5% to –4.6%).[47] In the 56-week SCALE Intensive Behavioral Therapy study, adding liraglutide to intensive lifestyle intervention yielded 7.5% weight loss vs 4% with placebo (ED, –3.4%; 95% CI, –5.3% to –1.6%).[48] Across the program, liraglutide consistently promoted clinically meaningful weight loss, with a substantial proportion of participants achieving over 5% or 10% weight reduction compared to placebo or behavioral intervention alone.

The LEADER trial evaluated the safety of liraglutide in patients with T2D and high cardiovascular risk.[50] This double-blind trial randomized 9,340 patients to receive liraglutide 1.8 mg once daily or placebo, with a median follow-up period of 3.8 years. The primary composite endpoint was the first occurrence of major adverse cardiovascular events (MACE), defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Liraglutide significantly reduced the incidence of this MACE endpoint compared to placebo (13.0% vs 14.9%; hazard ratio [HR], 0.87; 95% CI, 0.78 to 0.97). However, the specific cardiovascular benefit observed in the LEADER trial has not been established for the higher 3-mg once-daily liraglutide dose approved for chronic weight management in individuals without diabetes.

Semaglutide. Semaglutide is another GLP-1 RA approved for chronic weight management in adults. It is initiated at 0.25 mg once weekly and gradually titrated up in 4-week intervals to the 2.4-mg once-weekly maintenance dose, with the option to reduce to 1.7 mg if 2.4 mg is not tolerated (Table 1).[31] Dose escalation can be delayed by 4 weeks if adverse effects occur. Discontinuation is recommended if the 1.7-mg dose cannot be tolerated.

The STEP program evaluated the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg for weight management through several trials.[45,51] STEP 1 was a 68-week, double-blind trial in 1,961 adults with obesity or overweight having at least 1 weight-related comorbidity who did not have diabetes.[45] Patients were randomized to semaglutide or placebo plus lifestyle intervention. Semaglutide led to substantially greater mean weight loss vs placebo (–14.9% vs –2.4%; ED, –12.4%; 95% CI, –13.4% to –11.5%). In the semaglutide group, 86.4% achieved at least 5% weight loss vs 31.5% in the placebo group ($P < 0.001$). Additionally, 50.5% achieved at least 15% weight loss with semaglutide vs 4.9% with placebo ($P < 0.001$). STEP 4 was a 68-week randomized trial evaluating weight regain after a 20-week semaglutide run-in period.[51] Continued semaglutide promoted further mean weight loss of 7.9% vs 6.9% weight regain with placebo (ED, –14.8%; 95% CI, –16.0% to –13.5%). Across trials, semaglutide consistently delivered clinically meaningful weight loss alongside improvements in cardiometabolic parameters such as glycated hemoglobin, blood pressure, and cholesterol. The results of the STEP 4 trial highlight the importance of long-term adherence to weight loss medications.

The OASIS 1 study evaluated the efficacy of oral semaglutide 50 mg once daily vs placebo in adults with obesity or overweight and weight-related complications without diabetes.[52] This 68-week trial randomized participants to receive semaglutide or placebo in conjunction with lifestyle intervention. Oral semaglutide led to significantly greater mean weight loss than placebo (–15.1% vs –2.4%, respectively; ED, –12.7%; 95% CI, –14.2% to –11.3%). The majority achieved at least 5% weight reduction with semaglutide (85% vs 26% with placebo), and a substantial proportion of participants reached 10% (69% vs 12%), 15% (54% vs 6%), and 20% (34% vs 3%) weight loss thresholds. An

oral GLP-1 RA like semaglutide could increase patient acceptance of this highly effective drug class for chronic weight management by avoiding the need for injections.

The cardiovascular safety and potential benefit of semaglutide have been evaluated across several clinical trials in patients both with and without diabetes. In the SUSTAIN-6 trial, subcutaneous semaglutide demonstrated cardiovascular benefit in patients with T2D.[53] In contrast, the PIONEER 6 trial evaluated once-daily oral semaglutide 14 mg in patients with diabetes at high cardiovascular risk and found no cardiovascular benefit compared to placebo, although it met noninferiority for cardiovascular safety.[54] The SELECT trial specifically assessed the effect of subcutaneous semaglutide 2.4 mg once weekly on cardiovascular outcomes in 17,604 overweight or obese individuals without diabetes.[55] This double-blind trial enrolled patients aged 45 years of age or older with preexisting cardiovascular disease and a BMI of ≥27 kg/m^2. Over a mean 39.8-month follow-up period, MACE occurred significantly less frequently with semaglutide than with placebo (6.5% vs 8.0%; HR, 0.80; 95% CI, 0.72 to 0.90). These findings suggest a potential cardiovascular benefit of the 2.4-mg subcutaneous semaglutide dose in overweight or obese patients, irrespective of diabetes status.

Tirzepatide

Representing the latest advancement in the GLP-1 RA class, tirzepatide received FDA approval as a treatment for weight management in November 2023. Tirzepatide is a novel glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA administered as a once-weekly subcutaneous injection. The recommended dosing regimen starts at 2.5 mg for the first 4 weeks, followed by an increase to 5 mg weekly (Table 1).[33] Further dose escalation in 2.5-mg increments every 4 weeks up to a maximum of 15 mg weekly may be considered based on clinical response and tolerability. The initial 2.5-mg dose is intended to mitigate potential gastrointestinal adverse effects but does not provide clinically meaningful weight loss on its own.

Consistent with the GLP-1 RA class, the most commonly reported adverse effects with tirzepatide in clinical trials were gastrointestinal (Table 1).[33] The majority of these gastrointestinal events were mild to moderate in severity and tended to occur during the dose escalation phase, leading to treatment discontinuation in a minority of patients. Contraindications are similar to those for other GLP-1 RAs.

The efficacy of tirzepatide was evaluated in the SURMOUNT studies. The SURMOUNT-1 trial evaluated tirzepatide across 3 doses (5 mg, 10 mg, and 15 mg) vs placebo in 2,539 adults with obesity or overweight and weight-related complications over 72 weeks.[46] Tirzepatide led to significantly greater mean weight reductions of –15.0% (95% CI, –15.9% to –14.2%) with 5 mg, –19.5% (95% CI, –20.4% to –18.5%) with 10 mg, and –20.9% (95% CI, –21.8% to –19.9%) with 15 mg compared to –3.1% (95% CI, –4.3% to –1.9%) with placebo (P < 0.001 vs placebo for all comparisons). The proportion achieving at least 5% weight loss was 85% to 91% across the tirzepatide doses vs 35% with placebo. Approximately half achieved at least 20% weight reduction with the 10-mg (50.1%; 95% CI, 46.0% to 54.2%) and 15-mg (56.7%; 95% CI, 52.6% to 60.8%) doses, compared to only 3% with placebo. In SURMOUNT-2, involving 938 adults with T2D, the change in weight at 72 weeks was –12.8% and –14.7% with tirzepatide 10 and 15 mg, respectively, vs –3.2% with placebo.[56] SURMOUNT-3 evaluated weight regain prevention after initial weight loss with a 12-week intensive lifestyle intervention, demonstrating continued mean weight reduction at 72 weeks of –18.4% with tirzepatide vs 2.5% gain with placebo (ED, –20.8%; 95% CI, –23.2% to –18.5%).[57]

SURMOUNT-4 assessed the effects of long-term maintenance treatment with tirzepatide. This study had a 36-week open-label lead-in phase during which participants received the maximum tolerated tirzepatide dose of 10 or 15 mg weekly.[58] At week 36, participants were randomized to either continue tirzepatide or switch to placebo for 52 weeks. From week 36 to 88, those continuing tirzepatide experienced further mean weight reduction of –5.5%, whereas those switched to placebo regained 14.0% on average (ED, –19.4%; 95% CI, –21.2% to –17.7%). Notably, 89.5% of participants maintained at least 80% of their initial weight loss on continued tirzepatide vs only 16.6% of those on placebo (P < 0.001). These findings demonstrated the substantial weight regain that occurs after withdrawing tirzepatide, highlighting the need for long-term maintenance therapy to preserve weight loss achieved during the initial treatment period.

While the weight loss efficacy of tirzepatide is well established, there are limited data on its cardiovascular effects. The SURPASS-4 trial in adults with T2D and high cardiovascular risk found that tirzepatide did not increase the frequency of cardiovascular events compared to insulin glargine (HR, 0.74; 95% CI, 0.51 to 1.08), suggesting cardiovascular safety in this population.[59] Although there was a potential trend toward lower risk with tirzepatide, this did not reach statistical significance. The ongoing SURPASS-CVOT trial, expected to complete in October 2024, is directly comparing long-term cardiovascular outcomes with tirzepatide vs dulaglutide in patients with T2D to provide more definitive data on the effects of tirzepatide.

Metformin for off-label use

Metformin, widely known for its role in diabetes management, has shown potential as a weight loss aid. However, the evidence remains mixed and inconclusive. The most compelling data come from the Diabetes Prevention Program (DPP), a landmark study involving 3,234 individuals at high risk for T2D.[60] In this study, participants (mean age of 51 years, weight of 94.2 kg, and BMI of 34 kg/m^2)

were randomly assigned to placebo, metformin 850 mg twice daily, or a lifestyle modification program. After an average follow-up period of 2.8 years, the metformin group demonstrated significant weight loss compared to the placebo group (2.06% vs 0.02%; $P < 0.001$). The long-term follow-up DPP Outcomes Study showed that this weight loss was maintained, with participants receiving metformin sustaining an average weight reduction of 2.5 kg over a median period of 10 years.[61]

Moreover, other studies have shown inconsistent outcomes. A retrospective study of 222 patients with a mean BMI of 35 kg/m^2 found similar mean weight loss percentages for the euglycemic and T2D/prediabetes groups using metformin (1,000-2,000 mg daily).[62] Both groups lost an average of 6.5% body weight ($P = 0.97$) after 6 months. This similarity persisted at 1 year, with the euglycemic group losing 7.4% and the T2D/prediabetes group losing 7.3% ($P = 0.92$). These findings suggest that metformin's weight loss effects may be independent of glycemic status.

Despite these encouraging results, the overall evidence for metformin as a weight loss agent remains inconclusive. FDA has not approved metformin for this purpose, highlighting the need for more robust, long-term studies. Clinicians should consider metformin for weight management primarily in patients who are at high risk for diabetes or have prediabetes, as these groups may benefit most from its dual effects on glucose regulation and modest weight reduction.

Discussion

Historically, 4% to 5% weight loss within 12 weeks was the standard measure of effectiveness for an AOM. However, new information indicates that achieving a greater than 10% reduction in overall body weight might be needed to experience improvement in health outcomes. Individuals who lose at least 10% of their bodyweight have been shown to have a lower risk of a primary cardiovascular composite outcome (including death from cardiovascular causes, nonfatal acute myocardial infarction, nonfatal stroke, or hospitalization for angina) compared to those with stable weight or weight gain.[63] Most approved weight loss medications have modest effects, but newer medications such as semaglutide and tirzepatide result in impressive weight loss of 15% and 20.9%, respectively.[45,46] Notably, the SELECT trial demonstrated cardiovascular benefits with semaglutide in overweight or obese patients, emphasizing the potential advantages of significant weight loss with these potent medications.[55]

Compared to individuals who are not overweight or obese, those with these conditions incur substantially higher healthcare costs, including 46% greater inpatient expenses, 27% more physician visits, and an 80% increase in spending on medications.[64] However, the financial hurdles in obtaining AOMs represent a key obstacle in the management of obesity. Several health insurance plans, including Medicare Part D, do not include coverage for AOMs. The extent of Medicaid coverage for AOMs differs from state to state, with certain states not categorizing obesity as a medical issue, thereby restricting the availability of such treatments. The only AOM with generic availability is orlistat, which may not be suitable or effective for every patient.

The lack of insurance coverage for AOMs is partly due to concerns about the potential costs exceeding insurance budgets. Nevertheless, ongoing research is needed to assess the long-term efficacy and advantages of AOMs, as a combination approach that includes lifestyle modifications along with FDA-approved treatments might be beneficial for health outcomes. It is essential that individuals have access to affordable and comprehensive obesity treatment, including AOMs when needed, to address this public health challenge. Collaboration among healthcare providers, policymakers, and insurance companies is important to overcome the challenges of insurance coverage and affordability for individuals with obesity, leading to better quality of care and outcomes.

Conclusion

Combining lifestyle modification and/or surgical interventions with AOMs could be a successful approach for long-term weight management. However, providing economical options for obesity treatment continues to be a major obstacle in tackling this public health problem. By collaborating closely with other healthcare professionals, pharmacists can assist in identifying the most appropriate therapies for obesity, ensuring proper dosing and monitoring and ultimately optimizing health outcomes.

Data availability

No new data were generated or analyzed in support of this article.

Disclosures

The author has declared no potential conflicts of interest.

References

1. Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960-1962 through 2017-2018. National Center for Health Statistics. Published February 8, 2021. Accessed July 1, 2024. https://www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm
2. Centers for Disease Control and Prevention. Adult obesity facts. Accessed July 1, 2024. https://www.cdc.gov/obesity/php/data-research/adult-obesity-facts.html
3. Gorber SC, Tremblay M, Moher D, Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev*. 2007;8(4):307-326. doi:10.1111/j.1467-789X.2007.00347.x
4. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. *N Engl J Med*. 2019;381(25):2440-2450. doi:10.1056/NEJMsa1909301
5. Stierman B, Afful J, Carroll MD, et al. National Health and Nutrition Examination Survey 2017–March

2020 prepandemic data files development of files and prevalence estimates for selected health outcomes. National Center for Health Statistics. Published June 14, 2021. Accessed July 1, 2024. https://stacks.cdc.gov/view/cdc/106273
6. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157-163. doi:10.1016/S0140-6736(03)15268-3
7. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(suppl 3):1-203. doi:10.4158/EP161365.GL
8. Cameron AJ, Magliano DJ, Söderberg S. A systematic review of the impact of including both waist and hip circumference in risk models for cardiovascular diseases, diabetes and mortality. *Obes Rev*. 2013;14(1):86-94. doi:10.1111/j.1467-789X.2012.01051.x
9. Caleyachetty R, Barber TM, Mohammed NI, et al. Ethnicity-specific BMI cutoffs for obesity based on type 2 diabetes risk in England: a population-based cohort study. *Lancet Diabetes Endocrinol*. 2021;9(7):419-426. doi:10.1016/S2213-8587(21)00088-7
10. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med*. 2008;359(20):2105-2120. doi:10.1056/NEJMoa0801891
11. Staiano A, Reeder B, Elliott S, et al. Body mass index versus waist circumference as predictors of mortality in Canadian adults. *Int J Obes*. 2012;36(11):1450-1454. doi:10.1038/ijo.2011.268
12. Jacobs EJ, Newton CC, Wang Y, et al. Waist circumference and all-cause mortality in a large US cohort. *Arch Intern Med*. 2010;170(15):1293-1301. doi:10.1001/archinternmed.2010.201
13. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology consensus statement: comprehensive type 2 diabetes management algorithm—2023 update. *Endocr Pract*. 2023;29(5):305-340. doi:10.1016/j.eprac.2023.02.001
14. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. *Circulation*. 2014;129(25 suppl 2):S102-S138. doi:10.1161/01.cir.0000437739.71477.ee
15. Camelon KM, Hådell K, Jämsén PT, et al. The Plate Model: a visual method of teaching meal planning. DAIS Project Group. Diabetes Atherosclerosis Intervention Study. *J Am Diet Assoc*. 1998;98(10):1155-1158. doi:10.1016/s0002-8223(98)00267-3
16. Jayawardena R, Swarnamali H, Ranasinghe P, Hills AP. Impact of portion-control plates (PCP) on weight reduction: a systematic review and meta-analysis of intervention studies. *Obes Res Clin Pract*. 2021;15(2):106-113. doi:10.1016/j.orcp.2021.01.008
17. Armstrong MJ, Mottershead TA, Ronksley PE, Sigal RJ, Campbell TS, Hemmelgarn BR. Motivational interviewing to improve weight loss in overweight and/or obese patients: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev*. 2011;12(9):709-723. doi:10.1111/j.1467-789X.2011.00892.x
18. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362. doi:10.1210/jc.2014-3415
19. Grunvald E, Shah R, Hernaez R, et al. AGA clinical practice guideline on pharmacological interventions for adults with obesity. *Gastroenterology*. 2022;163(5):1198-1225. doi:10.1053/j.gastro.2022.08.045
20. Eisenberg D, Shikora SA, Aarts E, et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): indications for metabolic and bariatric surgery. *Surg Obes Relat Dis*. 2022;18(12):1345-1356. doi:10.1016/j.soard.2022.08.013
21. Dagan SS, Goldenshluger A, Globus I, et al. Nutritional recommendations for adult bariatric surgery patients: clinical practice. *Adv Nutr*. 2017;8(2):382-394. doi:10.3945/an.116.014258
22. Aills L, Blankenship J, Buffington C, Furtado M, Parrott J. ASMBS allied health nutritional guidelines for the surgical weight loss patient. *Surg Obes Relat Dis*. 2008;4(5):S73-S108. doi:10.1016/j.soard.2008.03.002
23. Noria SF, Shelby RD, Atkins KD, Nguyen NT, Gadde KM. Weight regain after bariatric surgery: scope of the problem, causes, prevention, and treatment. *Curr Diab Rep*. 2023;23(3):31-42. doi:10.1007/s11892-023-01498-z
24. Rothman RB, Baumann MH, Dersch CM, et al. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*. 2001;39(1):32-41. doi:10.1002/1098-2396(20010101)39:1<32::AID-SYN5>3.0.CO;2-3
25. Lomaira (phentermine). Package insert. KVK-Tech; 2023.
26. Phentermine. Package insert. Epic Pharma; 2017.
27. Xenical (orlistat). Package insert. H2-Pharma; 2022.
28. Alli (orlistat). Package insert. Haleon US Holdings; 2024.
29. Qsymia (phentermine/topiramate extended-release). Package insert. Vivus; 2023.
30. Contrave (naltrexone/bupropion extended-release). Package insert. Nalpropion Pharmaceuticals; 2021.
31. Wegovy (semaglutide). Package insert. Novo Nordisk; 2023.
32. Saxenda (liraglutide). Package insert. Novo Nordisk; 2023.
33. Zepbound (tirzepatide). Package insert. Eli Lilly and Company; 2023.
34. Lewis KH, Fischer H, Ard J, et al. Safety and effectiveness of longer-term phentermine use: clinical outcomes from an electronic health record cohort. *Obesity*. 2019;27(4):591-602. doi:10.1002/oby.22430
35. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. Xenical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27(1):155-161. doi:10.2337/diacare.27.1.155
36. Cosentino G, Conrad AO, Uwaifo GI. Phentermine and topiramate for the management of obesity: a review. *Drug Des Devel Ther*. 2013;7:267-278. doi:10.2147/DDDT.S31443
37. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9774):1341-1352. doi:10.1016/S0140-6736(11)60205-5
38. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized,

placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012;95(2):297-308. doi:10.3945/ajcn.111.024927
39. Lei XG, Ruan JQ, Lai C, Sun Z, Yang X. Efficacy and safety of phentermine/topiramate in adults with overweight or obesity: a systematic review and meta-analysis. *Obesity*. 2021;29(6):985-994. doi:10.1002/oby.23152
40. Billes SK, Sinnayah P, Cowley MA. Naltrexone/bupropion for obesity: an investigational combination pharmacotherapy for weight loss. *Pharmacol Res*. 2014;84:1-11. doi:10.1016/j.phrs.2014.04.004
41. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595-605. doi:10.1016/S0140-6736(10)60888-4
42. Onakpoya IJ, Lee JJ, Mahtani KR, Aronson JK, Heneghan CJ. Naltrexone-bupropion (Mysimba) in management of obesity: a systematic review and meta-analysis of unpublished clinical study reports. *Br J Clin Pharmacol*. 2020;86(4):646-667. doi:10.1111/bcp.14210
43. Pannacciulli N, Le DSNT, Salbe AD, et al. Postprandial glucagon-like peptide-1 (GLP-1) response is positively associated with changes in neuronal activity of brain areas implicated in satiety and food intake regulation in humans. *Neuroimage*. 2007;35(2):511-517. doi:10.1016/j.neuroimage.2006.12.035
44. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373(1):11-22. doi:10.1056/NEJMoa1411892
45. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA*. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224
46. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205-216. doi:10.1056/NEJMoa2206038
47. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes*. 2013;37(11):1443-1451. doi:10.1038/ijo.2013.120
48. Wadden TA, Tronieri JS, Sugimoto D, et al. Liraglutide 3.0 mg and intensive behavioral therapy (IBT) for obesity in primary care: the SCALE IBT randomized controlled trial. *Obesity*. 2020;28(3):529-536. doi:10.1002/oby.22726
49. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;389(10077):1399-1409. doi:10.1016/S0140-6736(17)30069-7
50. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827
51. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183
52. Knop FK, Aroda VR, do Vale RD, et al. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;402(10403):705-719. doi:10.1016/S0140-6736(23)01185-6
53. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.
54. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381(9):841-851. doi:10.1056/NEJMoa1901118
55. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563
56. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2023;402(10402):613-626. doi:10.1016/S0140-6736(23)01200-X
57. Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nat Med*. 2023;29(11):2909-2918. doi:10.1038/s41591-023-02597-w
58. Aronne LJ, Sattar N, Horn DB, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. *JAMA*. 2024;331(1):38-48. doi:10.1001/jama.2023.24945
59. Del Prato S, Kahn SE, Pavo I, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet*. 2021;398(10313):1811-1824. doi:10.1016/S0140-6736(21)02188-7
60. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403. doi:10.1056/NEJMoa012512
61. Knowler WC, Fowler SE, Hamman RF, et al; Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677-1686. doi:10.1016/S0140-6736(09)61457-4
62. Chukir T, Mandel L, Tchang BG, et al. Metformin-induced weight loss in patients with or without type 2 diabetes/prediabetes: a retrospective cohort study. *Obes Res Clin Pract*. 2021;15(1):64-68. doi:10.1016/j.orcp.2020.12.005
63. Gregg E, Jakicic J, Blackburn G, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2016;4(11):913-921. doi:10.1016/S2213-8587(16)30162-0
64. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. *Health Aff*. 2009;28(5):w822-w831. doi:10.1377/hlthaff.28.5.w822