

An Overview of Existing and Emerging Weight-Loss Drugs to Target Obesity-Related Complications: Insights from Clinical Trials

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Abstract

Obesity requires treatment as it is associated with health problems such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular diseases, and some cancers, which increase mortality rates. Achieving sufficient weight loss to reduce obesity-related diseases requires a variety of interventions, including comprehensive lifestyle modification of diet and exercise, change in behavior, anti-obesity medications, and surgery. To date, anti-obesity agents with various mechanisms of action have been developed, and mostly reduce energy intake, resulting in weight loss of about 5% to 10% compared to baseline. Recently developed drugs and those currently under development have been shown to reduce body weight by more than 10% and are expected to reduce obesity-related complications. This article summarizes existing and emerging anti-obesity medications, with a particular focus on those evaluated in clinical trials.

Key Words: Obesity, Anti-obesity agents, Weight loss, Clinical trial

INTRODUCTION

The prevalence of obesity is increasing globally: the World Health Organization estimates that obesity more than doubled between 1990 and 2020, with 890 million people living with obesity in 2020 (World Health Organization, 2024). Obesity is associated with several health related problems. People with obesity are at an increased risk for comorbidities stemming from metabolic abnormalities, such as hypertension, cardiovascular disease, type 2 diabetes mellitus (T2DM), dyslipidemia, metabolic syndrome, gallbladder disease, gout, and some types of cancer. They are also at higher risk of developing weight-related conditions such as arthritis, low back pain, and obstructive sleep apnea than normal-weight individuals. Therefore, the goal of obesity treatment is not exclusively centered on achieving weight loss, but rather on reducing the risk of obesity-related diseases and improving overall health. Specifically, weight loss of 5% to 10%, along with improvements in lifestyle, has clinically significant benefits in achieving these goals. Therefore, guidelines recommend that obese individuals lose 5% to 10% of their initial body weight within 6 months of starting a weight-loss intervention (Kim *et al.*, 2023). If patients with a BMI ≥ 30 kg/m² (or ≥ 25 kg/m² for certain ethnici-

ties, including Koreans) fail to lose weight through diet, physical activity, and behavior counseling, the use of anti-obesity medications can be considered (Garvey *et al.*, 2016; Kim *et al.*, 2023). However, if the use of an anti-obesity drug does not result in the loss of >5% body mass within 3 months, then the drug should be changed or discontinued (Kim *et al.*, 2023).

Given the increasing prevalence of obesity and the need for effective medications to promote weight loss and improve the overall health of people with obesity, this article sought to review the clinical trial-based evidence for existing therapies, as well as to highlight emerging therapies and ongoing trials that may influence the way obesity and obesity-related diseases are treated in the future.

ANTI-OBESITY MEDICATIONS CURRENTLY IN USE

Although many anti-obesity medications have been developed, several have been withdrawn because of adverse events (Wen *et al.*, 2022). Currently available long-term anti-obesity medications for adults include orlistat, naltrexone/bupropion (NAL/BUP) extended release (ER), liraglutide, phen-termine/topiramate ER, semaglutide, and tirzepatide (Table

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Table 1. Anti-obesity medication currently in-use for long term management

Drugs - Clinical trial	Mechanism	BW change from baseline (%)	
		Intervention	Placebo
Orlistat – XENDOS (Torgerson <i>et al.</i> , 2004)	Reversible inhibitor of lipases	–6.9	–4.1
Naltrexone/bupropion extended release – COR-1 (Greenway <i>et al.</i> , 2010)	Naltrexone: an opioid receptor antagonist	–6.1	–1.3
	Bupropion: a dopamine and norepinephrine reuptake inhibitor		
Phentermine/topiramate ER - EQUIP (Allison <i>et al.</i> , 2012)	Phentermine: a centrally acting sympathomimetic	–10.9	–1.6
	Topiramate: a gamma-aminobutyric acid agonist, glutamate antagonist, and carbonic anhydrase inhibitor		
Liraglutide - SCLAE (Pi-Sunyer <i>et al.</i> , 2015)	GLP-1 receptor agonist	–8.0	–2.6
Semaglutide - STEP (Wilding <i>et al.</i> , 2021)	GLP-1 receptor agonist	–14.9	–2.4
Tirzepatide - SURMOUNT (Jastreboff <i>et al.</i> , 2022)	GLP-1/GIP receptor agonist	–20.9	–3.1

ER, extended release; GLP-1, Glucagon-like peptide-1; GIP, Glucose-dependent insulinotropic polypeptide.

1). Short-term treatment options include phentermine, diethylpropion, phendimetrazine, and mazindol (Jeon *et al.*, 2023). However, evidence suggests that short-term treatment (3 to 6 months) with weight-loss medications does not produce long-term health benefits (Garvey *et al.*, 2016); therefore, this review focuses on long-term weight-loss anti-obesity medications.

Orlistat

Orlistat was approved for long-term weight management by the Food and Drug Administration (FDA) in 1999 and the Korea Ministry of Food and Drug Safety in 2000 (Jeon *et al.*, 2023). It is a reversible inhibitor of lipases, which exerts its therapeutic activity in the lumen of the stomach and the small intestine by binding covalently to the active serine residue site of gastric and pancreatic lipases. This results in the partial inhibition of triglyceride hydrolysis; undigested triglycerides are then excreted in feces (Guercioli, 1997). Orlistat inhibits approximately 30% of dietary fat absorption. The recommended therapeutic dosage is 120 mg taken three times a day (Jeon *et al.*, 2023).

In the 4-year XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) trial, the orlistat group achieved a 6.9% reduction in body weight compared with a 4.1% reduction in the placebo group at the end of the study. In addition, the incidence of T2DM was 45% lower in the orlistat group than in the placebo group over 4 years (Torgerson *et al.*, 2004). Common adverse events are gastrointestinal symptoms such as stool incontinence, oily stool, and fatty stool, with frequency rates ranging from 15% to 30% in most studies (Padwal *et al.*, 2004). Supplementation with multivitamins is recommended to compensate for the potential malabsorption of fat-soluble vitamins with orlistat therapy (Jeon *et al.*, 2023).

Naltrexone/bupropion (NAL/BUP) extended release (ER)

Bupropion (BUP) is a dopamine and norepinephrine reuptake inhibitor known for its role in the management of depression and smoking cessation. Its weight loss effects likely result from a combined dopaminergic and noradrenergic effect on proopiomelanocortin signaling; however, when administered alone, BUP's weight loss benefits are modest. Naltrexone (NAL) is an opioid receptor antagonist approved as a treat-

ment for opioid dependency and alcohol dependence. NAL monotherapy also has minimal weight loss effects; however, when combined with other weight-loss drugs, it prevents the classic weight loss plateau observed with monotherapies (such as BUP) by blocking β -endorphin-mediated proopiomelanocortin autoinhibition (Greenway *et al.*, 2009). This makes NAL an attractive combination therapy for obesity (Greenway *et al.*, 2009). The NAL/BUP combination was approved by the FDA in 2014 and by the Korea Ministry of Food and Drug Safety in 2016 (Jeon *et al.*, 2023).

One clinical trial reported 1.3% weight loss in the placebo group and 6.1% weight loss after NAL/BUP administration at a dose of 32 mg for 56 weeks. The most frequent adverse events associated with NAL/BUP administration were gastrointestinal symptoms such as nausea, especially during dose escalation; this was transient and generally mild to moderate in intensity. Headaches, constipation, dizziness, vomiting, and dry mouth were also frequent in the NAL/BUP group. Combination treatment was not associated with increased depression or suicidality events compared with placebo (Greenway *et al.*, 2010).

Phentermine/topiramate ER

Phentermine is a centrally acting sympathomimetic that enhances the release of serotonin, norepinephrine, and dopamine (Pilitsi *et al.*, 2019). It was approved in 1959 for short-term obesity treatment at a dose of 15.0 to 37.5 mg/day (Gadde *et al.*, 2011). Topiramate is a gamma-aminobutyric acid agonist, glutamate antagonist, and carbonic anhydrase inhibitor; it is a drug used for epilepsy treatment and migraine prophylaxis (Pilitsi *et al.*, 2019). In addition, topiramate has weight loss effects caused by an incompletely understood mechanism; however, dose-dependent adverse neuropsychiatric events such as depression limit its use as a single agent for weight loss (Allison *et al.*, 2012). Multiple neuronal and peripheral pathways are implicated in the regulation of food intake, satiety, and energy homeostasis. If only one pathway is targeted, as in monotherapy, this can lead to the occurrence of compensatory mechanisms, which reduces drug efficacy; the use of phentermine/topiramate as a combined therapy can overcome these compensatory mechanisms. The maximum dose of phentermine/topiramate ER is 15 mg of phentermine

and 92 mg of topiramate; these doses are lower than those marketed or studied as monotherapies in obesity (Allison *et al.*, 2012). The EQUIP study reported 10.9% body weight loss with the maximum dose of phentermine/topiramate ER, compared to 1.6% with placebo, while the CONQUER study, which included individuals with T2DM, reported 1.2% body weight loss in the individuals assigned to placebo and 9.8% body weight loss with the maximum dose (Gadde *et al.*, 2011). Common adverse events associated with phentermine/topiramate ER administration were paresthesia, dry mouth, constipation, dysgeusia, insomnia, depression, and anxiety. In addition, phentermine/topiramate ER increases heart rate, might affect renal function, and may lead to the development of metabolic acidosis and nephrolithiasis; therefore, monitoring heart rate, electrolytes, and creatinine is needed when administering this therapy (Pilitsi *et al.*, 2019). Phentermine/topiramate ER is contraindicated in pregnancy, uncontrolled hypertension, cardiovascular disease, chronic kidney disease, glaucoma, hyperthyroidism, and in patients on monoamine oxidase inhibitors (Pilitsi *et al.*, 2019).

Liraglutide

Glucagon-like peptide-1 (GLP-1), an incretin peptide, is synthesized in and secreted from enteroendocrine L cells. Its release increases rapidly after the ingestion of nutrients including carbohydrates, fats, and proteins. GLP-1 potentiates insulin release and suppresses glucagon release in a glucose-dependent manner (Campbell and Drucker, 2013; Bailey, 2021). In addition, it delays gastric emptying and modulates central hunger-satiety controls, which, in turn, create a feeling of fullness, reduce food intake, and promote weight loss (Bailey, 2021). As a result, GLP-1 receptor agonists (RAs) are an attractive target in the development of drugs for obesity and diabetes.

Liraglutide is a GLP-1RA with 97% homology to human GLP-1. It has a substitution of lysine for arginine at position 34 and palmitic acid conjugated via a glutamate spacer to lysine at position 26 (Meier, 2012). It was approved for chronic weight management in adults in December 2014 and in patients aged 12 and older in December 2020 by the FDA. The Satiety and Clinical Adiposity-Liraglutide (SCALE) Obesity and Prediabetes study was a key trial in determining liraglutide efficacy. The results demonstrated significant body weight

reductions in individuals taking liraglutide at a dose of 3 mg compared with those taking the placebo (8.0% vs. 2.6%); in addition, more people in the liraglutide group achieved a $\geq 5\%$ reduction in body weight than in the placebo group (63.2% vs. 27.1%). The most frequently reported adverse events were nausea and diarrhea, which were mild or moderate (Pi-Sunyer *et al.*, 2015). A 3-year follow-up study of the SCALE Obesity and Prediabetes study showed that more individuals from the liraglutide group than from the placebo group sustained their weight loss long term (le Roux *et al.*, 2017).

Semaglutide

Semaglutide is a GLP-1RA with 94% structural homology to native human GLP-1 (Lau *et al.*, 2015). Modifications include acylation of the peptide backbone with a spacer, conjugation of a C18 fatty di-acid chain to lysine at position 26, and an amino acid substitution at position 8. These modifications extend the half-life to approximately 1 week in humans, which enables once-weekly administration (Marbury *et al.*, 2017).

The Semaglutide Treatment Effect in People with Obesity (STEP) program was designed to comprehensively explore the efficacy of once-weekly subcutaneous semaglutide administration (2.4 mg) in people with overweight or obesity and consists of eight different trials (Bergmann *et al.*, 2023) (Table 2). The STEP 1 study was a 68-week trial that evaluated the efficacy and safety of semaglutide, as an adjunct to lifestyle intervention, on reducing body weight and other related endpoints including waist circumference, blood pressure, quality of life and body composition in adults with overweight or obesity without T2DM. Participants who received semaglutide 2.4 mg had a mean weight loss of 14.9%, while weight loss $\geq 5\%$ was achieved by 86%-89% of participants; participants who received the placebo had a mean weight loss of 2.4% (Wilding *et al.*, 2021). The STEP 2 trial (Davies *et al.*, 2021) was conducted in people with obesity and T2DM; the mean weight loss was 9.6% with semaglutide and 3.4% weight loss with placebo and 69% of participants with semaglutide achieved weight loss $\geq 5\%$. The STEP 6 (Kadowaki *et al.*, 2022) and STEP 7 trials (Mu *et al.*, 2024) were conducted in Asian populations and included people with T2DM; they demonstrated a mean weight loss of 13.2% and 12.1% in semaglutide and 2.1% and 3.6% in placebo, respectively. More of the population achieved $\geq 5\%$ weight loss (83%) than STEP 2 trials (67%).

Table 2. The Semaglutide Treatment Effect in People with Obesity (STEP) programs

Conditions		Comparator	BW change from baseline (%)	
			Semaglutide	Placebo
STEP 1 (Wilding <i>et al.</i> , 2021)	Obesity	Placebo	-14.9	-2.4
STEP 3 (Wadden <i>et al.</i> , 2021)	Obesity	Placebo	-16	-5.7
STEP 4 (Rubino <i>et al.</i> , 2021)	Obesity	Placebo	-14.4	6.9
STEP 5 (Garvey <i>et al.</i> , 2022)	Obesity	Placebo	-15.2	-2.6
STEP 8 (Rubino <i>et al.</i> , 2022)	Obesity	Liraglutide	-15.8	Liraglutide: -6.4
		Placebo		Placebo: -1.9
STEP 2 (Davies <i>et al.</i> , 2021)	Obesity and T2DM	Placebo	-9.6	-3.4
STEP 6 (Kadowaki <i>et al.</i> , 2022)	Obesity and T2DM	Asian	1.7 mg: -9.6	-2.1
			2.4 mg: -13.2	
STEP 7 (Mu <i>et al.</i> , 2024)	Obesity and T2DM	Asian	-12.1	-3.6

BW, body weight; T2DM, type 2 diabetes mellitus.

Secondary endpoint results from the STEP trials indicated improvement in cardiometabolic risk factors, including waist circumference, blood pressure, lipids, and C-reactive protein with semaglutide administered at a dose of 2.4 mg, as well as benefits on physical function and quality of life. Improvements in body composition were observed by dual-energy X-ray absorptiometry in STEP 1, while reductions in visceral fat areas were observed in a subpopulation of participants assessed by computed tomography in STEP 6. In addition, glycemic status shifted from prediabetes to normoglycemia in people receiving semaglutide. The most common adverse events experienced with semaglutide were gastrointestinal events; similar to other GLP-1 RAs, these were transient and mild or moderate in severity.

The significant weight reduction and improved metabolic parameters observed with semaglutide administration would be expected to result in the reduction of adverse cardiovascular outcomes. The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial (Lincoff *et al.*, 2023) was a randomized, placebo-controlled trial. It tested whether, when added to standard care, semaglutide was superior to placebo in reducing the risk of major adverse cardiovascular events among patients with overweight or obesity and preexisting cardiovascular disease who did not have T2DM. The primary cardiovascular endpoint was a composite of death from cardiovascular causes, non-fatal myocardial infarction, and nonfatal stroke in a time-to-first-event analysis. The mean duration of semaglutide 2.4 mg administration was 34.2 ± 13.7 months; the mean duration of follow-up was 39.8 ± 9.4 months. In the semaglutide group, the primary cardiovascular endpoint incidence was 20% lower than in the placebo group, which was a statistically significant effect (Lincoff *et al.*, 2023). Semaglutide also has a beneficial effect on heart failure and kidneys. Semaglutide 2.4 mg reduced the physical limitations and improved exercise function compared with placebo (Kosiborod *et al.*, 2023, 2024); semaglutide 1.0 mg delayed the progression of diabetic kidney disease, which is lower than that recommended for people with obesity (Perkovic *et al.*, 2024).

Tirzepatide

Glucose-dependent insulinotropic polypeptide (GIP) is a nutrient-stimulated hormone secreted from K cells in the upper small intestine in response to food. It regulates energy balance through cell surface receptor signaling in the brain and adipose tissue (Samms *et al.*, 2020). Results from studies that used transgenic GIP-overexpressing mice or that administered GIP to humans show that GIP results in weight loss and improved insulin sensitivity (Hojberg *et al.*, 2009; Kim *et al.*, 2012), suggesting that GIP could be a therapeutic target for obesity.

In November 2023, tirzepatide became the first GLP-1/GIP dual RA approved by the FDA for chronic weight management. It is approved for use in adults with obesity (BMI ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) and at least one weight-related condition alongside a reduced calorie diet and increased physical activity. It is a once-weekly subcutaneous injectable peptide engineered from the native GIP sequence, with agonist activity at both the GIP and GLP-1 receptors. It is a 39 amino acid linear peptide conjugated to a C20 fatty diacid moiety via a linker connected to the lysine residue at position 20. The peptide sequence contains two non-coded amino acid residues at positions 2 and 13 (α-aminoisobutyric acid) and the C-terminus is amidated; the molecular weight of tirzepatide is 4810.52 Da (Coskun *et al.*, 2018).

Several phase 3 programs have investigated tirzepatide; these are titled the SURMOUNT development programs (Table 3). These placebo-controlled trials aimed to evaluate the efficacy and safety of tirzepatide, as an adjunct to lifestyle intervention, in chronic weight management in adults with a BMI ≥27 kg/m² with or without T2DM. Mean weight loss from baseline with tirzepatide administration (10 mg or 15 mg) in SURMOUNT 1 to SURMOUNT 3 was 12.8% to 20.9%; this weight loss was significantly higher than in the placebo group (−3.1% to −2.5%) (Jastreboff *et al.*, 2022; Garvey *et al.*, 2023; Wadden *et al.*, 2023). Body fat reduction in SURMOUNT 1 was 33.9% with tirzepatide administration, compared with 8.2% with placebo administration. The ratio of total fat mass to total lean mass decreased significantly more from baseline with tirzepatide than with placebo (Jastreboff *et al.*, 2022). In addition, tirzepatide resulted in significantly lower blood pressure

Table 3. The SURMOUNT development programs

	Conditions	Comparator	BW change from baseline (%)	
			Tirzepatide	Placebo
SURMOUNT 1 (Jastreboff <i>et al.</i> , 2022)	Obesity	Placebo	15 mg: −20.9 10 mg: −19.5 5 mg: −15.0	−3.1
SURMOUNT 2 (Garvey <i>et al.</i> , 2023)	Obesity and T2DM	Placebo	15 mg: −14.7 10 mg: −12.8	−3.2
SURMOUNT 3 (Wadden <i>et al.</i> , 2023)	Obesity	After intensive lifestyle intervention Placebo	MTD: −18.4	2.5
SURMOUNT 4 (Aronne <i>et al.</i> , 2024)	Obesity	Phase 3 randomized withdrawal study with a 36-week, open-label tirzepatide lead-in period followed by a 52-week follow-up	−5.5	14.0

BW, body weight; MTD, maximum tolerated dose; T2DM, type 2 diabetes mellitus.

and blood sugar levels and improved lipid profiles compared to placebo (Qin *et al.*, 2024). Similar to other GLP-1 RAs, the most common adverse events with tirzepatide were gastrointestinal symptoms including nausea, diarrhea, and constipation. These symptoms were transient and mild to moderate in severity. There were four reported cases of adjudication-confirmed pancreatitis, which were evenly distributed across treatment groups, including the placebo group. There were no cases of medullary thyroid cancer. However, acute cholecystitis was reported more frequently in the tirzepatide groups than in the placebo group (Jastreboff *et al.*, 2022).

Tirzepatide is one of the most effective anti-obesity medications tested to date. Tirzepatide not only results in approximately 20% weight loss but also improves cardiovascular risk factors such as blood glucose levels, blood pressure, and blood lipid profiles, which could decrease metabolic syndrome and cardiovascular disease. Therefore, tirzepatide is likely to be particularly effective in improving obesity and its related complications; clinical trials of tirzepatide's effects on obesity and obesity-related complications are ongoing.

EMERGING ANTI-OBESITY MEDICATIONS UNDERGOING CLINICAL TRIALS

GLP-1 RAs

Oral semaglutide: Most clinically used GLP-1 analogs are administered via subcutaneous injections. Despite the high efficacy of GLP-1-based anti-obesity medications, the need for regular injections is still a significant barrier for many patients. Therefore, oral treatments that are easy to use and have a similar weight reduction efficacy to currently approved medications are required. Oral semaglutide is the first tablet-based oral GLP-1 analog. It is co-formulated with the absorption enhancer sodium N-[8-(2-hydroxybenzoyl)amino] caprylate and is absorbed in the stomach, where sodium N-[8-(2-hydroxybenzoyl)amino] caprylate causes a localized increase in pH, which leads to higher solubility and protection against proteolytic degradation (Davies *et al.*, 2017).

Although phase 2 trials have used oral semaglutide at a dose of 40 mg, the Oral Semaglutide Treatment Effect in People with Obesity (OASIS) 1 trial used oral semaglutide at a dose of 50 mg once a day; this dose can cause greater reductions in body weight with a similar safety profile to 40 mg. The OASIS 1 trial reported a mean weight loss of 15.1% in the oral semaglutide group and 2.4% weight loss in the placebo group; this weight loss, as well as improvements in cardiometabolic risk factors, including waist circumference, hemoglobin A1c, blood pressure, and high sensitivity C-reactive protein, were significantly greater than in the placebo group. The most frequently reported adverse events were gastrointestinal-related symptoms similar to those reported after the administration of subcutaneous semaglutide (Knop *et al.*, 2023). Semaglutide absorption is significantly affected by food and fluid in the stomach; therefore, the tablet must be administered after an overnight fast with a prescribed volume of water at least 30 min before the consumption of breakfast or other medicines (Kawai *et al.*, 2020).

Orforglipron (LY3502970): Orforglipron, a once-daily oral nonpeptide GLP-1 RA, is a partial agonist biased toward G protein activation over β -arrestin recruitment at the GLP-1R. The molecule is highly potent and selective against other

class B G protein-coupled receptors (Kawai *et al.*, 2020).

Phase 2 studies have used four different doses of orforglipron (12, 24, 36, and 45 mg); at week 26, the mean weight loss from baseline ranged from 8.6% to 12.6% across the orforglipron dose cohorts compared to 2.0% weight loss in the placebo group. At week 36, the loss of body weight ranged from 9.4% to 14.7% compared to 2.3% reduction in the placebo group. A weight reduction of at least 10% by week 36 occurred in 46% to 75% of the participants who received orforglipron. The most common adverse events reported with orforglipron were gastrointestinal events, which were mild to moderate. The safety profile of orforglipron is consistent with that of the GLP-1 RA class (Wharton *et al.*, 2023). Phase 3 studies of orforglipron in people with overweight or obesity coupled with T2DM, obstructive sleep apnea, or Asian ethnicity are ongoing (Table 4).

Ecnoglutide: Ecnoglutide (XW003) is once-weekly administered GLP-1 RA. It is a modified GLP-1 (7-37) peptide containing an alanine-for-valine substitution at position 8, as well as a C18 fatty acid conjugation at the side chain of lysine at position 30. These modifications promote the stability and activity of the peptide. Like the potent dual GLP-1/GIP agonist tirzepatide, the ecnoglutide valine substitution also biases GLP-1 receptor signaling towards cyclic adenosine monophosphate induction over β -arrestin recruitment and receptor internalization (Guo *et al.*, 2023).

A preclinical study reported that ecnoglutide reduced blood glucose and body weight and increased insulin secretion significantly more than semaglutide (Guo *et al.*, 2023). A phase 1 study reported that ecnoglutide was safe and generally well tolerated for up to 6 weeks; the most common adverse events were nausea, decreased appetite, and headaches, similar to other GLP-1 RAs (Guo *et al.*, 2023). Phase 2 studies using ecnoglutide for T2DM showed a 2.26 kg body weight reduction after ecnoglutide 1.2 mg administration (Zhu *et al.*, 2024). A phase 3 clinical trial (NCT05813795) for obesity (SLIMMER) is planned; in addition, a phase 1 trial of oral ecnoglutide (XW004, NCT05184322) is recruiting participants.

Other GLP-1 Ras: GSBR-129, Danuglipron, Dapigliptide (oral), and TG103, have also been developed and are undergoing phase 1 or 2 studies (Table 4).

GLP-1/GIP RAs

HRS9531 is a novel GLP-1/GIP RA. A phase 2 clinical study reported that HRS9531 given at a dose of 6 mg resulted in a 16.8% reduction in body weight from baseline at 24 weeks compared to 0.1% reduction in the placebo group. The most common adverse events were gastrointestinal symptoms, including nausea, diarrhea, decreased appetite, and vomiting, primarily during dose escalation (Zhao *et al.*, 2024).

Another GLP-1/GIP RA, NNC0519-0130 from Novo Nordisk, is undergoing phase 1 and 2 trials (Table 4).

Amylin analog/GLP-1 RA

Amylin is a pancreatic β -cell peptide hormone composed of 37 amino acids. It is co-synthesized and co-released with insulin in response to nutrient intake and acts in the central nervous system, including the lateral hypothalamus, as a satiation signal. In addition, it affects hedonic aspects of eating, such as reward-guided behaviors, and may directly or indirectly contribute to food selection (Boyle *et al.*, 2018). It also slows gastric emptying and reduces the postprandial glucagon response to meals (Zakariassen *et al.*, 2020). Therefore,

Table 4. Ongoing clinical trials

NCT Number	Study Title	Study Status	Conditions	Interventions	Sponsor	Phase	Start Date
GLP-1 receptor agonists							
NCT06440980	A Study to Compare Tablets and Capsules of Orforglipron (LY3502970) in Healthy Participants Who Are Obese or Overweight	Recruiting	Healthy obesity or overweight	Orforglipron	Eli Lilly and Company	Phase 1	2024-06-24
NCT05931380	A Study of Once-Daily Oral Orforglipron (LY3502970) in Japanese Adult Participants With Obesity Disease	Active, not recruiting	Obesity	Orforglipron, placebo		Phase 3	2023-07-31
NCT06672939	A Study of Orforglipron (LY3502970) in Adolescent Participants With Obesity, or Overweight With Related Comorbidities	Not yet recruiting	Overweight or obesity	Orforglipron, placebo		Phase 3	2024-12-01
NCT05869903	A Study of Orforglipron (LY3502970) in Adult Participants With Obesity or Overweight With Weight-Related Comorbidities	Active, not recruiting	Overweight or obesity	Orforglipron, placebo		Phase 3	2023-06-05
NCT06584916	A Study of Orforglipron for the Maintenance of Body Weight Reduction in Participants Who Have Obesity or Overweight With Weight-Related Comorbidities (ATTAIN-MAINTAIN)	Enrolling by invitation	Overweight or obesity	Orforglipron, placebo		Phase 3	2024-09-13
NCT06672549	A Platform Trial for Pediatric Participants With Obesity or Overweight (LY900040)	Not yet recruiting	Overweight or obesity	Orforglipron, placebo		Phase 3	2024-12-01
NCT06649045	A Master Protocol for Orforglipron in Participants With Obstructive Sleep Apnea (OSA) and Obesity or Overweight	Recruiting	Overweight or obesity, OSA	Orforglipron, placebo		Phase 3	2024-10-22
NCT05872620	A Study of Orforglipron in Adult Participants With Obesity or Overweight and Type 2 Diabetes	Active, not recruiting	Overweight or obesity, T2DM	Orforglipron, placebo		Phase 3	2023-06-05
NCT05803421	A Study of Daily Oral Orforglipron (LY3502970) Compared With Insulin Glargine in Participants With Type 2 Diabetes and Obesity or Overweight at Increased Cardiovascular Risk	Active, not recruiting	Overweight or obesity, T2DM, cardiovascular diseases, CKD	Orforglipron, insulin glargine		Phase 3	2023-04-03
GLP-1/GIP dual receptor agonists							
NCT06287437	HRS9531 Controls Weight Regain in Obese Subjects	Active, not recruiting	Obesity	HRS9531, placebo	Shanghai Zhongshan Hospital	Phase 2	2024-01-01
NCT06054698	Efficacy and Safety of HRS9531 Injections in Overweight or Obese Subjects	Not yet recruiting	Overweight or obesity	HRS9531, placebo		Phase 2	2023-10-01
NCT05881837	Efficacy and Safety of HRS9531 Injection in Obese Subjects Without Diabetes	Active, not recruiting	Overweight or obesity	HRS9532, placebo		Phase 2	2023-06-13
NCT06396429	To Compare the Efficacy and Safety of HRS9531 and Placebo in Subjects With Overweight or Obese	Recruiting	Overweight or obesity	HRS9533, placebo		Phase 3	2024-05-13
NCT06391710	HRS9531 Injection in Obese Subjects With Heart Failure With Preserved Ejection Fraction	Recruiting	Heart failure with preserved ejection fraction	HRS9534, placebo		Phase 2	2024-05-06
NCT06565871	A Study of HRS9531 Injection in Obese Subjects With Obstructive Sleep Apnea	Not yet recruiting	Weight management	HRS9535, placebo		Phase 2	2024-08-01
NCT06595797	A Multicenter, Randomized, Double-blind, Placebo-parallel-controlled Phase II Clinical Study Evaluating the Efficacy and Safety of HRS9531 Injection in Obese Subjects With Polycystic Ovary Syndrome	Not yet recruiting	Obese subjects with polycystic ovary syndrome	HRS9536, placebo		Phase 2	2024-09-01
NCT06642571	A Research Study to Compare How Much of the Medicine NNC0519-0130 is in the Blood of People With Overweight or Obesity Who Receive 2 Preparations of the Medicine	Not yet recruiting	Obesity	NNC0519-0130 B, NNC0519-0130 C	Novo Nordisk	Phase 1	2024-10-15
NCT06326060	A Research Study Comparing How Well Different Doses of the Medicine NNC0519-0130 Help People With Excess Body Weight Lose Weight	Active, not recruiting	Obesity	NNC0519-0130, placebo, tirzepatide		Phase 2	2024-03-18
NCT06567041	A Research Study of How Safe a New Medicine Called NNC0519 0130 is and to Test Its Effect in People Living With Excess Body Weight With or Without Type 2 Diabetes	Recruiting	Obesity, T2DM	NNC0519-0130, placebo		Phase 1	2024-08-07
GLP-1 receptor agonists/Amylin							
NCT06267092	A Study of How CagriSema Works on Appetite in People With Excess Body Weight	Recruiting	Overweight or obesity	Cagrilintide and semaglutide, placebo	Novo Nordisk	Phase 1	2024-02-15
NCT06131437	A Research Study to See How Well CagriSema Compared to Tirzepatide Helps People With Obesity Lose Weight	Active, not recruiting	Obesity	Cagrilintide, semaglutide, tirzepatide		Phase 3	2023-11-27

Table 4. Continued 1

NCT Number	Study Title	Study Status	Conditions	Interventions	Sponsor	Phase	Start Date
NCT05567796	A Research Study to See How Well CagriSema Helps People With Excess Body Weight Lose Weight	Active, not recruiting	Obesity	Cagrilintide and semaglutide, placebo to cagrilintide,	Novo Nordisk	Phase 3	2022-11-01
NCT06207877	A Research Study to Look at How CagriSema Influences Food Intake, Appetite and Emptying of the Stomach in People With Excess Body Weight	Recruiting	Obesity	Cagrilintide, semaglutide, placebo to semaglutide,		Phase 1	2024-02-23
NCT05996848	A Research Study to See How Well CagriSema Helps People in China With Excess Body Weight Lose Weight	Recruiting	Overweight or obesity	Cagrilintide, semaglutide, placebo to semaglutide,		Phase 3	2023-08-15
NCT06388187	A Research Study to See How Well Different Doses of CagriSema Help People With Excess Body Weight Lose Weight	Recruiting	Obesity	Cagrilintide, Semaglutide, Placebo		Phase 3	2024-06-24
NCT05813925	A Research Study to See How Well CagriSema Helps People in East Asia With Excess Body Weight Lose Weight	Recruiting	Overweight or obesity	Cagrilintide, semaglutide, placebo to Semaglutide		Phase 3	2023-04-03
NCT06289504	A Study on How CagriSema Affects Levels of Atorvastatin and Warfarin in the Blood of Participants With Excess Body Weight	Recruiting	Obesity	Cagrilintide, semaglutide, atorvastatin, warfarin		Phase 1	2024-02-27
NCT05394519	A Research Study to See How Well CagriSema Helps People With Type 2 Diabetes and Excess Body Weight Lose Weight	Active, not recruiting	Overweight or obesity, T2DM	Cagrilintide, semaglutide, placebo to cagrilintide, placebo to semaglutide		Phase 3	2023-02-01
NCT06131372	A Research Study to See if Kidney Damage in People With Chronic Kidney Disease and Type 2 Diabetes Living With Overweight or Obesity Can be Reduced by CagriSema Compared to Semaglutide, Cagrilintide and Placebo	Recruiting	Obesity, T2DM, CKD	Cagrilintide, semaglutide, placebo		Phase 2	2024-04-01
GLP-1/GOG receptor agonists							
NCT06176365	A Study to Test Whether Survodutide Helps Japanese People Living With Obesity Disease	Active, not recruiting	Obesity	Survodutide, placebo	Boehringer Ingelheim	Phase 3	2023-12-19
NCT06492135	A Study in Chinese People With Overweight or Obesity to Test How Different Doses of Survodutide Are Taken up in the Body	Active, not recruiting	Overweight or obesity	Survodutide		Phase 1	2024-07-15
NCT06066515	A Study to Test Whether Survodutide (BI 456906) Helps People Living With Overweight or Obesity Who do Not Have Diabetes to Lose Weight	Active, not recruiting	Obesity	Survodutide, placebo		Phase 3	2023-11-15
NCT06077864	A Study to Test the Effect of Survodutide (BI 456906) on Cardiovascular Safety in People With Overweight or Obesity (SYNCHRONIZE??- CVOT)	Recruiting	Obesity	Survodutide, placebo		Phase 3	2023-11-17
NCT06309992	A Study to Test Whether Survodutide Helps People Living With Obesity or Overweight and With a Confirmed or Presumed Liver Disease Called Non-alcoholic Steatohepatitis (NASH) to Reduce Liver Fat and to Lose Weight	Recruiting	Obesity, non-alcoholic steatohepatitis	Survodutide, placebo		Phase 3	2024-03-13
NCT06066528	A Study to Test Whether Survodutide (BI 456906) Helps People Living With Overweight or Obesity Who Also Have Diabetes to Lose Weight	Active, not recruiting	Obesity, T2DM	Survodutide, placebo		Phase 3	2023-11-15
NCT06564441	A Study to Test Whether BI 456906 (Survodutide) Influences the Amount of Bupropion, Caffeine and Midazolam in the Blood in People With Overweight or Obesity	Recruiting	Overweight or obesity	Survodutide, bupropion, caffeine, midazolam		Phase 1	2024-09-05
NCT05202353	A Study in People With Obesity to Test the Effects of BI 456906 Compared With Semaglutide on Glucagon Receptor Activity in the Liver	Recruiting	Obesity	BI 456906, semaglutide		Phase 1	2024-06-28
NCT06214741	A Study to Test Whether Survodutide (BI 456906) Helps Chinese People Living With Overweight or Obesity to Lose Weight	Active, not recruiting	Overweight or obesity	Survodutide, placebo		Phase 3	2024-01-15
NCT06200467	A Study to Test Whether Multiple Doses of BI 456906 Have an Effect on Cardiac Safety in People With Overweight or Obesity	Recruiting	Overweight or obesity	BI 456906, placebo to BI 456906, moxifloxacin, placebo to moxifloxacin		Phase 1	2024-03-04
NCT05896384	A Study in Women With Overweight or Obesity to Test Whether Different Doses of BI 456906 Influence the Amount of a Contraceptive in the Blood	Active, not recruiting	Overweight or obesity	BI 456906, Microgynon®		Phase 1	2023-12-07

Table 4. Continued 2

NCT Number	Study Title	Study Status	Conditions	Interventions	Sponsor	Phase	Start Date
NCT06164873	A Study of IBI362 9 mg in Chinese Adults With Obesity	Active, not recruiting	Obesity	IBI362, placebo	Innovent Biologics (Suzhou) Co. Ltd.	Phase 3	2023-12-27
NCT06184568	A Study Comparing IBI362 vs Semaglutide in Chinese Adults With Early Type 2 Diabetes and Obesity	Recruiting	Obesity, T2DM	IBI362, semaglutide		Phase 3	2024-02-29
NCT065636023	This is a Study to Evaluate the Pharmacokinetics and Safety of IBI362 in Chinese Adolescents With Obesity	Recruiting	Adolescents with obesity	IBI362, placebo		Phase 1	2024-08-30
NCT06313528	A Study to Measure Calorie Consumption and Usage in Participants With Obesity Using LY3437943	Recruiting	Obesity	LY3437943, placebo	Eli Lilly and Company	Phase 1	2024-03-20
NCT05936151	A Study of Retatrutide (LY3437943) on Renal Function in Participants With Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes	Recruiting	Overweight or obesity, T2DM, CKD	Retatrutide, placebo		Phase 2	2023-07-20
NCT05882045	A Study of Retatrutide (LY3437943) in Participants With Obesity and Cardiovascular Disease	Active, not recruiting	Obesity, cardiovascular diseases	Retatrutide, placebo		Phase 3	2023-05-30
NCT05931367	A Study of Retatrutide (LY3437943) Once Weekly in Participants Who Have Obesity or Overweight and Osteoarthritis of the Knee	Active, not recruiting	Overweight or obesity, knee osteoarthritis	Retatrutide, placebo		Phase 3	2023-08-01
NCT05929066	A Study of Retatrutide (LY3437943) in Participants Who Have Obesity or Overweight	Active, not recruiting	Overweight or obesity, knee pain, chronic knee osteoarthritis, OSA	Retatrutide, placebo		Phase 3	2023-07-10
NCT06662383	A Study of Retatrutide (LY3437943) Compared to Tirzepatide (LY3298176) in Adults Who Have Obesity	Not yet recruiting	Obesity	Retatrutide, tirzepatide		Phase 3	2024-11-01
NCT05929079	A Study of Retatrutide (LY3437943) in Participants With Type 2 Diabetes Mellitus Who Have Obesity or Overweight	Recruiting	Overweight or obesity, T2DM, OSA	Retatrutide, placebo		Phase 3	2023-07-11
NCT06383390	The Effect of Retatrutide Once Weekly on Cardiovascular Outcomes and Renal Function in Adults Living With Obesity (TRIUMPH-OUTCOMES)	Recruiting	Overweight or obesity	Retatrutide, placebo		Phase 3	2024-04-30
GLP-1/GIP receptor agonists							
NCT05669599	Dose-ranging Study to Evaluate the Efficacy, Safety, and Tolerability of AMG 133 in Adult Subjects With Overweight or Obesity, With or Without Type 2 Diabetes Mellitus	Active, not recruiting	Overweight or obesity, T2DM	Maridebart cafraglutide, placebo	Amgen	Phase 2	2023-01-18
NCT06660173	A Study of Maridebart Cafraglutide in Adult Participants With Type 2 Diabetes Mellitus (T2DM)	Not yet recruiting	T2DM	Maridebart cafraglutide, placebo		Phase 2	2024-11-21

CKD, chronic kidney disease; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; OSA, obstructive sleep apnea; T2DM, type 2 diabetes mellitus.

chronic administration of amylin reduces total energy intake, which results in body weight loss.

Cagrilintide is the first long-acting amylin analog and is administered as a subcutaneous injection once weekly (Kruse *et al.*, 2021). A phase 2 trial reported that cagrilintide 0.3 mg to 4.5 mg significantly reduced body weight by 6.0% to 10.8% at 26 weeks and was well tolerated. The most frequent adverse events were gastrointestinal disorders and administration-site reactions (Lau *et al.*, 2021). In a phase 2 dose-finding trial in people with overweight or obesity and hypertension or dyslipidemia without T2DM, cagrilintide at a dose of 2.4 mg, as an adjunct to diet and exercise, resulted in a body weight reduction of 10% after 26 weeks; the placebo resulted in a body weight reduction of 3% (Lau *et al.*, 2021).

When co-administrated with other therapies, the weight loss effect of cagrilintide is more prominent. For example, after 20 weeks, cagrilintide 2.4 mg co-administered with semaglutide 2.4 mg resulted in a body weight reduction of 17%; when semaglutide 2.4 mg was co-administered with placebo, body weight reduction was 10% (Enebo *et al.*, 2021). In addition, compared with monotherapies of cagrilintide 2.4 mg or semaglutide 2.4 mg, cagrilintide 2.4 mg/semaglutide 2.4 mg (CagriSema) resulted in a significant reduction of hemoglobin A1c in individuals with T2DM and overweight or obesity. Furthermore, body weight reduction with CagriSema administration was 15.6%, compared with 5.1% and 8.1% with semaglutide and cagrilintide alone, respectively (Frias *et al.*, 2023). The safety profile of CagriSema is consistent with the GLP-1 RA and amylin analog drug classes, which means gastrointestinal adverse events are the most common adverse events (Frias *et al.*, 2023). Currently, CagriSema is undergoing phase 3 trials in people with overweight or obesity and various related conditions (Table 4).

GLP-1/Glucagon RAs

BI 456906 (Survodutide): Glucagon is secreted from pancreatic α -cells and acts principally as a counter-regulatory hormone to insulin. It is released in response to physiological challenges that threaten adequate blood glucose levels and drives glucose production to restore euglycemia (Sandoval and D'Alessio, 2015). Glucagon also activates vagal afferents that subsequently suppress food intake via central nervous system mechanisms. In addition, it activates brown adipose tissue to increase energy expenditure. Thus, glucagon action can reduce body weight both by increasing energy expenditure and reducing food intake (Sandoval and D'Alessio, 2015). Based on this concept, Cegla *et al.* investigated the acute effects of intravenous infusion of a subanorectic dose of GLP-1 and glucagon on food intake. The results showed that co-administration of GLP-1 and glucagon reduced food intake significantly and ameliorated the hyperglycemic effects of glucagon. In addition, co-administration of GLP-1 and glucagon increased energy expenditure, supporting the concept of a dual GLP-1/glucagon RA as a possible therapeutic for obesity (Cegla *et al.*, 2014).

BI 456906 (survodutide) is a dual glucagon/GLP-1 RA and a potent, acylated peptide containing a C18 fatty acid to enable once-weekly dosing in humans (Zimmermann *et al.*, 2022). Preclinical studies show that it reduces body weight by increasing energy expenditure and reducing food intake compared to the maximally effective dose of semaglutide (Zimmermann *et al.*, 2022). In phase 2 clinical trials for obesity,

survodutide (0.6, 2.4, 3.6, or 4.8 mg) reduced body weight dose-dependently and resulted in a body weight loss of 6.2% to 14.9%, compared with -2.8% after placebo, at 46 weeks. Gastrointestinal disorders were the most common adverse event following survodutide administration, although there were no cases of pancreatitis or hepatic injury. In addition, heart rate was higher on average in the survodutide group than in the placebo group (le Roux *et al.*, 2024). In a recent study, survodutide resulted in significant improvement in metabolic dysfunction-associated steatohepatitis without a worsening of fibrosis, in fact, some participants experienced an improvement in fibrosis, which suggests that survodutide could be a potential treatment for patients with metabolic dysfunction-associated steatohepatitis and liver fibrosis (Sanyal *et al.*, 2024). Phase 3 trials for survodutide are ongoing (Table 4).

Mazdutide (IBI362, LY3305677): Mazdutide is another once-weekly administered dual GLP-1/glucagon RA for the treatment of obesity and T2DM; it is a mammalian oxyntomodulin analog with a fatty acid side chain attached (Ji *et al.*, 2023). Phase 1b and phase 2 trials have been conducted in China, where BMI cutoffs are lower: overweight is defined as a BMI ≥ 24 kg/m² and obesity is defined as a BMI ≥ 28 kg/m². In a phase 1b clinical trial in Chinese adults with overweight or obesity, mazdutide up to a dose of 10 mg was well tolerated and had an overall safety profile similar to those of other GLP-1-based therapies. At week 12, participants receiving mazdutide at 6 and 9 mg had body weight losses of 6.1% and 11.7%, respectively (Ji *et al.*, 2021, 2022). A phase 2 trial demonstrated body weight changes from baseline to week 24 of -6.7% with mazdutide 3 mg, -10.4% with mazdutide 4.5 mg, -11.3% with mazdutide 6 mg, and 1.0% with placebo. All mazdutide doses were well tolerated; the most common adverse events were diarrhea, nausea, and upper respiratory tract infection. However, heart rate tended to increase more with mazdutide than with placebo (Ji *et al.*, 2023), similar to the phase 1 trial (Ji *et al.*, 2021, 2022). The end-of-treatment heart rate increase was similar to or slightly higher than that observed with placebo (Ji *et al.*, 2023). Considering that 6 mg was not enough to achieve the desired weight loss target for individuals with a higher BMI, mazdutide administration at a dose of 9 mg, exclusively for adults with a BMI ≥ 30 kg/m², is under evaluation (Table 4).

GLP-1/GIP/Glucagon RAs

Retatrutide (LY3437943) has a triple agonist activity at the GLP-1, GIP, and glucagon receptors. Based on the benefits of dual GLP-1/GIP RAs and dual GLP-1/glucagon RAs, the effect of triple GLP-1/GIP/glucagon RAs on weight loss and glycemic control has also been investigated. Retatrutide is a 39 amino acid single peptide conjugated to a C20 fatty diacid moiety with a peptide sequence engineered from a GIP peptide backbone. Retatrutide has more potent human GIP receptor activity and less potent human glucagon and GLP-1 receptor activity, which are similar (Urva *et al.*, 2022). The half-life of retatrutide is approximately 6 days, which enables once-weekly dosing (Coskun *et al.*, 2022). In obese mice, retatrutide results in greater body weight loss and energy expenditure than tirzepatide through glucagon receptor activation.

In a phase 2 trial in people with obesity, treatment with a 12 mg dose of retatrutide resulted in a mean weight reduction of 24.2% after 48 weeks as compared with -2.1% in the placebo group. Participants who were receiving retatrutide continued

to lose weight until treatment was stopped at 48 weeks, and the trajectory of the weight-reduction curves indicated that a plateau had not yet been reached. The most common adverse events were gastrointestinal symptoms. Heart rate increased dose-dependently up to 24 weeks and reduced thereafter (Jastreboff *et al.*, 2023). The safety and side effect profiles of retatrutide are similar to those observed with GLP-1 and GIP/GLP-1 RAs. Phase 3 trials of retatrutide in various obesity-related conditions are underway (Table 4).

Others

AMG 133 is a GIPR/GLP-1R bispecific molecule. It was created by conjugating a fully human monoclonal anti-human GIPR-antibody with two GLP-1 analog agonist peptides using amino acid linkers. A phase 1 study showed AMG 133 had an acceptable safety and tolerability profile and resulted in dose-dependent weight loss (Veniant *et al.*, 2024). Phase 2 trials are now underway (Table 4).

Other novel drugs like neuropeptide Y receptor type 2 agonists, cannabinoid receptor-1 inverse agonists, and gut-brain axis-targeting therapeutics are under development.

PERSPECTIVES AND CONCLUSIONS

Weight loss aims to improve obesity-related complications and patients' health and quality of life. At least 5% weight loss is required to prevent obesity-related complications, and it is reflected in the guidelines for weight management drugs. Currently, available anti-obesity medications for long-term management meet this criterion. However, guidelines suggest different weight targets are set depending on the complications, such as 5-15% weight loss for metabolic syndrome, type 2 DM and cardiovascular disease, 7-8% for obstructive sleep apnea and asthma, and 10-40% for steatohepatitis (Garvey *et al.*, 2016). Especially recently developed incretin-based drugs semaglutide and tirzepatide result in dramatic reductions in body weight comparable to bariatric surgery (Fig. 1).

Until now, most drugs have primarily focused on reducing energy intake through appetite suppression. Drugs that

were developed to increase energy expenditure have failed (Christoffersen *et al.*, 2022). Although current anti-obesity medications are expected to improve obesity-related complications and cause weight loss, for weight loss maintenance, a strategy that promotes both appetite suppression and energy expenditure is most likely to succeed. Body weight often plateaus before increasing again after treatment cessation (Christoffersen *et al.*, 2022). For example, 1 year after the withdrawal of semaglutide in the STEP 1 trial, two-thirds of participants regained their body weight (Wilding *et al.*, 2022); the withdrawal of tirzepatide also resulted in substantial regain of lost weight, whereas continued treatment maintained initial weight reduction (Aronne *et al.*, 2024). The most common adverse events to overcome are gastrointestinal symptoms. Although they are generally well-tolerated, there is currently not enough data regarding potential long-term safety issues. For example, there is a concern about the increased risk of pulmonary aspiration in the peri-operative period (Milder *et al.*, 2024). The FDA updated drug safety-related labeling for liraglutide, semaglutide, and tirzepatide on November 5th, 2024. The labels for these drugs include a warning about pulmonary aspiration during general anesthesia or deep sedation (Food and Drug Administration, 2024).

To date, several anti-obesity drugs have been developed that show efficacy in promoting weight loss and improving obesity-associated diseases. With technical advances, novel therapeutic drugs are being developed to target different mechanisms underlying the pathogenesis of obesity; this could significantly impact the treatment of obesity and lead to more sustainable changes in weight and overall health.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

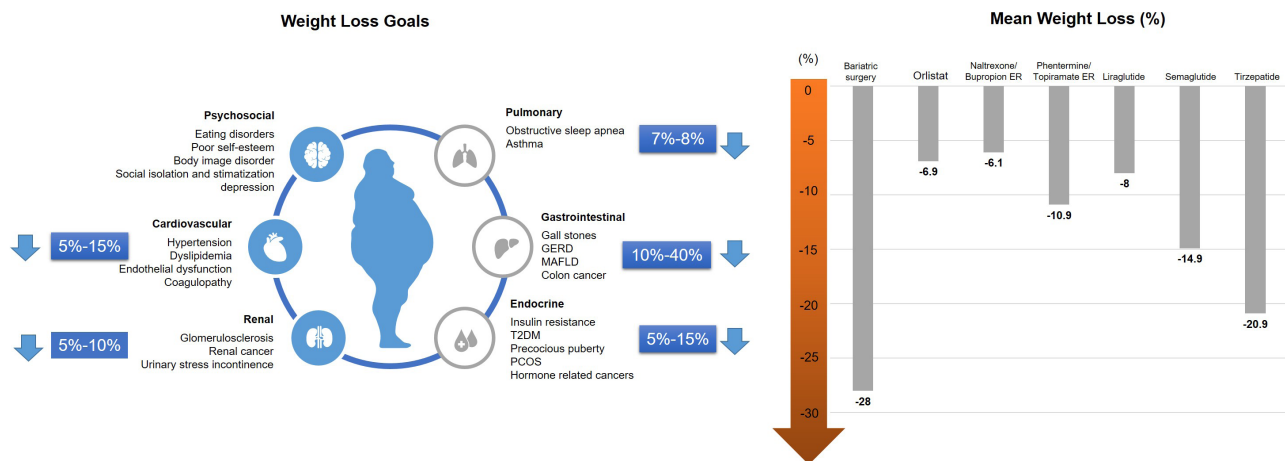


Fig. 1. The expected weight loss required to improve obesity-related complications and mean weight loss according to treatment. ER, extended-release; GERD, gastroesophageal reflux disease; MAFLD, metabolic dysfunction-associated fatty liver disease; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

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