

Pharmacotherapy for Obesity: Recent Updates

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Abstract: In this narrative review we describe the recent updates regarding anti-obesity medications as of February 2025. We describe the physiologic mechanisms underpinning the development of hunger, satiation, and maintenance of satiety to address targets for anti-obesity medications. The efficacy, mechanism, and additional beneficial effects of anti-obesity medications are then further detailed. For this review, we focus on FDA-approved medications for obesity and on select medications currently under development and undergoing Phase 2 and 3 trials. We start by focusing on the non-incretin anti-obesity medications orlistat, phentermine, phentermine-topiramate, and naltrexone-bupropion. We also highlight setmelanotide for heritable obesity. The mechanism of action and comparative efficacy of the GLP-1 receptor agonists liraglutide and semaglutide are reviewed. Tirzepatide, the GLP-1 and GIP-receptor dual agonist is described, and weight loss is compared to alternative anti-obesity medications. Additional incretin targets in the pipeline include dual co-agonists to glucagon and GLP-1 receptors, triple agonists targeting glucagon, GLP-1 and GIP, novel GLP-1 agonists, oral formulations of GLP-1 agonists, and amylin agonists. Finally, we provide best practices for adjuncts to pharmacologic treatments of obesity, monitoring efficacy of obesity treatments, and adjusting medication regimens for providers.

Keywords: obesity, pharmacotherapy, glucagon-like peptide-1, obesity management

Introduction

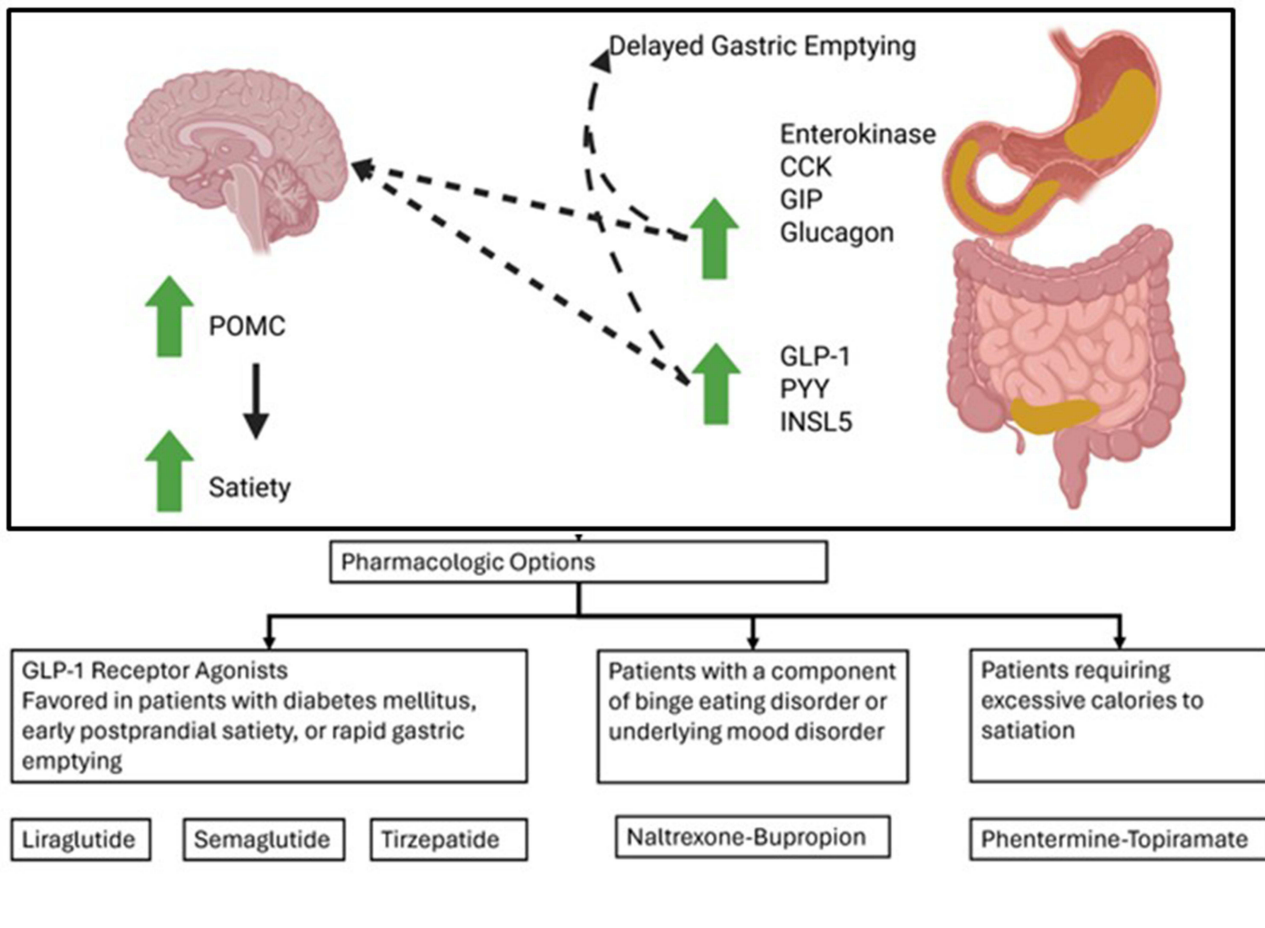
Obesity remains a disease of epidemic proportions, with up to 43% of the United States population affected and rates worldwide doubling from 1990 to 2022.^{1,2} This rising prevalence of obesity brings significant costs to the healthcare system, estimated to be up to \$172 billion in annual expenditures.³

Obesity is a disease of excess adiposity, but the diagnostic criteria remain an area of debate.⁴ Obesity has traditionally been classified based upon body mass index (BMI), as described in Table 1.⁵ BMI is a simple and reliable, population-based, metric for measuring body size, but comes with limitations for identifying individuals at increased risk of complications of obesity, particularly within different ethnic groups.⁶ Additional methods of measuring adiposity are detailed in Table 1. Most studies investigating obesity treatments rely on BMI, which will be the criterion used in this paper.

Untreated obesity is associated with significant additional health consequences (Figure 1),^{7,15–29} and obesity is an independent risk factor for increased all-cause mortality.³⁰ The 2013 joint American Heart Association (AHA), Obesity Society (TOS) and American College of Cardiology (ACC) guidelines for management of overweight and obesity state that “the greater the BMI, the higher the risk of fatal coronary heart disease” and “that the higher the BMI, the greater the risk of all-cause mortality”.^{31,32} Additionally, “overweight and obese adults with type 2 diabetes who intentionally lost 9 kg to 13 kg had a 25% decrease in mortality rate” and “there is a dose–response relationship between the amount of weight loss achieved by lifestyle intervention and the improvement in lipid profile”. Thus, treatments aimed at both correcting weight management and optimizing metabolic risk profiles can have the largest benefit in improving health outcomes.

At a fundamental level, obesity arises from caloric imbalance where intake exceeds expenditure. Food intake regulation and signaling between the gut-adipose-brain axis are important targets for treatment of obesity.³³ Historically, options for treatment of obesity focused on dietary modification and exercise.³⁴ Many of the comorbidities associated with obesity can be effectively managed with a sustained 5–10% body weight loss, which is a reasonable first step for most patients.³⁵ Bariatric surgical options, which result in more than 25% total body weight loss, are not widely adopted due to costs and side effect profile.^{36,37}

Graphical Abstract



Fortunately, there has been substantial expansion of pharmacological therapies for obesity in the last decade. In this article, we briefly review the pathophysiology and pertinent signals associated with food intake, the recently approved pharmacological treatments for obesity, and several novel treatments currently under investigation.

Methods

This narrative review was performed utilizing targeted literature search of PubMed, MEDLINE, and Google Scholar searches and recent high-impact reviews.^{38,39} We began our narrative review by reviewing the included references and searching the above registries with pertinent keywords including obesity, pharmacotherapy, phentermine, naltrexone, bupropion, topiramate, GLP-1, bariatric, anti-obesity, weight loss, and nutrition among others. Included studies were available up to February 1st, 2025. References from retrieved articles were also evaluated to extract relevant studies. Active obesity trials were identified through Clinicaltrials.gov.

Regulation of Appetite

The details regarding the physiology of appetite and caloric consumption have been well described.^{40,41} However, a brief review is essential to understanding the mechanism of action of novel pharmacologic treatments of obesity.

Food intake is mainly regulated by a homeostatic and a hedonic process. The homeostatic food intake regulation has three phases: hunger, satiation, and postprandial satiety. These three homeostatic phases drive food intake or appetite behavior of seek, consume, and rest. The hypothalamic arcuate nucleus (ARC) contains orexigenic neurons secreting

Table 1 Definitions of Obesity and Processes of Measuring Obesity

Direct Adiposity Measurements		
Measurement	Diagnostic Criteria for Obesity	Notes
Dual X-ray Imaging (DXA)	Measures percentage of body fat, Body fat $\geq 25\%$ in men and $\geq 30\%$ in women. ⁷	Since it generates a 2-dimensional image, cannot measure visceral or ectopic fat well. ⁸
CT	Various thresholds capable of diagnosing visceral adiposity.	Radiation Exposure. Capable of accurately evaluating ectopic fat.
MRI	Various thresholds that can provide information about visceral fat area. ⁹	No radiation. Time-consuming. Can provide detailed information about adipose tissue breakdown. ¹⁰
Indirect Adiposity Measurements		
Measurement	Diagnostic Criteria for Obesity	Notes
World Health Organization (WHO) Criteria		
Weight Category	BMI Range (kg/m^2)	
Underweight	Less than 18.5	
Healthy Weight	18.5 to less than 25	18.5 to <23 in individuals of Asian descent.
Overweight	25 to less than 30	23 to <27.5 in individuals of Asian descent.
Class 1 Obesity	30 to less than 35	27.5 to <35 in individuals of Asian descent.
Class 2 Obesity	35 to less than 40	
Class 3 Obesity (severe obesity)	40 or greater	
Waist Circumference – Defining abdominal obesity	Greater than 102 cm (men) or 88 cm (women)	More reliable in men than in women
Waist to Hip Ratio (WHR) - defining abdominal obesity	WHR ≥ 0.85 in women and ≥ 0.9 - in men	
Sagittal Abdominal Diameter (SAD)	SAD ≥ 25 cm associated with abdominal obesity ¹¹	Strongest association with visceral adiposity irrespective of age, sex, and degree of obesity ¹²
Body impedance assessment	Measures percentage of body fat, Body fat $\geq 30\%$ in men and $\geq 42\%$ in women ¹³	Less reliable in morbid obesity. ¹⁴

neuropeptide Y (NPY) and agouti-related peptide (AgRP) which increase appetite^{38,42,43} (Figure 2A). Additional hypothalamic pathways contributing to hunger involve the lateral hypothalamus and the parabrachial nucleus via calcitonin gene-related peptide (CGRP) neurons.^{44,45}

With food entry into the stomach, afferents in the vagus nerve signals to the nucleus tractus solitarius (NTS), and reflexively induces gastric accommodation.⁴⁶ This relaxation (Figure 2B) results in distention of the stomach and vagal signals fire to induce the sensation of fullness and terminate the meal. This phenomenon is known as satiety, and individuals perceive this as a sensation of fullness and freedom from hunger.

As food is digested, incretin signals and other enzymes or hormones are released, leading to a fasting state called satiety. The signals start with changes in gastric distention, leading to decreased acyl-ghrelin, increased deacyl-ghrelin, and increased gastric leptin.⁴⁷ As food enters the duodenum, other enzymes or hormones including enterokinase, cholecystokinin (CCK), glucose-dependent insulintropic peptide (GIP, previously called gastric inhibitory polypeptide) and glucagon are all secreted and act systemically to promote postprandial satiety (Figure 2C).⁴⁸ With food entry into the small intestine, intestinal L-cells release glucagon-like peptide 1 (GLP-1), which has wide ranging systemic effects promoting satiety.^{49–51} Once food reaches the terminal ileum, enterocytes release peptide YY (PYY), oxyntomodulin and

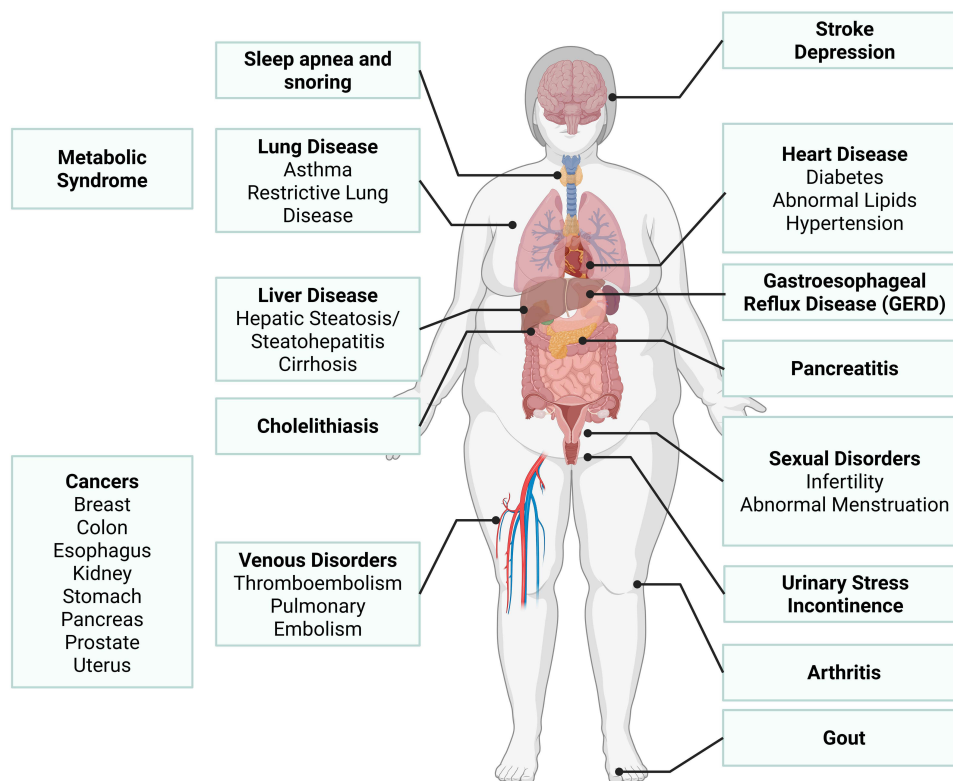


Figure 1 Complications of obesity. Created in BioRender. Fredrick, T. (2025) <https://BioRender.com/or5mft>.

insulin-like peptide 5 (INSL5), which constitute the “ileal brake” and further delay gastric emptying and enteric motility.⁵² The cumulative effect is a central sensation of postprandial satiety, (Figure 2C). As food leaves of the stomach, the anorexigenic signaling is reduced, and orexigenic signals from the hypothalamus start to promote hunger, driving the cycle again.

Adipose tissue secretes the hormone leptin, which promotes satiety. After years of excessive intake, adipose tissue stores increase throughout the body, with significant deposition in subcutaneous, liver, and mesenteric tissues. Obesity leads to changes in adipose tissue signaling through upregulation of pro-inflammatory cytokines and induces increased insulin resistance.^{53,54}

Regulation of this neurohormonal signaling forms the basis for novel pharmacologic treatments for obesity and obesity-related conditions. When describing the beneficial and adverse effects of each anti-obesity medication, we will highlight the novel mechanisms behind their induction of weight loss.

Pharmacologic Treatments for Obesity

Details of FDA-approved anti-obesity medications are described in Tables 2 and 3, and medications in development are highlighted in Table 4. We will classify pharmacologic treatments based on their mechanisms of action and explicitly characterize those treatments which are approved by the US Food and Drug Administration (FDA) for treatment of obesity.

Anti-Absorptive Treatments

Orlistat

Orlistat was approved by the FDA in 1999 for treatment of obesity in adults.⁸⁶ Orlistat inhibits gastric and pancreatic lipase, preventing triglycerides from being hydrolyzed and decreasing the absorption of free fatty acids from the diet. Weight reduction (denoted henceforth with the minus [-] sign) ranges from -2.8 to -4.8% total body weight loss (TBWL).^{55,56,70,87} Additional benefits of orlistat include reduced total cholesterol, LDL, fasting glucose, and systolic and diastolic blood pressure

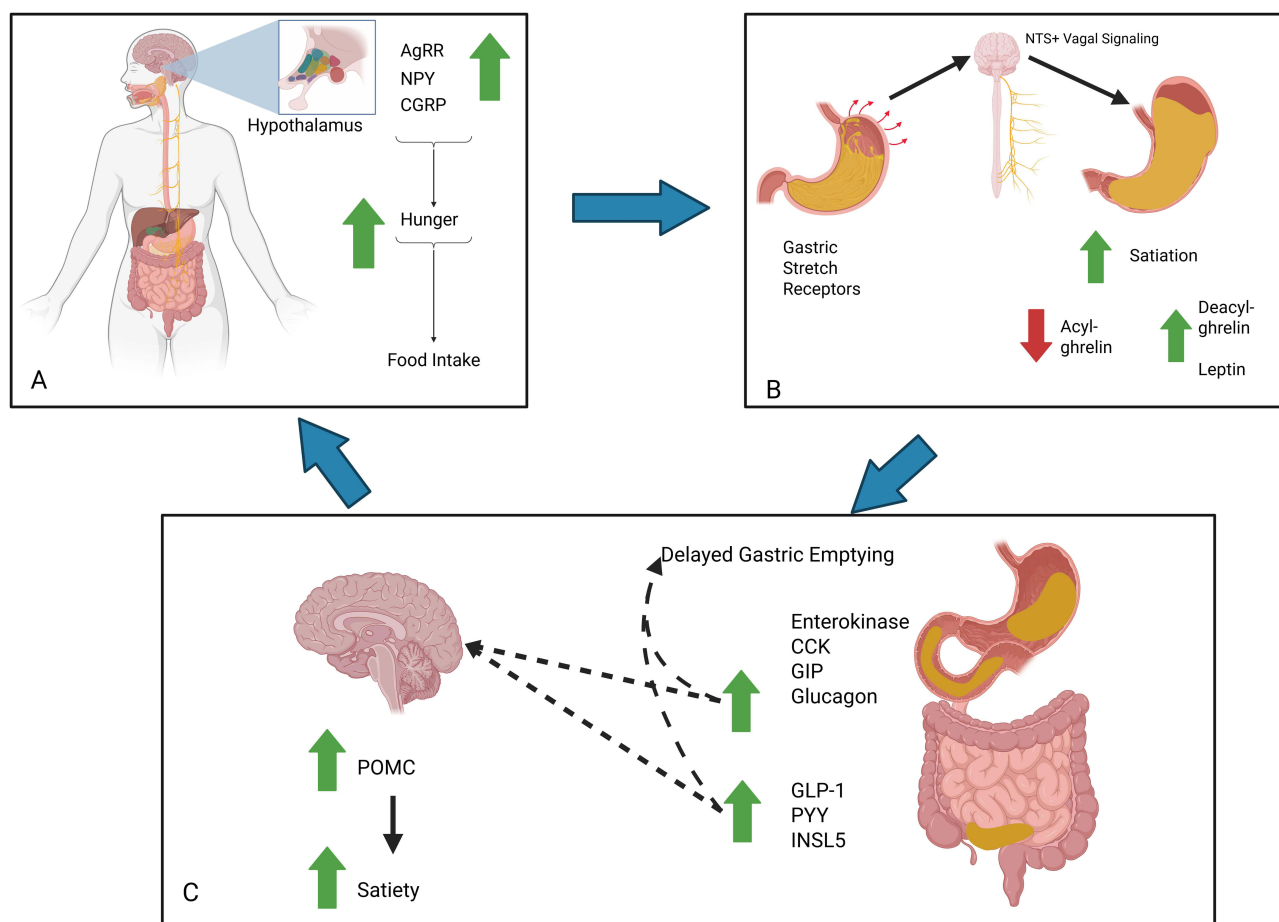


Figure 2 Mechanisms of Hunger, Satiety, and Satiation. **(A)** In the fasting state, hunger arises starting with increased signaling arising from hypothalamic hormones Agouti-related peptide (AgRP), Neuropeptide Y (NPY), and Calcitonin-Gen Related Peptide (CGRP). These hormones contribute to the hunger sensation, which causes individuals to consume food. Upon food entry to the stomach **(B)**, the stomach expands, which signals the nucleus tractus solitarius (NTS) in the brainstem. Nerve fibers then signal the stomach fundus to relax and accommodate more food. Changes in gastric hormones, including increased leptin and deacyl-ghrelin and decreased acyl-ghrelin promote changes in satiety (green arrow). As food enters the duodenum **(C)**, enterocytes secrete additional hormones, enterokinase, CCK, GIP, and glucagon which both slow gastric emptying and promote satiety. As the bolus reached the ileum, PYY, GLP-1, and INSL5 hormones are secreted and further delay gastric emptying. The end result of these hormones is action at the level of the hypothalamus to increase POMC secretion and promote satiety. Upward green arrows reflect increases, and downward red arrow reflects decreases. Created in BioRender. Fredrick, T. (2025) <https://BioRender.com/gd6ph92>.

(Table 5).^{88–90} Side effects arise from the reduced fat absorption, including flatulence, fecal urgency, fecal incontinence, and fat-soluble vitamin deficiencies, which result in high rates of treatment discontinuation, and low clinical use.^{87,91}

Centrally Acting Medications

Phentermine

Phentermine is a sympathomimetic medication with amphetamine-like stimulant effects initially FDA approved in 1959 for short-term weight loss.¹¹² Through increasing extracellular dopamine, norepinephrine, and serotonin in the brain, it reduces appetite.^{113,114} Side effects arising from the sympathomimetic nature of phentermine include insomnia, palpitations, elevated blood pressure, and gastrointestinal distress.¹¹⁵ Phentermine is contraindicated in individuals with underlying cardiovascular disease given risk of arrhythmias.¹¹⁶

Weight loss with phentermine varies from -6.7 to -8.1 kg after 12 weeks of treatment.^{71,117} While phentermine is only approved by FDA for 12 weeks use for weight loss, treatment can be continued longer via either continuous or intermittent use, with no increased cardiovascular risk.⁵⁸

Phentermine-Topiramate (Phen-Top)

Topiramate is an anticonvulsant and anti-migraine treatment that induces weight loss of -6 to -8 kg,¹¹⁸ through unclear

Table 2 Details on FDA Approved Medications for Weight Loss

Medication	Mechanism of Action	Formulation and Maximum Dosing	Weight Loss Efficacy	Common Adverse Events
Orlistat	Inhibits pancreatic lipase	120 mg orally, 3 times daily for each meal with fat	2.8–4.8% body weight loss relative to placebo at 52 weeks ^{55–57}	Steatorrhea (20%), abdominal pain (40%), defecation urgency (22–38%)
Phentermine	Increased adrenergic signaling in the CNS	Oral, can be given up to 37.5 mg daily for maximum of 12 weeks	7–8.3% body weight loss at 12 months. ⁵⁸	Increased blood pressure, tachycardia, prolonged QT interval, ventricular arrhythmias, CNS agitation
Phentermine-Topiramate	Increased adrenergic signaling in CNS (phentermine); unknown mechanism of topiramate, but potentially changes in glutamate neurotransmission	Orally, can be given to a maximum of phentermine 15mg/topiramate 92 mg	9.8–10.9% body weight loss at 12 months. ^{59,60}	Paresthesias (4–20%), Xerostomia (7–19%), Constipation (8–16%), Upper Respiratory Infection (12–16%)
Naltrexone-Bupropion	Opioid antagonist and dopaminergic and noradrenergic effects on POMC	Oral daily medication, up to a maximum of naltrexone 32 mg/ bupropion 360 mg per day	6.1–9.3% total body weight loss. ^{61,62}	Nausea (32%), constipation (19%), headache (17%), vomiting (10%), dizziness (9%)
Liraglutide	GLP-I Receptor Agonist	Subcutaneous (SC) injection up to 3 mg once daily	6–8% body weight loss at 12 months. ^{63,64}	Nausea (39–42%), vomiting (34%), headache 9–13%), diarrhea (10–22%), constipation (4–19%)
Semaglutide	GLP-I Receptor Agonist	Subcutaneous (SC) injection up to 2.4 mg weekly	10.76–14.9% total body weight loss at 52 weeks. ^{65,66}	Nausea (42–44%), vomiting (24–36%), headache (14–17%), diarrhea 8–10%), constipation 6–24%), abdominal pain (15–20%)
Tirzepatide	GLP-I and GIP receptor co-agonist	Weekly subcutaneous injection up to 15 mg weekly.	13.9–17.5% total body weight loss at 52 weeks, and up to 18.4% at 72 weeks. ^{67–69}	Nausea (12–29%), vomiting (5–14%), diarrhea 12–23%), constipation (6–17%), abdominal pain (5–10%)

Table 3 Pivotal Trials Results

Medication	Pivotal Trials	Weight Loss Observed in Trial	Additional Health Benefits
Orlistat	Xendos ⁷⁰	<ul style="list-style-type: none"> • Mean weight loss at 4 years: 5.8 kg with orlistat vs 3.0 kg with placebo • 52% completion rate with orlistat vs 34% with placebo 	<ul style="list-style-type: none"> • 37.3% reduction in risk of developing type 2 diabetes • Cumulative diabetes incidence: 6.2% with orlistat vs 9.0% with placebo
Phentermine	Kang et al 2010 ⁷¹ Lewis et al 2019 ⁵⁸	<p>Kang 2010 (12 weeks):</p> <ul style="list-style-type: none"> • Mean weight loss: 8.1 kg with phentermine vs 1.7 kg with placebo • ≥5% weight loss: 95.8% vs 20.8%; ≥10% weight loss: 62.5% vs 4.7% <p>Lewis 2019 (observational):</p> <ul style="list-style-type: none"> • Continuous use >12 months: 7.4% more weight loss at 24 months vs ≤3 months use 	<p>Kang 2010:</p> <ul style="list-style-type: none"> • Significant improvements in total cholesterol and LDL-C • Improved waist circumference reduction <p>Lewis 2019:</p> <ul style="list-style-type: none"> • No increased risk of cardiovascular disease or death with longer-term use
Phentermine- Topiramate	Equip, Conquer, Sequel ^{59,60,72}	<p>EQUIP (56 weeks):</p> <ul style="list-style-type: none"> • 10.9% weight loss vs 1.6% in placebo <p>CONQUER (56 weeks):</p> <ul style="list-style-type: none"> • 9.8% weight loss vs 1.2% in placebo <p>SEQUEL (108 weeks):</p> <ul style="list-style-type: none"> • 10.5% weight loss vs 1.8% in placebo 	<ul style="list-style-type: none"> • Significant improvements in waist circumference, blood pressure, fasting glucose • Improved lipid profiles (triglycerides, total cholesterol, LDL, HDL) • Decreased rates of incident diabetes
Naltrexone- Bupropion	COR-I, COR-II, ^{61,73}	<p>COR-I (56 weeks):</p> <ul style="list-style-type: none"> • 6.1% weight loss vs 1.3% in placebo <p>COR-II (56 weeks):</p> <ul style="list-style-type: none"> • 6.4% weight loss vs 1.2% in placebo weight loss • ≥5% weight loss: 50.5% vs 17.1% 	<ul style="list-style-type: none"> • Improvements in cardiometabolic risk markers • Improved weight-related quality of life • Better control of eating • Small reduction in blood pressure (~1 mm Hg) • No increased depression or suicidality
Liraglutide	SCALE (Diabetes Mellitus) SCALE Obesity ^{63,64}	<p>SCALE Diabetes (56 weeks):</p> <ul style="list-style-type: none"> • 6.0% (6.4 kg) weight loss vs 2.0% (2.2 kg) in placebo <p>Scale Obesity (56 weeks):</p> <ul style="list-style-type: none"> • 8.4 kg weight loss vs 2.8 kg in placebo • >10% weight loss: 33.1% vs 10.6% 	<ul style="list-style-type: none"> • Improved glycemic control in diabetes patients • Improved metabolic parameters (triglycerides, cholesterol) • Reduction in prediabetes progression • Improvements in blood pressure and lipid profiles
Semaglutide	STEP 1–5 trials. ^{65,74,75}	<p>STEP 1 (68 weeks):</p> <ul style="list-style-type: none"> • 14.9% weight vs 2.4% in placebo <p>STEP 5 (104 weeks):</p> <ul style="list-style-type: none"> • 15.2% weight loss vs 2.6% in placebo <p>STEP 8 vs Liraglutide (68 weeks):</p> <ul style="list-style-type: none"> • 15.8% weight loss vs 6.4% in liraglutide 	<ul style="list-style-type: none"> • Improvements in waist circumference • Reduced systolic blood pressure (3.9 mm Hg) • Improved physical functioning scores • Superior to liraglutide for weight loss • Sustained weight loss with continued treatment
Tirzepatide	SURMOUNT and SURPASS ^{67–69,76}	<p>SURMOUNT-1 (72 weeks):</p> <ul style="list-style-type: none"> • 15 mg: 20.9% weight loss vs 3.1% with placebo • ≥20% weight loss: 57% (15 mg) vs 3% <p>SURMOUNT-2 (T2D, 72 weeks):</p> <ul style="list-style-type: none"> • 15 mg: 14.7% weight loss vs 3.2% in placebo <p>SURMOUNT-3 (after lifestyle):</p> <ul style="list-style-type: none"> • Additional 18.4% weight loss • 87.5% achieved ≥5% additional loss 	<ul style="list-style-type: none"> • Improvements in all cardiometabolic measures • In T2D: Mean HbA1c reduction of 2.34% (15 mg) • Significant improvements in blood pressure, lipids • Effective even after initial lifestyle intervention success

Table 4 Selected Anti-Obesity Medications Under Development

Medication	Mechanism of Action	Current Status	Weight Loss Efficacy
Peripheral Tissue Actors			
Bimagrumab	Anti activin type II receptor (ActRII) monoclonal antibody	Phase 2 trials ongoing	Reduced fat mass by -7.9% relative to placebo at 10 weeks. ⁷⁷
Oral GLP-I Receptor Agonists			
Danuglipron	Daily oral small-molecule GLP-I RA	Phase 2 trials ongoing	TBWL: -8% to -13% after 32 weeks (NCT04707313).
Orforglipron	Daily oral small-molecule GLP-I RA	Phase 3 trials ongoing	TWBL: -14.7% vs -2.3% placebo at 36 weeks ⁷⁸
Rybelsus (semaglutide)	Daily oral peptide GLP-I RA	Approved in Diabetes Mellitus, Phase 3 trials in obesity ongoing	TBWL: -15.1% vs -2.4% in placebo at 68 weeks ⁷⁹
Subcutaneous (SQ) GLP-I Receptor Agonists			
Ecnoglutide (XW03)	Weekly SQ GLP-I RA	Phase 3 trials ongoing	TBWL: -14.7% TBWL at 26 weeks ⁸⁰
GZR18	Bi-weekly SQ GLP-I RA	Phase 2 trials completed	-17.29% TBWL at 30 weeks (CTR20231695)
GLP-I/ Glucagon Receptor (GCG) Dual Agonists			
Mazdutide	Weekly SQ GLP-I/GCG dual agonist	Phase 2 trials completed	-11.3% vs 1% in placebo at 24 weeks. ⁸¹
Pemvidutide	Weekly SQ GLP-I/GCG dual agonist	Phase 3 trials ongoing	-15.6% TBWL vs placebo at week 48 ⁸²
Survodutide	Weekly SQ GLP-I/GCG dual agonist	Undergoing Phase 3 trials	-14.9% weight loss vs -2.8% weight loss in placebo at 46 weeks
GLP-I and GIP Receptor Agonists			
Maridebart cafraglutide (AMG 133/MariTide)	Weekly SQ GLP-I/GIP dual agonist	Phase 2 trials completed	-20% weight loss at 52 weeks ⁸³
GLP-I, GIP, GCG Receptor Agonists			
Retatrutide	Weekly SQ GLP-I/GCG/GIP Triple Agonist	Undergoing Phase 3 trials	-24.2% weight loss vs -2.1% in placebo at 48 weeks ⁸⁴
GLP-I and Amylin Receptor Agonists			
Cagrisema (cagrilintide and semaglutide)	Weekly subcutaneous injection of GLP-I and Amylin dual agonist	Undergoing phase 3 trials	-12.6% weight loss at 32 weeks. ⁸⁵

mechanisms, but likely by modulating GABA in the hypothalamus.¹¹⁹ Combination 15 mg/92 mg phentermine-topiramate resulted in -10.92% weight loss vs -1.55% in placebo at 56 weeks,⁵⁹ and was confirmed in patients followed up to 108 weeks.^{60,72}

Secondary benefits include a weight-loss mediated reduction in blood pressure, reduced triglycerides and LDL, improved fasting glucose, fasting insulin, and high-sensitivity C-reactive protein (HS-CRP).⁶⁰ In a small randomized controlled trial (RCT), followed by a pragmatic trial, phentermine-topiramate was shown to work best in those with abnormal satiation, defined as need for high calorie intake to reach fullness.^{33,120}

Table 5 Additional Benefits of FDA-Approved Anti-Obesity Treatments. Summary of Potential Additional Benefits From AOM Which Have Previously Been Investigated

Medication	Steatohepatitis	Liver Fibrosis	Kidney Disease	Cardiovascular MACE (in diabetes)	Cardiovascular MACE (in obesity)	Heart Failure	Sleep Apnea	Arthritis	Stroke	Infertility
Orlistat	?	?	?	N/A	? ^{92,93}	? ⁹³	?	?	? ⁹³⁻⁹⁴	?
Phentermine-Topiramate	?	?	?	N/A	? ⁹⁵	?	?	?	?	?
Naltrexone-Bupropion	? ⁹⁶	?	?	N/A	X ⁷³	X ⁷³	?	?	?	?
Liraglutide	+ ⁹⁷	- ⁹⁷	+ ⁹⁸	+ ⁹⁹	?	?	¹⁰⁰⁻¹⁰¹	?	?	?
Semaglutide	+ ¹⁰²	- ¹⁰²	+ ¹⁰³	+ ⁹⁹	¹⁰⁴	? ¹⁰⁵	?	¹⁰⁶	?	?
Tirzepatide	+ ¹⁰⁷	- ¹⁰⁷	+ ¹⁰⁸	+ ¹⁰⁹	?	+ ¹¹⁰	+ ¹¹¹	?	?	?

Notes: + = High quality evidence that this medication can clinically improve the listed condition. ? = Further investigations are needed. - = Adequate evidence that AOM does not promote either enough weight loss or improve clinical parameters enough to improve outcome.

Naltrexone-Bupropion (NB)

Bupropion increases hypothalamic dopamine and norepinephrine signaling, reducing food intake,^{121–124} and naltrexone is approved for opioid abuse and helps reduce cravings for alcohol. The combination therapy naltrexone-bupropion (NB) has been shown to result in TBWL up to -6.1% compared to -1.3% in the placebo group at 56 weeks.^{61,73} When combined with intensive lifestyle changes, NB weight loss was -9.3% compared to -5.1% with placebo.⁶² The most common adverse events with NB include nausea, headache, constipation, dizziness, vomiting, and dry mouth. NB improves central obesity and LDL levels but without significant improvement in other cardiovascular parameters.^{61,62,73,125} NB is effective in binge eating disorder, which presents a patient population potentially best served by this medication.¹²⁶

Setmelanotide

Setmelanotide is a daily subcutaneous injection which acts as a melanocortin-4 (MC4) receptor agonist, and was approved by the FDA in 2020 in patients with obesity arising from genetically confirmed Bardet-Biedl syndrome (BBS), POMC, PCSK1, or LEPR deficiency.^{127,128} Human studies of setmelanotide showed significant weight loss and improved hunger scores.¹²⁹ A phase 2 study of 18 patients with hypothalamic obesity found that setmelanotide led to 80% experiencing $\geq 5\%$ body weight loss at 16 weeks.¹³⁰ Adverse events of setmelanotide include nausea, depression, suicidal ideation, and hyperpigmentation.^{127,129–131} Its use remains limited for these genetic alterations in MC4R signaling and given its specific actions is unlikely to be effective in the general population.

Incretin Agonists

GLP-1 Receptor Agonists

One class of anti-obesity medications experiencing a large rise in prescriptions are the GLP-1 receptor agonists (GLP-1RAs, [Figure 3](#)). GLP-1 RAs have been shown to impact functions associated with metabolism and energy balance by delaying gastric emptying, reducing hunger, increasing postprandial satiety, and reducing ad libitum food intake.^{132–134} In addition, GLP-1 activation in the CNS via the hypothalamus and medulla drives reduced appetite.^{135–137} GLP-1 directly acts on pancreatic B-cells to increase insulin secretion and on hepatic cells to decrease glucagon excretion and regulate blood glucose levels, leading to reductions in body fat.^{138–140}

Liraglutide

Liraglutide was developed by modifying GLP-1 protein to include a free fatty acid side chain bound to the peptide, allowing for albumin binding and (longer) half- allowing for daily dosing.¹⁴² Five randomized controlled trials of liraglutide in individuals with obesity have shown weight loss of -4.4 kg to -6.1 kg relative to placebo.^{63,64,143–145}

Semaglutide

Semaglutide is a GLP-1 RA with significantly longer half-life supporting weekly SQ administration. Like liraglutide, the GLP-1 sequence of semaglutide is bound to a free fatty acid side chain, mediating even stronger coupling to albumin.^{146,147}

The STEP trials were the pivotal trials evaluating semaglutide for obesity.⁶⁵ The STEP 1 randomized controlled trial investigated semaglutide 2.4 mg weekly and found a body weight loss of -14.9% vs -2.4% with placebo at 68 weeks.¹⁴⁸ Similar effects were seen across STEP 2–5 and STEP 8 (which included both overweight and obese without diabetes), with sustained weight loss seen at 104 weeks in the STEP 5 trial.^{149,150}

Additional benefits of semaglutide include reduced incidence of cardiovascular complications in individuals with type 2 diabetes and chronic kidney disease.^{151,152} The SELECT RCT showed improvement in a composite endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke in individuals receiving semaglutide relative to placebo (HR=0.80, 95% CI 0.72–0.90).¹⁵² Pooling results from additional trials including SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM confirmed improvement in composite outcomes in patients with heart failure (HF) with preserved ejection fraction, but no significant reduction in cardiovascular death alone in individuals receiving semaglutide.¹⁰⁵ Notably, these studies included variable dosages of semaglutide, with few individuals on the maximum dosage used for obesity treatment. Recommendations from the American College of Cardiology have yet to support empiric GLP-1 RA use for HF.^{153,154}

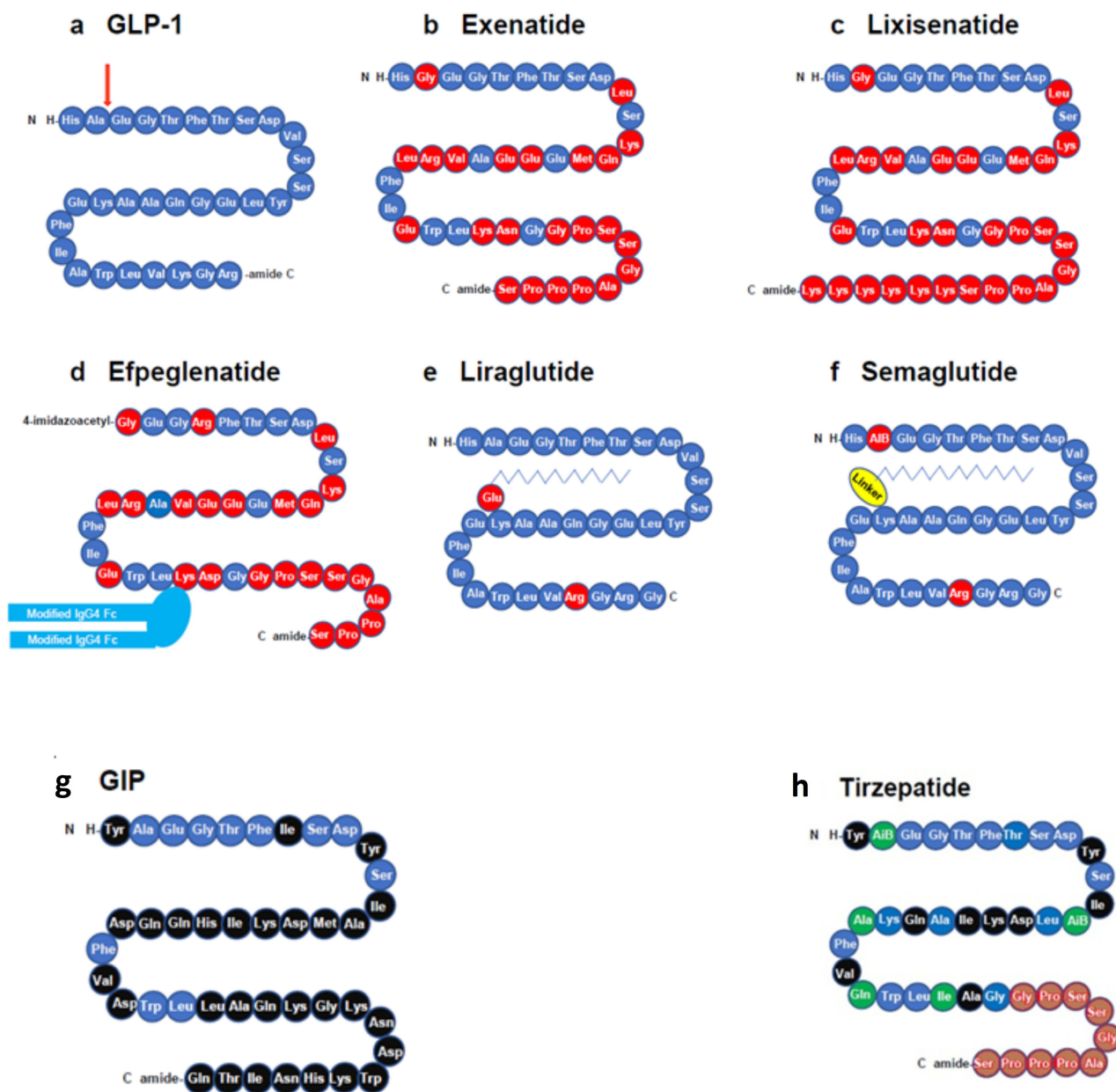


Figure 3 Composition of Different Incretin Agonists. Structures of formulations of GLP-1 receptor agonists (a) GLP-1, (b) exenatide, (c) lixisenatide, (d) efglenatide, (e) liraglutide, (f) semaglutide, (g) GIP and (h) tirzepatide. Amino acids are illustrated in circles; red circles show amino acids that are different from those in GLP-1; blue circles show amino acids that are identical to those in GLP-1; black circles show amino acids that are present in GIP and tirzepatide but not in GLP-1; brown circles show amino acids that are identical in tirzepatide and exenatide, and green circles show amino acids that are present in tirzepatide but not in GLP-1, GIP or exenatide. AiB, aminoisobutyric acid. The red arrow in (a) illustrates the site of DPP-4 inactivation. Adapted from Tschöp M, Nogueiras R, Ahren B. Gut hormone-based pharmacology: novel formulations and future possibilities for metabolic disease therapy. *Diabetologia*. 2023/10/01 2023;66(10):1796–1808. Creative Commons.¹⁴¹

Secondary benefits of GLP-1 receptor agonists and other anti-obesity medications remain an active area of investigation and are summarized in Table 5. These include improvement in MASLD-related steatohepatitis and steatosis,^{155,156} knee pain in osteoarthritis,¹⁰⁶ cardiovascular outcomes,⁹⁹ and potentially substance use disorders.¹⁵⁷

Common side effects of GLP-1 agonists include nausea, constipation, diarrhea, vomiting, abdominal discomfort, and reduced appetite.^{63,67,148,158} Side effects tend to be transient and resolve with time, but impact real-world adherence.¹⁵⁹ Patients on GLP-1 receptor agonists do lose muscle mass, as is commonly seen with all forms of weight loss.¹⁶⁰ Serious adverse events include gallbladder and biliary disease, which are believed to be dose-related and result from GLP-1 inhibiting gallbladder emptying through CCK suppression.^{120,140} Contraindications to use of GLP-1 receptor agonists

include medullary thyroid carcinoma, family history of MEN type 2 syndrome, pancreatitis, and relative contraindications include diabetic retinopathy and uncontrolled diabetes.^{161,162}

Given the recent approvals of these anti-obesity medications, providers and patients are undoubtedly concerned about what long-term safety data is available. Human studies have shown these medications are safe, and even protective when patients are followed for up to 5 years.¹⁶³

GIP

GIP acts in synergy with GLP-1 to regulate postprandial insulin secretion.¹⁶⁴ The effect of GIP agonism in obesity is most significant when combined with GLP-1 agonism. GIP-induced inhibition of centrally mediated emesis signals triggered by GLP-1 administration enhances weight loss seen with GLP-1 RA administration.¹⁶⁵ Unlike GLP-1, GIP by itself does not retard gastric emptying.¹⁶⁶

Tirzepatide

The GLP-1/GIP co-agonist, tirzepatide, has shown efficacy for both management of diabetes mellitus and weight loss.¹⁶⁷ The SURMOUNT-1 trial found mean 72-week weight loss up to -20.9% at 15 mg weekly compared to -3.1% with placebo.⁶⁷ Similar results were seen in the 5 SURPASS trials.^{76,168–171}

Tirzepatide was approved by the FDA for weight loss in 2022.^{172,173} Significant benefits for obesity-associated diseases are also being reported (Table 5) including reduced heart failure events at 104 weeks of follow up (hazard ratio [HR] 0.62 compared to placebo),¹¹⁰ improved management of obstructive sleep apnea at 52 weeks,¹¹¹ and improved management of metabolic-dysfunction associated steatohepatitis (MASH) with a decrease of ≥ 1 fibrosis stage with no worsening of MASH at 52 weeks.¹⁰⁷ Side effects of tirzepatide are similar to those of the GLP-1 receptor agonists.^{169,172,173}

Real-World Impacts

Although weight loss is significant in clinical trials of these medications, real-world evidence has shown significant variability in weight loss.¹⁷⁴ Given high costs of these medications, discontinuation rates are as high as 50%, resulting in most real-world studies showing weight loss lower than clinical trials.¹⁷⁴ Desire for these medications led to high levels of compounded formulations, potentially representing increased safety events reported in adverse events reported in Europe.¹⁷⁵

AOMs Under Investigation

With advances in understanding of the incretin system, there has been substantial development of new agents for obesity. Currently there are over 100 agents being investigated in human trials.¹⁷⁶ While each potential agent is beyond the scope of this review, we will focus on selected compounds anticipated for phase 3 trials, grouped by their mechanism of action and detailed in Table 4.

Peripheral Tissue Actors

Bimagrumab

Bimagrumab is a human monoclonal antibody that binds to the activin type II receptor (ActRII), which inhibits ligands which negatively regulate skeletal muscle growth.¹⁷⁷ A single dose of bimagrumab increased lean mass by 2.7% and reduced fat mass by -7.9% at 10 weeks relative to placebo, and improved markers of insulin sensitivity.¹⁷⁸ Bimagrumab also led to significant reductions in fat mass, waist circumference, improved lean mass, and reduced hemoglobin A1C. Side effects include respiratory tract infections (in elderly), rashes, and diarrhea, and muscle spasms.¹⁷⁷

Additional GLP-1 RAs

Oral formulations of GLP-1 RAs with absorption enhancers have been developed, with semaglutide (Rybelsus) currently approved for management of diabetes mellitus.¹⁵⁶ To investigate weight loss, the OASIS trials pursued higher doses of up to 50 mg daily, which led to up to -15.1% body weight loss vs -2.4% in placebo.¹⁷⁹

Orforglipton is a non-peptide oral GLP-1 RA which has completed phase 2 trials and has shown weight reduction ranging from -8.6% to -12.6% along with improved hemoglobin A1C.^{78,180,181} Danuglipron represents another non-peptide oral GLP-1 RA shown to lead to -8% to -13% weight loss after 32 weeks of treatment.¹⁸²

Novel subcutaneous GLP-1 RA competitors are also being investigated. Ecnoglutide (XW03), is in phase 3 trials after phase 2 trials showed up to -14.7% TBWL at 26 weeks (80). GZR18 is a novel GLP-1 injection with bi-weekly dosing in phase 2 trials that has demonstrated up to -17.29% TBWL at 30 weeks (CTR20231695).

Glucagon

Glucagon presents an important target for weight management and metabolism. Excess adiposity causes glucagon resistance, and leads to MASLD by reducing lipid metabolism in the liver.¹⁸³ The glucagon receptor (GCGR) also plays a key role in thermogenesis, or the burning of calories.¹⁸⁴ Thus, changes in the incretin signaling process can drive changes in body composition.

Several GLP-1 and glucagon receptor (GCGR) co-agonists are in development. Phase 3 trials of Mazdutide showed -14.0% TBWL vs 0.3% body weight gain in placebo group at 48 weeks.¹⁸⁵ Survodutide has also demonstrated an average TBWL of -14.9% vs -2.8% on placebo after 46 weeks.¹⁸⁶ Treatment was also associated with improvement in MASH with no worsening of fibrosis after 48 weeks treatment.¹⁸⁷ Phase 3 trials are ongoing to assess survodutide for obesity and MASH.¹⁸⁸

Triple Agonism

Given the additive effect of GCGR agonism to GLP-1 agonism, combining these with GIP agonism presented a novel therapeutic target. One “triple agonist” to GLP-1/GIP/GCGR, retatrutide, is a single peptide conjugated to a fatty diacid moiety that showed a mean TWBL in obesity of -24.2% vs -2.1% in placebo after 48 weeks,⁸⁴ with significant reductions in liver fat after 24 weeks.¹⁸⁹ Adverse events were frequent and most commonly GI related. Phase 3 trials for obesity, diabetes mellitus, and cardiovascular outcomes are currently ongoing.

Amylin

Pramlintide is a synthetic amylin analog approved for management of diabetes with only modest weight loss.¹⁹⁰ Cagrilintide is a long-acting amylin analog administered once-weekly. Phase 2 trials of the combination of cagrilintide and semaglutide (CagriSema) have shown a synergistic effect on TWBL, showing -15.6% in combined treatment vs -5.1% in semaglutide only after 32 weeks.⁸⁵

Comparisons of Different Anti-Obesity Medications

Few studies have evaluated the medications detailed above in head-to-head comparisons, which remains an area of investigation. The STEP-8 RCT found greater weight loss with semaglutide than with liraglutide at 68 weeks (Table 3).⁷⁴

Comparisons of tirzepatide to semaglutide head-to-head remain limited to few studies.^{169,191,192} However, both the randomized clinical trial of Frias et al from 2021¹⁶⁹ and the Bayesian meta-analysis of Ding et al from 2024¹⁹¹ did not evaluate the maximum dose of semaglutide, but rather the 1 mg weekly dosing. Results from the SURMOUNT-5 RCT are anticipated to be available this year and will reflect a direct comparison of tirzepatide 15 mg and semaglutide 2.4 mg weekly.¹⁹³

One head-to-head trial compared orlistat to liraglutide at up to 1 year and found that patients on liraglutide lost -3.8 kg more than those on orlistat.¹⁴⁴

Treatment Adjuncts to Pharmacological Agents in Obesity

A proposed framework for treating obesity is outlined in Figure 4. When starting individuals on anti-obesity treatment, we recommend first starting to ascertain the reasons for which individuals are obese. Readily reversible causes and causative medications should be evaluated and addressed.¹⁹⁴ All patients benefit from dietary and lifestyle modification.⁶⁶ Reducing caloric intake to 1200–1500 or 1500–1800 calories per day for women and men respectively,¹⁹⁵ with incorporation of moderate-intensity exercise of 150 minutes per week.¹⁹⁶ Administration of anti-obesity medications alone, without incorporating lifestyle treatments limits effectiveness and fails to provide the lifelong changes needed to promote weight maintenance.¹⁹⁷ Failing to address the role of dietary changes and exercise adoption when treating obesity would not be within the ethical guidelines of most societies. Medications are not without side effects, and providers must always weigh potential risks and benefits prior to prescription.¹⁹⁸

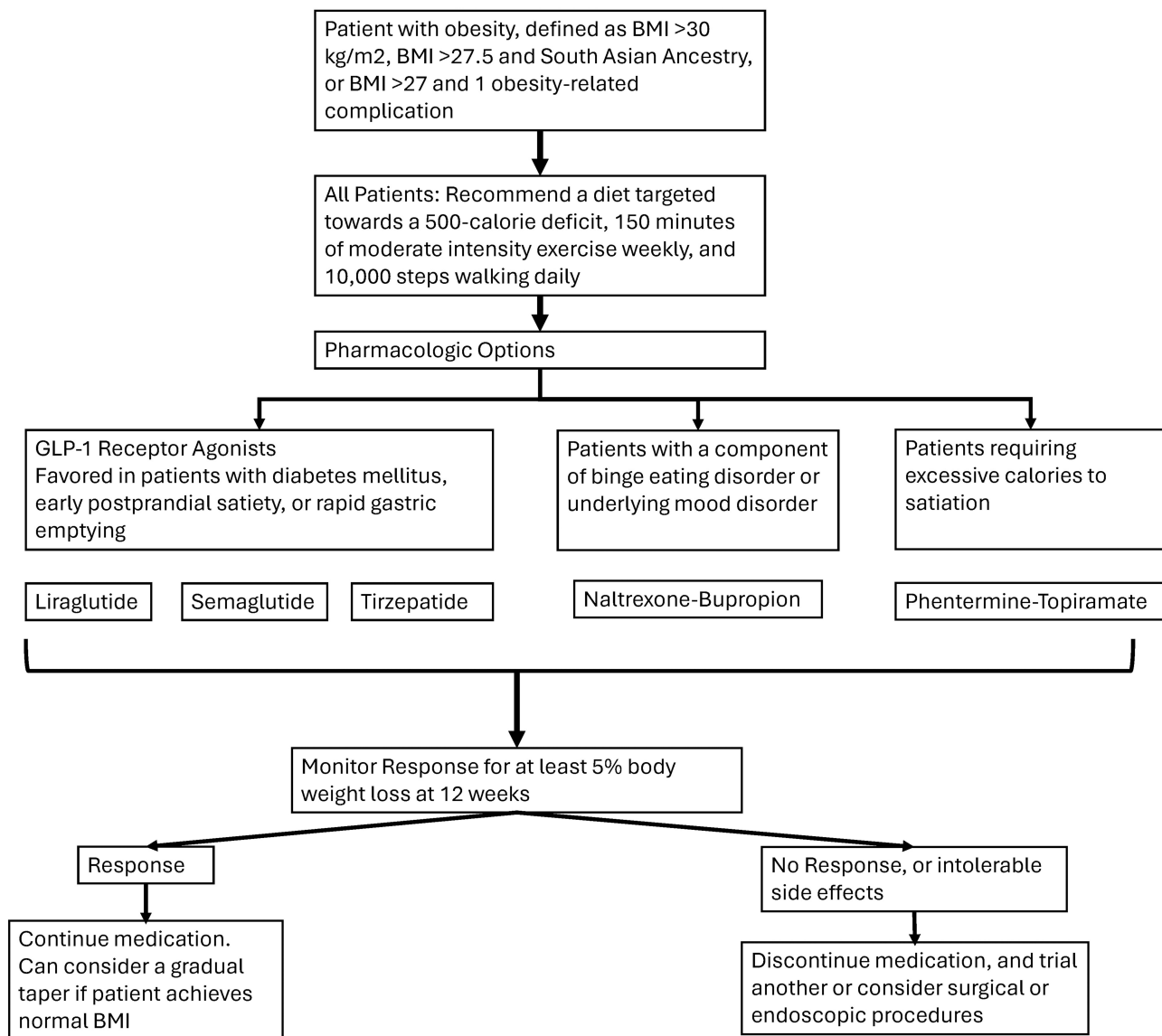


Figure 4 A proposed treatment scheme for anti-obesity medications.

Our practice aims to personalize the treatment for obesity to each patient (Figure 4). Certain patients tend to get hungry quickly after meals, or have abnormal postprandial satiety and may benefit from medications that slow gastrointestinal transit such as the GLP-1 RAs.¹⁹⁹ Those with diabetes also benefit greater from GLP-1 RAs and tirzepatide given the positive effects on insulin sensitivity. Patients who require more calories to feel full at any one meal may benefit from the effects on satiation signaling observed with phentermine-topiramate.²⁰⁰ Individuals with binge-eating traits or anxiety disorders may benefit from NB over other therapies.¹²⁰

Bariatric surgery has been one of the longest-studied treatments for obesity, with up to 25–30% TBWL after Roux-en-Y gastric bypass and 18–20% TBWL after sleeve gastrectomy, and recent research shows that weight regain is associated with increased morbidity and mortality.^{31,201} Endoscopic procedures have presented a novel alternative for weight loss, showing up to 15% TBWL at 1 year.²⁰² The positioning of pharmacologic therapies relative to bariatric and endoscopic procedures remains to be determined.

Assessment of Pharmacologic Response to Selected Strategies

It is important to evaluate treatment response shortly after starting pharmacologic treatment for obesity early to ensure effectiveness. Patients who are likely to demonstrate long-term response to GLP-1 RAs will likely lose a significant amount of weight within the first month.^{203–205}

Patients who fail to lose weight on treatment initiation should be evaluated for side effects, cost, or other factors impairing medication adherence. If side effects are unbearable, or they truly do not respond well it is reasonable to pursue a medication with an alternative pharmacological action.^{206,207}

One important aspect of GLP-1 RA use is weight regain that occurs with stopping the medication.^{75,208,209} Strategies to combat this weight loss include aggressive dietary management, cognitive behavioral therapy, and switching to different anti-obesity medications.^{210–212}

When switching from one once-weekly GLP-1 RA to another, it is ideal to stop the current GLP-1 RA, then begin the new GLP-1 RA one week later. It is recommend to restart the new GLP-1 RA at a reduced dose and titrate to the maximum tolerated dose, since side effects are more likely if starting immediately at the higher dose.²¹³ When switching between GLP-1 RAs, providers should meet with patients within 2–3 months to assess for side effects and monitor for treatment efficacy.

The duration of the use of pharmacological agents including incretin agonists for longer than 68 weeks is not based on clinical trial evidence and requires full discussion between the patient and provider. The risks of weight regain compared to continued incretin agonist use should be evaluated, and dietary and lifestyle modifications should play an instrumental role in preventing weight regain in those who discontinue incretin agonists. Weight loss can also alter pharmacokinetics of many medications, and medication doses may require adjustment in patients receiving these medications.²¹⁴

Economic Analysis of Pharmacotherapy

Many of the newer agents discussed in this review are not without high cost. The cost of novel GLP-1 agonists can be between \$10-20,000 annually. Economic analysis comparing different anti-obesity medications has found inconclusive evidence of cost-effectiveness of semaglutide and liraglutide, with some support suggesting phentermine and orlistat are cost-effective.²¹⁵ When comparing anti-obesity medications to bariatric surgery, multiple analysis have shown that bariatric surgery is more cost-effective than pharmacologic therapies, particularly the GLP-1 RAs.²¹⁶ Additionally, it remains to be determined if reimbursement modules should vary based upon severity of an individual patient's obesity. As further treatments are developed, additional analyses into cost effectiveness are certainly warranted.

Conclusion

The realm of pharmacologic treatments for obesity continues to expand rapidly. With the development of additional incretin agonists, we can expect the range of options for obesity and related comorbidities to improve dramatically. Further investigations are needed to address long-term use of incretin agonists and to provide recommendations for prevention of weight regain.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

- World Health Organization. Obesity and Overweight. 2024. Available from: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>. Accessed September 11, 2025.
- Obesity and severe obesity prevalence in adults: United States, August 2021–August 2023, <https://dx.doi.org/10.15620/cdc/159281>. 2024. Available from: <https://stacks.cdc.gov/view/cdc/159281>. Accessed September 11, 2025.
- Ward ZJ, Bleich SN, Long MW, Gortmaker SL. Association of body mass index with health care expenditures in the United States by age and sex. *PLoS One*. 2021;16(3):e0247307. doi:10.1371/journal.pone.0247307
- Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol*. 2025;13(3):221–262. doi:10.1016/S2213-8587(24)00316-4
- World Health Organization. Obesity: preventing and managing the global epidemic. *World Health Organ Tech Rep Ser*. 2000;894(i–xii):1–253.
- Tan TC. 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
- Cornier M-A, Després J-P, Davis N, et al. Assessing Adiposity. *Circulation*. 2011;124(18):1996–2019. doi:10.1161/CIR.0b013e318233bc6a
- Chaves L, Gonçalves TJM, Bitencourt AGV, Rstom RA, Pereira TR, Velludo SF. Assessment of body composition by whole-body densitometry: what radiologists should know. *Radiol Bras*. 2022;55(5):305–311. doi:10.1590/0100-3984.2021.0155-en
- Zhang QH, Xie LH, Zhang HN, et al. Magnetic resonance imaging assessment of abdominal ectopic fat deposition in correlation with cardiometabolic risk factors. *Front Endocrinol*. 2022;13:820023. doi:10.3389/fendo.2022.820023
- Borga M, West J, Bell JD, et al. Advanced body composition assessment: from body mass index to body composition profiling. *J Invest Med*. 2018;66(5):1–9. doi:10.1136/jim-2018-000722
- Rådholm K, Tengblad A, Dahlén E, et al. The impact of using sagittal abdominal diameter to predict major cardiovascular events in European patients with type 2 diabetes. *Nutr Metab Cardiovasc Dis*. 2017;27(5):418–422. doi:10.1016/j.numecd.2017.02.001
- Kahn HS. Replacing the body mass index with the sagittal abdominal diameter (abdominal height). *Obesity*. 2023;31(11):2720–2722. doi:10.1002/oby.23889
- Potter AW, Chin GC, Looney DP, Friedl KE. Defining overweight and obesity by percent body fat instead of body mass index. *J Clin Endocrinol Metab*. 2024;110(4):e1103–7. doi:10.1210/clinem/dgae341
- Dehghan M, Merchant AT. Is bioelectrical impedance accurate for use in large epidemiological studies? *Nutr J*. 2008;7(1):26. doi:10.1186/1475-2891-7-26
- Reaven GM. Insulin resistance: the link between obesity and cardiovascular disease. *Endocrinol Metab Clinics North Am*. 2008;37(3):581–601. doi:10.1016/j.ecl.2008.06.005
- Karaouzen N, Merzouk H, Aribi M, et al. Effects of the association of aging and obesity on lipids, lipoproteins and oxidative stress biomarkers: a comparison of older with young men. *Nutr Metab Cardiovasc Dis*. 2011;21(10):792–799. doi:10.1016/j.numecd.2010.02.007
- Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365(9468):1415–1428. doi:10.1016/S0140-6736(05)66378-7
- Després J-P, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444(7121):881–887. doi:10.1038/nature05488
- Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM. The metabolic syndrome as predictor of type 2 diabetes: the san antonio heart study. *Diabetes Care*. 2003;26(11):3153–3159. doi:10.2337/diacare.26.11.3153
- Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet*. 2014;384(9945):755–765. doi:10.1016/S0140-6736(14)60892-8
- Renahan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569–578. doi:10.1016/S0140-6736(08)60269-X
- Pillar G, Shehadeh N. Abdominal fat and sleep apnea: the chicken or the egg? *Diabetes Care*. 2008;31(Supplement_2):S303–S309. doi:10.2337/dc08-s272
- Wolk R, Shamsuzzaman AS, Somers VK. Obesity, sleep apnea, and hypertension. *Hypertension*. 2003;42(6):1067–1074. doi:10.1161/01.HYP.0000101686.98973.A3
- Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and nutrition examination survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. *Am J Epidemiol*. 1988;128(1):179–189. doi:10.1093/oxfordjournals.aje.a114939
- Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med*. 2007;175(7):661–666. doi:10.1164/rccm.200611-1717OC
- Hunnskaar S. A systematic review of overweight and obesity as risk factors and targets for clinical intervention for urinary incontinence in women. *Neurol Urodynamics*. 2008;27(8):749–757. doi:10.1002/nau.20635
- Chiu S, Birch DW, Shi X, Sharma AM, Karmali S. Effect of sleeve gastrectomy on gastroesophageal reflux disease: a systematic review. *Surg Obesity Related Dis*. 2011;7(4):510–515. doi:10.1016/j.soard.2010.09.011
- Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67(3):220–229. doi:10.1001/archgenpsychiatry.2010.2

29. Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology*. 2002;123(1):134–140. doi:10.1053/gast.2002.34168
30. Khan SS, Ning H, Wilkins JT, et al. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol*. 2018;3(4):280–287. doi:10.1001/jamacardio.2018.0022
31. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. *Circulation*. 2014;129(25_suppl_2):S102–S138. doi:10.1161/01.cir.0000437739.71477.ee
32. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American heart association. *Circulation*. 2021;143(21):e984–e1010. doi:10.1161/CIR.0000000000000973
33. Acosta A, Camilleri M, Shin A, et al. Quantitative gastrointestinal and psychological traits associated with obesity and response to weight-loss therapy. *Gastroenterology*. 2015;148(3):537–546.e4. doi:10.1053/j.gastro.2014.11.020
34. Freire R. Scientific evidence of diets for weight loss: different macronutrient composition, intermittent fasting, and popular diets. *Nutrition*. 2020;69:110549. doi:10.1016/j.nut.2019.07.001
35. Garvey WT, Mechanick JL, 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;22:1–203. doi:10.4158/EP161365.GL
36. Conaty EA, Denham W, Haggerty SP, Linn JG, Joehl RJ, Ujiki MB. Primary care physicians' perceptions of bariatric surgery and major barriers to referral. *Obes Surg*. 2020;30(2):521–526. doi:10.1007/s11695-019-04204-9
37. Surgery ASfMaB. Estimate of bariatric surgery numbers, 2011–2022. Available from: <https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers/>. Accessed September 11, 2025.
38. Elmaleh-Sachs A, Schwartz JL, Bramante CT, Nicklas JM, Gudzone KA, Jay M. Obesity management in adults: a review. *JAMA*. 2023;330(20):2000–2015. doi:10.1001/jama.2023.19897
39. Melson E, Ashraf U, Papamargaritis D, Davies MJ. What is the pipeline for future medications for obesity? *Int J Obesity*. 2025;49(3):433–451. doi:10.1038/s41366-024-01473-y
40. Lupianez-Merly C, Dilmaghani S, Vosoughi K, Camilleri M. Review article: pharmacologic management of obesity - updates on approved medications, indications and risks. *Aliment Pharmacol Ther*. 2024;59(4):475–491. doi:10.1111/apt.17856
41. Camilleri M. Incretin impact on gastric function in obesity: physiology, and pharmacological, surgical and endoscopic treatments. *J Physiol*. 2024. doi:10.1113/JP287535
42. Sternson SM, Eiselt AK. Three pillars for the neural control of appetite. *Annu Rev Physiol*. 2017;79(1):401–423. doi:10.1146/annurev-physiol-021115-104948
43. Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature*. 2000;404(6778):661–671. doi:10.1038/35007534
44. Campos CA, Bowen AJ, Schwartz MW, Palmiter RD. Parabrachial CGRP neurons control meal termination. *Cell Metab*. 2016;23(5):811–820. doi:10.1016/j.cmet.2016.04.006
45. Petrovich GD, Setlow B, Holland PC, Gallagher M. Amygdalo-hypothalamic circuit allows learned cues to override satiety and promote eating. *J Neurosci*. 2002;22(19):8748–8753. doi:10.1523/jneurosci.22-19-08748.2002
46. Gillis RA, Dezfuli G, Bellusci L, Vicini S, Sahibzada N. Brainstem neuronal circuitries controlling gastric tonic and phasic contractions: a review. *Cell Mol Neurobiol*. 2022;42(2):333–360. doi:10.1007/s10571-021-01084-5
47. Mason BL, Wang Q, Zigman JM. The central nervous system sites mediating the orexigenic actions of ghrelin. *Annu Rev Physiol*. 2014;76(1):519–533. doi:10.1146/annurev-physiol-021113-170310
48. Suzuki K, Simpson KA, Minnion JS, Shillito JC, Bloom SR. The role of gut hormones and the hypothalamus in appetite regulation. *Endocr J*. 2010;57(5):359–372. doi:10.1507/endocrj.K10E-077
49. Coveleskie K, Kilpatrick LA, Gupta A, et al. The effect of the GLP-1 analogue Exenatide on functional connectivity within an NTS-based network in women with and without obesity. *Obesity Sci Pract*. 2017;3(4):434–445. doi:10.1002/osp4.124
50. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest*. 2014;124(10):4473–4488. doi:10.1172/jci75276
51. Shah M, Vella A. Effects of GLP-1 on appetite and weight. *Rev Endocr Metab Disord*. 2014;15(3):181–187. doi:10.1007/s11154-014-9289-5
52. Camilleri M. Peripheral mechanisms in appetite regulation. *Gastroenterology*. 2015;148(6):1219–1233. doi:10.1053/j.gastro.2014.09.016
53. Cypess AM. Reassessing Human Adipose Tissue. *N Engl J Med*. 2022;386(8):768–779. doi:10.1056/NEJMra2032804
54. Taylor EB. The complex role of adipokines in obesity, inflammation, and autoimmunity. *Clin Sci*. 2021;135(6):731–752. doi:10.1042/cs20200895
55. Berne C; Group tOSTdS. A randomized study of orlistat in combination with a weight management programme in obese patients with Type 2 diabetes treated with metformin. *Diabetic Med*. 2005;22(5):612–618. doi:10.1111/j.1464-5491.2004.01474.x
56. Foxcroft DR, Milne R. Orlistat for the treatment of obesity: rapid review and cost-effectiveness model. *Obesity Rev*. 2000;1(2):121–126. doi:10.1046/j.1467-789x.2000.00011.x
57. LeBlanc ES, O'Connor E, Whitlock EP, et al. Effectiveness of primary care-relevant treatments for obesity in adults a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011;155:434–447. doi:10.7326/0003-4819-155-7-201110040-00006
58. 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
59. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity*. 2012;20(2):330–342. doi:10.1038/oby.2011.330
60. 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
61. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595–605. doi:10.1016/S0140-6736(10)60888-4
62. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity*. 2011;19(1):110–120. doi:10.1038/oby.2010.147

63. 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
64. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the scale diabetes randomized clinical trial. *JAMA.* 2015;314(7):687–699. doi:10.1001/jama.2015.9676
65. Kushner RF, Calanna S, Davies M, et al. Semaglutide 2.4 mg for the Treatment of Obesity: key Elements of the STEP Trials 1 to 5. *Obesity.* 2020;28(6):1050–1061. doi:10.1002/oby.22794
66. Grunwald 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
67. 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
68. 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
69. 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
70. Torgerson JS, Hauptman J, Boldrin MN, Sjörström 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
71. Kang JG, Park CY, Kang JH, Park YW, Park SW. Randomized controlled trial to investigate the effects of a newly developed formulation of phentermine diffuse-controlled release for obesity. *Diabetes Obes Metab.* 2010;12(10):876–882. doi:10.1111/j.1463-1326.2010.01242.x
72. 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
73. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity.* 2013;21(5):935–943. doi:10.1002/oby.20309
74. Rubino DM, Greenway FL, Khalid U, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *JAMA.* 2022;327(2):138–150. doi:10.1001/jama.2021.23619
75. 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
76. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. *JAMA.* 2022;327(6):534–545. doi:10.1001/jama.2022.0078
77. Heymsfield SB, Coleman LA, Miller R, et al. Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. *JAMA Network Open.* 2021;4(1):e2033457–e2033457. doi:10.1001/jamanetworkopen.2020.33457
78. Wharton S, Blevins T, Connery L, et al. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. *N Engl J Med.* 2023;389(10):877–888. doi:10.1056/NEJMoa2302392
79. Harris E. Oral semaglutide led to similar weight loss as injection, company says. *JAMA.* 2023;329(23):2011. doi:10.1001/jama.2023.9601
80. Zhu Z, Li Y, Zheng Q, et al. 79-LB: an open-label, active-controlled phase 2 evaluation of novel GLP-1 analog ecnoglutide in adults with obesity. *Diabetes.* 2023;72(Supplement_1). doi:10.2337/db23-79-LB
81. Ji L, Jiang H, Cheng Z, et al. A phase 2 randomised controlled trial of mazdutide in Chinese overweight adults or adults with obesity. *Nat Commun.* 2023;14(1):8289. doi:10.1038/s41467-023-44067-4
82. Aronne L, Harris MS, Roberts MS, et al. Pemvidutide, a GLP-1/glucagon dual receptor agonist, in subjects with overweight or obesity—A 48-week, placebo-controlled, phase 2 (MOMENTUM) trial. *Diabetes.* 2024;73(Supplement_1). doi:10.2337/db24-262-OR
83. Amgen announces robust weight loss with maritide in people living with obesity or overweight at 52 weeks in a Phase 2 study. 2024. Available from: <https://www.amgen.com/newsroom/press-releases/2024/11/amgen-announces-robust-weight-loss-with-maritide-in-people-living-with-obesity-or-overweight-at-52-weeks-in-a-phase-2-study>. Accessed September 11, 2025.
84. Jastreboff AM, Kaplan LM, Frias JP, et al. Triple-hormone-receptor agonist retatrutide for obesity — a phase 2 trial. *N Engl J Med.* 2023;389(6):514–526. doi:10.1056/NEJMoa2301972
85. Frias JP, Deenadayalan S, Erichsen L, et al. Efficacy and safety of co-administered once-weekly cagrilintide 2.4 mg with once-weekly semaglutide 2.4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial. *Lancet.* 2023;402(10403):720–730. doi:10.1016/S0140-6736(23)01163-7
86. Administration USFD. Orlistat (marketed as Alli and Xenical) Information. Available from: <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/orlistat-marketed-alli-and-xenical-information>. Accessed September 11, 2025.
87. Davidson MH, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat randomized controlled trial. *JAMA.* 1999;281(3):235–242. doi:10.1001/jama.281.3.235
88. Rössner S, Sjörström L, Noack R, Meinders AE, Nosedá G; Study obotEOO. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. *Obesity Res.* 2000;8(1):49–61. doi:10.1038/oby.2000.8
89. Sahebkar A, Simental-Mendía LE, Kovanen PT, Pedone C, Simental-Mendía M, Cicero AFG. Effects of orlistat on blood pressure: a systematic review and meta-analysis of 27 randomized controlled clinical trials. *J Am Soc Hypertens.* 2018;12(2):80–96. doi:10.1016/j.jash.2017.12.002
90. Sahebkar A, Simental-Mendía LE, Reiner Ž, et al. Effect of orlistat on plasma lipids and body weight: a systematic review and meta-analysis of 33 randomized controlled trials. *Pharmacol Res.* 2017;122:53–65. doi:10.1016/j.phrs.2017.05.022
91. Broom I, Wilding J, Stott P, Myers N; Group UKMS. Randomised trial of the effect of orlistat on body weight and cardiovascular disease risk profile in obese patients: UK multimorbidity study. *Int J Clin Pract.* 2002;56(7):494–499. doi:10.1111/j.1742-1241.2002.tb11307.x
92. Swinburn BA, Carey D, Hills AP, et al. Effect of orlistat on cardiovascular disease risk in obese adults. *Diabetes Obes Metab.* 2005;7(3):254–262. doi:10.1111/j.1463-1326.2004.00467.x
93. Ardissino M, Vincent M, Hines O, et al. Long-term cardiovascular outcomes after orlistat therapy in patients with obesity: a nationwide, propensity-score matched cohort study. *Eur Heart J Cardiovasc Pharmacother.* 2021;8(2):179–186. doi:10.1093/ehjcvp/pvaa133

94. Pavli P, Triantafyllidou O, Kapantais E, Vlahos NF, Valsamakis G. Infertility improvement after medical weight loss in women and men: a review of the literature. *Int J Mol Sci.* 2024;25(3):1909. doi:10.3390/ijms25031909
95. Hsia DS, Gosselin NH, Williams J, et al. A randomized, double-blind, placebo-controlled, pharmacokinetic and pharmacodynamic study of a fixed-dose combination of phentermine/topiramate in adolescents with obesity. *Diabetes Obes Metab.* 2020;22(4):480–491. doi:10.1111/dom.13910
96. Winokur A, Halseth A, Dybala C, Lam H, Chen S, Chalasani NP. Naltrexone/Bupropion Extended-Release 32 mg/360 mg significantly improves liver enzymes in obese/overweight individuals with elevated liver enzymes. Wiley-Blackwell 111 River St, Hoboken 07030-5774, NJ USA. 2015;1268A.
97. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet.* 2016;387(10019):679–690. doi:10.1016/S0140-6736(15)00803-X
98. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med.* 2017;377(9):839–848. doi:10.1056/NEJMoa1616011
99. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* 2021;9(10):653–662. doi:10.1016/S2213-8587(21)00203-5
100. Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obesity.* 2016;40(8):1310–1319. doi:10.1038/ijo.2016.52
101. Gudbergsen H, Overgaard A, Henriksen M, et al. Liraglutide after diet-induced weight loss for pain and weight control in knee osteoarthritis: a randomized controlled trial. *Am J Clin Nutrition.* 2021;113(2):314–323. doi:10.1093/ajcn/nqaa328
102. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med.* 2021;384(12):1113–1124. doi:10.1056/NEJMoa2028395
103. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med.* 2024;391(2):109–121. doi:10.1056/NEJMoa2403347
104. 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
105. Kosiborod MN, Deanfield J, Pratley R, et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. *Lancet.* 2024;404(10456):949–961. doi:10.1016/s0140-6736(24)01643-x
106. Bliddal H, Bays H, Czernichow S, et al. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. *N Engl J Med.* 2024;391(17):1573–1583. doi:10.1056/NEJMoa2403664
107. Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for metabolic dysfunction–associated steatohepatitis with liver fibrosis. *N Engl J Med.* 2024;391(4):299–310. doi:10.1056/NEJMoa2401943
108. Bosch C, Carriazo S, Soler MJ, Ortiz A, Fernandez-Fernandez B. Tirzepatide and prevention of chronic kidney disease. *Clin Kidney J.* 2022;16(5):797–808. doi:10.1093/ckj/sfac274
109. Chuang M-H, Chen J-Y, Wang H-Y, Jiang Z-H, Wu V-C. Clinical outcomes of tirzepatide or GLP-1 receptor agonists in individuals with type 2 diabetes. *JAMA Network Open.* 2024;7(8):e2427258–e2427258. doi:10.1001/jamanetworkopen.2024.27258
110. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. *N Engl J Med.* 2024;392(5):427–437. doi:10.1056/NEJMoa2410027
111. Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N Engl J Med.* 2024;391(13):1193–1205. doi:10.1056/NEJMoa2404881
112. Ryan D, Bray G. Sibutramine, phentermine, and diethylpropion sympathomimetic drugs in the management of obesity. In: *Handbook of Obesity - Volume 2: Clinical Applications.* 4th ed. London: CRC Press; 2014. doi:10.1201/b16472
113. Baumann MH, Ayestas MA, Dersch CM, Brockington A, Rice KC, Rothman RB. Effects of phentermine and fenfluramine on extracellular dopamine and serotonin in rat nucleus accumbens: therapeutic implications. *Synapse.* 2000;36(2):102–113. doi:10.1002/(sici)1098-2396(200005)36:2<102::Aid-syn3>3.0.Co;2-%23
114. Nelson DL, Gehlert DR. Central nervous system biogenic amine targets for control of appetite and energy expenditure. *Endocrine.* 2006;29(1):49–60. doi:10.1385/ENDO:29:1:49
115. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA.* 2014;311(1):74–86. doi:10.1001/jama.2013.281361
116. Prasad M, El Sabbagh A, Rihal C, Lerman A. Phentermine and coronary vasospasm–induced myocardial infarction. *Mayo Clin Proc.* 2019;94(7):1374–1377. doi:10.1016/j.mayocp.2018.08.029
117. Kim KK, Cho HJ, Kang HC, Youn BB, Lee KR. Effects on weight reduction and safety of short-term phentermine administration in Korean obese people. *Yonsei Med J.* 2006;47(5):614–625. doi:10.3349/ymj.2006.47.5.614
118. Kramer CK, Leitão CB, Pinto LC, Canani LH, Azevedo MJ, Gross JL. Efficacy and safety of topiramate on weight loss: a meta-analysis of randomized controlled trials. *Obesity Rev.* 2011;12(5):e338–e347. doi:10.1111/j.1467-789X.2010.00846.x
119. White HS. Molecular pharmacology of topiramate: managing seizures and preventing migraine. *Headache.* 2005;45(s1):S48–S56. doi:10.1111/j.1526-4610.2005.4501006.x
120. Acosta A, Camilleri M, Abu Dayyeh B, et al. Selection of antiobesity medications based on phenotypes enhances weight loss: a pragmatic trial in an obesity clinic. *Obesity.* 2021;29(4):662–671. doi:10.1002/oby.23120
121. Sinnayah P, Wallingford N, Evans A, Cowley MA. Bupropion and naltrexone interact synergistically to decrease food intake in mice. *Obesity.* 2007;15(9):A179.
122. Greenway FL, Whitehouse MJ, Guttadauria M, et al. Rational design of a combination medication for the treatment of obesity. *Obesity.* 2009;17(1):30–39. doi:10.1038/oby.2008.461
123. Hasegawa H, Meeusen R, Sarre S, Diltoer M, Piacentini MF, Michotte Y. Acute dopamine/norepinephrine reuptake inhibition increases brain and core temperature in rats. *J Appl Physiol.* 2005;99(4):1397–1401. doi:10.1152/japplphysiol.00435.2005
124. Billes SK, Cowley MA. Inhibition of dopamine and norepinephrine reuptake produces additive effects on energy balance in lean and obese mice. *Neuropsychopharmacology.* 2007;32(4):822–834. doi:10.1038/sj.npp.1301155

125. Nissen SE, Wolski KE, Prcela L, et al. Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. *JAMA*. 2016;315(10):990–1004. doi:10.1001/jama.2016.1558
126. Moawad MH-E, Sadeq MA, Abbas A, et al. Efficacy of naltrexone/bupropion in treatment of binge eating: a systematic review and meta-analysis. *Psychiatry Int*. 2024;5(3):323–337. doi:10.3390/psychiatryint5030022
127. Administration USFD. IMCIVREE® (setmelanotide) injection, for subcutaneous use initial U.S. approval: 2020. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213793s007lbl.pdf. Accessed September 11, 2025.
128. Blüher S, Ziotopoulou M, Bullen JW, et al. Responsiveness to peripherally administered melanocortins in lean and obese mice. *Diabetes*. 2004;53(1):82–90. doi:10.2337/diabetes.53.1.82
129. Clément K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol*. 2020;8(12):960–970. doi:10.1016/s2213-8587(20)30364-8
130. Roth CL, Scimia C, Shoemaker AH, et al. Setmelanotide for the treatment of acquired hypothalamic obesity: a phase 2, open-label, multicentre trial. *Lancet Diabetes Endocrinol*. 2024;12(6):380–389. doi:10.1016/s2213-8587(24)00087-1
131. Haqq AM, Chung WK, Dollfus H, et al. Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. *Lancet Diabetes Endocrinol*. 2022;10(12):859–868. doi:10.1016/s2213-8587(22)00277-7
132. Maselli DB, Camilleri M. Effects of GLP-1 and its analogs on gastric physiology in diabetes mellitus and obesity. *Adv Exp Med Biol*. 2021;1307:171–192. doi:10.1007/5584_2020_496
133. Jalleh RJ, Marathe CS, Rayner CK, et al. Physiology and pharmacology of effects of GLP-1-based therapies on gastric, biliary and intestinal motility. *Endocrinology*. 2024;166(1). doi:10.1210/endo/bqae155
134. Verdich C, Flint A, Gutzwiller JP, et al. A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. *J Clin Endocrinol Metab*. 2001;86(9):4382–4389. doi:10.1210/jcem.86.9.7877
135. Larsen PJ, Tang-Christensen M, Holst JJ, Orskov C. Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem. *Neuroscience*. 1997;77(1):257–270. doi:10.1016/s0306-4522(96)00434-4
136. Hayes MR, Bradley L, Grill HJ. Endogenous hindbrain glucagon-like peptide-1 receptor activation contributes to the control of food intake by mediating gastric satiation signaling. *Endocrinology*. 2009;150(6):2654–2659. doi:10.1210/en.2008-1479
137. Zhao S, Kanoski SE, Yan J, Grill HJ, Hayes MR. Hindbrain leptin and glucagon-like-peptide-1 receptor signaling interact to suppress food intake in an additive manner. *Int J Obes Lond*. 2012;36(12):1522–1528. doi:10.1038/ijo.2011.265
138. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368(9548):1696–1705. doi:10.1016/S0140-6736(06)69705-5
139. Halawi H, Khemani D, Eckert D, et al. Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial. *Lancet Gastroenterol Hepatol*. 2017;2(12):890–899. doi:10.1016/s2468-1253(17)30285-6
140. Maselli D, Atieh J, Clark MM, et al. Effects of liraglutide on gastrointestinal functions and weight in obesity: a randomized clinical and pharmacogenomic trial. *Obesity*. 2022;30(8):1608–1620. doi:10.1002/oby.23481
141. Tschöp M, Nogueiras R, Ahrén B. Gut hormone-based pharmacology: novel formulations and future possibilities for metabolic disease therapy. *Diabetologia*. 2023;66(10):1796–1808. doi:10.1007/s00125-023-05929-0
142. Damholt B, Golor G, Wierich W, Pedersen P, Ekblom M, Zdravkovic M. An open-label, parallel group study investigating the effects of age and gender on the pharmacokinetics of the once-daily glucagon-like peptide-1 analogue liraglutide. *J Clin Pharmacol*. 2006;46(6):635–641. doi:10.1177/0091270006288215
143. Astrup A, Rössner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet*. 2009;374(9701):1606–1616. doi:10.1016/s0140-6736(09)61375-1
144. Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes Lond*. 2012;36(6):843–854. doi:10.1038/ijo.2011.158
145. 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
146. Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem*. 2015;58(18):7370–7380. doi:10.1021/acs.jmedchem.5b00726
147. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab*. 2021;46:101102. doi:10.1016/j.molmet.2020.101102
148. 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
149. Bergmann NC, Davies MJ, Lingvay I, Knop FK. Semaglutide for the treatment of overweight and obesity: a review. *Diabetes Obes Metab*. 2023;25(1):18–35. doi:10.1111/dom.14863
150. Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nat Med*. 2022;28(10):2083–2091. doi:10.1038/s41591-022-02026-4
151. Pratley RE, Tuttle KR, Rossing P, et al. Effects of semaglutide on heart failure outcomes in diabetes and chronic kidney disease in the flow trial. *J Am Coll Cardiol*. 2024;84(17):1615–1628. doi:10.1016/j.jacc.2024.08.004
152. Deanfield J, Verma S, Scirica BM, et al. Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial. *Lancet*. 2024;404(10454):773–786. doi:10.1016/s0140-6736(24)01498-3
153. Kittipibul V, Mentz RJ. Effects of GLP-1 receptor agonists on heart failure outcomes. *J Am College Cardiol*. 2024;84(17):1629–1631. doi:10.1016/j.jacc.2024.08.016
154. Khan MS, Fonarow GC, McGuire DK, et al. Glucagon-like peptide 1 receptor agonist and heart failure. *Circulation*. 2020;142(12):1205–1218. doi:10.1161/CIRCULATIONAHA.120.045888
155. Davies M, Pieber TR, Hartoft-Nielsen M-L, Hansen OKH, Jabbour S, Rosenstock J. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA*. 2017;318(15):1460–1470. doi:10.1001/jama.2017.14752

156. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. *Diabetes Care*. 2019;42(9):1724–1732. doi:10.2337/dc19-0749
157. Bruns Vi N, Tressler EH, Vendruscolo LF, Leggio L, Farokhnia M. IUPHAR review – glucagon-like peptide-1 (GLP-1) and substance use disorders: an emerging pharmacotherapeutic target. *Pharmacol Res*. 2024;207:107312. doi:10.1016/j.phrs.2024.107312
158. Long B, Pelletier J, Koefman A, Bridwell RE. GLP-1 agonists: a review for emergency clinicians. *Am J Emergency Med*. 2024;78:89–94. doi:10.1016/j.ajem.2024.01.010
159. Sikirica MV, Martin AA, Wood R, Leith A, Piercy J, Higgins V. Reasons for discontinuation of GLP1 receptor agonists: data from a real-world cross-sectional survey of physicians and their patients with type 2 diabetes. *Diabetes Metab Syndr Obes*. 2017;10:403–412. doi:10.2147/dmso.S141235
160. Linge J, Birkenfeld AL, Neeland IJ. Muscle mass and glucagon-like peptide-1 receptor agonists: adaptive or maladaptive response to weight loss? *Circulation*. 2024;150(16):1288–1298. doi:10.1161/CIRCULATIONAHA.124.067676
161. Bezin J, Gouverneur A, Pénichon M, et al. GLP-1 receptor agonists and the risk of thyroid cancer. *Diabetes Care*. 2022;46(2):384–390. doi:10.2337/dc22-1148
162. Marso SP, Bain SC, Consoi A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834–1844. doi:10.1056/NEJMoa1607141
163. Huang YN, Liao WL, Huang JY, et al. Long-term safety and efficacy of glucagon-like peptide-1 receptor agonists in individuals with obesity and without type 2 diabetes: a global retrospective cohort study. *Diabetes Obes Metab*. 2024;26(11):5222–5232. doi:10.1111/dom.15869
164. Hayes MR, Borner T, De Jonghe BC. The role of GIP in the regulation of GLP-1 satiety and nausea. *Diabetes*. 2021;70(9):1956–1961. doi:10.2337/dbi21-0004
165. Borner T, Geisler CE, Fortin SM, et al. GIP receptor agonism attenuates GLP-1 receptor agonist-induced nausea and emesis in preclinical models. *Diabetes*. 2021;70(11):2545–2553. doi:10.2337/db21-0459
166. Meier JJ, Goetze O, Anstipp J, et al. Gastric inhibitory polypeptide does not inhibit gastric emptying in humans. *Am J Physiol Endocrinol Metab*. 2004;286(4):E621–5. doi:10.1152/ajpendo.00499.2003
167. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet*. 2018;392(10160):2180–2193. doi:10.1016/S0140-6736(18)32260-8
168. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet*. 2021;398(10300):583–598. doi:10.1016/S0140-6736(21)01443-4
169. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;385(6):503–515. doi:10.1056/NEJMoa2107519
170. 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
171. Rosenstock J, Wysham C, Frias JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet*. 2021;398(10295):143–155. doi:10.1016/s0140-6736(21)01324-6
172. Administration USFD. MOUNJAROTM (tirzepatide) Injection, for subcutaneous use initial U.S. Approval: 2022. 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215866s000lbl.pdf. Accessed September 11, 2025.
173. Administration USFD. ZEPBOUND™ (tirzepatide) Injection, for subcutaneous use Initial U.S. Approval: 2022. 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217806s000lbl.pdf. Accessed September 11, 2025.
174. Thomsen RW, Mailhac A, Løhde JB, Pottegård A. Real-world evidence on the utilization, clinical and comparative effectiveness, and adverse effects of newer GLP-1RA-based weight-loss therapies. *Diabetes Obes Metab*. 2025;27 Suppl 2(Suppl 2):66–88. doi:10.1111/dom.16364
175. Raičević BB, Belančić A, Mirković N, Janković SM. Analysis of reporting trends of serious adverse events associated with anti-obesity drugs. *Pharmacol Res Perspectives*. 2025;13(2):e70080. doi:10.1002/prp2.70080
176. Dolgin E. Dozens of new obesity drugs are coming: these are the ones to watch. *Nature*. 2025;638(8050):308–310. doi:10.1038/d41586-025-00404-9
177. Rooks D, Petricoul O, Praetstgaard J, Bartlett M, Laurent D, Roubenoff R. Safety and pharmacokinetics of bimagrumab in healthy older and obese adults with body composition changes in the older cohort. *J Cachexia Sarcopenia Muscle*. 2020;11(6):1525–1534. doi:10.1002/jcsm.12639
178. Garito T, Roubenoff R, Hompesch M, et al. Bimagrumab improves body composition and insulin sensitivity in insulin-resistant individuals. *Diabetes Obes Metab*. 2018;20(1):94–102. doi:10.1111/dom.13042
179. 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
180. Nauck MA, Horowitz M. Non-peptide, once-per-day oral orforglipron to compete with established peptide-based, injectable GLP-1 receptor agonists. *Lancet*. 2023;402(10400):429–431. doi:10.1016/S0140-6736(23)01201-1
181. Frias JP, Hsia S, Eyde S, et al. Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study. *Lancet*. 2023;402(10400):472–483. doi:10.1016/S0140-6736(23)01302-8
182. Saxena AR, Frias JP, Brown LS, et al. Efficacy and safety of oral small molecule glucagon-like peptide 1 receptor agonist danuglipron for glycemic control among patients with type 2 diabetes: a randomized clinical trial. *JAMA Network Open*. 2023;6(5):e2314493–e2314493. doi:10.1001/jamanetworkopen.2023.14493
183. McGlone ER, Bloom SR, Tan TM. Glucagon resistance and metabolic-associated steatotic liver disease: a review of the evidence. *J Endocrinol*. 2024;261(3). doi:10.1530/joe-23-0365
184. Conceição-Furber E, Coskun T, Sloop KW, Samms RJ. Is glucagon receptor activation the thermogenic solution for treating obesity? *Front Endocrinol*. 2022;13:868037. doi:10.3389/fendo.2022.868037
185. Innovent presents the results of the first phase 3 study of mazdutide for weight management at the ADA's 84th scientific sessions. 2024. Available from: <https://www.prnewswire.com/news-releases/innovent-presents-the-results-of-the-first-phase-3-study-of-mazdutide-for-weight-management-at-the-adas-84th-scientific-sessions-302180995.html>. Accessed September 11, 2025.

186. le Roux CW, Steen O, Lucas KJ, Startseva E, Unsel A, Hennige AM. Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial. *Lancet Diabetes Endocrinol.* 2024;12(3):162–173. doi:10.1016/S2213-8587(23)00356-X
187. Sanyal AJ, Bedossa P, Fraessdorf M, et al. A Phase 2 randomized trial of survodutide in MASH and fibrosis. *N Engl J Med.* 2024;391(4):311–319. doi:10.1056/NEJMoa2401755
188. Boehringer receives U.S. FDA breakthrough therapy designation and initiates two Phase III trials in MASH for survodutide. 2024. Available from: <https://www.boehringer-ingenheim.com/human-health/metabolic-diseases/survodutide-us-fda-breakthrough-therapy-phase-3-trials-mash>. Accessed September 11, 2025.
189. Sanyal AJ, Kaplan LM, Frias JP, et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. *Nature Med.* 2024;30(7):2037–2048. doi:10.1038/s41591-024-03018-2
190. Ryan G, Briscoe TA, Jobe L. Review of pramlintide as adjunctive therapy in treatment of type 1 and type 2 diabetes. *Drug Des Devel Ther.* 2009;2:203–214. doi:10.2147/dddt.s3225
191. Ding Y, Shi Y, Guan R, et al. Evaluation and comparison of efficacy and safety of tirzepatide and semaglutide in patients with type 2 diabetes mellitus: a Bayesian network meta-analysis. *Pharmacol Res.* 2024;199:107031. doi:10.1016/j.phrs.2023.107031
192. Rodriguez PJ, Goodwin Cartwright BM, Gratzl S, et al. Semaglutide vs tirzepatide for weight loss in adults with overweight or obesity. *JAMA Intern Med.* 2024;184(9):1056–1064. doi:10.1001/jamainternmed.2024.2525
193. Lilly's tirzepatide superior to Wegovy® (semaglutide) in head-to-head trial showing an average weight loss of 20.2% vs. 13.7%. 2024. Available from: <https://www.lilly.com/en-CA/news/press-releases/2024.12.4-tirzepatide-surmount-5-h2h>. Accessed September 11, 2025.
194. Allen G, Safranek SM. Secondary causes of obesity. *Am Family Phys.* 2011;83(8):972.
195. Acosta A, Streett S, Kroh MD, et al. White paper AGA: POWER — practice guide on obesity and weight management, education, and resources. *Clin Gastroenterol Hepatol.* 2017;15(5):631–649.e10. doi:10.1016/j.cgh.2016.10.023
196. Radić J, Belančić A, Đogaš H, et al. The power of movement: linking physical activity with nutritional health and blood sugar balance in a dalmatian type 2 diabetic population. *Nutrients.* 2025;17(1):187. doi:10.3390/nu17010187
197. Mozaffarian D, Agarwal M, Aggarwal M, et al. Nutritional priorities to support GLP-1 therapy for obesity: a joint advisory from the American college of lifestyle medicine, the American Society for Nutrition, the Obesity Medicine Association, and the Obesity Society. *Obesity.* 2025;n/a(n/a):100181. doi:10.1002/oby.24336
198. Rieder M, Belančić A. Past, present and future of drug safety: editorial. *Br J Clin Pharmacol.* 2024;90(8):1760–1762. doi:10.1111/bcp.16140
199. Gonzalez-Izundegui D, Campos A, Calderon G, et al. Association of gastric emptying with postprandial appetite and satiety sensations in obesity. *Obesity.* 2021;29(9):1497–1507. doi:10.1002/oby.23204
200. Cifuentes L, Ghun W, Feris F, et al. Phenotype tailored lifestyle intervention on weight loss and cardiometabolic risk factors in adults with obesity: a single-center, non-randomised, proof-of-concept study. *EClinicalMedicine.* 2023;58:101923. doi:10.1016/j.eclinm.2023.101923
201. Carlsson LMS, Arnetorp I, Andersson-Assarsson JC, et al. Health outcomes and their association with weight regain after substantial weight loss in Sweden: a prospective cohort study. *Lancet Reg Health Eur.* 2025;52:101261. doi:10.1016/j.lanepe.2025.101261
202. Štimac D, Klojučar Majanović S, Belančić A. Endoscopic Treatment of Obesity: from Past to Future. *Dig Dis.* 2020;38(2):150–162. doi:10.1159/000505394
203. Maccora C, Ciouli C, Goracci A, et al. One month weight loss predicts the efficacy of liraglutide in obese patients: data from a single center. *Endocr Pract.* 2020;26(2):235–240. doi:10.4158/EP-2019-0169
204. Sannaa W, Dilmaghani S, BouSaba J, et al. Factors associated with successful weight loss after liraglutide treatment for obesity. *Diabetes Obes Metab.* 2023;25(2):377–386. doi:10.1111/dom.14880
205. Acosta A, Camilleri M, Burton D, et al. Exenatide in obesity with accelerated gastric emptying: a randomized, pharmacodynamics study. *Physiol Rep.* 2015;3(11):e12610. doi:10.14814/phy2.12610
206. Lautenbach A, Wernecke M, Huber TB, et al. The potential of semaglutide once-weekly in patients without type 2 diabetes with weight regain or insufficient weight loss after bariatric surgery—a retrospective analysis. *Obesity Surg.* 2022;32(10):3280–3288. doi:10.1007/s11695-022-06211-9
207. Mok J, Adeleke MO, Brown A, et al. Safety and efficacy of liraglutide, 3.0 mg, once daily vs placebo in patients with poor weight loss following metabolic surgery: the bari-OPTIMISE randomized clinical trial. *JAMA Surg.* 2023;158(10):1003–1011. doi:10.1001/jamasurg.2023.2930
208. Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab.* 2022;24(8):1553–1564. doi:10.1111/dom.14725
209. Jensterle M, Ferjan S, Janez A. The maintenance of long-term weight loss after semaglutide withdrawal in obese women with PCOS treated with metformin: a 2-year observational study. *Front Endocrinol.* 2024;15:1366940. doi:10.3389/fendo.2024.1366940
210. Werrij MQ, Jansen A, Mulkens S, Elgersma HJ, Ament AJ, Hospers HJ. Adding cognitive therapy to dietetic treatment is associated with less relapse in obesity. *J Psychosom Res.* 2009;67(4):315–324. doi:10.1016/j.jpsychores.2008.12.011
211. Paddu NU, Lawrence B, Wong S, Poon SJ, Srivastava G. Weight maintenance on cost-effective antiobesity medications after 1 year of GLP-1 receptor agonist therapy: a real-world study. *Obesity.* 2024;32(12):2255–2263. doi:10.1002/oby.24177
212. Jensen SBK, Janus C, Lundgren JR, et al. Exploratory analysis of eating- and physical activity-related outcomes from a randomized controlled trial for weight loss maintenance with exercise and liraglutide single or combination treatment. *Nat Commun.* 2022;13(1):4770. doi:10.1038/s41467-022-32307-y
213. Almandoz JP, Lingvay I, Morales J, Campos C. Switching between glucagon-like peptide-1 receptor agonists: rationale and practical guidance. *Clin Diabetes.* 2020;38(4):390–402. doi:10.2337/cd19-0100
214. Belančić A, Al-Sallami HS. Spotlight commentary: changes in pharmacokinetics following significant weight loss. *Br J Clin Pharmacol.* 2025;91(3):678–680. doi:10.1111/bcp.16401
215. Finkelstein EA, Chodavadia PA, Strombotne K. A systematic review of the economic value proposition for commercially available nonsurgical weight-loss interventions. *Obesity.* 2023;31(7):1725–1733. doi:10.1002/oby.23760
216. Lauren BN, Lim F, Krikhely A, et al. Estimated cost-effectiveness of medical therapy, sleeve gastrectomy, and gastric bypass in patients with severe obesity and type 2 diabetes. *JAMA Network Open.* 2022;5(2):e2148317. doi:10.1001/jamanetworkopen.2021.48317

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