Review Article

Approved and Emerging Hormone-Based Anti-Obesity Medications: A Review Article

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Abstract

Obesity is a heterogeneous, complex, and chronic disease that has a detrimental impact on disability-adjusted life years across the globe. Recent advancements in our understanding of gut-brain communication at the molecular level have driven the development of next-generation anti-obesity medications (AOMs). Glucagon-like peptide-1 receptor agonists (GLP1RAs) remain the front-runners in this rapidly evolving landscape of hormone-based AOMs. Two GLP1RAs, namely Liraglutide and Semaglutide, have been approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) for use in clinical practice for weight loss. Three oral GLP1RAs, namely Semaglutide, Danuglipron, and Orforglipron, are undergoing advanced clinical trials in individuals with obesity. Amylin receptor agonist (AMYRA) Cagrilintide, when used alone or in combination with Semaglutide, has demonstrated substantial weight reduction in clinical trials. Tirzepatide, a dual agonist for the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, has been observed to be associated with a significant placebo-subtracted weight reduction of 17.8% in a 72-week randomized controlled trial. Novel approaches targeting glucagon signalling have also yielded promising preliminary results. Three long-acting GLP1R/glucagon receptor (GCGR) dual agonists, namely Survodutide, Mazdutide, and Pemvidutide, exhibited significant weight loss in clinical trials. Retatrutide, a GLP1R/GCGR/GIPR tri-agonist, has been associated with a placebo-subtracted weight reduction of -22.1% in a 48-week phase-II trial. As a note of caution, long-term data on such medications' safety and cardiovascular benefits is yet to be ascertained. Our review provides a comprehensive overview of the approved and emerging hormone-based AOMs, highlighting the diversity of options that might become available in the near future.

Keywords: Amylin, anti-obesity medication, dual receptor agonists, glucagon, glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, obesity, peptide tyrosine-tyrosine, triple receptor agonists, weight management

Introduction

Over the last decade, a renewed focus has been on the critical role played by the gastrointestinal (GI)-hypothalamic axis in influencing food intake and energy expenditure. Peptides secreted from the GI tract, such as glucagon-like peptide-1 (GLP-1), amylin, glucose-dependent insulinotropic polypeptide (GIP), glucagon, oxyntomodulin (OXM), and peptide tyrosine-tyrosine (PYY) have been targets for the development of novel anti-obesity medications (AOMs).[1]

GLP-1 receptor agonists (GLP1RAs) such as Liraglutide and Semaglutide have been observed to improve glycaemic control and promote weight loss.[2] These medications suppress appetite and enhance insulin secretion, offering dual-action benefits for obesity and diabetes management. In addition, emerging multi-agonist therapies, such as Tirzepatide, hold potential as these target multiple energy-regulating pathways, synergistically aiding weight loss and glycaemic control.[3]

Successful results of GLP-1-based therapies have spurred extensive research and development, leading to novel mono- and poly-agonist molecules.[4] Several compounds have progressed to advanced clinical trials, with some already approved for clinical use, such as Liraglutide and Semaglutide. The ongoing expansion of the drug development

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pipeline demonstrates a commitment to identifying safer and more effective treatments for obesity and type-2 diabetes mellitus (T2DM).[5]

GLP-1

GLP1RAs have been developed as a treatment for T2DM and have also been shown to promote weight loss. They are resistant to the actions of dipeptidyl peptidase-IV (DPP-IV), allowing for an extended duration of biologically active agonists and activation of accessible receptors throughout the body.[6] The mechanisms by which GLP1RAs reduce food intake and promote weight loss are incompletely understood. GLP1RAs have central actions. They are believed to promote satiation and weight loss through direct interaction with GLP1Rs in the circumventricular organs (CVOs) in the hypothalamus, hindbrain, and some brain areas adjacent to the ventricles. Access to area postrema (AP), subfornical organ (SFO), and median eminence (ME) has been observed for Liraglutide and Semaglutide, while Dulaglutide and Albiglutide are large-sized molecules and may have limited access to these brain areas.[7,8] The effects of Liraglutide and Semaglutide on food intake are more pronounced than those of Dulaglutide and Albiglutide, supporting the perspective that the impact of GLP1RAs on appetite occurs centrally, while the effects on glycaemic control are peripherally mediated.[6,9]

Liraglutide, a GLP1RA, shares a 97% similarity with human GLP-1. Its molecular structure modifications make it less susceptible to DPP-IV, and it is administered subcutaneously once daily with a half-life of 11–15 hours.[10] Initially approved for T2DM treatment, it received additional approvals for obesity in adults (up to 3.0 mg) in 2014 and adolescents in 2020. For obesity treatment, Liraglutide underwent five double-blind placebo-controlled trials in adults, called SCALE trials,[11–15] involving over 5000 participants. Each trial lasted for 56 weeks, except for the SCALE Obesity and Prediabetes Extension trials, which spanned over 160 weeks.[15] In the SCALE trial (in individuals without diabetes), Liraglutide users achieved 8.0% weight reduction compared to 2.6% in the placebo group after 56 weeks (estimated treatment difference (ETD): −5.4%; 95% CI: −5.8% to −5.0%; $P < 0.001$).[11] Placebo-subtracted weight reduction was 4.0%, 3.4%, 6.1%, and 4.3% for SCALE Diabetes (in individuals with T2DM),[12] SCALE Intensive Behavioural Therapy (IBT),[13] SCALE Maintenance,[14] and SCALE Obesity and Prediabetes,[15] respectively. A subsequent trial in adolescents, the SCALE TEENS trial, showed promising results. At week 56, a more significant reduction was observed with Liraglutide than with placebo for the relative change in body weight (ETD: −5.01%; 95% CI: −7.63% to −2.39%).[16] The most commonly observed adverse events (AEs), affecting more than 10% of participants in the main trials for Liraglutide approval, included slightly increased heart rate, GI symptoms (constipation, diarrhoea, nausea, dyspepsia, decreased appetite, and vomiting), infections (nasopharyngitis, upper respiratory tract infection (URTI), and influenza), hypoglycaemia, and central nervous system (CNS) symptoms (dizziness and headaches).[11–15]

Individuals' responses to Liraglutide for weight management exhibit considerable variation. In the SCALE trial, the proportion of participants who achieved ≥10% weight loss with Liraglutide was 33.1% versus 10.6% with placebo, with the majority of participants failing to achieve this significant (≥10%) weight loss.[11]

Semaglutide, a next-generation GLP1RA, offers once-weekly subcutaneous administration with an extended half-life of 183 hours.[17] It was approved in varying doses for T2DM and chronic weight management in obesity. The STEP program assessed its efficacy and safety in treating obesity or overweight over a period of 68 weeks. In STEP 1,[18] Semaglutide users achieved a 14.9% weight reduction compared to 2.4% in the placebo group at week 68 (ETD: −12.4%; 95% CI: −13.4% to −11.5%; $P < 0.001$). STEP 2 (in individuals with T2DM)[19] and STEP 3 (IBT)[20] trials also showed weight loss benefits, with a placebo-subtracted weight loss of 6.2% and 10.3%, respectively. In the STEP 4-Maintenance trial, the participants followed a reduced-calorie diet (500-kcal/day deficit relative to estimated energy expenditure) and engaged in increased physical activity (150 min/week). They also received Semaglutide 2.4 mg weekly for 20 weeks, resulting in a mean body weight reduction of 10.6%. After randomization, the Semaglutide group achieved a weight loss of 7.9%, while the placebo group experienced a weight gain of 6.9%.[21] The STEP 8 trial compared weekly Semaglutide 2.4 mg to daily Liraglutide 3.0 mg with matched weekly and daily placebo in individuals with obesity (IWO) and revealed Semaglutide's superiority over Liraglutide for weight loss (ETD: −9.4%; 95% CI: −12.0% to −6.8%; $P < 0.001$). The proportion of participants who achieved ≥10% weight loss with Semaglutide was 70.9% versus 25.6% for Liraglutide in the STEP 8 trial.[22]

Common AEs observed in more than 10% of the participants in the STEP trials included GI symptoms (nausea, dyspepsia, vomiting, flatulence, diarrhoea, abdominal pain, abdominal distention, or constipation), infections (URTI, urinary tract infection (UTI), and nasopharyngitis), musculoskeletal and connective tissue disorders such as back pain, and CNS symptoms (dizziness and headaches).[18-22]

Several oral GLP1RAs are currently in clinical development. Most GLP1RAs are administered subcutaneously due to poor bioavailability and rapid degradation when taken orally.[23] However, oral Semaglutide, formulated with sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) technology, improves transcellular absorption and prevents stomach degradation.[24] It is the first daily oral GLP1RA approved by the Food and Drug Administration (FDA) for T2DM at doses up to 14 mg daily.[25] Higher doses are currently under investigation for weight management in IWO.[26]

Other two oral GLP1RAs under development for the management of obesity and T2DM include Danuglipron[27] (selective small-molecule GLP1RA) and Orforglipron[28] (non-peptide GLP1RA molecule).

Dapiglutide is a GLP1R/GLP2R dual agonist developed by Zealand Pharma for treating obesity (NCT05788601) and short bowel syndrome.

GLP1RAs, currently on the market or in clinical development, are summarized in Table 1.

Amylin

Human amylin's tendency to aggregate, causing pancreatic islet death, hampers its use.[29] However, rat-based amylin analogues, such as Pramlintide, have been developed to induce body weight loss.[30] In 2005, the FDA approved Pramlintide as an adjunct therapy to insulin or oral agents in individuals with type-1 diabetes mellitus (T1DM) and T2DM.[31] Pramlintide's effects on food intake and body weight extend beyond individuals with diabetes. Early studies showed modest weight reduction with Pramlintide independent of diabetes status.[32] However, when combined with the leptin analogue Metreleptin in pre-clinical studies, Pramlintide demonstrated a significant and potent body weight reduction and potential improvement of leptin resistance.[33] These results have made amylin an attractive target for obesity management.

Recent studies indicate various amylin-based drugs' high efficacy and safety in humans. A long-acting amylin receptor agonist (AMYRA) called Cagrilintide has specific structural modifications to enhance its properties, such as inhibiting amyloid fibril formation, increasing potency, solubility, and duration of action.[34] In clinical trials, Cagrilintide led to significant weight loss,[35] especially when combined with Semaglutide[36] in IWO.

As human amylin receptor (AMYR) subtypes consist of calcitonin receptor (CALCR) and receptor activity-modifying proteins (RAMP), dual-acting amylin and calcitonin receptor agonists (DACRAs) have emerged as potential AOMs [Table 2].

GIP

Various therapeutic interventions based on harnessing the metabolic potential of GIP are in the pre-clinical or clinical trials, such as GIP antagonists, GIP agonists, and dual- or poly-agonists with GLP-1.

The potential use of GIP receptor (GIPR) agonism to combat T2DM and obesity has initially been met with scepticism due to the reduced insulinotropic effect in T2DM patients[37] and the pre-clinical evidence related to using GIPR antagonism in diet-induced obesity (DIO) mice.[38–41] However, long-acting GIPR agonists (LA-GIPRAs) have demonstrated weight reduction in obese mice, signalling through the central nervous system (CNS) via GIPR-expressing neurons/cells in the hypothalamus and hindbrain. Centrally administered acylated GIP leads to weight loss and reduced food intake in obese mice. However, peripheral administration shows weight loss effects in wild-type and GLP1R knockout mice but diminished reduction in body weight in CNS GIPR knockout mice.[42–44] These findings support the potential of LA-GIPRAs in managing body weight and glucose control and question the notion that GIP promotes obesity.

Combined treatment with GIPR and GLP1R agonists has shown synergistic weight loss in pre-clinical models, leading to the development of GLP1R/GIPR dual agonists for T2DM and obesity. GLP1R/GIPR dual agonism has shown metabolic benefits and weight reduction in mice compared to GLP1R agonists with matched pharmacokinetics.[3,45] GIP agonism offers additional metabolic advantages to GLP1 therapy beyond weight reduction and food intake control through GLP1R-independent mechanisms.[43,44] GIP can counteract the emetic effects of GLP1R agonism in pre-clinical models,[46] while GLP1R agonism restores GIP's insulinotropic effect in individuals with T2DM.[47] Moreover, GIP agonism improves adipocyte storage capacity, protecting against adipocyte lipid spillover and abnormal lipid accumulation in other tissues.[48] Notably, not all GLP1R/GIPR dual agonists, such as NN9709, yield successful results. The beneficial effects of GLP1R/GIPR dual agonists *in vivo* may rely, in part, on altered signalling of the molecule towards biased profiles for one or both components. The effect could be even more significant if both mechanisms apply to the co-agonists. The weight-loss contribution of the GIP part in the co-agonist remains unclear, but if incorporating GIP activity changes GLP-1 signalling, it could enhance weight loss. Ongoing molecular pharmacological experiments aim to determine how the influence of one component (GIP) on the signalling pathways of the other contributes to the effectiveness of co-agonists such as Tirzepatide. Answers to this intriguing paradox are anticipated in the near future.[49]

Tirzepatide is the leading GLP1R/GIPR dual agonist, which exhibits biased GIPR over GLP1R with five times greater potency towards the human GIPR compared to GLP1R.[3] It has an approximately 117-hour half-life.[3,50] Its mechanism combines GLP-1 and GIP effects to regulate weight and blood glucose. Tirzepatide's approval by the FDA and European Medicine Agency (EMA) for T2DM is based on data from the SURPASS Diabetes trials.[50–54] During the SURMOUNT-1 trial, Tirzepatide showed promising results for weight reduction in IWO without diabetes. The 15-mg dose led to a remarkable −20.9% body weight loss compared to −3.1% in the placebo group (ETD, Tirzepatide 15 mg vs Placebo of −17.8%; 95% CI: −19.3% to −16.3%; $P < 0.001$).[55] The proportion of participants who achieved ≥10% weight loss for Tirzepatide 15 mg versus placebo was 83.5% versus 18.8%, respectively, with over 50% of the participants on 10 or 15 mg achieving ≥20% weight loss, demonstrating significant weight reduction in most participants. The most commonly documented AEs were GI symptoms (nausea, diarrhoea, and constipation). These AEs were more prevalent among individuals in the Tirzepatide groups compared to the placebo group, were of a short-lived and mild to moderate nature, and primarily manifested during the dosage escalation period.[55] In the SURMOUNT-2 trial,[56] Tirzepatide showed weight loss benefits in IWO and T2DM. The ongoing SURMOUNT trials, namely SURMOUNT-3 (NCT04657016) and

Table 1: GLP1RAs currently on the market or in clinical development

Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
Liraglutide (Saxenda)	Novo Nordisk	GLP1RA	FDA/EMA approved	• Based on the results of SCALE trials,[11-15] the FDA authorized the use of Liraglutide 3.0 mg in December 2014, and the EMA followed suit in March 2015. This medication, marketed as Saxenda by Novo Nordisk, is used for chronic weight management in IWO or overweight.
Semaglutide (Wegovy)	Novo Nordisk	GLP1RA	FDA/EMA approved	• Based on the results of STEP trials,[18-22] the FDA authorized the use of Semaglutide 2.4 mg in June 2021, and the EMA followed suit in January 2022. This medication, marketed as Wegovy by Novo Nordisk, is used for chronic weight management in IWO or overweight.
Semaglutide (Rybelsus)	Novo Nordisk	Oral GLP1RA	Phase III	• The OASIS trials are currently investigating higher doses (25 mg and 50 mg daily) of oral Semaglutide for obesity management in IWO or overweight but without T2DM. • The OASIS 1 trial demonstrated that oral Semaglutide 50 mg led to a significant weight loss in participants with overweight or obesity, as reported on 22nd May 2023. At week 68, oral Semaglutide 50 mg users achieved a body weight reduction of -15.1% compared to -2.4% in the placebo group (estimated treatment difference: 1 2.7%, 95% CI: −14.2% to −11.3%; P<0·0001).[26]
Danuglipron (PF-06882961)	Pfizer	Small-molecule GLP1RA (Oral)	Phase IIb	• In a phase I study, 98 participants with T2DM who were taking metformin were randomly assigned to receive different doses of Danuglipron or placebo for 28 days. The study evaluated the drug's safety, tolerability, and pharmacokinetic and pharmacodynamic profiles. Adverse effects such as nausea, dyspepsia, and vomiting were reported, but overall, the drug was well tolerated and showed dose-dependent improvements in glycaemic control. Notably, the 70 mg twice daily dose of Danuglipron resulted in a weight reduction of 4.4 kg at day 28 compared to 1.8 kg for placebo, with a lower incidence of adverse events.[27] • Further clinical development of the drug for the treatment of T2DM and obesity is currently underway. In January 2021, Pfizer initiated a phase IIb trial to evaluate the efficacy, safety, tolerability, and pharmacokinetics of Danuglipron administration in adults with obesity (NCT04707313).
Orforglipron (LY3502970)	Eli Lilly and Company	Non-peptide GLP1RA	Phase III Attain-2 trial (Active and recruiting)	• A phase II study was a 36-week, multi-centre, double-blind RCT comparing the efficacy and safety of Orforglipron (12 mg, 24 mg, 36 mg, or 45 mg) to placebo in IWO or overweight with at least one co-morbidity, excluding T2DM. At the 26-week primary endpoint, different doses of Orforglipron exhibited significant and dose-dependent reductions in body weight. The weight loss ranged from 8.6% to 12.6% (9.0–13.3 kg) compared to 2.0% (2.1 kg) for placebo. By the 36-week mark, individuals taking Orforglipron experienced further decreases in body weight, with reductions ranging from 9.4% to 14.7% (9.8–15.4 kg) compared to 2.3% (2.4 kg) for placebo.[28] • Eli Lilly and Company then launched the phase III Attain-2 trial (NCT05872620).
Dapiglutide	Zealand Pharma	Long-acting GLP1R/GLP2R dual agonist	Phase II (obesity) Phase I (Short bowel syndrome)	• Phase II DREAM trial to assess the effectiveness of once-weekly SC of 4 mg and 6 mg Dapiglutide compared to a placebo over a 12-week treatment period for managing obesity (NCT05788601).

EMA, European Medicines Agency; FDA, Food and Drug Administration; GLP1R, glucagon-like peptide-1 receptor; GLP1RA, glucagon-like peptide-1 receptor agonist; GLP2R, glucagon-like peptide-2 receptor; IWO, individuals with obesity; RCT, randomized controlled trial; SCALE, Satiety and Clinical Adiposity - Liraglutide Evidence; STEP, Semaglutide Treatment Effect in People with Obesity; T2DM, type-2 diabetes mellitus

SURMOUNT-4 (NCT04660643), are investigating the potential of GLP1R/GIPR dual agonism as a new approach to combat obesity. These positive outcomes underscore Tirzepatide's potential in combating obesity in phase III trials.

Another molecule, Maridebart Cafraglutide (AMG133), employs a novel bispecific mechanism targeting GLP1R and GIPR. Unlike Tirzepatide, which acts as an agonist for both receptors, AMG133 is an antagonist for GIPR, providing a distinct feature in the obesity treatment market. Studies have demonstrated that the combined agonism of GLP1R and antagonism of GIPR contribute to weight loss.[57]

Further details related to GLP1R/GIPR dual agonists in the drug development pipeline are summarized in Table 3.

Table 2: AMYRAs and DACRAs in clinical development

Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
Cagrilintide	Novo Nordisk	Long-acting AMYRA	Phase II (obesity)	• In a 26-week study, once-weekly SC injections of Cagrilintide in IWO or overweight resulted in significant weight loss with all doses of Cagrilintide (0.3–4.5 mg, 6.0%–10.8%) versus placebo (3.0%; placebo-subtracted weight reduction 3.0%–7.8%; $P<0.001$). Cagrilintide 4.5 mg resulted in greater weight reduction compared to Liraglutide 3.0 mg (10.8% vs 9.0%; estimated treatment difference: 1.8%, $P=0.03$).[35]
CagriSema	Novo Nordisk	AMYRA/ GLP1RA fixed-dose combination	Phase III (obese non-diabetic; REDEFINE 1) Phase III (obese diabetic; REDEFINE 2)	• Combined with Semaglutide, Cagrilintide produced a more substantial weight reduction in IWO. • In the phase 1b trial, the CagriSema combination for 20 weeks resulted in substantial weight loss (17.1%) compared to (9.8%) with Semaglutide monotherapy; estimated treatment difference of −7.3% [95% CI: −11.2% to −3.5%] for CagriSema 2.4/2.4 vs Placebo/Semaglutide.[36] • The REDEFINE 1 trial (NCT05567796) evaluates the efficacy and safety of CagriSema SC 2.4 mg/2.4 mg once weekly in individuals with obesity or overweight, while the participants in REDEFINE 2 trial (NCT03600480) are individuals with obesity and T2DM.
Petrelintide (ZP8396)	Zealand Pharma	Long-acting AMYRA	Phase 1a (obesity)	• A first-in-human, randomized, single ascending dose trial assessing the safety, tolerability, pharmacokinetics, and pharmacodynamics of ZP8396 administered to healthy subjects demonstrated dose-dependent weight loss of up to a mean of 4.2% in ZP8396-treated individuals compared to 0.6% body weight increase from baseline in placebo-treated individuals (NCT05096598).
LY3841136	Eli Lilly and Company	Long-acting AMYRA	Phase I (obesity)	• A study to evaluate the safety, tolerability, and pharmacokinetics of LY3841136 in healthy and overweight participants (NCT05295940).
LY3541105 (DACRA QW II)	Eli Lilly and Company	DACRA (AMYR/ CALCR dual agonist)	Phase I (obesity)	• A study to evaluate the safety, tolerability, and pharmacokinetics of LY3541105 following single doses in healthy/overweight volunteers and multiple doses in overweight volunteers. DACRA produced substantial weight reduction in preclinical trials (NCT05380323).

AMYR, amylin receptor; AMYRA, amylin receptor agonist; CagriSema, Cagrilintide/Semaglutide; CALCR, calcitonin receptor; DACRA, dual amylin and calcitonin receptor agonist; GLP1RA, glucagon-like peptide-1 receptor agonist; IWO, individuals with obesity; T2DM, type-2 diabetes mellitus

Glucagon

Targeting glucagon signalling has emerged as a potential therapeutic approach for obesity management. Despite its hyperglycaemic effects, the plethora of beneficial effects of glucagon on lipid and energy metabolism encouraged the pharmacological application of glucagon as AOM. Several experimental approaches, including GLP1R/glucagon receptor (GCGR) dual agonists and OXM analogues, have shown promise in pre-clinical and clinical studies. GLP1R/GCGR dual agonists show potential as therapies for obesity and diabetes. They can synergistically induce weight loss, increase energy expenditure, and improve glucose and lipid metabolism.[58] Prolonged use of glucagon boosts energy expenditure, potentially through increased hepatic production of fibroblast growth factor 21 (FGF21) and other central mechanisms.[59] In addition, glucagon decreases lipid stores in the liver and modifies hepatocyte metabolism to mitigate the severity of non-alcoholic steatohepatitis (NASH), a prevalent obesity-related condition.[60] Balanced GLP1R/GCGR dual agonists, resembling oxyntomodulin's effects, effectively enhance glycaemic regulation in mice and humans.[61,62] GLP1R/GCGR dual agonists in clinical development are summarized in Table 4.

Activation of GCGR affects amino acid metabolism, causing hypoaminoacidemia. Further research is needed to understand the impact of GCGR-targeted multi-agonists on whole-body protein turnover, energy expenditure, and lean body mass. Therefore, it is prudent to monitor for any detrimental effects of GCGR agonism on lean body mass and find ways to mitigate hypoaminoacidemia.[76]

The significant success of dual-agonistic strategies for both GLP1R/GIPR and GLP1R/GCGR in clinical trials and the structural similarity between these three peptide molecules (GLP-1, GIP, and glucagon) have encouraged pharmaceutical companies to create chimeric unimolecular triple-agonists for GLP1R, GIPR, and GCGR.[77] In 2014, a highly potent and balanced triple-agonist for these receptors was developed through iterative chemical refinement.[78] The GLP1R/GCGR/GIPR triple-agonist exhibits remarkable effectiveness by harnessing the synergistic actions of GCGR to boost energy expenditure, GLP1R to promote satiety and glycaemic control, and GIPR to enhance insulin release and promote satiety in DIO mice.[78]

Table 3: GLP1R/GIPR dual agonists in clinical development

Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
Tirzepatide (LY-3298176)	Eli Lilly and Company	Acylated long-acting GLP1R/ GIPR dual agonist	FDA/EMA approved (obesity) FDA/EMA approved (T2DM) Phase III (HF, SAS) Phase II (NASH)	• Substantial weight loss is achieved with a comparable safety profile to FDA-approved GLP1RAs. • It is FDA/EMA approved for T2DM based on SURPASS trials.[50–54] • It is FDA/EMA approved for chronic weight management based on the ongoing SURMOUNT trials.[55,56] • Currently, it is under investigation for NASH in the SYNERGY-NASH trial (NCT04166773).
Maridebart cafraglutide (AMG133)	Amgen	GLP1R agonist/ GIPR antagonist*	Phase II (obesity)	• Maridebart cafraglutide (AMG133) offers the advantage of a longer duration of action, requiring administration only once every four weeks (Q4W), reducing the frequency of treatment and potentially improving patient adherence. • Results of the phase I trial demonstrated substantial weight loss among the participants in the multiple ascending doses (MAD) cohort with a mean of−14.5% at its maximum dose (420 mg) compared to 1.49% in the placebo group by day 85 (NCT04478708).[57] • Currently, AMG133 is in phase II (NCT05669599).
CT388	Carmot Therapeutics	GLP1R/ GIPR modulator	Phase I/IIa (obesity)	• Double-blind RCT to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of CT-388 in otherwise healthy overweight and obese adult participants and in obese patients with T2DM (NCT04838405).

*Maridebart Cafraglutide (AMG133) is an antagonist at GIPR and an agonist at GLP1R, unlike Tirzepatide which is GLP1R/GIPR dual agonist.
EMA, European Medicines Agency; FDA, Food and Drug Administration; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP1R, glucagon-like peptide-1 receptor; GLP1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; NASH, non-alcoholic steatohepatitis; RCT, randomized controlled trial; SAS, sleep apnoea syndrome; T2DM, type-2 diabetes mellitus

Table 5 summarizes GLP1R/GCGR/GIPR triple agonists in clinical development.

The development of GLP1R/GCGR/GIPR tri-agonists is in its early stages, requiring further clinical trials to address safety concerns.[84] Nevertheless, the superior efficacy of these tri-agonists compared to dual agonists has been shown in pre-clinical and clinical trials, confirming the efficacy of this approach in maximizing outcomes against obesity and diabetes.

Alternative approaches to harness GCGR pharmacology involve delivering small molecules or nuclear hormones to the liver, such as the glucagon-T3 conjugate. The therapeutic application of these molecular hormones, such as T3, to combat obesity is limited due to the ubiquitous expression of nuclear hormone receptors in various tissues, leading to unintended off-target effects.[4]

T3 enhances lipid catabolism and boosts energy expenditure. However, it can also cause undesired effects such as cardiac hypertrophy, tachycardia, muscle loss, and bone resorption. To target specific tissues, DPP-IV-resistant glucagon was combined with T3, resulting in the Glucagon/T3 conjugate.[85] This innovative conjugate effectively decreased body weight, enhanced glycaemic control, and alleviated NASH symptoms in mice. Notably, the hepatic effects of targeted T3 exposure counteracted the hyperglycaemic impact of glucagon. The Glucagon/T3 conjugate facilitated significant T3 accumulation in the liver, reducing plasma and hepatic cholesterol levels and increasing energy expenditure.[85,86]

PYY

Given the involvement of PYY in appetite control and energy balance, targeting PYY signalling pathways has emerged as a potential therapeutic approach for managing obesity. Synthetic analogues of PYY3–36 are being investigated as potential AOMs. These analogues mimic the effects of endogenous PYY by activating the neuropeptide Y receptor type-2 (Y2R) on the hypothalamus, reducing appetite.[87] PYY analogues are currently being developed as AOMs, either as a monotherapy or combined with GLP1RAs or other receptor agonists. Combination therapies involving GLP1R/Y2R dual agonists, GIPR agonists, amylin, Y5 receptor antagonists, GLP1R/GCGR/Y2R triple agonists, and GLP-1/OXM/PYY triple agonists show promise in weight loss and glucose regulation, with reduced nausea and vomiting.[88] These therapies have synergistic effects, inhibit food intake, and improve metabolic control, making them potential candidates for the treatment of obesity and related conditions. PYY analogues, currently being tested in clinical trials, are summarized in Table 6.

Navigating the pursuit of the ultimate AOM: Benefits and challenges

Obesity is a heterogeneous, complex, and chronic disease that is associated with multiple metabolic, mechanical, and mental co-morbidities. Even a modest reduction in body weight can yield favourable results, and the extent of weight loss corresponds to the degree of improvement in obesity-related conditions.[89,90] [Figure 1].

Table 4: GLP1R/GCGR in clinical development

Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
Cotadutide (MEDI0382)	AstraZeneca/ Medimmune	GLP1R/GCGR dual agonist	Phase II (T2DM/Obesity) Phase II (T2DM) Phase II (T2DM)	• The daily injectable GLP1R/GCGR dual agonist, Cotadutide (MEDI0382), was being developed by AstraZeneca to treat T2DM, obesity, NAFLD, and NASH. Cotadutide exhibited a balanced agonist effect on the GLP1R and GCGR with a ratio of approximately 5:1 GLP1R to GCGR activity.[63] • Clinical trials were conducted in multiple countries and reached phase IIb/III in non-cirrhotic NASH with fibrosis (PROXYMO-ADV, NCT05364931). • Additionally, Cotadudite significantly improved glycaemic control and weight reduction among IWO and T2DM in a 54-week-phase IIb study.[64] • Due to strategic pipeline considerations, the development of Cotadutide has been discontinued in favour of focusing on AZD9550, a once-weekly injectable GLP1RA/GCGR. AstraZeneca will shift its focus to the ever-growing diabetes and obesity market due to the increased utilization of GLP1RA mono-agonists and dual agonists for both indications.[65] AstraZeneca's decision is surprising as NASH has no approved therapies. Other GLP1RAs being developed for NASH include Semaglutide and Tirzepatide.[66] Data suggests that dual agonists such as Cotadutide may be more effective in NASH than mono-agonists.
Survodutide (BI456906)	Boehringer Ingelheim/ Zeeland Pharma	GLP1R/GCGR dual agonist	Phase III (obesity; NASH; T2DM)	• The once-weekly long-acting GLP1R/GCGR dual agonist, Survodutide, is also undergoing development by Boehringer Ingelheim and Zealand Pharma. Initially focused on NASH, there is now a shift in attention towards obesity and its co-morbidities.[67] • Phase 1 studies of Survodutide showed a placebo-adjusted average body weight reduction of 13.8% ± 1.6% among participants in the DS7 group of the MRD study.[68] • In its phase 2 trial involving the obese non-diabetic population, Survodutide demonstrated a weight loss of 14.9% over 46 weeks and reached up to 18.7% in individuals who reached and stayed on the maximum dose of 4.8 mg compared to 2.0% with placebo (NCT04667377).[69] • These "encouraging data" support further study of Survodutide for weight reduction in larger Phase III trials. SYNCHRONIZE-1 (NCT06066515) and SYNCHRONIZE-2 (NCT06066528) are Phase III studies investigating Survodutide in IWO or overweight without T2DM and with T2DM, respectively.[69] • Survodutide has received FDA fast-track designation for adults with NASH.[69]
Mazdutide (IBI-362; LY-3305677; OXM-3)	Eli Lilly and Company; Innovent Biologics	Long-acting OXM analogue (GLP1R/GCGR dual agonist)	Phase III; ongoing (obesity) Phase III; ongoing (Diabetes) Phase II (Diabetes)	• Innovent Biologics conducted a phase I trial to evaluate the efficacy and safety of Mazdutide dosed up to 9 mg and 10 mg. High-dose Mazdutide demonstrated promising results in a 12-week trial, showing significant body weight loss. At week 12, the mean percent change in body weight from baseline was −11.7% in the Mazdutide 9 mg cohort compared to −1.8% in the placebo group (estimated treatment difference of −9.8%; 95% CI: −14.4% to −5.3%; *P*=0.0002). At week 16, the mean percent change in body weight from baseline was -9.5% in the Mazdutide 10 mg cohort compared to -3.3% in the placebo group (estimated treatment difference of −6.2%; 95% CI: −11.5% to −0.9%; *P*=0.024). This suggests its potential as a treatment for moderate-to-severe obesity.[70]

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Table 4: Contd...

Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
				• In a Phase II trial, the Mazdutide 9 mg regimen showed superior body weight loss compared to placebo. At week 24, the estimated treatment difference of the mean percent change in body weight from baseline, Mazdutide 9 mg vs placebo, was −15.4%; 95% CI: −18.8% to −11.9%; *P*<0.0001. This result is particularly encouraging for individuals with moderate to severe obesity.[71] • Phase III GLORY-1 trial to evaluate the efficacy and safety of Mazdutide in Chinese patients with overweight or obese (NCT05607680). The study status is active, not recruiting.
Pemvidutide (ALT-801)	Altimmune	GLP1R/GCGR dual agonist	Phase II (obesity) Phase I (NAFLD/NASH/ T2DM)	• Altimmune conducted a 12-week phase I trial in IWO and overweight volunteers, with participants achieving mean placebo-subtracted weight reductions of 3.3%, 8.7%, and 7.4% at the 1.2 mg, 1.8 mg, and 2.4 mg doses, respectively. AEs were mild to moderate, with no serious AEs nor discontinuation due to AEs reported.[72] • Altimmune started a phase II MOMENTUM trial in April 2022 to test Pemvidutide for obesity (NCT05295875, ALT-801-211). The trial is double-blind and aims to recruit 320 US patients. The main goal is to measure the change in body weight after 48 weeks. Secondary assessments include metabolic and lipid profiles, cardiovascular indicators, and glucose regulation. The first participant is already enrolled. As of August 2022, 167 patients have been assigned, and 25 more join weekly. By September 2022, enrolment was complete, and participants received the initial dosage. In March 2023, interim results on efficacy and safety were published. In September 2023, Altimmune announced the trial's patient dosing completion.
Efinopegdutide (JNJ-64565111; HM12525A)	Hanmi Pharmaceutical; Janssen Pharmaceuticals; Merck and Co	OXM analogue (GLP1R/GCGR dual agonist)	Phase II; discontinued (obesity/T2DM) Phase II; discontinued (obesity) Phase II (NASH)	• Due to issues related to company agreements, Hanmi Pharmaceutical and Merck and Co. entered into an exclusive licensing agreement to develop, manufacture, and commercialize Efinopegdutide to treat NASH. In June 2023, Hanmi Pharmaceutical received Fast Track designation for NASH (NCT04944992).
NN1177	Novo Nordisk	GLP1R/GCGR dual agonist	Phase I (Obesity) Phase I (Obesity) All discontinued	• Novo Nordisk conducted three phase I clinical trials to evaluate the efficacy and safety of NN1177 in IWO. The trial results indicated a significant weight loss of nearly 12.6%. However, unacceptable safety concerns such as tachycardia, reticulocytopenia, elevated inflammatory markers, hepatic disturbances, impaired glucose tolerance, and hypoaminoacidemia have been encountered.[73]
AZD9550	AstraZeneca/ Medimmune	GLP1R/GCGR dual agonist	Preclinical (passed) and recruiting for phase I	• Phase I, first-in-human, randomized single-blind placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of AZD9550 following single ascending dose administration to healthy participants (NCT05848440), is now recruiting.

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Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
DA-1726	NeuroBo pharmaceuticals	Long-acting OXM analogue (GLP1R/GCGR dual agonist)	Preclinical	• DA-1726 demonstrated superior weight loss efficacy compared to Semaglutide in DIO mice and rats, with a higher dose required in rats. It induced dose-dependent weight loss effects and increased the expression of energy metabolism-related genes in white adipose tissues, suggesting increased energy expenditure. After single dosing, DA-1726 resulted in significant weight loss and increased gene expression, indicating a direct effect. These findings suggest that DA-1726 may offer excellent weight loss effects in humans through a novel mechanism.[74]
MK-1462	Merck Sharp and Dohme LLC	GLP1R/GCGR dual agonist	Preclinical	• MK-1462 represents a promising avenue in the development of treatments for metabolic disorders, but it's important to note that its clinical use and approval status may evolve over time.[75]

AEs, adverse events; BMI, body mass index; DIO, diet-induced obesity; FDA, Food and Drug Administration; GCGR, glucagon receptor; GLP1R, glucagon-like peptide-1 receptor; GLP1RA, glucagon-like peptide-1 receptor agonist; IWO, individuals with obesity; MRD, multiple rising dose; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OXM, oxyntomodulin; T2DM, type-2 diabetes mellitus

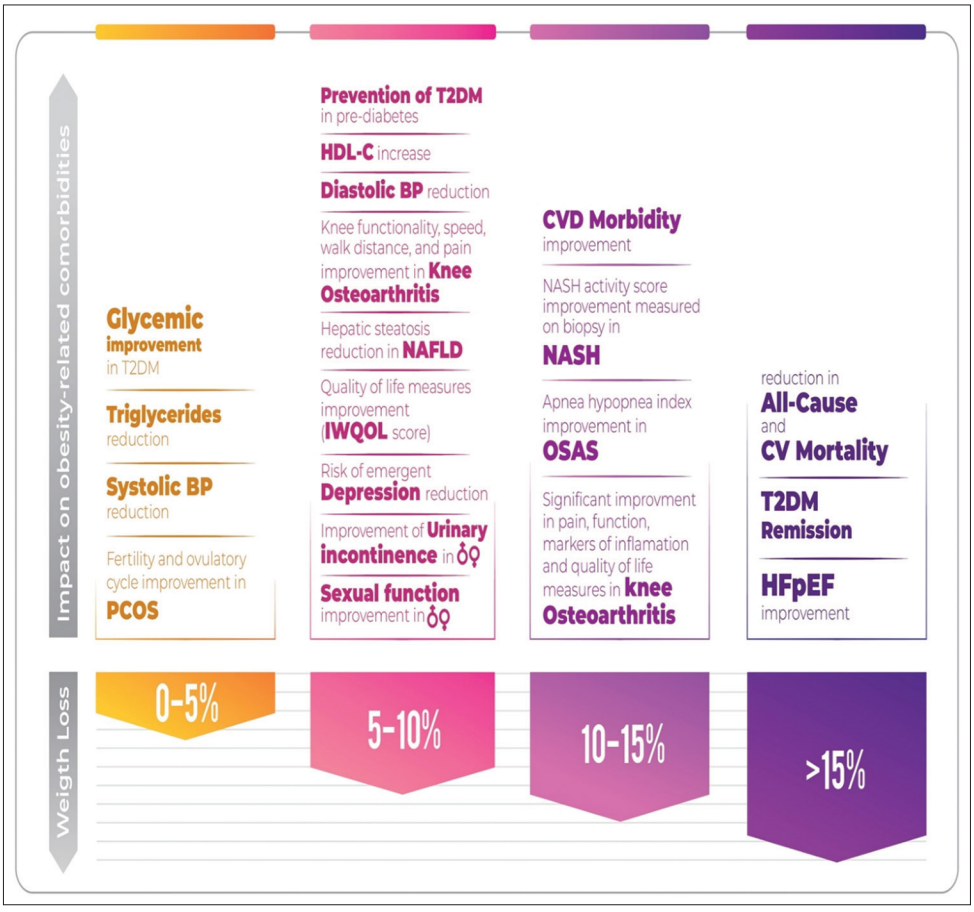

Figure 1: Weight loss impact on obesity-related co-morbidities. Further weight loss is associated with further improvements. BP, blood pressure; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HFpEF, heart failure with preserved ejection fraction; IWQOL, impact of weight on quality of life; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome; T2DM, type-2 diabetes mellitus

AOM development faces challenges [Figure 2]. The heterogeneity of obesity, where genetic and environmental factors impact drug responses, gives rise to considerable intricacies.[5,91] A significant obstacle in weight management is difficulty foreseeing how patients will react to AOMs. A substantial variation exists in how individuals' weight responds to a specific drug.[92] The causes of non-responsiveness have yet to be thoroughly examined. Much like diabetes,

Table 5: GLP1R/GCGR/GIPR triple agonists in clinical development

Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
Retatrutide (LY3437943)	Eli Lilly and Company	GLP1R/ GCGR/GIPR tri-agonist	Phase III (obesity/ CVD) Phase II (T2DM)	• Retatrutide (LY3437943), favouring GIPR but with balanced GLP1R and GCGR activity, demonstrates a safety profile similar to GLP1R mono-agonists. The GLP1R/GCGR/GIPR balance of LY3437943 is 1:1:10. It exhibits a similar safety profile to GLP1R mono-agonists, with mild tachycardia.[79] • In a phase I trial involving healthy individuals, administration of a single dose of LY3437943 was well tolerated and resulted in significant weight reduction, which was sustained for up to 43 days.[79] The results were comparable to four weeks of Tirzepatide injections.[3] The satisfactory safety, tolerability, and efficacy observed in this study support further investigation of LY3437943 using multiple doses in IWO and T2DM • A phase Ib trial involving individuals with T2DM confirmed a significant decrease in blood glucose and weight over 12 weeks of treatment while maintaining tolerability and safety.[80] • The latest findings from a Phase II trial (NCT04881760) revealed that after 48 weeks, the groups receiving 1 mg, 4 mg, 8 mg, and 12 mg doses experienced a decrease in body weight by −8.7%, −17.1%, −22.8%, and −24.2%, respectively, as compared to −2.1% in the placebo group (estimated treatment difference, Retatrutide 12 mg vs Placebo of −22.1%; 95% CI: −24.9% to −19.3%). Additionally, 60% of the participants achieved a weight reduction of 15% or above. In terms of safety, the most common AEs observed were gastrointestinal in nature, indicating that Retatrutide's safety profile is comparable to other incretin-based therapies.[81] Results of phase II were presented in ADA 2023. The historic debut of Retatrutide stole headlines, with weight loss rivalling that of bariatric and metabolic surgery, with weight loss reaching up to 24.2%.[81] • In May 2023, Eli Lilly and Company initiated • a phase III trial (TRIUMPH-3; NCT05882045) to investigate the effects of Retatrutide on individuals with severe obesity and existing CVD. This trial is expected to conclude in November 2025.
SAR 441255	Sanofi	GLP1R/ GCGR/GIPR tri-agonist	Phase I (obesity; T2DM)	• SAR441255 is a synthetic peptide triagonist developed to target multiple receptors, including GLP1R, GCGR, and GIPR. This triagonist is structurally based on the exendin-4 sequence and has shown potential in various studies for improving weight loss and glycaemic control in individuals, particularly in those with obesity and diabetes.[82] • SAR441255 has demonstrated the ability to ameliorate body weight in obese individuals, including diabetic cynomolgus monkeys.[82] • In October 2019, Sanofi reported discontinuation of SAR 441255 development in type 2 diabetes mellitus and obesity
Efocipegtrutide (HM15211)	Hanmi Pharmaceutical	GLP1R/ GCGR/GIPR tri-agonist	Phase II (NASH)	• HM15211, a third GLP1R/GCGR/GIPR tri-agonist peptide, effectively reduces hepatic lipid and body weight in IWO and NAFLD. It is being evaluated in phase II trials (NCT04505436) to treat NASH.[83]

ADA, American Diabetes Association; AEs, adverse events; CVD, cardiovascular disease; GCGR, glucagon receptor; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP1R, glucagon-like peptide-1 receptor; GLP1RA, glucagon-like peptide-1 receptor agonist; IWO, individuals with obesity; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type-2 diabetes mellitus

precision medicine could be the forthcoming approach to weight management, suggesting a personalized strategy based on a patient's profile.[93]

In addition, neuroendocrine systems are central to food regulation. Still, they can impede weight loss by defending against negative energy balance, favouring weight recidivism, and turning obesity into a chronic disease that requires long-term management plans.[94,95] The data concerning weight recidivism observed in the STEP 1 extension study[96] and STEP 4,[21] where participants discontinued Semaglutide, strongly imply that lifelong pharmacological treatment is necessary to counter the adaptive physiological factors that impede long-term weight reduction.[94,95]

The complex phenotype of obesity constitutes another challenge to achieving the desirable weight loss and usually needs combination therapies besides lifestyle modifications.[97] Multi-agonist AOMs, currently in the pre-clinical and clinical trials, exhibit simultaneous activity at several metabolically relevant receptors, offering hope to counteract this complex underlying pathophysiology.[4]

Table 6: PYY analogues in clinical development

Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
PYY 1875 (NN 9775; NNC01651875)	Novo Nordisk	PYY analogue; Y2R agonist	Phase II (obesity)	• The efficacy and safety of PYY 1875 were investigated in a phase II trial as an add-on to semaglutide (NCT04969939).
Nisotirostide (LY3457263)	Eli Lilly and Company	PYY analogue; Y2R agonist	Phase I	• Eli Lilly and company just finished a phase I study that examined the safety, pharmacokinetics, and pharmacodynamics of various quantities of Nisotirostide used together with tirzepatide. The trial, which was randomized, parallel, double-blind, and placebo-controlled, started in November 2022 and included 38 adult and elderly participants in the United States (NCT05582096).

PYY, peptide tyrosine-tyrosine; Y2R, neuropeptide Y receptor type-2

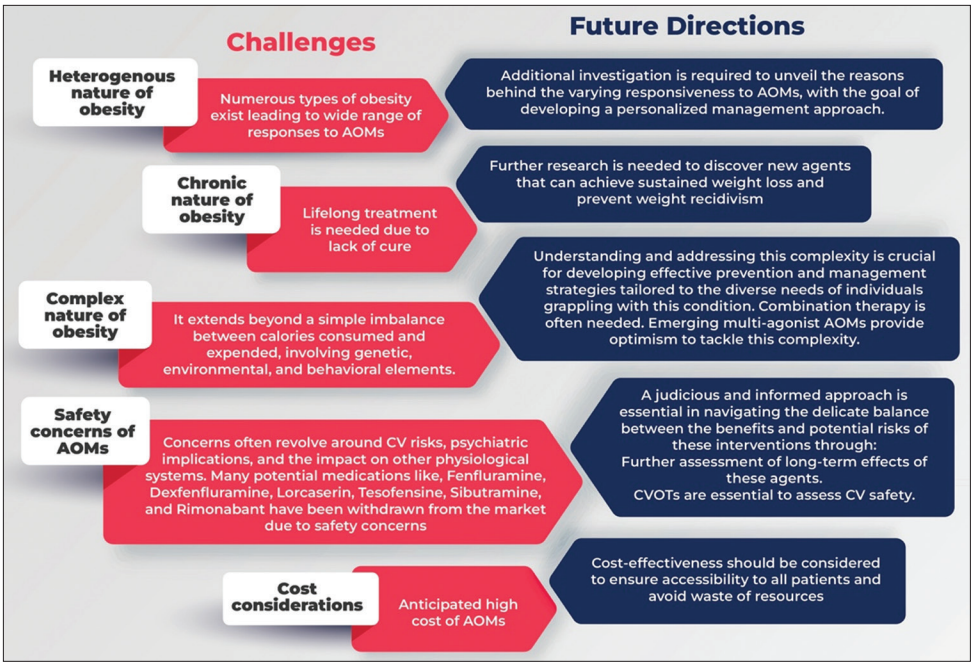

Figure 2: Challenges confronting the development of AOMs and future directions. AOMs, anti-obesity medications; CV, cardiovascular; CVOTs, cardiovascular outcome trials

Safety is paramount for next-generation AOMs, posing a significant challenge for developers.[5] Further long-term clinical trials and evaluation with post-marketing surveillance studies are required to determine the risk-benefit ratio accurately. Cardiovascular safety is a growing concern while developing AOMs, where cardiovascular disease (CVD) is the leading cause of morbidity and mortality in IWO.[98] Many potential medications, such as Sibutramine and Rimonabant, have been withdrawn from the market due to cardiovascular safety concerns.[5,99,100] The need for rigorous evaluation of the cardiovascular safety and benefits of pharmacotherapy has led to the initiation of Cardiovascular Outcome Trials (CVOTs) for AOMs, which aim to assess their cardiovascular safety and benefits. Despite several CVOTs in obesity, many have failed to demonstrate cardiovascular benefits, leading regulatory agencies to establish stringent requirements.[101–103] GLP1RAs have shown cardiovascular risk reduction in T2DM, informing ongoing CVOTs in obesity. The SELECT trial with subcutaneous Semaglutide is an example of such efforts.[104] Table 7 summarizes the CVOTs in obesity that have been conducted to date and those underway.

The high anticipated cost of such AOMs currently in clinical trials, similar to current Liraglutide and Semaglutide costs, adds complexity and should be considered while evaluating the overall cost-effectiveness.[111] This presents a challenge for drug developers, patients, and healthcare systems. Developing effective and safe AOMs demands extensive research and development without guaranteed success. It often takes years of work to bring a new medication to market.

The ideal AOM should produce a sizeable and sustained weight reduction while offering tolerability, safety, and cost-effectiveness.

Take-Home Messages for Healthcare Practitioners (HCPs):

The landscape of obesity management is undergoing a transformative shift with the FDA/EMA approval of novel pharmacotherapies, such as Semaglutide and Tirzepatide,

Table 7: Comprehensive Overview of CVOTs for Hormone-Based AOMs: Completed and ongoing studies

Name	CVOTs/References
Liraglutide 3.0 mg (Saxenda)	• No CVOT directly evaluates the impact of Liraglutide on CV outcomes in IWO without T2DM; all evidence originates from trials carried out among those with both obesity and T2DM, as well as from *post-hoc* analysis of trials conducted in IWO without T2DM. • In the LEADER trial, with 9340 patients with T2DM and established CVD over 3.8 years, Liraglutide demonstrated superior outcomes. The primary composite outcome (3P MACE) occurred less in the Liraglutide group (13.0%) compared to the placebo group (14.9%) (hazard ratio 0.87; 95% CI: 0.78–0.97; P<0.001 for non-inferiority; P=0.01 for superiority). Cardiovascular deaths were fewer in the Liraglutide group (4.7%) than in the placebo group (6.0%) (hazard ratio: 0.78; 95% CI: 0.66–0.93; P=0.007). Overall mortality, non-fatal myocardial infarction, stroke, and heart failure hospitalization rates were also lower with Liraglutide. Gastrointestinal events were the primary adverse events leading to liraglutide discontinuation; pancreatitis incidence was non-significantly lower.[105] • A post hoc analysis using pooled data from a 2-year Phase 2 trial and four Phase 3a (SCALE) RCTs (n=5908). The primary outcome of this analysis was the first occurrence of 3P MACE. This analysis revealed that Liraglutide 3.0 mg was not associated with an increased risk of CV outcomes compared to placebo (hazard ratio: 0.42; 95% CI: 0.17–1.08). Nevertheless, it's crucial to acknowledge that the statistically insignificant outcome stems from the wide confidence intervals and the retrospective assessment of events in two of the included trials.[106]
Semaglutide 2.4 mg (Wegovy)	• Semaglutide 0.5 mg and 1 mg reduced MACE in individuals with T2DM (SUSTAIN 6).[107] • In the Phase-III SELECT trial, with 17,604 participants aged ≥45 years and a BMI ≥27 kg/m^2 with established CVD (MI, stroke, symptomatic PAD) but without established T2DM or HbA1c ≥6.5% over a mean follow-up duration of 38.9 months, Semaglutide 2.4 mg was superior to placebo and met the primary endpoint with a 20% reduction in 3P MACE for patients with overweight or obesity and established CVD (hazard ratio: 0.8; 95% CI: 0.72–0.90; P<0.001). Adverse events leading to Semaglutide discontinuation occurred in 16.6% in the Semaglutide group versus 8.2% in the placebo group (P<0.001).[104]
Oral Semaglutide (Rybelsus)	• No CVOT directly evaluates the impact of oral Semaglutide on CV outcomes in IWO without T2DM • In the PIONEER 6 trial, oral Semaglutide was not inferior to placebo in individuals with T2DM at a high CV risk.[108] • Novo Nordisk initiated the phase III SOUL trial in June 2019 to assess the risk CV events of once-daily oral Semaglutide 14 mg in individuals with T2DM and established ASCVD and/or CKD (NCT03914326). The estimated completion date is July 2024. The primary outcome measure is the time to the first occurrence of any of the adjudicated components of the composite endpoint (3P MACE).[109]
Orforglipron (LY3502970)	• Eli Lilly and Company initiated the ACHIEVE-4 phase III trial in April 2023 to assess the safety and efficacy of Orforglipron compared with insulin glargine in individuals with T2DM and obesity or overweight at increased CV risk (NCT05803421).
CagriSema	• Novo Nordisk initiated the phase III REDEFINE 3 trial in March 2023 to assess the CV safety of once-weekly Cagrilintide/Semaglutide in IWO and established CVD (NCT05669755).
Tirzepatide (LY3298176)	• Eli Lilly and Company initiated the SURPASS-CVOT phase III trial in April 2020 to assess the effect of Tirzepatide compared with Dulaglutide on MACE in individuals with T2DM (NCT04255433).[110] The estimated completion date is October 2024 • Eli Lilly and Company initiated the SURMOUNT-MMO phase III trial in October 2022 to assess the effect of Tirzepatide on the reduction of morbidity and mortality in IWO (NCT05556512). The estimated completion date is October 2027. The primary outcome measure is the time to first occurrence of any component event of composite (all-cause death, non-fatal MI, non-fatal stroke, coronary revascularization, or HF events), while the time to first occurrence of any component event of the 3P MACE is among the secondary outcome measures.
Survodutide (BI456906)	• Boehringer Ingelheim initiated the SYNCHRONIZE-CVOT phase III trial in November 2023 to assess the effect of Survodutide on CV safety in IWO or overweight (NCT06077864). The estimated completion date is April 2026. The primary outcome measure is the time to first occurrence of any of the adjudicated components of the composite endpoint (5P MACE) consisting of CV death, non-fatal stroke, non-fatal MI, ischaemia related coronary revascularisation, or HFE (to demonstrate non-inferiority), while the time to first occurrence of any component event of the 3P MACE (to demonstrate non-inferiority and superiority) are among the secondary outcome measures.
Retatrutide (LY3437943)	• Eli Lilly and Company initiated the TRIUMPH-3 phase III trial in May 2023 to assess the efficacy and safety of Retatrutide in IWO and established CVD (NCT05882045). The estimated completion date is February 2026.

ASCVD, Atherosclerotic Cardiovascular Disease; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CVD, Cardiovascular Disease; CV, Cardiovascular; CVOT, Cardiovascular Outcome Trial; HFE, Heart Failure Event; HF, Heart Failure; IWO, individuals with obesity; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; PAD, Peripheral Arterial Disease; PIONEER, Peptide InnOvatioN for Early diabEtes tReatment; REDEFINE; Research Study to See the Effects of CagriSema in People Living With Diseases in the Heart and Blood Vessels; SCALE, Satiety and Clinical Adiposity - Liraglutide Evidence; SELECT, Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes; SURMOUNT-MMO, A Study of Tirzepatide on the Reduction on Morbidity and Mortality in Adults With Obesity; SURPASS-CVOT, A study comparing Tirzepatide with Dulaglutide in assessing major cardiovascular events in participants with type 2 diabetes; SYNCHRONIZE-CVOT, A Study to Test the Effect of Survodutide on Cardiovascular Safety in People With Overweight or Obesity; T2DM, type-2 diabetes mellitus; TRIUMPH, A Study of Retatrutide in Participants With Obesity and Cardiovascular Disease

opening up new avenues for effective weight loss in IWO without T2DM.[112–115] These advancements mark a new era in obesity care, offering a range of treatment options with diverse mechanisms of action and routes of administration. Clinicians can now tailor obesity treatment towards individualized targets, similar to approaches seen in managing T2DM.[116]

- It is crucial for HCPs to recognize the heterogeneity in treatment responses, with approximately 10%–30% of participants achieving <10% weight loss, especially among those with T2DM.[117,118]
- Adverse events leading to treatment discontinuation are notable, emphasizing the need for a personalized and adaptive approach over time.[118]
- As the field progresses, there is a need for HCPs to actively engage in monitoring and counselling. Monitoring parameters, including heart rate, mood changes, blood glucose, liver function, lipid profiles, and renal function, is essential for the safe use of AOMs. In addition, continuous patient counselling, initiated through empathetic discussions, is crucial. HCPs should guide patients on the indications, risks, benefits, drug interactions, compliance, and necessary lifestyle changes to maximize the benefits of AOMs.[119]
- Moreover, the integration of lifestyle interventions remains pivotal. While new pharmacotherapies offer substantial mean weight loss (15%–25%), a comprehensive approach combining medication with intensive lifestyle interventions can provide additional benefits. HCPs should emphasize the importance of a healthy lifestyle, including increased physical activity and a balanced diet, to optimize overall health outcomes.[118]
- The availability of multiple pharmacological options empowers clinicians to identify effective personalized regimens, considering patient preferences, co-morbidities, safety profiles, and response to treatment. Personalized pharmacotherapy can be further informed by identifying how molecules can directly target specific organ fat deposits. For example, GLP1R/GCGR dual agonists can effectively reduce liver fat content in individuals with NAFLD/NASH compared to using GLP1RAs alone,[60,120] while GLP1RAs, such as Semaglutide 2.4 mg, can reduce epicardial fat, improve physical function, and alleviate symptoms in individuals with heart failure with preserved ejection fraction (HFpEF).[121]
- The long-term efficacy and safety of these new pharmacotherapies, especially in individuals with established CVD, require further investigation. CVOTs will shed light on the benefits and potential risks associated with each molecule.[103]
- Cost-effectiveness and equitable access to these therapies pose challenges, urging HCPs to advocate for fair access and explore strategies for long-term weight loss maintenance.[111]

In summary, HCPs are entering a dynamic phase in obesity management, armed with a spectrum of effective pharmacotherapies. Embracing a personalized, adaptive, and multi-disciplinary approach, combining medication with lifestyle interventions, will be pivotal in optimizing outcomes for IWO. The role of HCPs extends beyond prescription to continuous monitoring, counselling, and advocacy for equitable access to these transformative therapies.

Conclusion

Addressing the obesity epidemic demands a comprehensive understanding of its complexities. The gut-brain axis represents a critical piece of this puzzle, and future research should focus on harnessing metabolic signals to craft innovative and personalized interventions. Moreover, ongoing trials exploring hormone-based therapies offer hope for more effective and targeted treatments. By uniting efforts across various disciplines, we can pave the way towards more successful strategies in combating obesity and improving the overall health and well-being of populations worldwide.

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Authors' contributions

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Conflicts of interest

There are no conflicts of interest.

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