

The evolving landscape of obesity pharmacotherapy

Jonas Petersen¹, Brian Finan², Valdemar B. I. Johansen¹, Timo D. Müller^{3,4,5} & Christoffer Clemmensen¹✉

Abstract

Obesity is a chronic, relapsing disease driven by complex interactions between genetic, environmental, neuroendocrine and behavioural factors. The advent of incretin-based therapies and the expansion to multi-receptor agonist peptides targeting glucagon-like peptide 1 (GLP1), glucose-dependent insulinotropic polypeptide (GIP), glucagon, and amylin receptors has transformed obesity treatment, demonstrating average weight loss of more than 20% in humans and improvements in a broad range of obesity-related comorbidities. In this Review, we trace the recent evolution of obesity pharmacotherapy from GLP1 receptor agonists to next-generation multi-receptor agonists, alongside strategies that incorporate oral formulations, weight-loss quality approaches and tissue-specific drug targeting. We outline major translational and biological challenges, identify key gaps for future research and discuss emerging approaches aimed at achieving durable and scalable obesity treatment.

Sections

Introduction

Obesity drug development landscape

Benefits beyond weight loss and glycaemic control

Emerging treatment concepts

Grand challenges

Concluding remarks

¹Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. ²Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA.

³Institute for Diabetes and Obesity, Helmholtz Diabetes Center, Helmholtz Center Munich, Munich, Germany.

⁴Walther-Straub-Institute for Pharmacology and Toxicology, Ludwig-Maximilians-University (LMU), Munich, Germany.

⁵German Center for Diabetes Research (DZD), Neuherberg, Germany. ✉e-mail: chc@sund.ku.dk

Introduction

The capacity to efficiently store excess energy in adipose tissue has been fundamental to human evolution¹. Although this adaptation, shaped across long timescales, supported survival under conditions of food scarcity, it has become maladaptive in modern environments^{2,3}. Today, obesity is recognized as a complex, chronic disease characterized not solely by excess adiposity but also by ectopic and dysfunctional fat deposits that contribute to physical and metabolic health complications, including type 2 diabetes (T2D), cardiovascular disease, sleep apnoea, joint damage and certain cancers^{4,5}.

Since the 1980s, global obesity rates have risen dramatically^{5,6}. Initially concentrated in urban areas, the prevalence has also increased in rural populations, fuelling the global epidemic and posing one of the most significant health challenges of the twenty-first century⁶. Today, it is estimated that more than one billion people live with obesity, typically defined as a body mass index (BMI) of 30 kg m⁻² or higher⁶. Despite the emergence of more nuanced diagnostic methods⁴ that account for both regional and organ-specific fat deposition, the scale of the obesity epidemic remains overwhelming. Indeed, obesity prevalence is projected to nearly double by 2035, affecting approximately 1.9 billion people, or roughly 25% of the global population⁷.

The widespread belief that obesity is simply the result of eating too much and exercising too little has reinforced stigma by implying that individuals are solely responsible for their condition⁸. This reductionist view ignores the powerful genetic, environmental, neuroendocrine, psychological and socioeconomic factors that shape body size, fat distribution and cardiometabolic health². In reality, lifestyle interventions such as dieting and exercise have been insufficient to achieve sustained weight loss in most individuals^{9,10}. More concerning, although prevention remains the ultimate goal, no effective or scalable preventive public health strategies have yet been identified. Consequently, treatment options are currently limited to two main approaches: bariatric surgery and pharmacotherapy. Although bariatric surgery is effective, it is invasive and impractical to address the scale of the medical need. This underscores the need for safe, accessible, effective pharmacological interventions capable of facilitating weight loss, maintaining it over time and improving overall cardiometabolic health.

Despite the need for effective therapies, the history of obesity therapy has been marked by significant challenges¹¹. Throughout the twentieth century, most attempts to develop obesity medications were unsuccessful owing to either lack of efficacy or intolerable side effects¹¹. This is perhaps not surprising, given that much of our understanding of the physiological and neuroendocrine regulation of energy homeostasis only began to emerge in the 1990s, with discoveries such as leptin, the hypothalamic melanocortin system and the appetite-regulating role of gut hormones, followed by advances in human genetics and the neurobiology of obesity in the early twenty-first century². After decades of limited progress, 2021 marked a major advance with the approval of the once-weekly glucagon-like peptide 1 receptor (GLP1R) agonist semaglutide for the treatment of obesity. With a mean placebo-subtracted weight loss of 10–15% in people with obesity^{12–14}, semaglutide set a benchmark for efficacy, helped to transform obesity care and demonstrated health benefits beyond obesity^{13,15–17}. Tirzepatide, a glucose-dependent insulinotropic polypeptide receptor (GIPR)–GLP1R co-agonist, has shown greater weight-lowering efficacy in people with obesity than semaglutide, reaching mean placebo-corrected weight loss in the region of 15–20%^{14,18}, and additional benefits on certain obesity-related complications^{19,20} and diabetes prevention²¹. We are now witnessing the emergence of next-generation molecules,

including GLP1R–glucagon receptor (GCGR)^{22,23}, GLP1R–GIPR–GCGR tri-agonists²⁴, amylin receptor (AMLNR) agonists^{25–27} and combined GLP1R–AMLNR co-agonists²⁸. These advances are complemented by a diverse pipeline of preclinical and clinical innovations, ranging from oral peptide formulations, oral small molecules, unimolecular peptide–drug conjugates (PDCs), to novel pharmacological targets with differential effects on body composition, energy expenditure, sustained weight loss, feeding behaviours and systemic inflammation that are orthogonal to incretins, offering continued hope for the future management of obesity and cardiometabolic diseases to enhance health-span²⁹.

In this Review, we outline the current landscape of pharmacotherapies for obesity management, focusing on drug candidates currently in clinical development, and examine the potential of emerging obesity therapies to address a broad spectrum of chronic comorbidities beyond weight loss. Ongoing challenges, and novel preclinical concepts with the potential to address them, are discussed.

Obesity drug development landscape

Pharmacological treatments for obesity date back to the late nineteenth century¹¹. Throughout most of the twentieth century, drug development focused primarily on small molecules that suppress appetite via modulation of central monoaminergic pathways, including dopamine, noradrenaline (also known as norepinephrine) and serotonin¹¹. Although a few agents from this era remain in clinical practice, such as phentermine–topiramate and bupropion–naltrexone, these therapies typically achieve no more than ~10% reduction in body weight at tolerable doses when used chronically^{30–34}. Their long-term use is further limited by adverse effects, including cardiovascular risks (for example, hypertension, valvular heart disease) and neuropsychiatric complications (for example, mood changes, anxiety, insomnia)^{30–34}. Other approaches, such as lipase inhibitors and α -glucosidase inhibitors, act by limiting nutrient absorption and provide an alternative mechanism for modest weight reduction^{35,36}.

At the start of the twenty-first century, peptide-based drug development emerged with the intention to capture the physiological effects of neuroendocrine hormones³⁷. The advent of half-life-extending technologies³⁸ (Box 1) and the roadmap to the rational design of unimolecular peptide-based multi-agonists³⁹ represented transformative advances in peptide drug discovery during this era (Fig. 1). These innovations, building on improved understanding of incretin biology and energy homeostasis, enabled the development of highly effective therapies for the management of both obesity and T2D. Furthermore, these therapies are capable of inducing more than 10% weight loss, with a potential beyond 20%⁴⁰ (Fig. 2), and normalizing glycated haemoglobin (HbA_{1c}) levels in individuals with and without obesity⁴¹.

GLP1R agonism

The story of GLP1 has unfolded over several decades. For much of this time, research focused on its role in glucose homeostasis and its therapeutic potential in T2D, with comparatively little attention to body weight regulation and obesity. In the 1980s, scientists identified GLP1 as an incretin hormone that enhances glucose-dependent insulin secretion^{42–47}, catalysing drug discovery programmes targeting GLP1R agonism for T2D. The inherent pharmacokinetic limitations of native GLP1, which result from rapid proteolytic inactivation by dipeptidyl peptidase 4 (DPP-IV)⁴⁸ and fast renal clearance⁴⁹, necessitated chemical optimization to create molecules with viable therapeutic properties. The first GLP1R agonist to gain regulatory approval in the USA in 2005

Box 1 | Half-life-extending technologies for biopharmaceuticals

The clinical utility of peptides and proteins has long been limited by short plasma half-lives due to proteolytic digestion, renal excretion and receptor-mediated clearance³⁹⁰. Coupled with poor oral bioavailability, these modalities often necessitate frequent injections, compromising patient adherence and efficacy. To overcome these limitations, molecular engineering strategies have been developed to increase molecular size or enable endosomal recycling via the neonatal Fc receptor, resulting in prolonged systemic exposure. Among these, fatty acid acylation and Fc-fusion represent the most clinically advanced and widely adopted strategies within obesity drug development.

Fatty acid acylation has emerged as a versatile strategy to prolong the half-life of peptide therapeutics by leveraging albumin's natural role as a fatty acid transporter to retain peptides in systemic circulation and by promoting oligomerization at the injection depot to slow absorption into the bloodstream³⁸. The strategy was originally devised within the context of diabetes research by coupling a myristic acid directly to the side chain of LysB29 of human insulin³⁹¹. Importantly, it was found that the length of the fatty acid chain profoundly influenced both the rate of absorption to the bloodstream and the binding affinity towards albumin, and consequently the *in vivo* half-life^{392–394}. Additional insights were obtained from structure–activity relationship studies, leading to the development of liraglutide and insulin degludec, showing that the insertion of a hydrophilic γ -Glu spacer between the fatty acids and the peptides improved parameters such as albumin binding affinity, oligomerization and aqueous solubility^{53,395}. Finally, pivotal studies leading to the discovery of semaglutide revealed that fatty diacids confer significantly stronger binding to human serum albumin than the corresponding fatty monoacids⁵⁹. Moreover, further exploration of the chemical nature of the spacer revealed that incorporation of a hydrophilic linker with two amino-3,6-dioxoactanoic acid (OEG) units further enhanced albumin binding affinity, proteolytic stability

and overall pharmacokinetic properties, enabling once-weekly dosing in humans^{12,59}. Notably, although the presence of 2% albumin has been shown to reduce the *in vitro* GLP1R affinity of semaglutide and similar analogues, this reduction does not impact their efficacy *in vivo*⁵⁹. Notably, variations of the fatty diacid protraction strategy and extended hydrophilic linkers are now used in most long-acting peptides in clinical development for obesity treatment, including cagrilintide²⁵, tirzepatide¹¹⁰, retatrutide²⁴ and survodutide¹⁶².

Fc-fusion represents another clinically well-established strategy for extending the half-life of biologics by harnessing the intrinsic pharmacokinetic properties of the IgG Fc domain³⁹⁶, a feature that has been successfully applied in several approved therapeutics, including the once-weekly GLP1 analogue, dulaglutide, approved for management of T2D³⁹⁷. The prolonged systemic exposure observed with Fc-fusion proteins arises from two key mechanisms. First, the addition of the Fc domain increases the hydrodynamic radius of the fusion construct by approximately 50 kDa, thereby reducing renal filtration³⁹⁰. Secondly, the Fc domain interacts with neonatal Fc receptors in the endosomal compartments, enabling selective recycling of the protein back into systemic circulation, thus escaping degradation via lysosomal pathways^{398,399}. Recent studies have demonstrated that combining fatty acid acylation with Fc-fusion synergistically improves the pharmacokinetics of insulin, suggesting that this dual approach could be a promising and universally applicable strategy to develop once-monthly peptide-based obesity therapies⁴⁰⁰. Albumin similarly converges on the neonatal Fc-receptor recycling pathway, and chemical conjugation of peptides to albumin has emerged as a half-life extension strategy analogous to Fc-fusion, most notably demonstrated by albiglutide for the treatment of T2D⁴⁰¹. Furthermore, engineering efforts aimed at enhancing Fc receptor binding affinity at acidic pH have opened avenues to extend half-life beyond native levels, applicable to both Fc- and albumin-based platforms^{402–404}.

was exenatide for the treatment of T2D⁵⁰. It is a synthetic version of a 39-mer peptide isolated from the saliva of the Gila monster that has a glycine residue instead of an alanine residue at position 2, making it more resistant to DPP-IV cleavage; however, its circulatory half-life remains relatively short owing to rapid elimination via glomerular filtration⁵¹. In people with T2D, exenatide administered as twice-daily subcutaneous injections, typically before meal ingestion, showed promising glycaemic effects that coincided with a modest reduction in body weight⁵². Exenatide marked the first therapeutic proof of concept that GLP1R agonism could be translated into meaningful clinical benefit, validating decades of physiological research, but at the same time highlighted the fundamental pharmacokinetic challenges of short half-life and frequent dosing that would drive the next wave of molecular innovation³⁷.

To improve the pharmacokinetics of GLP1 analogues, fatty acids were used to convey reversible binding to serum albumin with the goal of extending the circulatory half-life of biopharmaceuticals (Box 1). Positional scanning of the GLP1 peptide sequence identified several sites amenable to fatty acid derivatization, and through iterative chemical optimization, the first once-daily GLP1R agonist, liraglutide, was developed and approved for T2D in 2009 in Europe, and in 2014 as

the first GLP1R agonist for obesity treatment⁵³. The anorectic actions of GLP1 were discovered in 1996 (refs. 54,55), but at the time, obesity was not widely recognized as a disease, and drug development during this era was fraught with challenges¹¹. These factors might have limited prioritization of, and investment in, GLP1-based approaches for obesity therapy. However, in the landmark SCALE obesity and pre-diabetes trial, once-daily administration of 3.0 mg of liraglutide for 56 weeks in people with obesity without diabetes resulted in a placebo-corrected weight loss of 5.4%⁵⁶, and continuation for 3 years maintained weight loss and reduced the risk of developing T2D⁵⁷. Importantly, during the clinical development of liraglutide, gradual dose escalation was found to reduce the rate of gastrointestinal adverse effects, allowing patients to tolerate higher doses and potentially achieve additional therapeutic benefits⁵⁸.

To improve the relationship between the pharmacokinetics and pharmacodynamics of liraglutide, further chemical refinement of the half-life-extending technology was undertaken, most notably by introducing a C20 diacid that confers stronger binding affinity to human serum albumin (Box 1), and incorporating protection against DPP-IV cleavage, resulting in the discovery of the once-weekly analogue semaglutide⁵⁹. Both liraglutide and semaglutide were engineered to

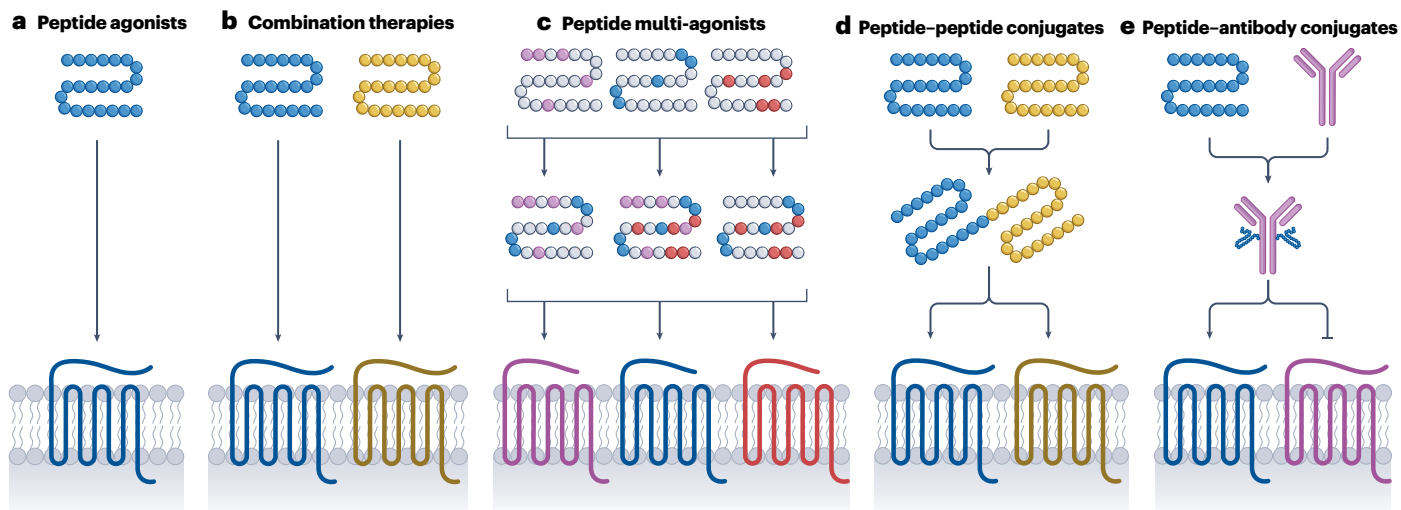


Fig. 1 | Peptide-based molecular formats in obesity pharmacotherapy. **a**, Short- and long-acting peptide receptor agonists (for example, semaglutide, dulaglutide, cagrilintide). **b**, Combination therapy of two or more molecules in a single formulation (for example, CagriSema, tirzepatide + eloralintide). **c**, Unimolecular peptide receptor agonists are single molecules engineered to activate two or more hormonal pathways (for example, tirzepatide, retatrutide,

survodutide) within one peptide backbone. **d**, Peptide-peptide fusion conjugates are engineered formats in which two distinct bioactive peptides (for example, amycretin/zenagamtide) are covalently linked head to tail. **e**, Peptide-antibody conjugates comprise one or more peptides covalently linked to an antibody (for example, maridebart cafraglutide or Fc-fusion conjugates).

structurally resemble native GLP1, minimizing amino acid substitutions in the peptide backbone, partly to reduce the likelihood of anti-drug antibodies that had been observed for exenatide and taspoglutide^{60–62} and partly to simplify biosynthetic manufacturing.

Semaglutide 1.0 mg was initially evaluated in patients with T2D, where it delivered significant glycaemic control alongside a modest placebo-subtracted weight loss of 3.9% over 30 weeks⁶³. These results marked a step change in the chronic management of obesity in patients with T2D, and suggested that greater weight loss might be achievable at higher dose levels. In the STEP 1 trial, 68 weeks of treatment with semaglutide 2.4 mg reduced body weight by 12.5% relative to placebo in people with obesity without T2D¹². Additional weight loss can be achieved with three times higher doses, resulting in an 18.3% placebo-adjusted body weight reduction over 72 weeks in people with obesity without T2D⁶⁴. Based on these clinical data, semaglutide 7.2 mg gained regulatory approval for weight loss in 2026⁶⁵. In contrast, reduced efficacy has been observed in patients with obesity and T2D, resulting in a 6.2% placebo-corrected body weight reduction over the course of 68 weeks⁶⁶. A dose-ranging trial demonstrated that escalating the weekly dose of semaglutide from 2.4 mg to 16.0 mg could generate a greater placebo-subtracted weight loss of 7.8% over 40 weeks (including 24 weeks of dose escalation)⁶⁷. However, the trial also revealed that dose escalation amplifies treatment-emergent gastrointestinal adverse effects and discontinuation rates, highlighting that greater efficacy may come at the cost of compromising tolerability. Cessation of semaglutide treatment results in weight regain and recurrence of obesity and associated risk factors for cardiometabolic diseases^{68,69}, and hence, weight loss maintenance is intrinsically dependent on long-term adherence to treatment⁷⁰. Emerging clinical data indicate that tapering off semaglutide slowly instead of abruptly may support the maintenance of lost weight for at least 26 weeks⁷¹. However, the evidence base is limited, and the causal contribution of drug tapering remains uncertain.

Innovation in the field of GLP1R agonism continues with advances in peptide design and receptor pharmacology converging to enhance efficacy, durability and tolerability. Biased agonism offers the opportunity to selectively modulate intracellular signalling to optimize clinical benefit (Box 2), and breakthroughs in absorption enhancement and small-molecule chemistry have enabled the development of the first peptide-based and non-peptide, orally active GLP1R agonists, respectively. Furthermore, continued efforts to improve the pharmacokinetics of GLP1R agonists have yielded molecules with progressively longer half-lives and sustained receptor engagement. The clinical candidate MET-097i, leveraging a lipidation-based, ultra-high-affinity albumin binding strategy, exemplifies this progress with a half-life of 15–16 days supporting once-monthly dosing in humans⁷². This molecule induced a 14.1% placebo-subtracted weight loss over 28 weeks in people with obesity without T2D, approaching the efficacy of unimolecular dual incretins despite acting selectively through the GLP1R⁷³. Furthermore, oral once-quarterly GLP1 therapies are being explored for enhanced weight-loss maintenance⁷⁴, alongside gene-encoded incretin approaches designed to achieve durable, physiological GLP1 secretion⁷⁵.

Central pathways mediating the weight-reducing effects of GLP1R agonists. Central to the anorexigenic effect of GLP1R agonists is their ability to modulate both homeostatic and hedonic feeding circuits across various brain regions, with particular emphasis on direct signalling in the hypothalamus and brainstem^{76–78}. A cumulative body of evidence suggests that systemically administered GLP1R agonists achieve direct central nervous system (CNS) target engagement predominantly at circumventricular and periventricular-adjacent sites with limited penetration of the intact blood–brain barrier, including the area postrema and median eminence, with downstream recruitment of broader hindbrain and hypothalamic circuits^{76,77,79,80}. Where hypothalamic access is observed, it may involve tanycyte-mediated transport at the median eminence⁸¹.

Initial studies using loss-of-function rodent models and fluorescently labelled liraglutide highlighted a crucial role for GLP1Rs on pro-opiomelanocortin (POMC) neurons in mediating the weight-lowering effects of this drug class^{77,82}. However, more recent preclinical evidence suggests that brainstem GLP1R-expressing glutamatergic neurons are the primary mediators of the appetite- and weight-reducing effects of long-acting GLP1R agonists^{83–86}. Yet, no single brain region has been identified as solely responsible for these effects in rodents, nor should it be expected, and studies unravelling the nuanced central mechanisms behind the weight-lowering actions of GLP1R agonists are ongoing^{76,83,84,87}. It is clear, however, that activation of GLP1Rs in the area postrema of the brainstem in rodents contributes to the gastrointestinal aversive effects of GLP1R activation^{83,84,88}. Some studies suggest that selectively targeting GLP1Rs in the nucleus of the solitary tract could be a strategy to achieve appetite suppression without nausea, whereas others indicate that the food intake-lowering effects are inseparable from the aversive effects^{83,84}.

GLP1R and GIPR co-targeting

It remains enigmatic that both GIPR agonism and antagonism, whether alone or in combination with GLP1R agonism, result in comparable weight-loss outcomes. The rationale for GIPR antagonism derives from human genetic studies linking inactivating mutations in the receptor to a lower BMI^{89,90}. However, attempts to leverage pharmacological GIPR antagonism for obesity treatment using antibody- and peptide-based modalities have only yielded moderate weight-loss efficacy in preclinical studies^{91–95}. Instead, co-treatment with GLP1R agonists results in synergistic metabolic improvements in both mice and non-human primates^{91,92,95}. The investigational drug maridebart cafraglutide (MariTide), constructed by conjugation of two GLP1 analogues to a GIPR antagonist antibody⁹⁴, reached maximum plasma concentrations after 4–6 days with a half-life of 23 days in humans following subcutaneous administration, enabling once-monthly dosing⁹⁶. Phase II clinical trials with maridebart cafraglutide revealed an average placebo-adjusted weight loss of 17.3% in individuals with obesity without T2D and 15.6%

loss in individuals with obesity and T2D over 52 weeks⁹⁷. Gastrointestinal adverse events were common and moderately less frequent with dose escalation and a lower starting dose. An extension of this study showed that a large majority of patients who had achieved significant weight loss in the initial 52-week period were able to maintain their weight loss when given lower or less frequent doses of the drug in the second year of treatment, with favourable tolerability and no new safety signals reported⁹⁸.

Somewhat counterintuitively, transgenic overexpression of endogenous glucose-dependent insulinotropic polypeptide (GIP) and pharmacological dosing of long-acting GIPR agonists both effectively promote weight loss and improve glucose homeostasis in rodents^{99–104}. Mounting preclinical evidence indicates that the pharmacological effects of GIPR agonism on food intake suppression are mediated via the CNS^{103–105}, whereas the glucometabolic benefits appear to involve both direct weight loss-independent actions on the endocrine pancreas^{106,107} and weight loss-dependent improvements in insulin sensitivity¹⁰⁸. Biochemically optimized GIPR agonists lower body weight and food intake in *Gip1r*-knockout mice, but not in *Gipr*-knockout mice, supporting the therapeutic utility of coordinated agonism at both receptor systems^{100,104}.

The first unimolecular peptide designed to harness coordinated activation of the GLP1R and GIPR was reported in 2013¹⁰². This molecule demonstrated superior metabolic outcomes in both rodents and non-human primates relative to an appropriately matched GLP1R agonist; however, the translational benefits in humans were underwhelming, demonstrating only marginal improvements in body weight and glycaemic control relative to open-label liraglutide¹⁰⁹. Although this prototypical peptide was discontinued, it demonstrated the feasibility of the dual-incretin concept, fuelling the continued drug development efforts that led to tirzepatide, the first dual agonist molecule to gain regulatory approval for treatment of obesity. Tirzepatide was engineered by chemically modifying the peptide sequence of human GIP to confer GLP1R activity, and conjugating a C20 fatty diacid-based half-life extender to the lysine in position 20

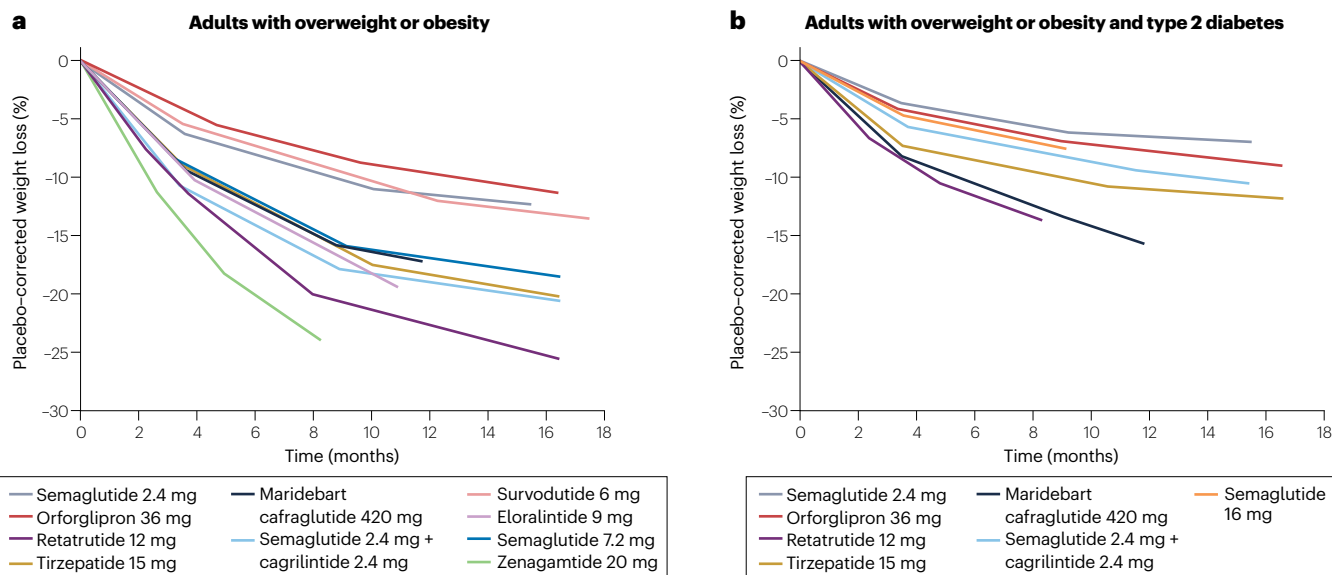


Fig. 2 | Placebo-corrected efficacy estimand weight loss in advanced obesity pharmacotherapy trials. a, Schematic of placebo-corrected weight loss in people with overweight or obesity without type 2 diabetes. **b**, Schematic

of placebo-corrected weight loss in people with overweight or obesity and type 2 diabetes.

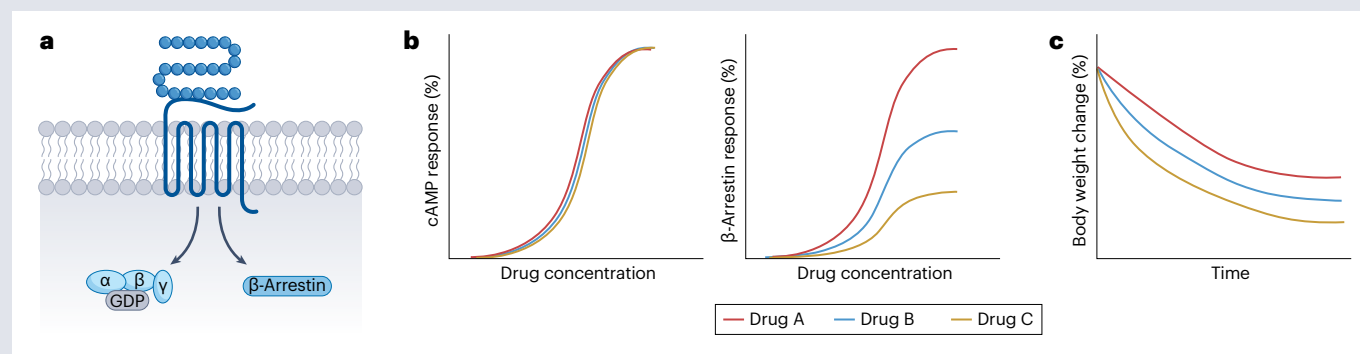
Box 2 | Biased agonism

Historically, obesity drug development emphasized sustained receptor activation through pharmacokinetic optimization. However, accumulating evidence indicates that signalling bias, that is, preferential activation of specific intracellular G protein-coupled receptor (GPCR) pathways (panels **a** and **b**), can meaningfully influence therapeutic outcomes (panel **c**). Tirzepatide, for instance, exhibits biased agonism at the glucagon-like peptide 1 receptor (GLP1R), favouring GPCR signalling over β -arrestin recruitment, a feature that contributes to its glucose- and weight-lowering effects in preclinical models¹¹¹. This may be explained by the fact that β -arrestin facilitates receptor desensitization and internalization, a process leading to lower receptor availability at the plasma membrane and, consequently, reduced GLP1R signalling^{111,112}. These pivotal findings prompted a shift in anti-obesity drug discovery towards harnessing biased signalling⁴⁰⁵.

Although the interpretation of tirzepatide data is complicated by its dual GLP1R and GIPR activity, human pharmacogenomic evidence supports the translational relevance of biased GLP1R agonism¹¹³. Individuals carrying rare β -arrestin 1 loss-of-function variants confer enhanced glycaemic responsiveness to GLP1R agonists, achieving greater HbA_{1c} reductions despite similar baseline blood glucose levels¹¹³. Although the weight-lowering effects in these individuals remain untested, preclinical studies show that biased GLP1R agonists elicit more efficacious and durable improvements in glycaemic control and body weight than unbiased agonists^{115,406}. However, to fully comprehend whether biased signalling results in improved clinical outcomes, dedicated head-to-head trials comparing

pharmacokinetically matched biased and unbiased agonists are warranted.

As multi-receptor agonists advance, detailed pharmacological profiling becomes increasingly complex, and nuanced evaluation is crucial for candidate selection in early drug development. However, biased signalling at other class B GPCRs than the GLP1R remains comparatively underexplored. For example, although several studies have shown that genetic deletion of β -arrestin in isolated pancreatic β -cells and in vivo impairs glucose-dependent insulinotropic polypeptide (GIP)-mediated insulin secretion and glucose regulation^{89,111,407}, more recent pharmacological evidence suggests that signalling bias towards cAMP at the glucose-dependent insulinotropic polypeptide receptor (GIPR) may provide more sustained metabolic benefits¹³⁶. However, minimal β -arrestin recruitment may not always be beneficial. For instance, β -arrestin engagement at the glucagon receptor (GCGR) can promote receptor internalization⁴⁰⁸, potentially limiting hepatic glucose output and dampening glucose excursions⁴⁰⁹. Finally, fatty acid acylation is commonly used to extend the circulatory half-life of peptides; however, prolonged activation of the GLP1R and GIPR has been proposed to drive temporal receptor desensitization^{410,411}. Hence, biased signalling may provide a solution to overcome this challenge and achieve more sustained therapeutic efficacy. Optimizing multiple parameters across several target receptors presents a complex challenge for traditional structure–activity relationship campaigns, akin to solving a Rubik’s Cube in which each move affects the entire system.



to support once-weekly administration in humans¹¹⁰. Mechanistically, tirzepatide activates the human GIPR with similar potency to native GIP, but differs in its molecular pharmacology at the human GLP1R, with 13-fold lower potency compared with native GLP1¹¹¹. Of note for preclinical testing, tirzepatide is 75-fold less potent at the mouse GIPR relative to the human isoform, corresponding to the observation that co-administration of a mouse GIPR agonist and tirzepatide results in additional weight loss in diet-induced obese mice¹⁰⁵. Tirzepatide acts as a biased agonist at the GLP1R, strongly promoting intracellular cAMP production while eliciting reduced β -arrestin recruitment^{111,112} (Box 2). The biased signalling profile may beneficially impact receptor desensitization to provide sustained activation of the GLP1R and may explain the observation that tirzepatide displays superior

weight-lowering efficacy relative to semaglutide in GIPR-deficient mice^{105,113–115}.

The effectiveness of tirzepatide has been characterized in multiple clinical trials evaluating its efficacy for the management of both obesity and weight-related comorbidities^{41,116–120}. After 72 weeks of treatment, tirzepatide reduced body weight in individuals with obesity by 20.1% relative to placebo¹⁸. In participants with obesity and T2D, the same treatment duration resulted in a lower placebo-corrected body weight reduction of 12.4%¹²¹. A clinical trial is currently investigating whether higher doses of tirzepatide (20.0 mg and 25.0 mg) may provide additional weight-loss benefits in patients with obesity and T2D (NCT06037252). A real-world analysis, alongside findings from the SURMOUNT 5 trial, demonstrated that treatment with

tirzepatide resulted in significantly greater weight loss compared with semaglutide with a generally similar incidence of gastrointestinal adverse event-related treatment discontinuations^{12,14,18,122}. The enhanced efficacy of tirzepatide relative to semaglutide may arise from several mechanisms, such as engagement of complementary GIPR-driven satiety pathways^{103,104}, stimulation of adipose tissue futile cycling¹²³, biased agonism at the GLP1R^{105,111,115}, the anti-aversive effects of GIP enabling escalation of the GLP1R agonism component^{124–126} or a combination thereof. Tirzepatide was also associated with greater weight loss compared with the combination therapy CagriSema in an open-label head-to-head phase III clinical trial¹²⁷. Preceding tirzepatide therapy with intensive lifestyle intervention enhanced maximal attainable weight-loss outcomes¹²⁸, although this strategy appears to be broadly effective for incretin-based therapies^{129,130}. Sustained weight loss requires continued treatment; that is, treatment with tirzepatide for up to 3 years was able to maintain an 18.4% placebo-corrected weight loss²¹, whereas a switch to placebo resulted in immediate and rapid weight regain¹³¹ and recurrence of cardiometabolic risk factors¹³². Adherence to treatment was further associated with a 94% reduction in the risk of developing T2D in adults with obesity and prediabetes²¹.

Several other GLP1R–GIPR co-agonist programmes are advancing through clinical development. KAI-9531 is a long-acting GLP1R–GIPR dual agonist with a half-life of 7–8 days in healthy people, demonstrating substantial improvements in glycaemic control and 21.1% placebo-subtracted weight loss in individuals with obesity over 36 weeks¹³³. Based on these results, KAI-9531 is now advancing into phase III clinical trials for the treatment of obesity and T2D. Roche is advancing two dual GLP1R–GIPR co-agonist molecules with promising clinical profiles, namely CT-868 and CT-388^{134,135}. These molecules were identified using chemotype evolution, a fragment-based drug discovery platform that enables rapid synthesis and screening of target-focused chemical libraries, and differ from other GLP1R–GIPR co-agonists by having an N-terminal cap that confers dually biased agonism at the human isoforms of both target receptors¹³⁶. In preclinical studies, a tool compound exhibiting comparable dually biased agonism at the murine isoforms of the GLP1R and GIPR produced superior improvements in glycaemic control and body weight compared with pharmacokinetically matched, biased mono-agonist control compounds¹³⁶. Treatment with CT-388, a once-weekly subcutaneous injectable for obesity and T2D, induced a 22.5% placebo-adjusted weight reduction after 48 weeks in a phase II trial without reaching a stable weight-loss plateau¹³⁷. Meanwhile, BGM0504, a C-terminally lipidated co-agonist designed with artificial intelligence to have enhanced receptor potency relative to tirzepatide¹³⁸, showed promising weight reduction in early-phase trials, supporting its potential as a next-generation therapy¹³⁹. Finally, olatorepatide, licensed by Regeneron, showed up to 19.0% weight loss at 48 weeks in a phase III trial in Chinese adults with overweight or obesity, positioning it among the more competitive late-stage obesity therapies pending global validation¹⁴⁰.

Central mechanisms engaged by GIPR-targeting therapies.

Although preclinical studies suggest that tirzepatide-induced weight loss reflects both appetite suppression and blunting of metabolic adaptation (a disproportionate decline in energy expenditure relative to the amount of weight lost), clinical data indicate that this metabolic protective effect is not preserved in humans¹⁴¹. Instead, a 6-week randomized phase I trial suggested that tirzepatide lowers body weight primarily by decreasing energy intake, suppressing appetite and food cravings, and dampening neural responses to high-fat and high-sugar

food cues, consistent with effects on ingestive behaviour and food reward¹⁴². In a single-participant intracranial recording case report, tirzepatide exposure was associated with changes in patient-reported food preoccupation, sometimes referred to as food noise¹⁴³, alongside modulation of nucleus accumbens activity, implicating the mesolimbic reward circuitry¹⁴⁴. Complementing these findings, emerging mechanistic data are beginning to map the differential and synergistic neural mechanisms that underlie the enhanced weight-loss benefits achieved by either coordinately agonizing or antagonizing GIPRs in combination with GLP1R agonism. Long-acting GIPR agonists act in the brain^{104,145–147}, with evidence implicating GABAergic neurons^{103,105}, to suppress appetite. This is consistent with findings showing that stimulation of endogenous GIP secretion lowers food intake and body weight, and that these effects are abolished by intracerebroventricular pre-treatment with a GIPR-blocking antibody¹⁴⁵. Similar to GLP1R agonists, emerging evidence implicates the hindbrain as a key site for GIPR agonism-induced weight loss^{103,146,148}, consistent with data showing that hypothalamic GIPRs are dispensable for the weight-lowering effects of combined GLP1 and GIP therapy and that hindbrain GIPR circuits can relay satiety signals to the hypothalamus¹⁴⁶.

Both GLP1R and GIPR agonists can indirectly suppress AgRP neuron activity, a key driver of feeding¹⁴⁹. Yet, GIP, but not GLP1, is required for the nutrient-dependent inhibition of AgRP neurons, underscoring the distinct central actions of the two incretin hormones¹⁴⁹. Divergent CNS actions of GLP1 and GIP are further supported by single-cell RNA sequencing in mouse and human hypothalamus. Whereas GLP1R is expressed in both neuronal and non-neuronal populations, GIPR expression appears to be comparatively enriched in non-neuronal cell types such as pericytes, oligodendrocytes and vascular smooth muscle cells^{150–152}. These distinct expression patterns and mechanisms suggest a molecular synergy that could explain the enhanced weight loss observed with dual GLP1R–GIPR co-agonists. For instance, studies conducted in mice indicate that pharmacological activation of GIPRs in oligodendrocytes increases vascular permeability at the barrier between the median eminence and arcuate nucleus, facilitating enhanced uptake of peripherally dosed GLP1R agonists into hypothalamic sites¹⁵³. Finally, GIPR agonism may also mitigate the nausea commonly associated with GLP1R agonists in both preclinical^{124,126} and clinical settings¹⁵⁴. One proposed mechanism involves GIPR expression in GABAergic neurons within the area postrema, which, upon activation, may inhibit excitatory glutamatergic GLP1R-expressing neurons to reduce aversive effects^{86,105}.

Conversely, the observation that GIPR antagonism also effectively enhances GLP1-induced weight loss in humans presents a contrasting, yet equally fascinating, mechanistic paradigm. This effect does not reflect a simple reversal of GIPR signalling; instead, antagonists appear to enhance weight loss through differential mechanisms that involve disinhibition of central anorectic pathways. This hypothesis is supported by studies revealing that disruption of GIPR signalling in rodents either globally or in the brain diminishes the efficacy of GIPR-blocking antibodies, whereas targeted deletion in the peripheral nervous system or in GABAergic neurons does not^{148,155}. In further support of this model, transcriptomic analysis of the dorsal vagal complex showed that pharmacologically agonizing or antagonizing the GIPR induces opposing gene expression signatures, with the transcriptional signature of GIPR antagonism closely resembling that of GLP1R agonism¹⁴⁸. This, combined with evidence that the body weight- and food intake-reducing effects of GIPR-blocking antibodies are abolished in both *Glp1r*- and *Gipr*-knockout mice, and the observation that the

weight-lowering efficacy of semaglutide is enhanced in *Gipr*-knockout mice¹⁰⁵, indicates that pharmacological GIPR antagonism fundamentally functions as a sensitizer for the anorectic signalling output of GLP1R-expressing neurons^{148,155}.

GLP1R–GCGR co-agonism

The historical framing of glucagon as the counter-regulatory hormone to insulin has long rendered it seemingly paradoxical in the context of obesity and T2D pharmacotherapy¹⁵⁶. However, the capacity of glucagon to stimulate lipid metabolism and energy expenditure presents a compelling metabolic advantage¹⁵⁷, provided its hyperglycaemic propensity can be effectively counterbalanced. Recognizing this challenge, the first fully synthetic, unimolecular GLP1R–GCGR co-agonist was developed in 2009 through iterative modification of the human glucagon peptide sequence to confer GLP1R activity¹⁵⁸. Independently, oxyntomodulin, an endogenous albeit pharmacologically imbalanced GLP1R–GCGR co-agonist, was used as a template for chemical optimization¹⁵⁹. Together, these advances established a rational multi-agonist design paradigm that has accelerated the clinical development of unimolecular GLP1R–GCGR co-agonists.

Mazdutide is a once-weekly GLP1R–GCGR dual agonist in clinical development for obesity and T2D. In a phase II trial, weekly doses of up to 6.0 mg induced a placebo-adjusted weight loss of 12.4% over 24 weeks of treatment¹⁶⁰. In a subsequent phase III study, 48 weeks of treatment with once-weekly mazdutide 6.0 mg resulted in a placebo-corrected weight loss of 14.7%, alongside improvements in biomarkers of cardiovascular and liver health²³. Beyond obesity and diabetes, mazdutide is also being evaluated for other indications, including alcohol use disorder (NCT06817356), and it was the first GLP1R–GCGR co-agonist to gain regulatory approval in China¹⁶¹.

Survodutide is a fatty acid acylated GLP1R–GCGR co-agonist engineered for once-weekly dosing in humans, with a receptor activity profile favouring GLP1R activation eightfold relative to the GCGR¹⁶². In people with obesity and without T2D, 46 weeks of treatment with survodutide dose-dependently lowered body weight by up to 12.1% relative to placebo, accompanied by improvements in blood pressure²². In another clinical trial investigating survodutide for the management of T2D, the molecule improved HbA_{1c} levels¹⁶³, perhaps mitigating some concerns about glucagon's potential hyperglycaemic liabilities. Furthermore, the actions of glucagon to stimulate hepatic lipolysis and suppress lipogenesis have served as a mechanistic rationale for the evaluation of survodutide for the treatment of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). In a phase II clinical trial of patients with biopsy-confirmed MASH, treatment with survodutide significantly reduced liver fat content and improved MASH without worsening of fibrosis by up to 62%¹⁶⁴. Albeit in this trial, one in five patients did not reach the maximal 6.0 mg dose level because of gastrointestinal adverse effects, which may be a consequence of the dose escalation used in the trial. Survodutide is currently being investigated in two phase III clinical trials for the treatment of patients with MASH and moderate or advanced fibrosis or cirrhosis (NCT06632444, NCT06632457).

A recent phase IIa study of another once-weekly GLP1R–GCGR co-agonist, pemvidutide, showed a 13.4% placebo-subtracted reduction in body weight over 48 weeks¹⁶⁵. Concerns about the potential negative impact of glucagon on lean mass were dampened, as only 25.5% of the weight loss came from fat-free mass, while 74.5% was from fat mass. This effect on body composition mirrors that observed with other

long-acting incretin receptor agonists¹⁶⁶. In a phase IIb trial of patients with biopsy-confirmed MASH, pemvidutide achieved significant resolution of steatohepatitis without worsening fibrosis, accompanied by hepatic fat reductions of up to 58% over 24 weeks¹⁶⁷. Pemvidutide is a balanced co-agonist, which may explain the rapid and robust effects on hepatic fat clearance relative to other co-agonists that are more imbalanced towards GLP1R potency.

Although the actions of glucagon seem to positively contribute to the efficacy and mode of action of both survodutide and pemvidutide, challenges have been encountered for other GLP1R–GCGR co-agonists. For example, the imbalanced co-agonist, NN1177, favouring GLP1R activation at a ratio of 3:1, was evaluated across three phase I clinical trials¹⁶⁸. Treatment with NN1177 over 12 weeks achieved a placebo-corrected weight reduction of up to 12.6%, but the emergence of safety signals, including elevated heart rate, adverse liver biomarkers and impaired glycaemic control, led to termination of its clinical development¹⁶⁸. These findings suggest that a central challenge in optimizing GLP1R–GCGR co-agonism lies in defining the relative receptor activity and dose level, which will likely differ by disease indication. In diabetes, for example, sufficient GLP1R signalling may be required to counter the hyperglycaemic drive of GCGR activation. Beyond glycaemia and cardiovascular risk, glucagon also stimulates hepatic amino acid catabolism and ureagenesis, raising the possibility of unfavourable shifts in body composition.

GLP1R–GIPR–GCGR tri-agonism

The success of the dual agonist approaches prompted the idea that integrated GLP1R, GIPR, and GCGR activity could further amplify weight-loss efficacy, and dual-incretin receptor activity could help offset the diabetogenic effects of glucagon^{169–173}. To test this concept, first-generation molecules such as NN1706 and SAR441255 were chemically engineered to display balanced activity at all three receptors and exhibit a pharmacokinetic profile conducive to once-daily human dosing^{172,173}. In preclinical studies, these molecules demonstrated hitherto unprecedented metabolic improvements, including profound weight loss, enhanced glycaemic control and improvements in fatty liver disease^{172–174}. Translational investigations with NN1706 demonstrated a placebo-subtracted weight loss of 6.6% at the highest dose level over 10 weeks of treatment, comparable to once-weekly semaglutide¹², tirzepatide¹⁸ and the combination therapy CagriSema¹⁷⁵ over a similar treatment duration. However, its development was halted owing to a persistent, dose-independent increase in heart rate, which dissipated upon treatment cessation. NN1706 is no longer in clinical development; therefore, the mechanisms for these effects have either not been studied or not communicated¹⁷⁶.

Retatrutide, the most advanced molecule in the tri-agonist class currently being evaluated in multiple phase III clinical trials¹⁷⁷, is based on the peptide sequence of human GIP, with amino acid substitutions conferring activity at all three receptors, albeit with an imbalance in relative potency profile favouring activation of the human GIPR²⁴. It is a polypeptide, modified with a C20 fatty diacid through a linker attached to the side chain of a lysine in position 17, achieving a half-life of approximately 6 days in humans, supporting once-weekly administration^{24,178}. In obese mice, the tri-agonist reduces body weight by up to ~45% and significantly outperforms the weight-loss efficacy of equimolarly dosed tirzepatide²⁴. Furthermore, the highest dose of retatrutide potently reduces food intake for up to 14 days in mice, and counters metabolic adaptation to prolong caloric restriction²⁴. However, whereas GCGR activation typically increases energy expenditure

as part of the weight-loss mechanism in rodents, retatrutide, consistent with its relatively weak potency at the GCGR, does not elevate energy expenditure in mice. This receptor balance is distinct from other co- and tri-agonists that more robustly engage the GCGR pathway.

In individuals with obesity without T2D, 48 weeks of treatment with retatrutide, at the highest dose of 12.0 mg, resulted in a 22.1% mean body weight reduction relative to placebo controls, with around half of the participants losing more than 25% of their initial body weight¹⁷⁷. A parallel 40-week phase III trial investigating once-weekly retatrutide in people with overweight or obesity and T2D showed a 14.3% weight loss and 1.9% reduction in HbA_{1c} levels at the highest dose level compared with placebo controls^{179,180}. In both trials, the safety and tolerability profile of retatrutide, including gastrointestinal and cardiovascular adverse effects, was generally comparable to that of other molecules in the GLP1 and GLP1–GIP classes. Corroborating these findings, retatrutide demonstrated up to a 26.6% placebo-adjusted body weight reduction over 68 weeks, with substantial relief from knee pain in people with obesity and knee osteoarthritis¹⁸¹. The safety profile of retatrutide was generally comparable to that of other incretin-based obesity therapies, with gastrointestinal adverse events being the most common. Dysaesthesia was observed in roughly one in five patients, but was generally mild and rarely led to treatment discontinuation¹⁸¹. In extension, a comprehensive phase III programme is ongoing to assess the safety and efficacy of retatrutide in adults with T2D (TRANSCEND-T2D), and overweight or obesity and weight-related comorbidities (TRIUMPH), to define further the efficacy and long-term safety of retatrutide across diverse patient populations.

Several additional GLP1R–GIPR–GCGR tri-agonists are in development. Eficopegtrutide, developed by Hanmi Pharmaceuticals, is optimized for once-weekly dosing and is currently in a phase IIb trial for biopsy-confirmed MASH^{182,183}. Hanmi is also advancing HM15275, another long-acting tri-agonist in phase I development, which has shown metabolic efficacy superior to that of existing dual agonists in preclinical studies¹⁸⁴. In addition, UBT251, licensed by Novo Nordisk, demonstrated a 17.7% placebo-corrected weight loss over 24 weeks in a phase II trial in Chinese people with overweight or obesity¹⁸⁵. In a parallel 24-week phase II trial in individuals with T2D, UBT251 achieved an 8.4% placebo-adjusted body weight reduction at the highest dose, compared with 3.4% for semaglutide 1.0 mg¹⁸⁶. Although this magnitude of weight loss over 24 weeks is notable, larger phase II/III trials are necessary to fully evaluate its efficacy and safety relative to other tri-agonists currently in clinical development.

Despite the metabolic benefits observed with glucagon-inclusive multifunctional incretin receptor agonists, their clinical development has highlighted important cardiac safety considerations, particularly related to GCGR activation and heart rate increase. In the phase II study of retatrutide in participants with obesity, heart rate increases were dose dependent and trended back towards baseline with continued treatment, peaking at an increase of 10 bpm at the midpoint of the study, declining to an increase of 6 bpm at 48 weeks with the highest dose¹⁷⁷. Furthermore, a small percentage of participants undergoing a fast dose-escalation regimen, a regimen not typically used in phase III studies, experienced arrhythmias, an effect that seemed to be partially managed in those following a slower dose-titration schedule, as arrhythmias were not observed in these participants. Hence, although it remains unknown how drug exposure and the molecular pharmacology of GLP1R–GIPR–GCGR tri-agonism impact haemodynamics, it seems that appropriate dose-titration regimens may mitigate some of the effects. Furthermore, activation of GCGR signalling pathways stimulates hepatic amino acid uptake and catabolism¹⁸⁷, which can

reduce circulating amino acid availability and may have implications for muscle maintenance. Studies in rodents suggest that the impact on lean body mass may be dose dependent, underscoring the importance of achieving the right balance to avoid excessive skeletal muscle loss¹⁸⁸. However, given the diversity in receptor potency ratios across tri-agonists in development, further human studies are necessary to delineate how differences in receptor balance impact cardiac outcomes and body composition. Such trials will be important to define therapeutic windows that maximize metabolic efficacy while minimizing cardiac impact, ultimately informing the rational design of next-generation tri-agonists optimized for both efficacy and safety.

Amylin-based weight-loss drugs

Amylin is a 37-mer peptide hormone produced and co-secreted with insulin from pancreatic β -cells in response to nutrient ingestion¹⁸⁹. Amylin exerts its anorectic effects via engagement of AMLNRs in the CNS, and amylin analogues are used clinically in diabetes and are being advanced as anti-obesity therapies, particularly in combination with GLP1R agonists. AMLNRs are not single proteins but instead heterodimeric complexes consisting of the calcitonin receptor (CalcR) paired with one of three receptor activity-modifying proteins (RAMP1, RAMP2, RAMP3) to form distinct AMLNR subtypes with unique pharmacological profiles (AMLNR1, AMLNR2, AMLNR3)¹⁹⁰. By shaping ligand specificity and signalling dynamics, RAMPs fulfil a central role in how amylin and related therapeutics regulate appetite and energy balance¹⁹¹. Pharmacological amylin regulates appetite suppression, delays gastric emptying and enhances glucose handling, making AMLNRs a long-standing target of interest for metabolic disease treatment¹⁸⁹. A major chemical challenge, however, has been to mitigate the fibrillating propensity of human amylin, which underlies the formation of cytotoxic amyloid deposits in the pancreatic islets of patients with late-stage T2D¹⁹². Rat amylin contains three proline residues that disrupt the secondary structure of the peptide, reducing its tendency to form fibrils¹⁹³. Incorporating these residues into the peptide sequence of human amylin led to the discovery of pramlintide, the first AMLNR agonist to gain approval for treatment of T2D in 2005. Although pramlintide demonstrated efficacy in reducing food intake and promoting weight loss in patients with T2D, the necessity for frequent high-dose injections rendered it undesirable for chronic weight management and it is primarily used as an add-on to mealtime insulin therapy^{194,195}.

Using pramlintide as a template, further chemical optimization and derivatization with a half-life-extending technology yielded the long-acting amylin analogue cagrilintide²⁵. Although cagrilintide was initially described as a long-acting amylin analogue, later studies revealed that it also activates the calcitonin receptor, classifying it as a dual amylin and calcitonin receptor agonist (DACRA) or otherwise unselective to calcitonin versus AMLNRs^{196,197}. In rodents, however, it was demonstrated that cagrilintide-induced anorexia and weight loss are fully dependent on the presence of the AMLNR1 and AMLNR3 subtypes¹⁹⁸.

In a dose-finding trial, once-weekly subcutaneous injections with cagrilintide 4.5 mg induced a placebo-corrected body weight reduction of 7.8% over 26 weeks in subjects with overweight or obesity¹⁹⁹. A key objective in the development of cagrilintide was to combine it with semaglutide to enhance weight loss and glycaemic control²⁵. A fixed-dose combination of cagrilintide 2.4 mg and semaglutide 2.4 mg (CagriSema) induced a mean placebo-corrected weight loss of 17.3% over 68 weeks, with participants completing the trial at the maximum dose achieving 20.4% weight reduction²⁰⁰. In parallel, a 68-week phase III trial of CagriSema in participants with overweight or obesity and T2D found

Table 1 | Selected amylin receptor agonists in discovery and development

Drug	Company	Class	Modality	Clinical status	Clinical trial identifier or reference
Cagrilintide	Novo Nordisk	DACRA	Peptide	Phase III	200
Eloralintide	Eli Lilly	SARA	Peptide	Phase III	NCT07282600
Zenagamtide ^a	Novo Nordisk	DACRA, GLP1RA	Peptide	Phase III	NCT06064006
NNC0662-0419	Novo Nordisk	SARA/DACRA, GLP1RA, GIPRA	Peptide	Phase II	NCT07184632
Petrelintide	Roche, Zealand Pharma	DACRA	Peptide	Phase II	NCT06662539
AZD6234	AstraZeneca	SARA	Peptide	Phase II	NCT06862791
MET-233i	Metsera	DACRA	Peptide	Phase II	NCT07022977, NCT06924320
KBP-336	KeyBioscience	DACRA	Peptide	Phase II	NCT06833749
NNC0638-0355	Novo Nordisk	DACRA	Peptide	Phase I	NCT06577766
NNC0174-1213	Novo Nordisk	SARA	Peptide	Phase I	NCT06719011
GUBamy	AbbVie, Gubra	DACRA	Peptide	Phase I	NCT06144684
ACCG-2671	Structure Therapeutics	DACRA	Small molecule	Phase I	NA
PTT-A	Pep2Tango	DACRA, GLP1RA, GIPRA	Peptide	Preclinical	NA
Structure Therapeutics	ACCG-3535	DACRA	Small molecule	Preclinical	NA
VRB-103	Verdiva Bio	DACRA	Small molecule	Preclinical	NA

For clinical trials see [ClinicalTrials.gov](https://clinicaltrials.gov). DACRA, dual amylin and calcitonin receptor agonist; GIPRA, glucose-dependent insulinotropic polypeptide receptor agonist; GLP1RA, glucagon-like peptide 1 receptor agonist; NA, not applicable; SARA, selective amylin receptor agonist. ^aZenagamtide is being developed both as a subcutaneous injectable and in tablet formulation.

that those reaching the maximal dose achieved a 10.3% placebo-adjusted weight loss²⁰¹. Both trials used a flexible dosing regimen to improve completion rates, resulting in approximately 60% of the participants reaching the maximum dose level. Accordingly, two additional phase III trials with a stricter design have been launched to evaluate the efficacy at full therapeutic exposure (NCT06780449). In addition, the REDEFINE phase III trial programme will assess the impact of CagriSema on cardiovascular outcomes (NCT05669755) and explore the potential for further weight loss with dose re-escalation and longer treatment duration²⁰².

Amylin-based obesity therapies are advancing rapidly, with several long-acting amylin analogues under investigation in clinical trials (Table 1). Two main classes exist based on receptor selectivity profiles, that is, selective AMLNR agonists (SARAs) targeting the heterodimeric AMLNR3 complex and unselective AMLNR agonists that target both the AMLNR3 complex and the calcitonin receptor (DACRAs). The most clinically advanced molecule in the selective AMLNR agonist class, eloralintide²⁰³, achieved placebo-corrected body weight reduction of 11.5% in a 12-week phase I multiple ascending-dose trial²⁰⁴. In a subsequent phase II trial, eloralintide demonstrated up to 19.7% placebo-subtracted weight loss over 48 weeks, with a tolerability profile that compares favourably with incretin-induced therapies and non-selective AMLNR agonists in similar patient populations²⁷, highlighting the potential of selective AMLNR agonism for obesity treatment. Eloralintide is currently undergoing clinical evaluation in combination with tirzepatide, a strategy that has the potential to further enhance metabolic outcomes (NCT06603571).

Other notable selective AMLNR agonists include AstraZeneca's molecule AZD6234, currently in phase IIb clinical development with the intention of pairing it with their long-acting GLP1R–GCCR co-agonist AZD9550 (NCT06862791) (ref. 205), and Novo Nordisk's second-generation compound, amylin 1213²⁶, which has entered phase I

clinical evaluation (NCT06719011). In a parallel phase I clinical trial, Novo Nordisk is evaluating an unselective AMLNR agonist named amylin 355, designed for oral formulation and with biophysical properties better supporting co-formulation with semaglutide and other incretin-based molecules (NCT06577766). Other unselective receptor agonists include petrelintide being co-developed by Zealand Pharma and Roche with the intention of pairing it with the GLP-1R–GIPR co-agonist CT-388^{206,207}, the phase I compound GUBamy being co-developed by Gubra and AbbVie^{208,209}, both of which engage the amylin and calcitonin receptors, akin to cagrilintide, as well as the phase II molecule, KBP-336, which, while also unselective, differs in its chemical design, being derived from a salmon calcitonin template rather than an amylin-based scaffold (NCT06833749)²¹⁰. This class also includes several innovative therapies in development, such as MET-233i, a once-monthly peptide-based unselective AMLNR agonist that demonstrated 8.4% body weight reduction over 36 days in a phase I trial (NCT07022977)²¹¹, and ACCG-2671 being developed by Structure Therapeutics, which is a small-molecule oral unselective AMLNR agonist^{212,213}.

There has been ongoing consideration as to whether purposefully designed DACRAs offer additional therapeutic benefits compared with more selective AMLNR agonists. Evidence from rodent studies showed that while both selective and unselective AMLNR agonists reduce body weight, unselective compounds more strongly induce behaviours indicative of malaise and aversion^{203,214}. Exploring such insights in humans will be instrumental in refining the design of next-generation amylin-based therapies, ensuring optimized efficacy and safety across diverse patient populations. Interestingly, a phase II clinical trial with the DACRA molecule petrelintide demonstrated up to 9.0% placebo-corrected weight loss with a favourable tolerability profile comparable to placebo, suggesting that it may be possible to achieve weight loss at dose levels that do not induce aversion²¹⁵.

As illustrated by the proglucagon-derived peptide class, a unimolecular multi-receptor agonist can offer practical advantages in obesity drug development by combining multiple activities within a single active pharmaceutical entity with a unified pharmacokinetic profile²¹⁶. This approach also reduces formulation and manufacturing complexity, obviating the need to co-formulate multiple peptides or biologics with distinct biophysical properties (solubility, stability, aggregation), and streamlines non-clinical and clinical characterization, as only one molecule must be assessed for safety, immunogenicity and metabolism. The clinical success of unimolecular incretin co-agonists has likely spurred renewed interest in the development of unimolecular GLP1 and amylin-based co-agonists.

As early as 2013, the first GLP1 and amylin fusion molecules were conceptualized, using a head-to-tail peptide linkage of exenatide and davalintide to preserve the N-terminal and C-terminal motifs essential for GLP1R and AMLNR engagement, respectively, and thereby generating the first short-acting unimolecular GLP1R–AMLNR co-agonist²¹⁷. Although the fusion resulted in a more than 20-fold decrease in potency at the AMLNR, this co-agonist molecule delivered comparable efficacy to co-administration of the monotherapies in obese rats. More recently, a long-acting unimolecular tri-agonist with balanced activity at the GLP1R, AMLN₃R and CalcR, termed zenagamtide, also known as amycretin, was developed by chemically fusing semaglutide with a DACRA^{28,218}. Preclinical investigations showed that peripherally administered zenagamtide accumulates in the hindbrain and hypothalamus, suggesting that it modulates energy homeostasis through neuronal mechanisms similar to CagRI-Sema²⁸. Zenagamtide is being developed as both subcutaneous and oral formulations, and has demonstrated promising results in early-phase clinical trials^{218,219}. In a phase Ib/IIa clinical trial enrolling participants with overweight or obesity, once-weekly subcutaneous injections with zenagamtide 20.0 mg induced a placebo-subtracted body weight reduction of 23.9% over a 36-week period, and a parallel trial with oral zenagamtide administered as two 50.0 mg tablets in a single daily dose delivered 11.8% weight loss over 12 weeks^{218,219}. Based on these results, both formulations are being developed in the global phase III clinical programme AMAZE for the treatment of obesity and weight-related comorbidities.

The encouraging results from early-stage clinical trials with zenagamtide have inspired the development of next-generation unimolecular amylin-based multi-receptor agonists. Among these, a tetra-agonist has been described, designed to combine the pharmacological actions of tirzepatide and cagrilintide in a single molecule under the name PTT-A²²⁰. In rats with diet-induced obesity, PTT-A has demonstrated superior weight loss compared with equimolarly dosed tirzepatide, while also yielding favourable improvements in body composition²²¹. Novo Nordisk is advancing a unimolecular amylin-based tri-agonist (NNC0662-0419) in phase II clinical development that chemically combines a selective AMLNR agonist with a GLP1R–GIPR co-agonist imbalanced in favour of GIPR activation²²². Furthermore, co-treatment with retatrutide and cagrilintide in diet-induced obese rats results in synergistic weight-loss benefits, indicating that adding CGCR agonism to the cocktail might confer additional metabolic improvements. Whether amylin-based pharmacotherapies confer benefits beyond additive anorectic effects remains an open question. Whereas GIP may attenuate gastrointestinal adverse events and glucagon enhances energy expenditure and exerts favourable effects on hepatic lipid metabolism, the unique mechanistic contributions of AMLNR agonism are less well defined. There is some evidence to implicate amylin in the modulation of mesolimbic reward pathways and

the restoration of leptin sensitivity in the context of obesity; however, these observations await robust clinical validation^{223–226}.

Next-generation oral obesity therapies

Oral medicines provide a less-invasive alternative to injectables and are generally more cost-effective to produce. This is due to both the elimination of injection devices and, in the case of small molecules, the typically lower synthesis costs compared with peptides. In addition, oral preparations may reduce health-care resource demands and have a broader geographical reach by avoiding cold chain logistics, injection training and medical waste disposal. These advantages could enhance the cost-effectiveness and accessibility of obesity medications, particularly in low-resource settings. Given the rapid proteolytic degradation of peptides in the gastrointestinal tract and their poor intestinal absorption, the development of effective oral peptide drugs has been notoriously difficult. As a result, small-molecule alternatives are increasingly being pursued.

Nevertheless, the challenge of oral peptides has led to the exploration of innovative solutions, such as the co-formulation of semaglutide in a tablet with the absorption enhancer, salcaprozate sodium (SNAC), which facilitates transcellular absorption through the gastric mucosa, resulting in an oral bioavailability of 0.5–1.0%²²⁷. As a result, oral semaglutide requires significantly higher doses given daily to achieve plasma exposure comparable to that of weekly subcutaneous semaglutide²²⁸. However, owing to its long plasma half-life, the relatively low concentration of the absorbed compound remains in circulation, gradually accumulating to steady-state levels. Furthermore, the long half-life of semaglutide can help to mitigate dose-to-dose variability in bioavailability evident with absorption enhancer-based oral delivery of peptides. In clinical trials, a daily dose of oral semaglutide 50.0 mg delivered comparable efficacy and tolerability to subcutaneous semaglutide, achieving a placebo-subtracted body weight reduction of 12.7% in adults with obesity without T2D²²⁹. In a parallel, smaller-sized phase III trial, it was found that once-daily oral semaglutide 25.0 mg in people with overweight or obesity led to an 11.4% placebo-corrected body weight reduction over 64 weeks, and based on these results it is the dose level that has gained regulatory approval by the FDA^{230,231}. However, the fact that oral semaglutide must be taken 30 min before breakfast for optimal absorption challenges the treatment burden and compliance of this type of oral obesity therapy²³². In parallel, Novo Nordisk is pursuing the GLP1R–AMLN₃R co-agonist, zenagamtide, in an oral two-tablet single-dose formulation, enabled by the SNAC co-formulation platform, as this was found to achieve higher drug exposure than an equidose single-tablet version²¹⁸. Finally, Viking Therapeutics is advancing an oral formulation of a peptide-based GLP1R–GIPR co-agonist, VK2735, that demonstrated 13.0% placebo-subtracted weight loss in a 13-week phase II study at the highest dose level, but with dose-limiting tolerability that may prohibit advancement of this dose level²³³.

Although the first synthetic small-molecule GLP1R agonists were reported almost two decades ago^{234,235}, concerns over their ability to replicate the receptor activation mechanisms of larger peptide ligands led commercial development to focus on peptide-based modalities. However, with the recent discoveries of the non-peptide agonists orforglipron and danuglipron, this long-held belief is being challenged as these molecules demonstrate potent activation of the human GLP1R in experimental models^{236–239}. Before the availability of the human, activated GLP1R crystal structure in 2017 (ref. 240), screening-based drug discovery had been a central strategy for identifying small-molecule

Table 2 | Selected oral obesity therapies in clinical development by USA trial status

Drug	Company	Target	Modality	Clinical status	Clinical trial identifier or references
Semaglutide 25.0 mg	Novo Nordisk	GLP1R	Peptide	Approved	13,15
Orforglipron	Eli Lilly	GLP1R	Small molecule	Approved	242
MDR-001	MindRank	GLP1R	Peptide	Phase III	NCT07274137
VK2735	Viking Therapeutics	GLP1R, GIPR	Peptide	Phase III	NCT07104500
Zenagamtide	Novo Nordisk	GLP1R, DACRA	Peptide	Phase III	NCT06049329
Elecoglipron	AstraZeneca	GLP1R	Small molecule	Phase II	NCT06579092
CT-996	Roche	GLP1R	Small molecule	Phase II	NCT07081958
Aleniglipron	Structure Therapeutics	GLP1R	Small molecule	Phase II	NCT06703021
HDM-1002	Huadong	GLP1R	Small molecule	Phase II	NCT06500299
VCT-220	Corxel/Vincentage	GLP1R	Small molecule	Phase II	NCT07011797
RGT-075	Regor	GLP1R	Small molecule	Phase II	NCT06277934
ASC30	Asclepis Pharma	GLP1R	Small molecule	Phase II	NCT07002905
Monlunabant	Novo Nordisk	CB1R	Small molecule	Phase II	NCT05891834
Enobosarm	Veru	SARM	Small molecule	Phase II	NCT06282458
PF-07976016	Pfizer	GIPR antagonist	Small molecule	Phase II	NCT06717425
HRS-7535	Kailera, Hengrui	GLP1R	Small molecule	Phase III	NCT06904105
IBI-3032	Innovent	GLP1R	Small molecule	Phase I	NCT07120425
MK-4082	Merck	GLP1R	Small molecule	Phase I	NCT07388667
ACCG-2671	Structure Therapeutics	AMLNR, CalcR	Small molecule	Phase I	Initiation ³⁸⁵
TLC-6740	OrsoBio	Uncoupler	Small molecule	Phase I	NCT05822544
ACCG-3535	Structure Therapeutics	AMLNR, CalcR	Small molecule	Preclinical	NA
ASC39	Asclepis Pharma	AMLNR	Small molecule	Preclinical	253
Danuglipron	Pfizer	GLP1R	Small molecule	Discontinued	252
TERN-601	Terns Pharmaceuticals	GLP1R	Small molecule	Discontinued	386

For clinical trials see [ClinicalTrials.gov](https://www.clinicaltrials.gov). AMLNR, amylin receptor; CalcR, calcitonin receptor; CB1R, cannabinoid receptor 1; DACRA, dual amylin and calcitonin receptor agonist; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP1R, glucagon-like peptide 1 receptor; NA, not applicable; SARM, selective androgen receptor modulator.

scaffolds that could be chemically optimized with the aim of improving pharmacological and pharmacokinetic properties^{236,238}. As several small-molecule GLP1R agonists progress through clinical development (Table 2), this emerging class of therapeutics has the potential to provide effective, convenient and more widely accessible treatments for people living with metabolic diseases.

Orforglipron is a high-affinity partial agonist of the human GLP1R, exhibiting low intrinsic efficacy for activating downstream cellular responses (canonical cAMP signalling) and negligible β -arrestin recruitment, which may contribute to minimal receptor desensitization^{236,237}. In humanized GLP1R rodent models, orforglipron elicits comparable receptor engagement in the brain and pancreas to peptide-based GLP1R agonists, and chronic pharmacological treatment results in equipotent improvements in body weight and glucose homeostasis²³⁷. With a half-life of 29–49 h in humans, orforglipron supports once-daily oral administration and, unlike oral semaglutide, does not require specific meal timing²⁴¹. In a phase III study involving adults with overweight or obesity and a weight-related medical problem without diabetes, once-daily oral administration of orforglipron 36.0 mg induced an 11.5% placebo-subtracted body weight reduction over

72 weeks of treatment²⁴². No hepatic safety concerns were identified. In a parallel phase III clinical trial, the safety and efficacy of orforglipron 36.0 mg was evaluated in adults living with overweight or obesity and T2D, revealing a placebo-corrected weight loss of 8.3% over a similar treatment duration²⁴³. In both of these trials, orforglipron treatment was discontinued by approximately 10% of the participants^{242,243}, which appears higher than the discontinuation rates for oral semaglutide 50.0 mg (6%)²²⁹ and subcutaneous 2.4 mg semaglutide (7%)^{12,66}. Corroborating these observations, a population-adjusted indirect treatment comparison study showed that oral semaglutide 25.0 mg treatment was associated with both superior weight loss efficacy and tolerability relative to orforglipron 36.0 mg (ref. 244). However, orforglipron does not require food and water restriction before administration, and it may represent an efficacious and more readily scalable alternative to oral peptide-based GLP-1R agonists, with potential advantages for manufacturing, storage and distribution. In a phase III maintenance trial, topline results indicated that switching from injectable incretin therapy (semaglutide 1.8–2.4 mg or tirzepatide 10–15 mg) to once-daily oral orforglipron (titrated up to 36 mg) reduced weight regain over 52 weeks versus placebo²⁴⁵. Orforglipron

was approved for weight loss in 2026 by the U.S. Food and Drug Administration²⁴⁶.

Structurally related to orforglipron, the molecule aleniglipron (GSBR-1290) is a fully biased, orally available and potent small-molecule GLP1R agonist, identified through a structure-based drug discovery approach²⁴⁷. Aleniglipron at 180.0 mg showed a placebo-adjusted mean weight loss of 16.3% after 44 weeks in a phase II clinical trial involving participants with overweight or obesity²⁴⁸. Elicoglipron is another clinical molecule from the same class of compounds that demonstrates a safety and tolerability profile comparable to that of other GLP1R agonists. This molecule is progressing to phase III clinical trials after demonstrating positive results in phase IIb trials for the treatment of obesity and T2D²⁴⁹. CT-996, originally discovered by Carmot Therapeutics and now being developed by Roche for obesity and T2D, is a high-affinity, selective and biased GLP1R agonist with pharmacokinetics supporting once-daily dosing in humans²⁵⁰. In a phase I multiple ascending-dose study, CT-996 achieved up to 6.1% placebo-subtracted weight loss over 4 weeks and, based on these results, is being advanced to phase II clinical development. A phase II trial is investigating the efficacy of CT-996 head to head with semaglutide in people with T2D (NCT07112872). Finally, Pfizer was progressing a biased GLP1R agonist, danuglipron, which was developed through consecutive high-throughput screening and hit-to-lead optimization²³⁸. Twice-daily dosing in patients with T2D improved glycaemic control and reduced body weight²⁵¹, but frequent gastrointestinal adverse events and high discontinuation rates halted its clinical development. Optimization of the release formulation resulted in a tablet amenable to once-daily dosing in humans, but this formulation was eventually shown to induce unpredictable liver injury at higher dose levels, associated with the metabolism of high concentrations of small molecule in the liver, and consequently the clinical development was terminated²⁵². These findings highlight that careful toxicological assessment is important for small-molecule weight-loss therapies, and that this modality may pose a larger developmental risk during early drug development, relative to peptide-based oral anti-obesity therapies that are metabolized to the constituent amino acids.

The development of high-affinity small-molecule GLP1R agonists has not only validated the feasibility of targeting this receptor with non-peptide molecules but has also sparked interest in designing low-molecular-weight, non-peptide agonists for other class B GPCRs. Accordingly, preclinical efforts are under way to develop small-molecule obesity therapies targeting the GIPR, GCGR, CalcR and AMLNR (Table 2), likely with the intention of pairing them with non-peptide GLP1R agonists, highlighting the broader therapeutic potential of this emerging drug class^{253,254}. Although no unimolecular non-peptide multi-receptor agonists have yet advanced to clinical development, early evidence suggests that such molecules may be feasible and could represent an innovative approach to enhance weight-loss efficacy while minimizing drug–drug interactions in the next generation of oral obesity therapies^{255,256}.

Resurrection of CB1R antagonism

The cannabinoid 1 receptor (CB1R) antagonist rimonabant emerged from growing interest in the role of the endocannabinoid system in appetite regulation. Although it improved weight and metabolic outcomes, it was withdrawn in Europe owing to serious neuropsychiatric adverse effects, including depression and anxiety^{257,258}. Recently, there has been renewed interest in CB1R pharmacology, focusing on strategies that separate central and peripheral effects through rational chemical design, guided in part by Lipinski's rule of five, to achieve

molecular properties that limit brain penetration^{259–261}. Many of the newer ligands act as de facto antagonists rather than inverse agonists, which may also contribute to reduced neuropsychiatric side effects by blocking receptor activation instead of suppressing constitutive CB1R activity. Data from a phase IIa dose-finding clinical trial with a first-generation peripherally restricted CB1R antagonist, monlunabant, demonstrated up to 7.4% placebo-corrected weight loss over 16 weeks²⁶². However, mild to moderate dose-dependent neuropsychiatric side effects such as anxiety and irritability were noted, questioning the restricted brain access, and a phase IIb trial has been initiated to interrogate the long-term safety of monlunabant.

Pharmacological strategies for lean mass preservation

The profound weight loss achieved with incretin-based obesity therapies has prompted concerns regarding the accompanying reductions in fat-free mass, which typically accounts for 25–40% of total weight reduction in clinical studies²⁶³. Because fat-free mass, and in particular skeletal muscle mass and function, is a key determinant of resting energy expenditure and physical capacity, these changes raise important questions about long-term metabolic health, physical function and the risk of treatment-emergent frailty. At the same time, reductions in fat-free mass are essentially an inevitable consequence of weight loss, irrespective of the type of intervention applied^{264–266}. The central challenge is perhaps therefore not to prevent any loss of lean mass, but to develop strategies that preserve or augment skeletal muscle quantity and function during pharmacologically induced weight loss.

Inhibitors that target myostatin or activin type II receptors (ActRIIs), originally developed to treat conditions characterized by muscle atrophy, are now being explored in combination with incretin-based drugs as a therapeutic strategy to preserve lean mass during weight loss. Bimagrumab, a human monoclonal antibody that blocks ActRII to stimulate muscle growth, has been shown to selectively reduce body fat, increase lean mass and result in a total weight loss of 6.5% after 48 weeks in individuals with overweight or obesity²⁶⁷. Similarly, the co-administration of monoclonal antibodies that inhibit both myostatin and ActRII signalling was found to increase thigh muscle volume while simultaneously reducing total fat mass in healthy participants²⁶⁸. Studies in rodents and non-human primates suggest that combining blockers of the activin receptor signalling pathway with semaglutide could fully reverse the lean mass loss associated with semaglutide monotherapy^{269,270}. These findings were corroborated in a recent phase II trial, investigating intravenous bimagrumab in combination with subcutaneous semaglutide 2.4 mg (ref. 271). The combination therapy produced clinically meaningful weight loss over 72 weeks, with participants achieving an average 22.1% reduction in body weight, surpassing the effects of 10.8% for bimagrumab and 15.7% for semaglutide comparators²⁷². Fat mass reduction accounted for 92.8% of the weight loss, substantially higher than the 71.8% observed with the group receiving semaglutide monotherapy. The combination regimen also yielded greater reductions in abdominal adiposity and inflammation-related biomarkers, suggesting a potential for not only enhanced weight loss but also improved cardiometabolic health outcomes. A subcutaneous formulation of bimagrumab is currently being tested in combination with tirzepatide in adults with obesity without T2D, investigating each agent alone or in combination (NCT06643728). However, another separate phase IIb trial assessing bimagrumab, alone and with tirzepatide, in people with obesity and T2D was withdrawn for strategic reasons before enrolment. Hence, the clinical progression of bimagrumab may hinge on whether the combination demonstrates meaningful

Review article

Table 3 | Clinical trials for weight-related comorbidities

Company	Drug	Target	Trial name	Clinical status	Clinical trial identifier or references
Cardiovascular disease					
Novo Nordisk	Semaglutide	GLP1R		Approved	13,15
Novo Nordisk	CagriSema	GLP1R, AMLNR	REDEFINE-3	Phase III	NCT05669755
Eli Lilly	Tirzepatide	GLP1R, GIPR	SURMOUNT-MMO	Phase III	NCT05556512 ^{20,387}
Eli Lilly	Retatrutide	GLP1R, GIPR, GCGR	TRIUMPH-3, TRIUMPH-OUTCOMES	Phase III	NCT05882045, NCT06383390
Eli Lilly	Orforglipron	GLP1R	ACHIEVE-4	Phase III	NCT05803421
Zealand Pharma, Boehringer Ingelheim	Survodutide	GLP1R, GCGR	SYNCHRONIZE-CVOT	Phase III	NCT06077864
Amgen	Maridebart cafraglutide	GLP1R, GIPR	MARITIME-HF	Phase III	NCT07037459
Chronic kidney disease					
Novo Nordisk	Semaglutide	GLP1R	FLOW	Approved	16
Novo Nordisk	CagriSema	GLP1R, AMLNR		Phase II	NCT06131372
Eli Lilly	Tirzepatide	GLP1R, GIPR	TREASURE-CKD	Phase II	NCT05536804
Eli Lilly	Retatrutide	GLP1R, GIPR, GCGR	TRIUMPH-OUTCOMES	Phase III Phase II	NCT06383390 NCT05936151
Zealand Pharma, Boehringer Ingelheim	Survodutide	GLP1R, GCGR	SYNCHRONIZE-CVOT	Phase III	NCT06077864
Amgen	Maridebart cafraglutide	GLP1R, GIPR	MARITIME	Phase III	Not initiated
MASH					
Novo Nordisk	Semaglutide	GLP1R	ESSENCE	Phase III	17
Eli Lilly	Tirzepatide	GLP1R, GIPR	SYNERGY-OUTCOMES SYNERGY-NASH	Phase III Phase II	NCT07165028 (ref. 282)
Eli Lilly	Retatrutide	GLP1R, GIPR, GCGR	SYNERGY-OUTCOMES	Phase III Phase II	NCT07165028 (ref. 283)
Zealand Pharma, Boehringer Ingelheim	Survodutide	GLP1R, GCGR	LIVERAGE	Phase III	NCT06632457
Merck, Hanmi Pharmaceuticals	Efinopegdutide	GLP1R, GCGR		Phase II	NCT06465186
Osteoarthritis					
Novo Nordisk	Semaglutide	GLP1R	STEP-9	Phase III	288
Eli Lilly	Tirzepatide	GLP1R, GIPR	STOP KNEE-OA	Phase IV	NCT06191848
Eli Lilly	Retatrutide	GLP1R, GIPR, GCGR	TRIUMPH-4	Phase III	NCT05931367
Chronic low back pain					
Eli Lilly	Retatrutide	GLP1R, GIPR, GCGR	TRIUMPH-7	Phase III	NCT07035093
Obstructive sleep apnoea					
Eli Lilly	Tirzepatide	GLP1R, GIPR	OSA	Approved	388
Eli Lilly	Orforglipron	GLP1R	ATTAIN-OSA	Phase III	NCT06649045
Eli Lilly	Retatrutide	GLP1R, GIPR, GCGR	TRIUMPH-1	Phase III	NCT05929066
Amgen	Maridebart cafraglutide	GLP1R, GIPR	MARITIME-OSA1, MARITIME-OSA2	Phase III	NCT07225686, NCT07226765
Neurodegenerative disease					
Novo Nordisk	Oral semaglutide	GLP1R	EVOKE, EVOKE+	Discontinued	290

Table 3 (continued) | Clinical trials for weight-related comorbidities

Company	Drug	Target	Trial name	Clinical status	Clinical trial identifier or references
Neuropsychiatric disorders					
Eli Lilly	Brenipatide	GLP1R, GIPR	RENEW-ALC	Phase III	NCT07219966
Eli Lilly	Brenipatide	GLP1R, GIPR	RENEW-Bipolar	Phase II	NCT07826175
Eli Lilly	Brenipatide	GLP1R, GIPR	RENEW-Smk	Phase II	NCT07223840
Inflammatory diseases					
Eli Lilly	Tirzepatide	GLP1R, GIPR	TOGETHER AMPLIFY-PsO	Phase IV	NCT06857942
Eli Lilly	Tirzepatide, Ixekizumab	GLP1R, GIPR	TOGETHER AMPLIFY-PsA	Phase IV	NCT06864026
Eli Lilly	Tirzepatide, Mirikizumab	GLP1R, GIPR	COMMIT-CD	Phase III	NCT06937099
Eli Lilly	Tirzepatide, Mirikizumab	GLP1R, GIPR	COMMIT-UC	Phase III	NCT06937086
Eli Lilly	Tirzepatide, Ixekizumab	GLP1R, GIPR	TOGETHER-PsA	Phase III	NCT06588296 (ref. 389)
Eli Lilly	Tirzepatide, Ixekizumab	GLP1R, GIPR	TOGETHER-PsO	Phase III	389
Eli Lilly	Brenipatide	GLP1R, GIPR	(Asthma)	Phase II	NCT07219173

For clinical trials see ClinicalTrials.gov. AMLNR, amylin receptor; GCGR, glucagon receptor; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP1R, glucagon-like peptide 1 receptor; MASH, metabolic dysfunction-associated steatohepatitis; NA, not applicable.

improvements in body composition and physical function beyond tirzepatide alone. In parallel, a phase II clinical trial is investigating apitegromab, a monoclonal antibody originally developed for spinal muscular atrophy that blocks myostatin, as an adjunctive therapy to tirzepatide (NCT06445075). Additionally, another phase II study is investigating dual blockade of GDF8 and activin A with monoclonal antibodies in combination with semaglutide 2.4 mg (NCT06299098), a strategy that has shown promising results in preclinical studies²⁷³.

These considerations raise an important question: are muscle-sparing co-therapies necessary for most patients on incretin-based treatment, or should they be reserved for defined high-risk subgroups, such as patients with advanced age or mobility limitations? Recent controlled data with semaglutide and CagriSema showed that weight loss was driven predominantly by fat mass reduction, with preservation of muscle function and reductions in intramuscular fat, and without evidence of a disproportionate loss of skeletal muscle relative to total weight loss^{15,64,200,274–276}. Furthermore, it is important to note that despite the measured decreases in fat-free mass in clinical trials, deficits in physical function have collectively not been observed in the patient populations typical of late-stage clinical trials. This is exemplified by the SEMALEAN study with semaglutide, in which measures of physical function showed improvement with treatment²⁷⁵. Therefore, a more pressing issue may be body composition changes in response to treatment discontinuation, for example, whether weight regain preferentially restores fat rather than muscle mass²⁷⁷, and whether long-term adverse outcomes are more closely linked to disproportionate fat mass regain than to modest treatment-associated reductions in lean mass.

Benefits beyond weight loss and glycaemic control

Increasing experimental and clinical evidence indicates that incretin-based drugs exert meaningful effects on symptoms, functional capacity and prognosis in multiple disease contexts beyond obesity and T2D, at least partly independent of weight loss. This has prompted evaluations of anti-obesity pharmacotherapies across a broad range of diseases (Table 3 and Fig. 3).

The strongest evidence of an effect on disease parameters is in obesity-related cardiometabolic comorbidities, where semaglutide is the best-studied compound and has been reported to lower major adverse cardiovascular events^{13,278}, improve symptoms and physical function in heart failure with preserved ejection fraction^{15,276}, and reduce the risk of worsening heart failure or the composite of worsening heart failure and cardiovascular death²⁷⁹. Tirzepatide was reported to be non-inferior to dulaglutide for major adverse cardiovascular events in people with T2D and established atherosclerotic cardiovascular disease²⁸⁰. There are also data supporting benefits of several compounds, including semaglutide^{17,281}, tirzepatide²⁸², survodutide¹⁶⁴, and retatrutide²⁸³, across multiple liver-related end points in MASH, with semaglutide currently the only agent among these to have received regulatory approval for MASH (accelerated FDA approval in the USA). Evidence for organ protection also extends to the kidney, with GLP1R and GLP1–GIPR agonists showing benefits on chronic kidney disease end points^{16,118,284,285}.

Building on these pleiotropic benefits, investigations now extend to additional disorders marked by systemic or neuroinflammation and metabolic dysfunction^{286,287}. Although the evidence is still maturing, clinical and preclinical data indicate that single- and multi-target incretin agonists may benefit obstructive sleep apnoea, osteoarthritis, neurodegenerative disease and substance use disorders (Table 3 and Fig. 3). Tirzepatide has obtained regulatory approval for moderate-to-severe obstructive sleep apnoea in adults with obesity¹⁹. In osteoarthritis, semaglutide use has been associated with lower risk of knee replacement²⁸⁸, and retatrutide has also shown clinically meaningful improvements in knee pain and physical function in a dedicated phase III trial¹⁸¹. For neurodegeneration, including Alzheimer disease and Parkinson disease, emerging evidence has suggested preventive or disease-modifying potential²⁸⁶. However, two phase III trials evaluating once-daily oral semaglutide 14.0 mg in mild cognitive impairment or early Alzheimer disease did not meet the primary end point for slowing disease progression in early symptomatic Alzheimer disease, despite effects on Alzheimer disease-related biomarkers^{289,290}. Finally, modulation of central reward pathways by GLP1R agonists has motivated trials in substance use disorders, with early signals of reduced cravings and consumption of alcohol, tobacco and opioids²⁹¹.

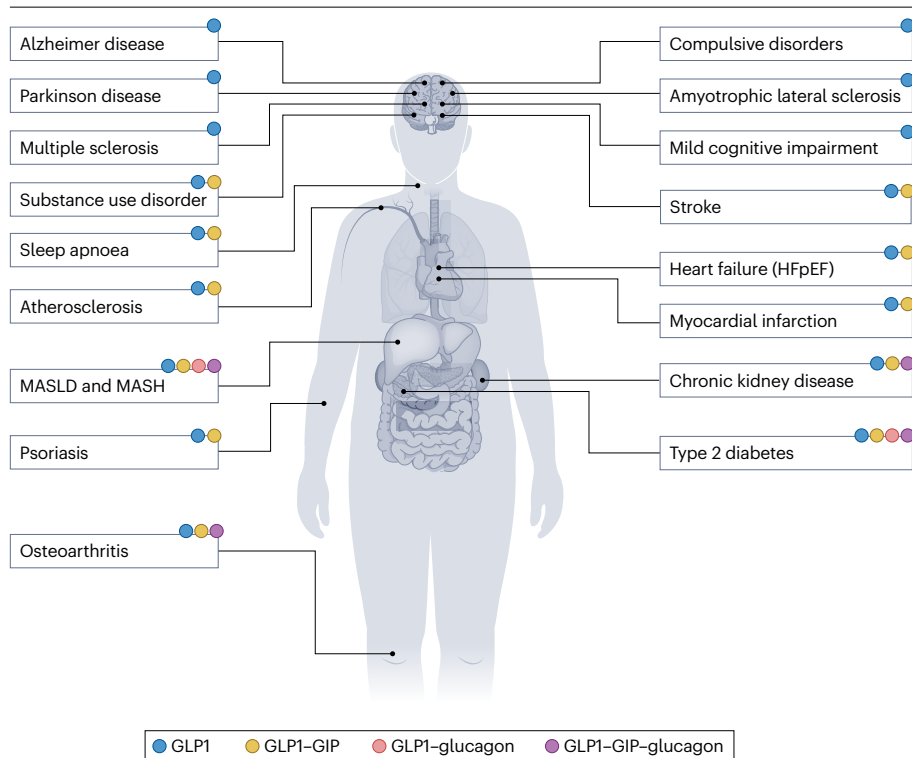


Fig. 3 | Expanding therapeutic scope of obesity pharmacotherapies. Additional disease indications for approved and late-stage obesity treatments. HFpEF, heart failure with preserved ejection fraction; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease.

Several key questions remain, including how GLP1R agonism produces systemic benefits beyond tissues with clear receptor engagement and to what extent these effects are independent of weight loss and glycaemic improvement. Proposed mechanisms include reduced systemic inflammation^{292–294}, improved insulin sensitivity and direct cardiovascular and renal actions^{292,295–302} (reviewed in^{303–305}), but clarification of causal pathways in humans is needed to enable biomarker-driven stratification, determine which mechanisms drive therapeutic benefit in which diseases and inform whether to pursue single, multi-agonist or combination therapies.

Emerging treatment concepts

Obesity pharmacotherapy is entering a new phase in which the focus extends beyond the dominant incretin paradigm towards mechanistic and technological innovations with the potential to complement, or even transcend, appetite suppression²⁹. After decades during which many alternative pathways were deprioritized, renewed attention is turning to energy expenditure, central reward signalling and tissue-specific metabolic modulation. At the same time, advances in peptide engineering, medicinal chemistry and high-throughput biology are enabling formats that range from higher-order multi-agonists to PDCs, and from genomics-driven target discovery to biomarker-guided patient stratification. These emerging concepts remain at various stages of maturity, from exploratory preclinical work to early-phase human studies, but together they outline a forward-looking landscape that may help to address the limitations of today's therapies (Fig. 4).

Genomics-driven target discovery

Leveraging human genetics offers a significant upside for novel target discovery and indication selection for clinical development. It is

estimated that the probability of success for novel investigational drugs to advance from phase I clinical study to eventual launch is 2.6 times greater for drug mechanisms in which there is human genetic support than for those without³⁰⁶. This appears to be even greater when looking at metabolic disorders, including obesity, where genetic evidence has helped improve the likelihood to progress from preclinical to clinical development, which may be a reflection of preclinical models and biomarkers that are more predictive of clinical outcomes relative to other indications. Genome-wide association studies (GWAS) of body weight and waist-to-hip ratio have identified hundreds of common genetic variants associated with obesity and body fat distribution, each with a small effect size, and established strong aetiological relationships to obesity-related complications such as diabetes and coronary artery disease^{307–309}. These analyses highlight the inherited basis of obesity and the role the CNS has in body mass regulation as most of these genes are expressed in the CNS³⁰⁹. Whole-exome sequencing has emerged as a leading approach for novel target discovery and has been utilized to identify naturally occurring yet rare loss-of-function variants associated with a large phenotypic impact and a degree of protection from disease. This approach has identified (and validated) an expanding number of new targets for pharmacological intervention across various indications, notably cardiovascular disease^{310–312}. For traits and targets relevant for obesity, when complemented with polygenic risk score analyses, fine-mapping and conventional wet lab validation, whole-exome sequencing led to the identification of *GPR75* (among 15 other genes, primarily CNS targets, associated with BMI) as an interesting anti-obesity target^{313,314} that is also predominantly expressed in the CNS³¹⁵.

Layering in analyses of traits reflective of adiposity and body fat distribution has further exemplified the power of leveraging

whole-exome sequencing to identify rare protein-coding variants as potential novel targets for obesity drug discovery, notably targets expressed in the periphery. As established by Mendelian randomization, increased adiposity, as proxied by waist-to-hip ratio adjusted for BMI, is causally linked to cardiometabolic disease risk³¹⁶. Multi-ancestry exome sequencing identified genes enriched for expression in adipose tissue, where rare coding variants are associated with robust differences in body fat distribution, as estimated from BMI-adjusted waist-to-hip circumference ratio^{315,317}. Inhibin subunit β E (*INHBE*) and activin receptor 1C (*ACVR1C*) were identified in both studies and are involved in the activin/inhibin and greater TGF β superfamily. *INHBE* encodes inhibin E subunit, which monodimerizes to form activin E, which can then activate ActRIIs, and is predominantly expressed in the liver. *ACVR1C* is predominantly expressed in adipose tissue and encodes activin receptor-like kinase 7 (ALK7), the activin type I co-receptor, which, together with ActRIIs, is a receptor complex mediating activin E signalling. For both of these targets several small interfering RNA (siRNA)-based therapies are currently in phase I testing or about to enter clinical development^{318–321}.

Human genomics is a powerful tool for identification of novel targets and prioritization of indications. However, reliance on genetics alone would have missed some of the most transformative obesity therapies, including GLP1R agonists. Although recent genomics-driven work has highlighted GIPR as a potential target³¹⁵, its biology was originally defined through physiology-based experimentation³²², and clinical data indicate that GIPR modulation is effective only when combined with GLP1R agonism, whether it is GIPR agonism or antagonism.

Conversely, mutations in leptin receptor (*LEPR*) and melanocortin 4 receptor (*MC4R*) are strongly correlated with obesity, but pharmacological targeting of these receptors for the treatment of general obesity has yielded only modest weight-loss effects in humans^{323–327}. Together, these examples highlight that although genomics can enrich discovery and improve the probability of success, it cannot substitute for physiology-driven experimentation and translational pharmacology, which must proceed in parallel.

Precision medicine

Obesity is multifactorial and heterogeneous, with respect to both disease drivers and health consequences, often manifesting as a spectrum of medical conditions with unique presentations. As such, individuals living with obesity have different health profiles and therapeutic needs, but are often discussed as a single entity, defined by one single parameter (BMI). In early 2025, the Lancet Diabetes & Endocrinology Commission proposed a diagnostic framework that defines obesity as excess adiposity (with or without abnormal distribution or function), distinguishes ‘preclinical obesity’ (increased risk without organ dysfunction) from ‘clinical obesity’ (adiposity with demonstrable organ impairment) and recommends moving beyond BMI by incorporating measures of fat distribution and, where available, imaging and biomarker-based risk stratification to enable prevention and precision care⁴. However, there is a general lack of standardized and validated criteria with sufficient accuracy and refinement for diagnosis and measurement of obesity that reflects the broad range of clinical manifestations and that also integrates risk factors of complications. Current medicinal treatment

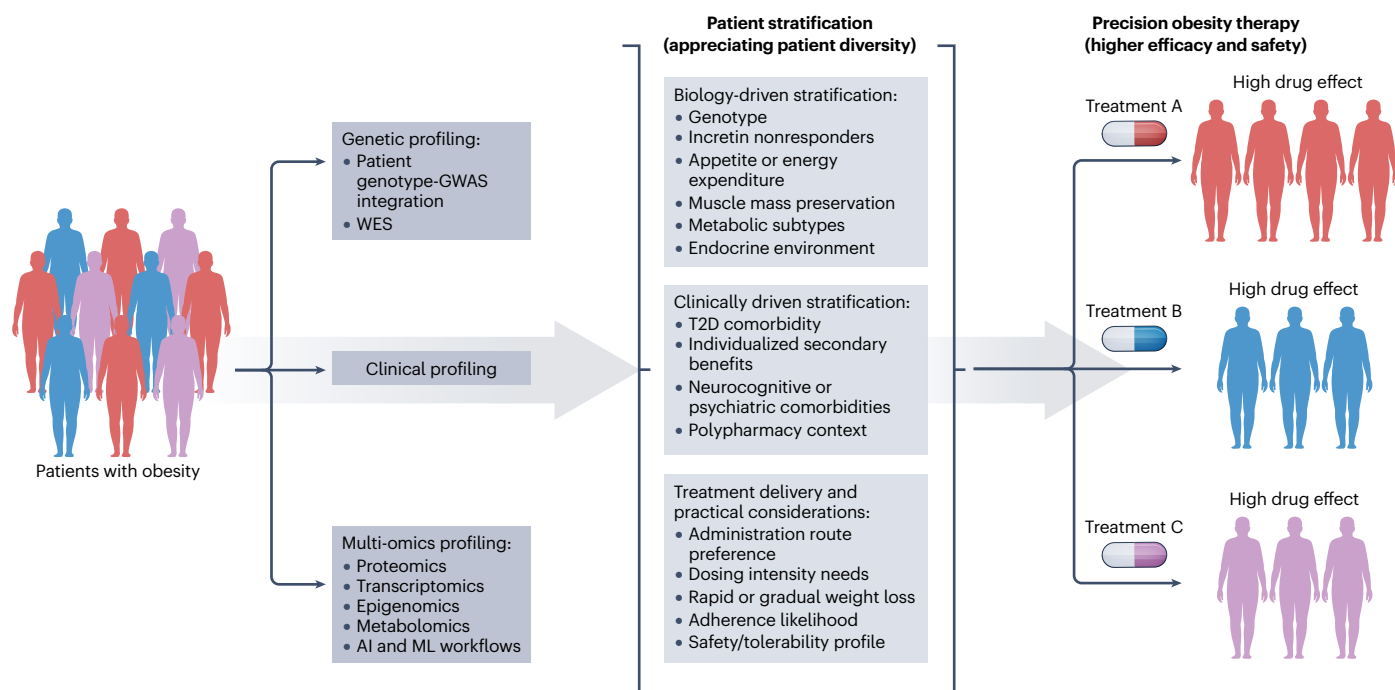


Fig. 4 | Conceptual framework for achieving precision medicine. A systematic, multistep process to optimize drug selection and maximize therapeutic outcomes for patients with obesity with and without weight-related comorbidities. The framework progresses from extensive patient characterization, including genetic, clinical and multi-omics profiling, to informed patient stratification based on biological, clinical and practical considerations. The ultimate goal is

to move beyond a ‘one-size-fits-all’ approach by matching individual patients to specific treatments (treatment A, B or C), thereby achieving higher drug effect and safety through personalized medicine. AI, Artificial intelligence; GWAS, genome-wide association studies; ML, machine learning; T2D, type 2 diabetes; WES, whole-exome sequencing.

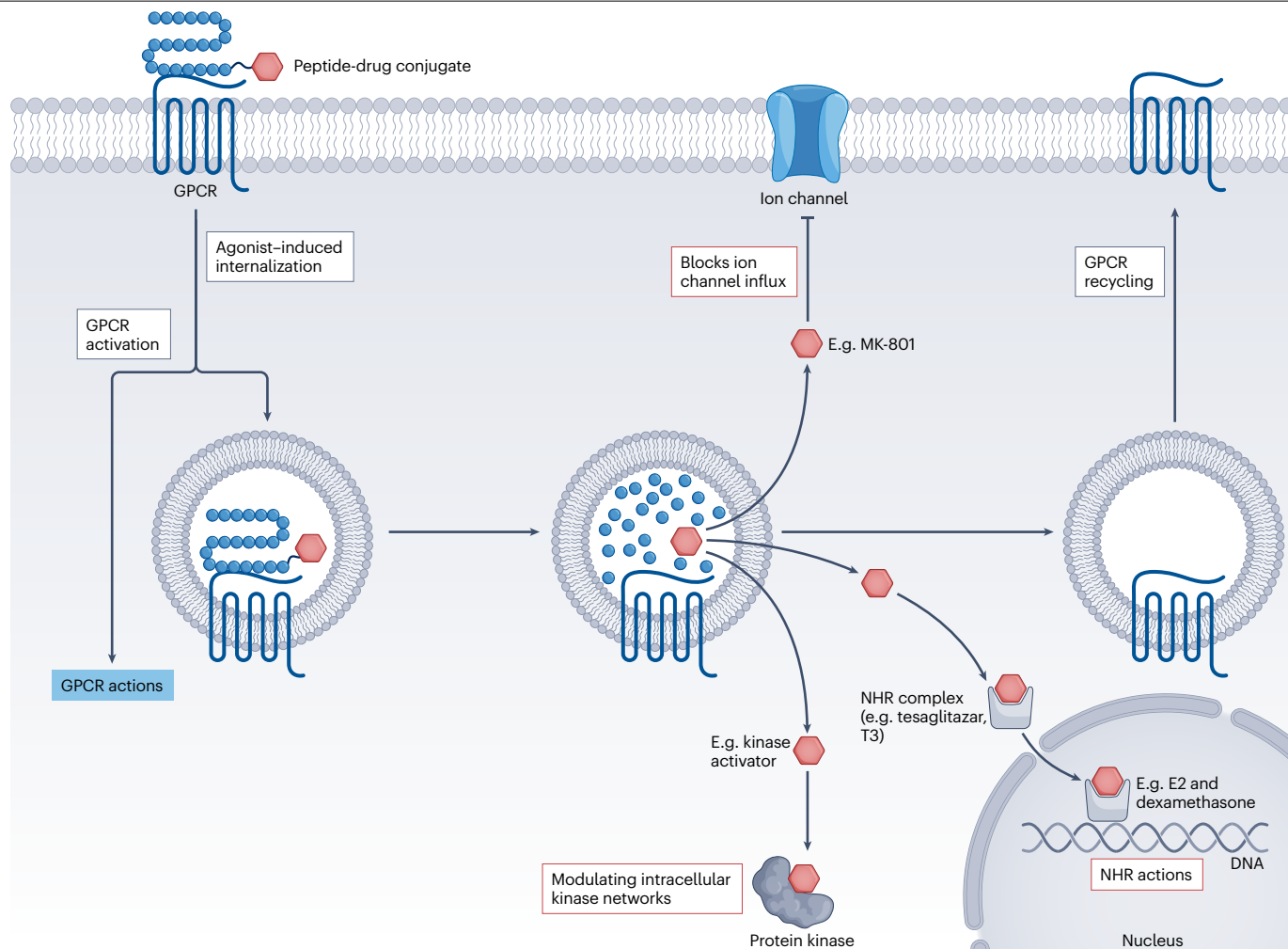


Fig. 5 | Mechanisms of tissue-specific targeting and intracellular delivery by peptide–drug conjugates. Peptide–drug conjugates (PDCs) enable the selective delivery of therapeutic payloads to specific tissues and cellular targets by exploiting receptor-mediated mechanisms. This schematic illustrates key processes involved in PDC function, that is, binding of the peptide moiety to G protein-coupled receptors (GPCRs) on the cell surface, leading to receptor activation and agonist-induced internalization of the GPCR–PDC complex and

subsequently intracellular trafficking to lysosomes, where the conjugated small-molecule drug is typically released. The released payload can then engage its target, including ion channels (for example, blockade by MK-801), kinase signalling pathways or nuclear hormone receptors (NHRs) affecting transcriptional regulation. Finally, internalized GPCRs may also be recycled back to the plasma membrane for subsequent rounds of activation. E2, oestrogen.

for obesity is based on a one-size-fits-all approach wherein treatment strategies are selected based on a small number of treatment choices available, and the therapy choice is often not predicated on biological mechanisms tied to underlying pathophysiology or disease state. There is substantial scope for stratification of clinical obesity into subtypes, potentially based on their clinical presentation or pathophysiology, but also genetically informed subtyping³²⁸, which should enable better disease management. Human pharmacogenetic analyses support this concept, showing that variation in drug target genes, including GLP1R and GIPR, contributes modestly to inter-individual variability in weight-loss efficacy and gastrointestinal tolerability during GLP1-based therapy³²⁹. Although understanding of human disease progression is advancing³³⁰, we have yet to identify first, causal subtypes of adiposity, and secondly, causal subtypes of obesity-related complications, so that

we can establish an evidence foundation and a framework for clinical guidelines of precision care⁴.

The degree of weight loss needed for clinically meaningful benefit across obesity-associated conditions may also help to guide treatment selection. This includes diversification of mechanisms of action, drug modality and delivery. Furthermore, optimal precision medicine for obesity, at least at a subgroup level, requires that treatment choice be based on biological and mechanistic rationale, combined with patient preference. Hence, a deeper understanding of the chronicity of human obesity, both aetiology and progression, as well as human behaviour, is a necessary next step. One such tactic to achieve this is to categorize patients into dynamic subgroups via biological markers (for example, multi-omics) and clinical measurements (for example, adiposity) (Fig. 4).

Although progress is being made at a relatively modest pace, current challenges to fully enable this include the limited availability of high-quality and high-resolution data from diversified patient groups that are relevant for different approaches of stratification. Deeper phenotyping, in particular more advanced clinical characterization paired with multi-omic analyses, of individuals living with obesity across diverse populations is needed. Much of the presiding work in this arena has included both retrospective and prospective analyses of cross-sectional or longitudinal cohorts, but often the collected data are limited in scope or the patient population studied is rather homogeneous. More recently, deeper phenotyping in a controlled, randomized clinical trial setting has provided insights into mechanisms of GLP1 therapy in obesity and cardiovascular complications, including body weight-dependent and independent effects, and offers evidence of potential indication expansion³³¹. Despite limitations to sample size and the finite time frame of such trials, it will be important to more deeply phenotype and characterize patients across many diverse randomized trials exploring different drug mechanisms, and subsequently harmonize that data with real-world evidence.

Peptide–drug conjugates

Alongside biomarker-driven patient stratification, new therapeutic modalities are being developed to expand the mechanistic and tissue-targeting options for obesity treatment, with PDCs as one example (Fig. 5). PDCs combine the tissue specificity and receptor selectivity of peptides with the pharmacological diversity of small molecules or other bioactive cargoes. This can enable targeted effects while potentially reducing systemic exposure and off-target toxicity.

GLP1 is the most widely used targeting vector, leveraging its potent anorectic effects and receptor expression in key metabolic tissues. The first reported GLP1-based PDC for obesity linked an aromatic oestrogen to a non-acylated GLP1 analogue (GLP1–E2), enabling receptor-mediated uptake, linker cleavage and local oestrogen receptor activation^{332,333}. Other GLP1 conjugates have targeted nuclear hormone receptors, such as glucocorticoid receptors, to reduce obesity-associated neuroinflammation^{334,335} and PPARs to improve glucose control³³⁶, or combined GLP1R agonism with *N*-methyl-D-aspartate (NMDA) receptor antagonism to modulate hypothalamic glutamatergic signalling³³⁷ (Fig. 5). GLP1 conjugates have also been developed to deliver antisense oligonucleotides or lysosome-targeting chimeras (LYTACs) for tissue-specific gene silencing^{338,339} or protein degradation³⁴⁰ in GLP1R-positive tissues.

Beyond GLP1, other peptides have also served as targeting vectors. Glucagon-based PDCs have been used to deliver thyroid hormones selectively to the liver, harnessing thermogenic and lipid-lowering effects while avoiding the diabetogenic risk of systemic glucagon agonism³⁴¹. Similarly, neuropeptide Y₁ receptor targeting has enabled delivery of the dual PPAR α / γ agonist tesaglitazar specifically to adipocytes, improving glycaemic control and adipogenesis in diabetic mice³⁴² (Fig. 5). Although these approaches show strong proof of principle in preclinical models, their clinical potential will depend on demonstrating sustained efficacy, acceptable safety and manufacturability for long-term obesity management in humans.

Grand challenges

Despite substantial advances in pharmacological interventions, obesity remains a chronic relapsing condition with complex multifactorial origins. The advent of highly effective weight-loss drugs has transformed the therapeutic landscape, yet durable and scalable solutions remain

elusive. Key obstacles include long-term safety, affordability and equitable access, as well as biological challenges such as variability in treatment response and the body's intrinsic resistance to sustained weight loss. Addressing these challenges will be essential not only to improve and expand current treatment options, but also to move towards a functional cure for obesity.

Translational barriers

Although GLP1R agonists and related incretin-based drugs have been used for more than two decades in diabetes, their widespread application to obesity is far more recent, and lifetime safety profiles remain uncertain. Rare adverse events may emerge after prolonged exposure in large, diverse populations, underscoring the importance of post-marketing surveillance and long-term safety studies.

Patient adherence remains a crucial determinant of real-world effectiveness. Weekly injections deter some individuals, and gastrointestinal side effects such as nausea or vomiting can delay or prevent dose escalation^{343–345}. Real-world data have shown that many patients never reach the trial-proven maintenance doses, and fewer than half remain on treatment after 1 year³⁴⁶. Reasons range from tolerability and cost to patients reaching a personal weight goal or shifting treatment priorities³⁴⁷. These barriers have also shaped patient behaviour, with some adopting adaptive, but largely untested, strategies to prolong treatment or reduce cost³⁴⁸. Reported examples include stretching dosing intervals beyond approved schedules, splitting doses to lower the effective dose or switching from newer, highly potent drugs to older, more affordable alternatives³⁴⁹. Others discontinue pharmacotherapy entirely, pursuing lifestyle-based maintenance through structured meal plans, app-based behavioural support or exercise programmes^{129,350–352}. Although such approaches may help to temporarily sustain weight loss, they may not provide the weight-independent benefits of current incretin-based therapies, such as cardiovascular risk reduction^{13,280}. Emerging evidence suggests that transitioning from high-potency drugs to less potent but more accessible agents can

Glossary

Energy homeostasis

The physiological processes that regulate energy intake, energy expenditure and energy storage to maintain energy balance in the body over time.

Incretin

A gut-derived hormone released after nutrient ingestion that enhances glucose-dependent insulin secretion.

Metabolic adaptation

A compensatory reduction in energy expenditure that exceeds that predicted from changes in body mass and body composition during and after weight loss.

Pharmacodynamics

The relationship between drug exposure and its biological effects over time.

Pharmacokinetics

The time course of drug absorption, distribution, metabolism and excretion.

Precision medicine

An approach to disease prevention and treatment that considers individual variability in genetics, biology, environment and lifestyle.

Unimolecular multi-receptor agonist

A single molecular entity engineered to activate two or more distinct receptors.

Weight-loss maintenance

Sustained maintenance of a reduced body weight after an initial period of weight loss.

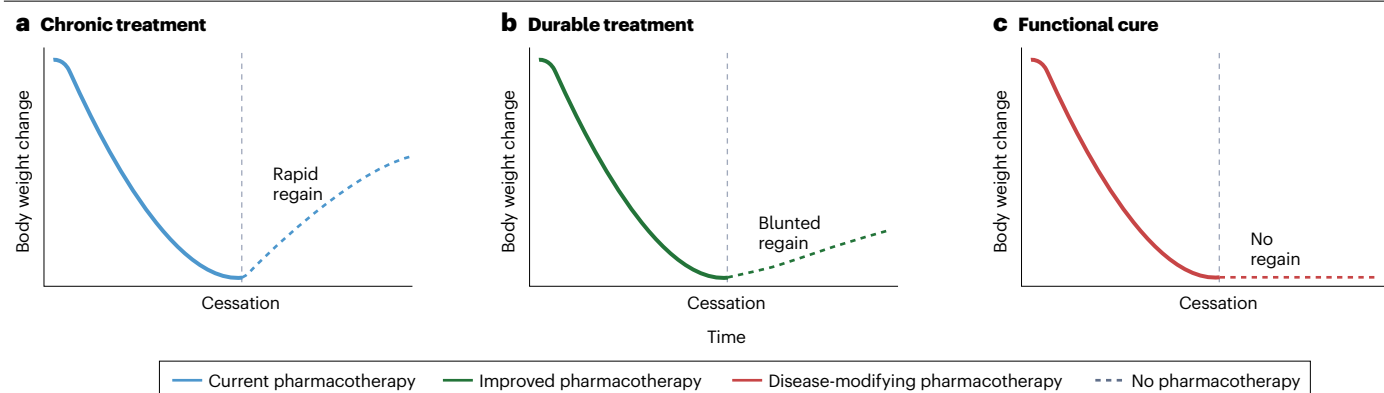


Fig. 6 | Conceptual body weight trajectories during and after obesity pharmacotherapy. **a**, Cessation of current obesity pharmacotherapies results in rapid body weight regain, reflecting the biological defence of adiposity against weight loss. **b**, A durable and improved pharmacotherapy blunts the rate of weight regain, consistent with partial modification of the defended level of

adiposity. **c**, Treatment with a disease-modifying therapy achieves weight loss with no subsequent regain after cessation, reflecting a permanent downward shift in defended adiposity and representing a functional cure for obesity. These trajectories are conceptual and do not reflect clinical validation for panels **b** and **c**.

preserve some weight loss³⁴⁹, and similar findings have been reported when switching from semaglutide or tirzepatide to oral orforglipron for 52-week maintenance, although the greater rebound after tirzepatide may be consistent with withdrawal of GIPR agonism²⁴⁵. Systematic evaluation of dose-modulation and step-down strategies will be crucial to inform evidence-based approaches for long-term weight maintenance and to broaden the reach of obesity pharmacotherapy.

Targeting energy expenditure

Whereas appetite-suppressing strategies have driven recent therapeutic successes, safe pharmacological enhancement of energy expenditure remains an unmet but high-priority goal³⁵³. Weight loss triggers metabolic adaptation, a disproportionate reduction in energy expenditure, which likely contributes to weight regain. Addressing this alongside appetite suppression could improve long-term weight maintenance^{2,354}.

Currently approved incretin-based drugs show no measurable effects on energy expenditure in humans, despite encouraging rodent data¹⁴¹. Glucagon-containing multi-agonists are anticipated to change this, with part of their weight-loss effect expected to derive from increased energy expenditure³⁵⁵. However, although both the GLP1R–GIPR–GCGR tri-agonist retatrutide and the GLP1R–GCGR co-agonist survodutide have progressed to phase III clinical trials, clear evidence of an impact on human energy expenditure is still lacking, leaving open whether this mechanism will translate clinically.

Historically, the mitochondrial uncoupler 2,4-dinitrophenol (DNP) proved that pharmacologically raising energy expenditure can drive substantial fat loss, but safety concerns precluded clinical use¹¹. Modern uncouplers such as BAM15 and controlled-release mitochondrial protonophores (CRMPs) show metabolic benefits in preclinical models^{356,357}, yet the narrow margin between effective and dangerous doses, whereby small increases in exposure can sharply raise systemic heat production, may limit enthusiasm for human trials. As an alternative, engaging endogenous thermogenic pathways, such as brown adipose tissue activation via β -adrenergic agonists, remains attractive, but systemic receptor expression limits tissue specificity, creating a similarly narrow therapeutic window in which efficacy and cardiovascular safety

risks must be carefully balanced³⁵⁸. Emerging work suggests that the development of selective or biased agonists could offer novel strategies to optimize outcomes in this space³⁵⁸.

Other approaches to elevate energy expenditure include targeting futile substrate cycling³⁵⁹, FGF21 analogues³⁶⁰, targeted thyroid hormone delivery³⁴¹ and modulation of the leptin–melanocortin axis³⁶¹. Additional emerging targets such as NK2R agonism³⁶², bile acid receptor (TGR5–FXR) modulation³⁶³, myostatin inhibition³⁶⁴, urocortin 2 (UCN2) analogues, prolactin-releasing peptide (PrP) analogues³⁶⁵ and GPR75 (refs. 313,314) antagonism may eventually broaden the therapeutic toolkit. Yet these concepts remain at a very early stage, and no clear path to a viable energy expenditure-stimulating therapy has emerged. At present, GCGR agonism stands out as the most clinically advanced and mechanistically plausible approach, with potential to counter metabolic adaptation via hepatic futile cycling and thermogenesis, although risks of cardiovascular adverse effects and lean mass loss require careful monitoring.

Variability in weight-loss efficacy

Distinct from inter-individual heterogeneity, another challenge in obesity treatment is the systematic variability observed across clinical subgroups. The most consistent example is T2D, for which clinical trials repeatedly show smaller average weight reductions with GLP1R agonists and related therapies compared with people without diabetes^{366,367} (Fig. 2). This pattern is observed across agents from semaglutide to newer multi-receptor agonists and likely reflects a combination of diabetes-associated biology, patient baseline characteristics, concomitant medications and trial-level differences rather than a single diabetes-intrinsic mechanism.

Emerging data from newer multi-agonist therapies suggest the absolute response in T2D may be improving, even if a gap persists. In SURMOUNT-1 and SURMOUNT-2, tirzepatide achieved 20.1% weight loss in participants without T2D versus 12.4% in those with T2D, but with the latter reaching a weight-loss magnitude generally comparable to that for semaglutide in non-diabetic obesity trials^{18,121}. Retatrutide has shown 26.6% placebo-corrected weight loss over 68 weeks in non-diabetic individuals in a phase III trial¹⁸¹ and 13.9% over 36 weeks in

those with overweight or obesity and T2D in a phase II trial^{177,179}. Maridebart cafraglutide and CagriSema have each produced double-digit weight loss in T2D populations, at a magnitude comparable to that of semaglutide in non-diabetic trials^{97,201}. Zenagamtide has shown promising early results in individuals without diabetes²¹⁹, with T2D data pending.

The same factors that drive variability between groups – for example, genetics, baseline adiposity, comorbidity burden, altered hormone sensitivity, concomitant therapies that promote weight gain, and ability to tolerate and adhere to target dosing – might also contribute to the variability observed in treatment responsiveness and adherence^{329,368–370}. Consequently, some high-responders in ‘obesity-only’ cohorts may be enriched for favourable tolerability and fewer weight-promoting co-medications, whereas low responders may share constraints commonly presented in people with T2D. Thus, group-level variability and individual heterogeneity are interconnected, and closing the efficacy gap will require strategies that address both.

Biological barriers to durable weight loss

Although incretin-based pharmacotherapies achieve unmatched weight loss, sustaining these effects remains challenging. Across clinical trials with semaglutide and tirzepatide, treatment discontinuation is followed by substantial weight regain, underscoring coordinated physiological adaptations that favour recovery of lost weight³⁷¹ (Fig. 6). The therapeutic goal is therefore not only to suppress appetite transiently, but to permanently lower the defended level of adiposity. A sustained downward shift in defended fat mass would represent a functional cure for obesity, but this remains to be demonstrated.

A nearer-term translational strategy is to treat maintenance as a planned second phase in the context of weight loss. In a phase III maintenance trial, participants who had completed 72 weeks of semaglutide or tirzepatide and reached a stable weight-loss plateau were switched to once-daily oral orforglipron or placebo for 52 weeks, with superior weight maintenance on orforglipron versus placebo²⁴⁵. Switching from semaglutide was associated with a 0.9 kg difference at week 52, and switching from tirzepatide was associated with a 5.0 kg difference. This approach does not alter defended adiposity, but it reframes durability as a maintenance regimen that may reduce injection burden and limit weight regain.

Beyond maintenance strategies, several biological mechanisms are being pursued to blunt relapse biology after weight loss. Early on it was found that leptin replacement can attenuate post-weight-loss adaptations³⁷² and may support maintenance when combined with other agents^{223,373–375}. Separately, the ghrelin–LEAP2 axis has emerged as a mechanistically distinct target^{376,377}, with preclinical LEAP2 analogues showing potential to blunt rebound hyperphagia, particularly in combination with GLP1R agonists^{377,378}. Finally, weight regain has been linked to neuroplasticity within hypothalamic hunger circuits, motivating efforts to modulate region-specific glutamatergic signalling more selectively than brain-wide NMDA antagonism^{337,379–384}. Collectively, these concepts support the premise that weight-regain biology may be pharmacologically modifiable and that future therapies may combine weight-loss induction with dedicated maintenance regimens to improve durability (Fig. 6).

Concluding remarks

The rapid evolution of obesity pharmacotherapy, from single-pathway appetite suppressants to multi-agonist peptides, genomics-guided

target discovery and tissue-specific drug delivery, marks a pivotal shift in the field. By clarifying the underlying pathophysiology and demonstrating durable therapeutic effects, these advances are reframing obesity as a treatable, biologically complex disease rather than a static lifestyle condition. Yet formidable challenges remain: maintaining weight loss after treatment withdrawal, extending efficacy to severe or treatment-resistant cases, ensuring long-term safety and securing equitable global access. Progress will depend on advancing emerging modalities, such as PDCs and precision biomarker strategies, alongside mechanistic innovations that enhance energy expenditure and counter the homeostatic drive to regain weight. Translation from preclinical discovery to lasting human benefit will also hinge on long-term studies in diverse populations, rigorous safety surveillance and strategies to preserve efficacy beyond controlled trial settings. The convergence of mechanistic insight, technological innovation and pragmatic health system solutions offers a credible path to therapies that are both effective and widely accessible. The ultimate measure of success will be to transform short-term pharmacological efficacy into durable health benefits that reduce the global burden of obesity-related disease.

Published online: 13 May 2026

References

- Gesta, S., Tseng, Y.-H. & Kahn, C. R. Developmental origin of fat: tracking obesity to its source. *Cell* **131**, 242–256 (2007).
- Johansen, V. B. I. et al. Brain control of energy homeostasis: implications for anti-obesity pharmacotherapy. *Cell* **188**, 4178–4212 (2025).
This article summarizes key neuroendocrine and neural circuit mechanisms underpinning current and emerging anti-obesity therapies.
- Magkos, F. et al. On the pathogenesis of obesity: causal models and missing pieces of the puzzle. *Nat. Metab.* <https://doi.org/10.1038/s42255-024-01106-8> (2024).
- Rubino, F. et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol.* **13**, 221–262 (2025).
- GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N. Engl. J. Med.* **377**, 13–27 (2017).
- NCD Risk Factor Collaboration (NCD-RisC) Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet* **403**, 1027–1050 (2024).
- World Obesity Federation. World Obesity Atlas 2025. [worldobesity.org https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2025](https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2025) (2025).
- Rubino, F. et al. Joint international consensus statement for ending stigma of obesity. *Nat. Med.* **26**, 485–497 (2020).
- Hall, K. D. & Kahan, S. Maintenance of lost weight and long-term management of obesity. *Med. Clin. North Am.* **102**, 183–197 (2018).
- Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity* **22**, 5–13 (2014).
- Müller, T. D., Clemmensen, C., Finan, B., DiMarchi, R. D. & Tschöp, M. H. Anti-obesity therapy: from rainbow pills to polyagonists. *Pharmacol. Rev.* **70**, 712–746 (2018).
- Wilding, J. P. H. et al. Once-weekly semaglutide in adults with overweight or obesity. *N. Engl. J. Med.* **384**, 989–1002 (2021).
This article reports landmark clinical trial evidence that supports the efficacy of semaglutide 2.4 mg for weight management in adults with overweight or obesity without T2D.
- Lincoff, A. M. et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N. Engl. J. Med.* **389**, 2221–2232 (2023).
This article shows the effect of semaglutide 2.4 mg on cardiovascular outcomes in people with overweight or obesity without T2D.
- Aronne, L. J. et al. Tirzepatide as compared with semaglutide for the treatment of obesity. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMoa2416394> (2025).
This article reports the landmark trial comparing the effects of semaglutide and tirzepatide at their maximum tolerated doses in adults with obesity, or with overweight and at least one prespecified comorbidity.
- Kosiborod, M. N. et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N. Engl. J. Med.* **389**, 1069–1084 (2023).
- Perkovic, V. et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N. Engl. J. Med.* **391**, 109–121 (2024).
- Sanyal, A. J. et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N. Engl. J. Med.* **392**, 2089–2099 (2025).
This article reports the effects of semaglutide 2.4 mg in individuals with biopsy-confirmed MASH and stage 2 or 3 fibrosis.

18. Jastreboff, A. M. et al. Tirzepatide once weekly for the treatment of obesity. *N. Engl. J. Med.* **387**, 205–216 (2022).
This article demonstrates the efficacy of tirzepatide 5, 10 and 15 mg in people with overweight or obesity without T2D.
19. Malhotra, A. et al. Tirzepatide for the treatment of obstructive sleep apnea: rationale, design, and sample baseline characteristics of the SURMOUNT-OSA phase 3 trial. *Contemp. Clin. Trials* **141**, 107516 (2024).
This article demonstrates the efficacy of tirzepatide in people with overweight or obesity and obstructive sleep apnoea.
20. Packer, M. et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. *N. Engl. J. Med.* **392**, 427–437 (2025).
21. Jastreboff, A. M. et al. Tirzepatide for obesity treatment and diabetes prevention. *N. Engl. J. Med.* **392**, 958–971 (2025).
This article reports the safety and efficacy of tirzepatide for obesity treatment and T2D prevention over 3 years of treatment in adults with obesity and prediabetes.
22. le Roux, C. W. et al. Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial. *Lancet Diabetes Endocrinol.* **12**, 162–173 (2024).
23. Ji, L. et al. Once-weekly mazdutide in chinese adults with obesity or overweight. *N. Engl. J. Med.* **392**, 2215–2225 (2025).
24. Coskun, T. et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: from discovery to clinical proof of concept. *Cell Metab.* **34**, 1234–1247.e9 (2022).
This article presents the discovery and preclinical characterization of retratutide, a unimolecular GLP1R-GIPR-CGGR tri-agonist.
25. Kruse, T. et al. Development of cagrilintide, a long-acting amylin analogue. *J. Med. Chem.* **64**, 11183–11194 (2021).
This article describes the medicinal chemistry optimization and early preclinical evaluation of cagrilintide.
26. Dahl, K. et al. NN1213 - a potent, long-acting, and selective analog of human amylin. *J. Med. Chem.* **67**, 11688–11700 (2024).
27. Billings, L. K. et al. Eloralintide, a selective amylin receptor agonist for the treatment of obesity: a 48-week phase 2, multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* **406**, 2631–2643 (2025).
This article demonstrates the weight loss efficacy of the selective AMLNR agonist, eloralintide, in people with obesity.
28. Kuhre, R. E. et al. The effect of amycretin, a unimolecular glucagon-like peptide-1 and amylin receptor agonist, on body weight and metabolic dysfunction in mice and rats. *EBioMedicine* **118**, 105862 (2025).
29. Clemmensen, C., Gerhart-Hines, Z., Schwartz, T. W., Zierath, J. R. & Sakamoto, K. Shaping the future of cardiometabolic innovation: advances and opportunities. *Nat. Metab.* **7**, 1495–1497 (2025).
30. Garvey, W. T. et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am. J. Clin. Nutr.* **95**, 297–308 (2012).
31. Gadde, K. M. et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* **377**, 1341–1352 (2011).
32. Allison, D. B. et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity* **20**, 330–342 (2012).
33. Greenway, F. L. et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **376**, 595–605 (2010).
34. Apovian, C. M. et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity* **21**, 935–943 (2013).
35. Sjöström, L. et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European multicentre orlistat study group. *Lancet* **352**, 167–172 (1998).
36. Khalili, N. & Safavi-pour, A. Evaluation of the effects of acarbose on weight and metabolic, inflammatory, and cardiovascular markers in patients with obesity and overweight. *Int. J. Prev. Med.* **11**, 140 (2020).
37. Treviskakis, J. L., Parkes, D. G. & Young, A. A. A salute to innovation: exenatide in diabetes and obesity drug development at Amylin Pharmaceuticals. *Nat. Metab.* <https://doi.org/10.1038/s42255-025-01383-x> (2025).
38. Kurtzhals, P., Østergaard, S., Nishimura, E. & Kjeldsen, T. Derivatization with fatty acids in peptide and protein drug discovery. *Nat. Rev. Drug Discov.* **22**, 59–80 (2023).
39. Clemmensen, C. et al. Emerging hormonal-based combination pharmacotherapies for the treatment of metabolic diseases. *Nat. Rev. Endocrinol.* **15**, 90–104 (2019).
40. Petersen, J., Ingemann Johansen, V. B. & Clemmensen, C. SnapShot: brain-targeting anti-obesity medications. *Cell Metab.* **37**, 790–790.e1 (2025).
41. Frias, J. P. et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N. Engl. J. Med.* **385**, 503–515 (2021).
42. Lund, P. K., Goodman, R. H., Dee, P. C. & Habener, J. F. Pancreatic preproglucagon cDNA contains two glucagon-related coding sequences arranged in tandem. *Proc. Natl Acad. Sci. USA* **79**, 345–349 (1982).
43. Mojsov, S. et al. Preproglucagon gene expression in pancreas and intestine diversifies at the level of post-translational processing. *J. Biol. Chem.* **261**, 11880–11889 (1986).
44. Mojsov, S. & Merrifield, R. B. An improved synthesis of crystalline mammalian glucagon. *Eur. J. Biochem.* **145**, 601–605 (1984).
45. Drucker, D. J., Philippe, J., Mojsov, S., Chick, W. L. & Habener, J. F. Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. *Proc. Natl Acad. Sci. USA* **84**, 3434–3438 (1987).
46. Holst, J. J., Orskov, C., Nielsen, O. V. & Schwartz, T. W. Truncated glucagon-like peptide I, an insulin-releasing hormone from the distal gut. *FEBS Lett.* **211**, 169–174 (1987).
47. Kreymann, B., Williams, G., Ghatei, M. A. & Bloom, S. R. Glucagon-like peptide-1 7-36: a physiological incretin in man. *Lancet* **2**, 1300–1304 (1987).
48. Vilsbøll, T., Agersø, H., Krarup, T. & Holst, J. J. Similar elimination rates of glucagon-like peptide-1 in obese type 2 diabetic patients and healthy subjects. *J. Clin. Endocrinol. Metab.* **88**, 220–224 (2003).
49. Deacon, C. F. et al. Dipeptidyl peptidase IV resistant analogues of glucagon-like peptide-1 which have extended metabolic stability and improved biological activity. *Diabetologia* **41**, 271–278 (1998).
50. Drucker, D. J. et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* **372**, 1240–1250 (2008).
51. Eng, J., Kleinman, W. A., Singh, L., Singh, G. & Raufman, J. P. Isolation and characterization of exendin-4, an exendin-3 analogue, from *Heloderma suspectum* venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas. *J. Biol. Chem.* **267**, 7402–7405 (1992).
52. DeFronzo, R. A. et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* **28**, 1092–1100 (2005).
53. Knudsen, L. B. et al. Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J. Med. Chem.* **43**, 1664–1669 (2000).
This article was among the first to describe the use of fatty acids to prolong the circulating half-life of GLP1 analogues.
54. Turton, M. D. et al. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* **379**, 69–72 (1996).
55. Tang-Christensen, M. et al. Central administration of GLP-1-(7-36) amide inhibits food and water intake in rats. *Am. J. Physiol.* **271**, R848–R856 (1996).
56. Pi-Sunyer, X. et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N. Engl. J. Med.* **373**, 11–22 (2015).
57. le Roux, C. W. et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* **389**, 1399–1409 (2017).
58. Davies, M. J. et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA* **314**, 687–699 (2015).
59. Lau, J. et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J. Med. Chem.* **58**, 7370–7380 (2015).
60. Rosenstock, J. et al. The fate of taspoglutide, a weekly GLP-1 receptor agonist, versus twice-daily exenatide for type 2 diabetes: the T-emerge 2 trial. *Diabetes Care* **36**, 498–504 (2013).
61. Fineman, M. S. et al. Clinical relevance of anti-exenatide antibodies: safety, efficacy and cross-reactivity with long-term treatment. *Diabetes Obes. Metab.* **14**, 546–554 (2012).
62. Buse, J. B. et al. Liraglutide treatment is associated with a low frequency and magnitude of antibody formation with no apparent impact on glycemic response or increased frequency of adverse events: results from the liraglutide effect and action in diabetes (LEAD) trials. *J. Clin. Endocrinol. Metab.* **96**, 1695–1702 (2011).
63. Sorli, C. et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol.* **5**, 251–260 (2017).
64. Wharton, S. et al. Once-weekly semaglutide 7.2 mg in adults with obesity (STEP UP): a randomised, controlled, phase 3b trial. *Lancet Diabetes Endocrinol.* **13**, 949–963 (2025).
This article demonstrates the efficacy of semaglutide 7.2mg in people living with obesity.
65. FDA approves fourth product under National Priority Voucher program, higher dose semaglutide. <https://www.fda.gov/news-events/press-announcements/fda-approves-fourth-product-under-national-priority-voucher-program-higher-dose-semaglutide> (19 March 2026).
66. Davies, M. et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* **397**, 971–984 (2021).
67. Aroda, V. R. et al. High-dose semaglutide (up to 16 mg) in people with type 2 diabetes and overweight or obesity: a randomized, placebo-controlled, phase 2 trial. *Diabetes Care* **48**, 905–913 (2025).
68. Rubino, D. et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA* **325**, 1414–1425 (2021).
This article reports that discontinuation of semaglutide 2.4 mg is followed by weight regain, supporting the need for continued treatment to maintain weight loss.
69. Wilding, J. P. H. et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diabetes, Obes. Metab.* **24**, 1553–1564 (2022).
This article reports the re-emergence of cardiometabolic risk factors following withdrawal of semaglutide 2.4 mg.

70. Ryan, D. H. et al. Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial. *Nat. Med.* **30**, 2049–2057 (2024).
71. Seier, S., Stamp-Larsen, K., Jensen, S. B. K., Torekov, S. S. & Gudbergson, H. Treat to target in weight management with semaglutide: Real-world evidence from an eHealth clinic. *Diabetes Obes. Metab.* **27**, 6979–6987 (2025).
72. Pfizer's ultra-long-acting injectable GLP-1 RA shows robust and continued weight loss with monthly dosing in phase 2b trial. Pfizer <https://www.pfizer.com/news/press-release/press-release-detail/pfizers-ultra-long-acting-injectable-glp-1-ra-shows-robust> (3 February 2026).
73. Metsera. Metsera reports positive phase 2b results for first- and best-in-class ultra-long acting GLP-1 RA candidate MET-0971, enabling rapid transition into phase 3. *GlobalNewswire* <https://www.globenewswire.com/news-release/2025/09/29/3158095/0/en/Metsera-Reports-Positive-Phase-2b-Results-for-First-and-Best-in-Class-Ultra-long-Acting-GLP-1-RA-Candidate-MET-0971-Enabling-Rapid-Transition-into-Phase-3.html> (2025).
74. Wu, J. J., Wang, V., Pharma, A. & Kong, H. ASC30, a once-monthly SQ injected small molecule GLP-1RA in participants with obesity: a Ph Ib study [Poster]. *Obesity Week* https://www.ascletis.com/data/upload/ueditor/20251030/Poster_ASC30_SQ_obesity_week_Obesity_week.pdf (2025).
75. Fractyl Health, Inc. news release. Fractyl Health reports positive 6-month REVEAL-1 open-label results showing sustained post-GLP-1 weight maintenance after a single Revita® procedure. *fractyl.com* <https://ir.fractyl.com/news-releases/news-release-details/fractyl-health-reports-positive-6-month-reveal-1-open-label/> (2025).
76. Gabery, S. et al. Semaglutide lowers body weight in rodents via distributed neural pathways. *JCI Insight* **5**, e133429 (2020).
77. Secher, A. et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J. Clin. Invest.* **124**, 4473–4488 (2014).
78. Hansen, H. H. et al. Whole-brain activation signatures of weight-lowering drugs. *Mol. Metab.* **47**, 101171 (2021).
79. Skovbjerg, G. et al. Uncovering CNS access of lipidated extendin-4 analogues by quantitative whole-brain 3D light sheet imaging. *Neuropharmacology* **238**, 109637 (2023).
80. de Bray, A. et al. Fluorescent GLP1R/GIPR dual agonist probes reveal cell targets in the pancreas and brain. *Nat. Metab.* **7**, 1536–1549 (2025).
81. Imbernon, M. et al. Tanycytes control hypothalamic liraglutide uptake and its anti-obesity actions. *Cell Metab.* **34**, 1054–1063.e7 (2022).
82. Sisley, S. et al. Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect. *J. Clin. Invest.* **124**, 2456–2463 (2014).
83. Huang, K.-P. et al. Dissociable hindbrain GLP1R circuits for satiety and aversion. *Nature* **632**, 585–593 (2024).
84. Yacawych, W. T. et al. A single dorsal vagal complex circuit mediates the aversive and anorectic responses to GLP1R agonists. Preprint at *bioRxiv* <https://doi.org/10.1101/2025.01.21.634167> (2025).
85. Adams, J. M. et al. Liraglutide modulates appetite and body weight through glucagon-like peptide 1 receptor-expressing glutamatergic neurons. *Diabetes* **67**, 1538–1548 (2018).
86. Ludwig, M. Q. et al. A genetic map of the mouse dorsal vagal complex and its role in obesity. *Nat. Metab.* **3**, 530–545 (2021).
87. Chen, Z. et al. GLP-1R-positive neurons in the lateral septum mediate the anorectic and weight-lowering effects of liraglutide in mice. *J. Clin. Invest.* **134**, e178239 (2024).
88. Zhang, C. et al. Area postrema cell types that mediate nausea-associated behaviors. *Neuron* **109**, 461–472.e5 (2021).
89. Kizilkaya, H. S. et al. Characterization of genetic variants of GIPR reveals a contribution of β -arrestin to metabolic phenotypes. *Nat. Metab.* **6**, 1268–1281 (2024).
90. Kizilkaya, H. S. et al. Loss of function glucose-dependent insulinotropic polypeptide receptor variants are associated with alterations in BMI, bone strength and cardiovascular outcomes. *Front. Cell Dev. Biol.* **9**, 749607 (2021).
91. Yang, B. et al. Discovery of a potent GIPR peptide antagonist that is effective in rodent and human systems. *Mol. Metab.* **66**, 101638 (2022).
92. Killion, E. A. et al. Anti-obesity effects of GIPR antagonists alone and in combination with GLP-1R agonists in preclinical models. *Sci. Transl. Med.* **10**, eaat3392 (2018).
93. Chen, M. et al. Chronic glucose-dependent insulinotropic polypeptide receptor (GIPR) agonism desensitizes adipocyte GIPR activity mimicking functional GIPR antagonism. *Nat. Commun.* **11**, 4981 (2020).
94. Lu, S.-C. et al. GIPR antagonist antibodies conjugated to GLP-1 peptide are bispecific molecules that decrease weight in obese mice and monkeys. *Cell Rep. Med.* **2**, 100263 (2021).
95. Jensen, M. H. et al. AT-7687, a novel GIPR peptide antagonist, combined with a GLP-1 agonist, leads to enhanced weight loss and metabolic improvements in cynomolgus monkeys. *Mol. Metab.* **88**, 102006 (2024).
96. Véniant, M. M. et al. A GIPR antagonist conjugated to GLP-1 analogues promotes weight loss with improved metabolic parameters in preclinical and phase 1 settings. *Nat. Metab.* **6**, 290–303 (2024).
97. Jastreboff, A. M. et al. Once-monthly maridebart cafraglutide for the treatment of obesity — a phase 2 trial. *N. Engl. J. Med.* **392**, 843–857 (2025).
This article demonstrates the weight loss efficacy of maridebart cafraglutide (MariTide), a long-acting peptide–antibody conjugate combining GLP1R agonism with GIPR antagonism, in adults with obesity with and without T2D.
98. Erman, M. & Beasley, D. Amgen says MariTide helped trial patients maintain weight loss. *Reuters* <https://www.reuters.com/business/healthcare-pharmaceuticals/amgen-says-maritide-helped-trial-patients-maintain-weight-loss-2026-01-13/> (2026).
99. Kim, S.-J. et al. GIP-overexpressing mice demonstrate reduced diet-induced obesity and steatosis, and improved glucose homeostasis. *PLoS ONE* **7**, e40156 (2012).
100. Mroz, P. A. et al. Optimized GIP analogs promote body weight lowering in mice through GIPR agonism not antagonism. *Mol. Metab.* **20**, 51–62 (2019).
101. Nørregaard, P. K. et al. A novel GIP analogue, ZP4165, enhances glucagon-like peptide-1 induced body weight loss and improves glycaemic control in rodents. *Diabetes Obes. Metab.* **20**, 60–68 (2018).
102. Finan, B. et al. Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. *Sci. Transl. Med.* **5**, 209ra151 (2013).
This article describes the discovery and preclinical characterization of the first long-acting GLP1R–GIPR co-agonist.
103. Liskiewicz, A. et al. Glucose-dependent insulinotropic polypeptide regulates body weight and food intake via GABAergic neurons in mice. *Nat. Metab.* **5**, 2075–2085 (2023).
104. Zhang, Q. et al. The glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS–GIPR signaling. *Cell Metab.* **33**, 833–844.e5 (2021).
105. Wean, J. et al. Specific loss of GIPR signaling in GABAergic neurons enhances GLP-1R agonist-induced body weight loss. *Mol. Metab.* **95**, 102074 (2025).
106. El, K. et al. The incretin co-agonist tirzepatide requires GIPR for hormone secretion from human islets. *Nat. Metab.* **5**, 945–954 (2023).
107. Samms, R. J. et al. GIPR agonism mediates weight-independent insulin sensitization by tirzepatide in obese mice. *J. Clin. Invest.* **131**, e146353 (2021).
108. Thomas, M. K. et al. Dual GIP and GLP-1 receptor agonist tirzepatide improves beta-cell function and insulin sensitivity in type 2 diabetes. *J. Clin. Endocrinol. Metab.* **106**, 388–396 (2021).
109. Frias, J. P. et al. The sustained effects of a dual GIP/GLP-1 receptor agonist, NNC0090-2746, in patients with type 2 diabetes. *Cell Metab.* **26**, 343–352.e2 (2017).
110. Coskun, T. et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. *Mol. Metab.* **18**, 3–14 (2018).
This article describes the discovery and preclinical characterization of tirzepatide.
111. Willard, F. S. et al. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight* **5**, e140532 (2020).
112. Novikoff, A. et al. Spatiotemporal GLP-1 and GIP receptor signaling and trafficking/recycling dynamics induced by selected receptor mono- and dual-agonists. *Mol. Metab.* **49**, 101181 (2021).
113. Dawed, A. Y. et al. Pharmacogenomics of GLP-1 receptor agonists: a genome-wide analysis of observational data and large randomised controlled trials. *Lancet Diabetes Endocrinol.* **11**, 33–41 (2023).
114. McNeill, S. M. et al. The role of G protein-coupled receptor kinases in GLP-1R β -arrestin recruitment and internalisation. *Biochem. Pharmacol.* **222**, 116119 (2024).
115. Douros, J. D. et al. A GLP-1 analogue optimized for cAMP-biased signaling improves weight loss in obese mice. *Mol. Metab.* **100**, 102124 (2025).
116. Rosenstock, J. et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* **398**, 143–155 (2021).
117. Ludvik, B. et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet* **398**, 583–598 (2021).
118. Del Prato, S. et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet* **398**, 1811–1824 (2021).
119. Dahl, D. et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. *JAMA* **327**, 534–545 (2022).
120. Rosenstock, J. et al. Tirzepatide vs insulin lispro added to basal insulin in type 2 diabetes: The SURPASS-6 randomized clinical trial. *JAMA* **330**, 1631–1640 (2023).
121. Garvey, W. T. et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* **402**, 613–626 (2023).
122. Rodriguez, P. J. et al. Semaglutide vs tirzepatide for weight loss in adults with overweight or obesity. *JAMA Intern. Med.* **184**, 1056–1064 (2024).
123. Yu, X. et al. The GIP receptor activates futile calcium cycling in white adipose tissue to increase energy expenditure and drive weight loss in mice. *Cell Metab.* **37**, 187–204.e7 (2025).
124. Borner, T. et al. GIP receptor agonism attenuates GLP-1 receptor agonist-induced nausea and emesis in preclinical models. *Diabetes* **70**, 2545–2553 (2021).
125. Knop, F. K. et al. A long-acting glucose-dependent insulinotropic polypeptide receptor agonist improves the gastrointestinal tolerability of glucagon-like peptide-1 receptor agonist therapy. *Diabetes Obes. Metab.* **26**, 5474–5478 (2024).
126. Borner, T. et al. Hypophagia and body weight loss by tirzepatide are accompanied by fewer GI adverse events compared to semaglutide in preclinical models. *Sci. Adv.* **11**, eadu1589 (2025).
127. Novo Nordisk A/S: CagriSema demonstrated 23% weight loss in an open-label head-to-head REDEFINE 4 trial in people with obesity, the primary endpoint was not achieved. *Novo Nordisk* <https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=916501> (23 February 2026).

128. Wadden, T. A. et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nat. Med.* **29**, 2909–2918 (2023).
129. Lundgren, J. R. et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. *N. Engl. J. Med.* **384**, 1719–1730 (2021).
130. Petersen, J., Merrild, C., Lund, J., Holm, S. & Clemmensen, C. Lead-in calorie restriction enhances the weight-lowering efficacy of incretin hormone-based pharmacotherapies in mice. *Mol. Metab.* **89**, 102027 (2024).
131. Aronne, L. J. et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. *JAMA* **331**, 38–48 (2024).
132. Horn, D. B. et al. Cardiometabolic parameter change by weight regain on tirzepatide withdrawal in adults with obesity: a post hoc analysis of the SURMOUNT-4 trial. *JAMA Intern. Med.* **186**, e256112 (2025).
133. Jiangsu Hengrui Pharmaceuticals and Kailera Therapeutics report positive topline data from 8 mg dose of phase 2 obesity trial of GLP-1/GIP receptor dual agonist HRS9531. Kailera <https://www.kailera.com/press-release/jiangsu-hengrui-pharmaceuticals-and-kailera-therapeutics-report-positive-topline-data-from-8-mg-dose-of-phase-2-obesity-trial-of-glp-1-gip-receptor-dual-agonist-hrs9531/> (2025).
134. Roche Pharma Day 2024. https://assets.roche.com/f/176343/x/f513f69de2/pharma_day_20240930_final_online_v02.pdf (2024).
135. Chakravarthy, M. V. et al. Effects of CT-388, a once-weekly signaling-biased dual GLP-1/GIP receptor agonist, on weight loss and glycemic control in preclinical models and participants with obesity. *Mol. Metab.* **103**, 102291 (2025).
136. Rodriguez, R. et al. Biased agonism of GLP-1R and GIPR enhances glucose lowering and weight loss, with dual GLP-1R/GIPR biased agonism yielding greater efficacy. *Cell Rep. Med.* **6**, 102156 (2025).
137. [Ad hoc announcement pursuant to Art. 53 LR] Roche announces positive Phase II results for its dual GLP-1/GIP receptor agonist CT-388 in people living with obesity. Roche <https://www.roche.com/media/releases/med-cor-2026-01-27> (27 January 2026).
138. Yuan, J. et al. Molecular dynamics-guided optimization of BGM0504 enhances dual-target agonism for combating diabetes and obesity. *Sci. Rep.* **14**, 16680 (2024).
139. Fan, Y. et al. The safety, tolerability, pharmacokinetics and pharmacodynamics of an optimized dual GLP-1/GIP receptor agonist (BGM0504) in healthy volunteers: a dose-escalation phase I study. *Diabetes Obes. Metab.* **27**, 2110–2119 (2025).
140. Olatorepatide obesity treatment licensed by Regeneron demonstrates positive phase 3 results in Chinese patients. Regeneron <https://investor.regeneron.com/news-releases/news-release-details/olatorepatide-obesity-treatment-licensed-regeneron-demonstrates> (9 March 2026).
141. Ravussin, E. et al. Tirzepatide did not impact metabolic adaptation in people with obesity, but increased fat oxidation. *Cell Metab.* **37**, 1060–1074.e4 (2025).
142. Martin, C. K. et al. Tirzepatide on ingestive behavior in adults with overweight or obesity: a randomized 6-week phase 1 trial. *Nat. Med.* **31**, 3141–3150 (2025).
143. Dhurandhar, E. J. et al. Food noise: definition, measurement, and future research directions. *Nutr. Diabetes* **15**, 30 (2025).
144. Choi, W. et al. Brain activity associated with breakthrough food preoccupation in an individual on tirzepatide. *Nat. Med.* **31**, 4038–4043 (2025).
145. Lewis, J. E. et al. Stimulating intestinal GIP release reduces food intake and body weight in mice. *Mol. Metab.* **84**, 101945 (2024).
146. Adriaenssens, A. et al. Hypothalamic and brainstem glucose-dependent insulinotropic polypeptide receptor neurons employ distinct mechanisms to affect feeding. *JCI Insight* **8**, e164921 (2023).
147. Adriaenssens, A. E. et al. Glucose-dependent insulinotropic polypeptide receptor-expressing cells in the hypothalamus regulate food intake. *Cell Metab.* **30**, 987–996.e6 (2019).
148. Gutgesell, R. M. et al. GIPR agonism and antagonism decrease body weight and food intake via different mechanisms in male mice. *Nat. Metab.* **7**, 1282–1298 (2025).
149. McMorrow, H. E. et al. Incretin receptor agonism rapidly inhibits AgRP neurons to suppress food intake in mice. *J. Clin. Invest.* <https://doi.org/10.1172/JCI186652> (2025).
150. Steuernagel, L. et al. HypoMap — a unified single-cell gene expression atlas of the murine hypothalamus. *Nat. Metab.* **4**, 1402–1419 (2022).
151. Tadross, J. A. et al. A comprehensive spatio-cellular map of the human hypothalamus. *Nature* <https://doi.org/10.1038/s41586-024-08504-8> (2025).
152. Smith, C. et al. A comparative transcriptomic analysis of glucagon-like peptide-1 receptor- and glucose-dependent insulinotropic polypeptide receptor-expressing cells in the hypothalamus. *Appetite* **174**, 106022 (2022).
153. Hansford, R. et al. Glucose-dependent insulinotropic polypeptide receptor signaling in oligodendrocytes increases the weight-loss action of GLP-1R agonism. *Cell Metab.* **37**, 1820–1834.e5 (2025).
154. Douras, J. D., Flak, J. N. & Knerr, P. J. The agony and the efficacy: central mechanisms of GLP-1 induced adverse events and their mitigation by GIP. *Front. Endocrinol.* **16**, 1530985 (2025).
155. Liu, C. M. et al. GIPR-Ab/GLP-1 peptide-antibody conjugate requires brain GIPR and GLP-1R for additive weight loss in obese mice. *Nat. Metab.* <https://doi.org/10.1038/s42255-025-01295-w> (2025).
156. Habegger, K. M. et al. The metabolic actions of glucagon revisited. *Nat. Rev. Endocrinol.* **6**, 689–697 (2010).
157. Wewer Albrechtsen, N. J. et al. 100 years of glucagon and 100 more. *Diabetologia* **66**, 1378–1394 (2023).
158. Day, J. W. et al. A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. *Nat. Chem. Biol.* **5**, 749–757 (2009).
159. Pocai, A. et al. Glucagon-like peptide 1/glucagon receptor dual agonism reverses obesity in mice. *Diabetes* **58**, 2258–2266 (2009).
160. Ji, L. et al. A phase 2 randomised controlled trial of mazdutide in Chinese overweight adults or adults with obesity. *Nat. Commun.* **14**, 8289 (2023).
161. Innovent. Innovent announces mazdutide received approval from China's NMPA for glycemic control in adults with type 2 diabetes. PR Newswire <https://www.prnewswire.com/news-releases/innovent-announces-mazdutide-received-approval-from-chinas-nmpa-for-glycemic-control-in-adults-with-type-2-diabetes-302561434.html> (2025).
162. Zimmermann, T. et al. BI 456906: discovery and preclinical pharmacology of a novel GCGR/GLP-1R dual agonist with robust anti-obesity efficacy. *Mol. Metab.* **66**, 101633 (2022).
163. Blüher, M., Rosenstock, J., Hoefler, J., Manuel, R. & Hennige, A. M. Dose-response effects on HbA1c and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomised clinical trial. *Diabetologia* **67**, 470–482 (2024).
164. Sanyal, A. J. et al. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N. Engl. J. Med.* **391**, 311–319 (2024).
165. Aronne, L. et al. 262-OR: Pemvidutide, a GLP-1/glucagon dual receptor agonist, in subjects with overweight or obesity—a 48-week, placebo-controlled, phase 2 (MOMENTUM) trial. *Diabetes* **73** (Suppl. 1), 262-OR (2024).
166. Conte, C., Hall, K. D. & Klein, S. Is weight loss-induced muscle mass loss clinically relevant? *JAMA* **332**, 9–10 (2024).
167. Noureddin, M. et al. Safety and efficacy of weekly pemvidutide versus placebo for metabolic dysfunction-associated steatohepatitis (IMPACT): 24-week results from a multicentre, randomised, double-blind, phase 2b study. *Lancet* **406**, 2644–2655 (2025).
168. Friedrichsen, M. H. et al. Results from three phase 1 trials of NNC9204-1177, a glucagon/GLP-1 receptor co-agonist: effects on weight loss and safety in adults with overweight or obesity. *Mol. Metab.* **78**, 101801 (2023).
169. Gault, V. A., Bhat, V. K., Irwin, N. & Flatt, P. R. A novel glucagon-like peptide-1 (GLP-1)/glucagon hybrid peptide with triple-acting agonist activity at glucose-dependent insulinotropic polypeptide, GLP-1, and glucagon receptors and therapeutic potential in high fat-fed mice. *J. Biol. Chem.* **288**, 35581–35591 (2013).
170. Bhat, V. K., Kerr, B. D., Vasu, S., Flatt, P. R. & Gault, V. A. A DPP-IV-resistant triple-acting agonist of GIP, GLP-1 and glucagon receptors with potent glucose-lowering and insulinotropic actions in high-fat-fed mice. *Diabetologia* **56**, 1417–1424 (2013).
171. Mansur, S. A. et al. A new stable GIP-Oxyntomodulin hybrid peptide improved bone strength both at the organ and tissue levels in genetically-inherited type 2 diabetes mellitus. *Bone* **87**, 102–113 (2016).
172. Finan, B. et al. A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. *Nat. Med.* **21**, 27–36 (2015).
- This article describes the discovery and preclinical characterization of the first long-acting GLP1R-GIPR-GCGR tri-agonist.**
173. Bossart, M. et al. Effects on weight loss and glycemic control with SAR441255, a potent unimolecular peptide GLP-1/GIP/GCG receptor triagonist. *Cell Metab.* **34**, 59–74.e10 (2022).
174. Jall, S. et al. Monomeric GLP-1/GIP/glucagon triagonism corrects obesity, hepatosteatosis, and dyslipidemia in female mice. *Mol. Metab.* **6**, 440–446 (2017).
175. Enebo, L. B. et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2.4 mg for weight management: a randomised, controlled, phase 1b trial. *Lancet* **397**, 1736–1748 (2021).
176. Knerr, P. J. et al. Next generation GLP-1/GIP/glucagon triple agonists normalize body weight in obese mice. *Mol. Metab.* **63**, 101533 (2022).
177. Jastreboff, A. M. et al. Triple-hormone-receptor agonist retatrutide for obesity - a phase 2 trial. *N. Engl. J. Med.* **389**, 514–526 (2023).
178. Urva, S. et al. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial. *Lancet* **400**, 1869–1881 (2022).
179. Rosenstock, J. et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. *Lancet* **402**, 529–544 (2023).
180. Lilly's triple agonist, retatrutide, demonstrated significant reductions in A1C and weight in first Phase 3 trial for treatment of type 2 diabetes. Lilly <https://investor.lilly.com/news-releases/news-release-details/lillys-triple-agonist-retatrutide-demonstrated-significant> (19 March 2026).
181. Eli Lilly and Company. News release. Lilly's triple agonist, retatrutide, delivered weight loss of up to an average of 71.2 lbs along with substantial relief from osteoarthritis pain in first successful phase 3 trial. [lilly.com https://investor.lilly.com/news-releases/news-release-details/lillys-triple-agonist-retatrutide-delivered-weight-loss-average](https://investor.lilly.com/news-releases/news-release-details/lillys-triple-agonist-retatrutide-delivered-weight-loss-average). **This article reports the weight loss efficacy of the unimolecular GLP1R-GIPR-GCGR tri-agonist retatrutide in people with obesity and osteoarthritis.**
182. Hanmi Pharmaceutical. Efciopegrutide. [hanmipharm.com https://www.hanmipharm.com/science/pipeline/focused/efciopegrutide.htm](https://www.hanmipharm.com/science/pipeline/focused/efciopegrutide.htm) (2025).
183. Hanmi Pharmaceutical. Potent body weight loss, and therapeutic efficacy in a NASH animal model by a novel long-acting GLP-1/GIP/glucagon tri-agonist (HM15211). In European Association for the Study of Diabetes (EASD) 53rd Annual Meeting https://www.hanmipharm.com/science-pdf/HM15211/3.2017_EASD_Oral%20presentation_HM15211.pdf (2017).

184. Hanmi Pharmaceutical. HM15275. *hanmipharm.com* <https://hanmipharm.com/science/pipeline/focused/hm15275.htm> (2025).
185. Novo Nordisk: Triple agonist UBT251 delivers up to 19.7% mean weight loss after 24 weeks in phase 2 trial in China. *Novo Nordisk* <https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=916503> (24 February 2026).
186. Novo Nordisk A/S: Triple agonist UBT251 showed a mean HbA1c reduction of up to 2.16% after 24 weeks in phase 2 trial in Chinese patients with type 2 diabetes. *Novo Nordisk* <https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=916519> (25 March 2026).
187. Winther-Sørensen, M. et al. Glucagon acutely regulates hepatic amino acid catabolism and the effect may be disturbed by steatosis. *Mol. Metab.* **42**, 101080 (2020).
188. Roell, W. et al. Characterization of LY3324954 a long-acting glucagon-receptor agonist. *Mol. Metab.* **91**, 102073 (2025).
189. Lutz, T. A. Creating the amylin story. *Appetite* **172**, 105965 (2022).
190. Poyner, D. R. et al. International union of pharmacology. XXXII. The mammalian calcitonin gene-related peptides, adrenomedullin, amylin, and calcitonin receptors. *Pharmacol. Rev.* **54**, 233–246 (2002).
191. Gostynska, S. E. et al. Amylin receptor subunit interactions are modulated by agonists and determine signaling. *Sci. Signal.* **18**, ead8127 (2025).
192. Westermark, P., Andersson, A. & Westermark, G. T. Islet amyloid polypeptide, islet amyloid, and diabetes mellitus. *Physiol. Rev.* **91**, 795–826 (2011).
193. Paulsson, J. F., Benoit-Biancamano, M.-O., Schäffer, L. & Dahl, K. Ferret islet amyloid polypeptide (IAPP): characterization of in vitro and in vivo amyloidogenicity. *Amyloid* **18**, 222–228 (2011).
194. Smith, S. R. et al. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care* **31**, 1816–1823 (2008).
195. Ryan, G., Briscoe, T. A. & Jobe, L. Review of pramlintide as adjunctive therapy in treatment of type 1 and type 2 diabetes. *Drug Des. Dev. Ther.* **2**, 203–214 (2009).
196. Fletcher, M. M. et al. AM833 is a novel agonist of calcitonin family G protein-coupled receptors: pharmacological comparison with six selective and nonselective agonists. *J. Pharmacol. Exp. Ther.* **377**, 417–440 (2021).
197. Larsen, A. T. et al. Does receptor balance matter? - Comparing the efficacies of the dual amylin and calcitonin receptor agonists cagrilintide and KBP-336 on metabolic parameters in preclinical models. *Biomed. Pharmacother.* **156**, 113842 (2022).
198. Carvas, A. O. et al. Cagrilintide lowers bodyweight through brain amylin receptors 1 and 3. *EBioMedicine* **118**, 105836 (2025).
199. Lau, D. C. W. et al. Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial. *Lancet* **398**, 2160–2172 (2021).
200. Garvey, W. T. et al. Coadministered cagrilintide and semaglutide in adults with overweight or obesity. *N. Engl. J. Med.* **393**, 635–647 (2025).
This article reports the weight loss efficacy of CagriSema (cagrilintide, an amylin analogue, in combination with semaglutide, a GLP1 analogue) in adults with overweight or obesity.
201. Davies, M. J. et al. Cagrilintide-semaglutide in adults with overweight or obesity and type 2 diabetes. *N. Engl. J. Med.* **393**, 648–659 (2025).
202. Novo Nordisk. Investor presentation. First three months of 2025. <https://www.novonordisk.com/content/dam/nncorp/global/en/investors/pdfs/financial-results/2025/Q1-2025-investor-presentation.pdf> (2025).
203. Briere, D. A. et al. Eloralintide (LY3841136), a novel amylin receptor agonist for the treatment of obesity: From discovery to clinical proof of concept. *Mol. Metab.* <https://doi.org/10.1016/j.molmet.2025.102271> (2025).
204. Bhattachar, S. N. et al. 882-P: Eloralintide, a selective, long-acting amylin receptor agonist for obesity—phase 1 proof of concept. *Diabetes* **74** (Suppl.1), 882-P (2025).
205. Geoghegan, G. et al. 88-OR: Long-acting amylin analog AZD6234 in combination with the GLP-1R agonist semaglutide enhances body weight and fat mass loss in diet-induced obese (DIO) rats. *Diabetes* **74** (Suppl. 1), 88-OR (2025).
206. Fischer Munch, H. et al. Development of petrelintide: a potent, stable, long-acting human amylin analogue. *J. Med. Chem.* **68**, 23925–23940 (2025).
207. Roche announces positive Phase II results for petrelintide, an amylin analog developed for people living with overweight and obesity. *Roche* <https://www.roche.com/media/releases/med-cor-2026-03-05> (5 March 2026).
208. Murray, A. et al. Amylin receptor (hAmy3r) agonists with improved chemical stability. World Patent WO2024003359A1 (2023).
209. AbbVie announces positive topline results from a phase 1 multiple ascending dose study of ABBV-295, a long-acting amylin analog, in adults. *AbbVie* <https://news.abbvie.com/2026-03-09-AbbVie-Announces-Positive-Topline-Results-from-a-Phase-1-Multiple-Ascending-Dose-Study-of-ABBV-295-a-Long-Acting-Amylin-Analog-in-Adults> (9 March 2026).
210. Mohamed, K. E. et al. The dual amylin and calcitonin receptor agonist KBP-336 elicits a unique combination of weight loss, antinociception and bone protection - a novel disease-modifying osteoarthritis drug. *Arthritis Res. Ther.* **26**, 129 (2024).
211. Pfizer to Acquire Metseara and its Next-Generation Obesity Portfolio. *pfizer.com* <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-acquire-metseara-and-its-next-generation-obesity> (2025).
212. Structure Therapeutics. Structure Therapeutics Reports Fourth Quarter and Full Year 2025 Financial Results and Recent Highlights. <https://ir.structuretx.com/news-releases/news-release-details/structure-therapeutics-reports-fourth-quarter-and-full-year-2025> (2026).
213. Fang, X. et al. 2184-LB: Novel oral small molecule ACCG-2671—a dual amylin and calcitonin receptor agonist development candidate for obesity therapy. *Diabetes* **74** (Suppl. 1), 2184-LB (2025).
214. Boccia, L. et al. Hypophagia induced by salmon calcitonin, but not by amylin, is partially driven by malaise and is mediated by CGRP neurons. *Mol. Metab.* **58**, 101444 (2022).
215. Genentech announces positive phase II results for petrelintide, an amylin analog developed for people living with overweight and obesity. *Business Wire* <https://www.businesswire.com/news/home/20260305198579/en/Genentech-Announces-Positive-Phase-II-Results-for-Petrelintide-an-Amylin-Analog-Developed-for-People-Living-With-Overweight-and-Obesity> (5 March 2026).
216. Tschöp, M. H. et al. Unimolecular polypharmacy for treatment of diabetes and obesity. *Cell Metab.* **24**, 51–62 (2016).
217. Trevasakis, J. L. et al. Improved glucose control and reduced body weight in rodents with dual mechanism of action peptide hybrids. *PLoS ONE* **8**, e78154 (2013).
218. Gasiorek, A. et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the first-in-class GLP-1 and amylin receptor agonist, amycretin: a first-in-human, phase 1, double-blind, randomised, placebo-controlled trial. *Lancet* **406**, 135–148 (2025).
219. Dahl, K. et al. Amycretin, a novel, unimolecular GLP-1 and amylin receptor agonist administered subcutaneously: results from a phase 1b/2a randomised controlled study. *Lancet* **406**, 149–162 (2025).
220. Ghosh, S., Valdecantos, P., Rada, P., Valverde, A. M. & Rondinone, C. M. 85-OR: A novel unimolecular peptide tetra-agonist (PTT-A) targeting GLP-1, GIP, amylin, and calcitonin receptors with superior weight loss effects vs. tirzepatide while preserving muscle in DIO rats. *Diabetes* **74** (Suppl. 1), 85-OR (2025).
221. Rondinone, C. Novel unimolecular tetra-agonist peptides targeting GLP-1, GIP, amylin, and calcitonin receptors with enhanced metabolic benefits in animal models of obesity. Oral presentation 81. EASD Media Centre. <https://www.easd.org/media-centre/#resources/b-novel-unimolecular-tetra-agonist-peptides-targeting-glp-1-gip-amylin-and-calcitonin-receptors-with-enhanced-metabolic-benefits-in-animal-models-of-obesity-b> (2024).
222. Kruse, T. et al. Tri-agonists of the glp-1, gip, and amylin receptors. World Patent WO2025114501A1 (2024).
223. Roth, J. D. et al. Leptin responsiveness restored by amylin agonism in diet-induced obesity: evidence from nonclinical and clinical studies. *Proc. Natl Acad. Sci. USA* **105**, 7257–7262 (2008).
224. Trevasakis, J. L. et al. Amylin-mediated restoration of leptin responsiveness in diet-induced obesity: magnitude and mechanisms. *Endocrinology* **149**, 5679–5687 (2008).
225. Moon, H.-S. et al. Leptin and amylin act in an additive manner to activate overlapping signaling pathways in peripheral tissues: in vitro and ex vivo studies in humans. *Diabetes Care* **34**, 132–138 (2011).
226. Miettlicki-Baase, E. G. et al. Amylin modulates the mesolimbic dopamine system to control energy balance. *Neuropsychopharmacology* **40**, 372–385 (2015).
227. Buckley, S. T. et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Sci. Transl. Med.* **10**, eaar7047 (2018).
This article describes the preclinical characterization of an absorption-enhancer strategy (SNAC) to enable oral delivery of semaglutide.
228. Overgaard, R. V., Hertz, C. L., Ingwersen, S. H., Navarra, A. & Drucker, D. J. Levels of circulating semaglutide determine reductions in HbA1c and body weight in people with type 2 diabetes. *Cell Rep. Med.* **2**, 100387 (2021).
229. Knop, F. K. et al. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **402**, 705–719 (2023).
230. Wharton, S. et al. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. *N. Engl. J. Med.* **393**, 1077–1087 (2025).
This article describes the weight loss efficacy of oral semaglutide 25 mg in people with overweight or obesity.
231. Novo Nordisk A/S. Company announcement: Wegovy® pill approved in the US as first oral GLP-1 for weight management. *Novo Nordisk* <https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=9165161> (2026).
232. Manjoo, P. & Sharma, A. M. Oral semaglutide: an OASIS from injectables. *Lancet* **402**, 670–671 (2023).
233. Bays, H. E. et al. Weekly subcutaneous VK2735, a GIP/GLP-1 receptor dual agonist, for weight management: Phase 2, randomized, 13-week VENTURE study. *Obesity* **34**, 537–549 (2026).
234. Knudsen, L. B. et al. Small-molecule agonists for the glucagon-like peptide 1 receptor. *Proc. Natl Acad. Sci. USA* **104**, 937–942 (2007).
235. Teng, M. et al. Small molecule ago-allosteric modulators of the human glucagon-like peptide-1 (hGLP-1) receptor. *Bioorg Med. Chem. Lett.* **17**, 5472–5478 (2007).
236. Kawai, T. et al. Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist. *Proc. Natl Acad. Sci. USA* **117**, 29959–29967 (2020).
237. Sloop, K. W. et al. The pharmacological basis for nonpeptide agonism of the GLP-1 receptor by orforglipron. *Sci. Transl. Med.* **16**, eadp5765 (2024).
This article describes the preclinical characterization of the non-peptide GLP1R agonist, orforglipron.
238. Griffith, D. A. et al. A small-molecule oral agonist of the human glucagon-like peptide-1 receptor. *J. Med. Chem.* **65**, 8208–8226 (2022).
239. Zhang, X. et al. Differential GLP-1R binding and activation by peptide and non-peptide agonists. *Mol. Cell* **80**, 485–500.e7 (2020).

240. Zhang, Y. et al. Cryo-EM structure of the activated GLP-1 receptor in complex with a G protein. *Nature* **546**, 248–253 (2017).
241. Pratt, E. et al. Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: a phase 1a, blinded, placebo-controlled, randomized, single- and multiple-ascending-dose study in healthy participants. *Diabetes Obes. Metab.* **25**, 2634–2641 (2023).
242. Wharton, S. et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMoa2511774> (2025). **This article describes the weight loss efficacy of orforglipron in adults with obesity.**
243. Eli Lilly & Co. News release. Lilly's oral GLP-1, orforglipron, is successful in third phase 3 trial, triggering global regulatory submissions this year for the treatment of obesity. *lilly.com* <https://investor.lilly.com/news-releases/news-release-details/lillys-oral-glp-1-orforglipron-successful-third-phase-3-trial> (2025).
244. Wegovy pill demonstrated greater weight loss than orforglipron and lower odds of stopping medication due to side effects in a new indirect comparison to be presented at Obesity Medicine Association 2026. *Novo Nordisk* <https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=916526> (2 April 2026).
245. Eli Lilly & Co. Lilly's orforglipron helped people maintain weight loss after switching from injectable incretins to oral GLP-1 therapy in first-of-its-kind phase 3 trial. *lilly.com* <https://investor.lilly.com/news-releases/news-release-details/lillys-orforglipron-helped-people-maintain-weight-loss-after> (2025). **This article describes the efficacy of using orforglipron as a maintenance therapy after treatment with semaglutide or tirzepatide at maximum tolerated dose.**
246. FDA approves Lilly's Founday (orforglipron), the only GLP-1 pill for weight loss that can be taken any time of day without food or water restrictions. *Lilly* <https://investor.lilly.com/news-releases/news-release-details/fda-approves-lillys-foundaytm-orforglipron-only-glp-1-pill> (1 April 2026).
247. Meng, Q. et al. Heterocyclic glp-1 agonists. World Patent WO2023016546A1 (2023).
248. Structure Therapeutics reports positive topline data from phase 2 ACCESS II trial with once-daily oral small molecule GLP-1 receptor agonist, aleniglipron. *Structure Therapeutics* <https://ir.structuretx.com/news-releases/news-release-details/structure-therapeutics-reports-positive-topline-data-phase-2> (16 March 2026).
249. Haggag, A. Z. et al. Non-clinical and first-in-human characterization of ECC5004/AZD5004, a novel once-daily, oral small-molecule GLP-1 receptor agonist. *Diabetes Obes. Metab.* **27**, 551–562 (2025).
250. Chakravarthy, M. V. et al. Press release: Safety, pharmacokinetics, and pharmacodynamics of CT-996, an oral small-molecule, signal-biased GLP-1 receptor agonist over 4 weeks in adults with obesity. *EASD* <https://www.easd.org/media-centre/#resources/b-safety-pharmacokinetics-and-pharmacodynamics-of-ct-996-an-oral-small-molecule-signal-biased-glp-1-receptor-agonist-over-4-weeks-in-adults-with-obesity-b> (2024).
251. Saxena, A. R. et al. Efficacy and safety of oral small molecule glucagon-like peptide 1 receptor agonist danuglipron for glycemic control among patients with type 2 diabetes: a randomized clinical trial. *JAMA Netw. Open* **6**, e2314493 (2023).
252. Pfizer. Pfizer provides update on oral GLP-1 receptor agonist danuglipron. *pfizer.com* <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-provides-update-oral-glp-1-receptor-agonist> (2025).
253. Asclelis announces fixed-dose combination of ASC30, once-daily oral small molecule GLP-1R agonist, and ASC39, once-daily oral small molecule amylin-selective amylin receptor agonist, for clinical development. *Asclelis* https://www.asclelis.com/news_detail/200/id/1363.html (7 April 2026).
254. Beauchamp, T. J. et al. GIP receptor agonist compounds. World Patent WO/2025/264700A1 (2025).
255. Yuliantie, E. et al. Isoquinoline small molecule ligands are agonists and probe-dependent allosteric modulators of the glucagon subfamily of GPCRs. *Biochem. Pharmacol.* **229**, 116483 (2024).
256. Kodra, J. T. et al. Novel glucagon receptor antagonists with improved selectivity over the glucose-dependent insulinotropic polypeptide receptor. *J. Med. Chem.* **51**, 5387–5396 (2008).
257. Després, J.-P., Golay, A. & Sjöström, L. Rimonabant in obesity-lipids study group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N. Engl. J. Med.* **353**, 2121–2134 (2005).
258. Gaal, L. F. V., Rissanen, A. M., Scheen, A. J., Ziegler, O. & Rössner, S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* **365**, 1389–1397 (2005).
259. Liu, Z. et al. Functional selectivity of a biased cannabinoid-1 receptor (CB1R) antagonist. *ACS Pharmacol. Transl. Sci.* **4**, 1175–1187 (2021).
260. Tam, J. et al. Peripheral cannabinoid-1 receptor inverse agonism reduces obesity by reversing leptin resistance. *Cell Metab.* **16**, 167–179 (2012).
261. Gammal, A. et al. Synthesis and pharmacological characterization of novel peripheral cannabinoid-1 receptor blockers based on a tricyclic scaffold. *J. Med. Chem.* **68**, 9431–9445 (2025).
262. Knop, F. K. et al. Efficacy and safety of monlunabant in adults with obesity and metabolic syndrome: a double-blind, randomised, placebo-controlled, phase 2a trial. *Lancet Diabetes Endocrinol.* **13**, 911–923 (2025).
263. Neeiland, I. J., Linge, J. & Birkenfeld, A. L. Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. *Diabetes Obes. Metab.* **26** (Suppl. 4), 16–27 (2024).
264. Karakasis, P., Patoulas, D., Fragakis, N. & Mantzoros, C. S. Effect of glucagon-like peptide-1 receptor agonists and co-agonists on body composition: systematic review and network meta-analysis. *Metabolism* **164**, 156113 (2025).
265. Keenan, S., Cooke, M. B. & Belski, R. The effects of intermittent fasting combined with resistance training on lean body mass: a systematic review of human studies. *Nutrients* **12**, 2349 (2020).
266. Haghighat, N. et al. Preservation of fat-free mass in the first year after bariatric surgery: a systematic review and meta-analysis of 122 studies and 10,758 participants. *Surg. Obes. Relat. Dis.* **18**, 964–982 (2022).
267. Heymsfield, S. B. et al. Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. *JAMA Netw. Open* **4**, e2033457 (2021).
268. Gonzalez Trotter, D. et al. 34-OR: the effect of combined activin a and myostatin blockade on body composition—a phase 1 trial. *Diabetes* **73** (Suppl. 1), 34-OR (2024).
269. Nunn, E. et al. Antibody blockade of activin type II receptors preserves skeletal muscle mass and enhances fat loss during GLP-1 receptor agonism. *Mol. Metab.* **80**, 101880 (2024).
270. Mastaitis, J. et al. 207-OR: Myostatin inhibition synergizes with GLP-1R agonism to accelerate weight loss in male, obese nonhuman primates. *Diabetes* **72** (Suppl. 1), 207-OR (2023).
271. American Diabetes Association. Press release. New GLP-1 therapies enhance quality of weight loss by improving muscle preservation. *diabetes.org* <https://diabetes.org/newsroom/press-releases/new-glp-1-therapies-enhance-quality-weight-loss-improving-muscle-0> (2025).
272. Heymsfield, S. B. et al. Bimagrumab plus semaglutide alone or in combination for the treatment of obesity: a randomized phase 2 trial. *Nat. Med.* **32**, 869–882 (2026).
273. Mastaitis, J. W. et al. GDF8 and activin A blockade protects against GLP-1-induced muscle loss while enhancing fat loss in obese male mice and non-human primates. *Nat. Commun.* **16**, 4377 (2025).
274. Langer, H. T. et al. Weight loss with GLP-1 medicines does not result in a disproportionate loss of muscle mass or function in obese mice and humans. *Cell Rep. Med.* **7**, 102665 (2026).
275. Alissou, M. et al. Impact of semaglutide on fat mass, lean mass and muscle function in patients with obesity: the SEMALEAN study. *Diabetes Obes. Metab.* **28**, 112–121 (2026).
276. Kosiborod, M. N. et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. *N. Engl. J. Med.* **390**, 1394–1407 (2024).
277. Beavers, K. M. et al. Is lost lean mass from intentional weight loss recovered during weight regain in postmenopausal women? *Am. J. Clin. Nutr.* **94**, 767–774 (2011).
278. Deanfield, J. et al. Semaglutide and cardiovascular outcomes by baseline and changes in adiposity measurements: a prespecified analysis of the SELECT trial. *Lancet* **406**, 2257–2268 (2025).
279. Kosiborod, M. N. et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. *Lancet* **404**, 949–961 (2024).
280. Nicholls, S. J. et al. Cardiovascular outcomes with tirzepatide versus dulaglutide in type 2 diabetes. *N. Engl. J. Med.* **393**, 2409–2420 (2025). **This article demonstrates the efficacy of tirzepatide relative to dulaglutide on cardiovascular outcomes in people with T2D.**
281. Jara, M. et al. Modulation of metabolic, inflammatory and fibrotic pathways by semaglutide in metabolic dysfunction-associated steatohepatitis. *Nat. Med.* **31**, 3128–3140 (2025).
282. Loomba, R. et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N. Engl. J. Med.* **391**, 299–310 (2024). **This article demonstrates the efficacy of tirzepatide for treatment of MASH.**
283. Sanyal, A. J. et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. *Nat. Med.* **30**, 2037–2048 (2024).
284. Apperloo, E. M. et al. Semaglutide in patients with overweight or obesity and chronic kidney disease without diabetes: a randomized double-blind placebo-controlled clinical trial. *Nat. Med.* **31**, 278–285 (2025).
285. Heerspink, H. J. L. et al. Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. *Lancet Diabetes Endocrinol.* **10**, 774–785 (2022).
286. Vear, A., Heneka, M. T. & Clemmensen, C. Incretin-based therapeutics for the treatment of neurodegenerative diseases. *Nat. Metab.* **7**, 679–696 (2025).
287. Drucker, D. J. The benefits of GLP-1 drugs beyond obesity. *Science* **385**, 258–260 (2024).
288. Bliddal, H. et al. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. *N. Engl. J. Med.* **391**, 1573–1583 (2024). **This article demonstrates the weight loss efficacy and improvements in knee osteoarthritis pain scores in people with obesity and knee osteoarthritis.**
289. Cummings, J. L. et al. Evoke and Evoke+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease. *Alzheimers Res. Ther.* **17**, 14 (2025).
290. Cummings, J. L. et al. Efficacy and safety of oral semaglutide 14 mg (flexible dose) in early-stage symptomatic Alzheimer's disease (evoke and evoke+): two phase 3, randomised, placebo-controlled trials. *Lancet* [https://doi.org/10.1016/S0140-6736\(26\)00459-9](https://doi.org/10.1016/S0140-6736(26)00459-9) (2026).

291. Hendershot, C. S. et al. Once-weekly semaglutide in adults with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry* **82**, 395–405 (2025).
292. Wong, C. K. et al. Central glucagon-like peptide 1 receptor activation inhibits Toll-like receptor agonist-induced inflammation. *Cell Metab.* **36**, 130–143.e5 (2024).
293. Wong, C. K. et al. Divergent roles for the gut intraepithelial lymphocyte GLP-1R in control of metabolism, microbiota, and T cell-induced inflammation. *Cell Metab.* **34**, 1514–1531.e7 (2022).
294. Greenberg, A. S. & Obin, M. S. Obesity and the role of adipose tissue in inflammation and metabolism. *Am. J. Clin. Nutr.* **83**, 461S–465S (2006).
295. McLean, B. A., Wong, C. K., Kaur, K. D., Seeley, R. J. & Drucker, D. J. Differential importance of endothelial and hematopoietic cell GLP-1Rs for cardiometabolic versus hepatic actions of semaglutide. *JCI Insight* **6**, e153732 (2021).
296. Wang, Y. et al. Exendin-4 decreases liver inflammation and atherosclerosis development simultaneously by reducing macrophage infiltration. *Br. J. Pharmacol.* **171**, 723–734 (2014).
297. Sourris, K. C. et al. Glucagon-like peptide-1 receptor signaling modifies the extent of diabetic kidney disease through dampening the receptor for advanced glycation end products-induced inflammation. *Kidney Int.* **105**, 132–149 (2024).
298. Hansen, J. et al. A reference tissue atlas for the human kidney. *Sci. Adv.* **8**, eabn4965 (2022).
299. McLean, B. A. et al. Revisiting the complexity of GLP-1 action from sites of synthesis to receptor activation. *Endocr. Rev.* **42**, 101–132 (2021).
300. Hviid, A. V. R. & Sørensen, C. M. Glucagon-like peptide-1 receptors in the kidney: impact on renal autoregulation. *Am. J. Physiol. Ren. Physiol.* **318**, F443–F454 (2020).
301. Chang, J.-T. et al. Glucagon-like peptide receptor agonists attenuate advanced glycation end products-induced inflammation in rat mesangial cells. *BMC Pharmacol. Toxicol.* **18**, 67 (2017).
302. Moschovaki Filippidou, F. et al. Glucagon-like peptide-1 receptor agonism improves nephrotic serum nephritis by inhibiting T-cell proliferation. *Am. J. Pathol.* **190**, 400–411 (2020).
303. Wong, C. K. & Drucker, D. J. Antiinflammatory actions of glucagon-like peptide-1-based therapies beyond metabolic benefits. *J. Clin. Invest.* **135**, e194751 (2025).
304. Drucker, D. J. The expanding landscape of GLP-1 medicines. *Nat. Med.* <https://doi.org/10.1038/s41591-025-04124-5> (2026).
- This article provides a summary of the pharmacological effects of GLP1-based medicines for treatment of obesity-associated complications.**
305. Drucker, D. J. GLP-1-based therapies for diabetes, obesity and beyond. *Nat. Rev. Drug Discov.* **24**, 631–650 (2025).
306. Minikel, E. V., Painter, J. L., Dong, C. C. & Nelson, M. R. Refining the impact of genetic evidence on clinical success. *Nature* **629**, 624–629 (2024).
307. Justice, A. E. et al. Protein-coding variants implicate novel genes related to lipid homeostasis contributing to body-fat distribution. *Nat. Genet.* **51**, 452–469 (2019).
308. Shungin, D. et al. New genetic loci link adipose and insulin biology to body fat distribution. *Nature* **518**, 187–196 (2015).
309. Locke, A. E. et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**, 197–206 (2015).
310. Pollin, T. I. et al. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. *Science* **322**, 1702–1705 (2008).
311. Cohen, J. C., Boerwinkle, E., Mosley, T. H. & Hobbs, H. H. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N. Engl. J. Med.* **354**, 1264–1272 (2006).
312. Dewey, F. E. et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N. Engl. J. Med.* **377**, 211–221 (2017).
313. Leeson-Payne, A. et al. Loss of GPR75 protects against non-alcoholic fatty liver disease and body fat accumulation. *Cell Metab.* **36**, 1076–1087.e4 (2024).
314. Hossain, S. et al. Gpr75-deficient mice are protected from high-fat diet-induced obesity. *Obesity* **31**, 1024–1037 (2023).
315. Akbari, P. et al. Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity. *Science* **373**, eabf8683 (2021).
316. Emdin, C. A. et al. Genetic association of waist-to-hip ratio with cardiometabolic traits, type 2 diabetes, and coronary heart disease. *JAMA* **317**, 626–634 (2017).
317. Deaton, A. M. et al. Rare loss of function variants in the hepatokine gene INHBE protect from abdominal obesity. *Nat. Commun.* **13**, 4319 (2022).
318. Rona Therapeutics. Rona Therapeutics advances INHBE siRNA into phase 1 clinical development. [ronatherapeutics.com/news/41](https://www.ronatherapeutics.com/news/41) (2025).
319. Kokoshi, A. Vial initiates phase 1 trial of Vial's INHBE siRNA for the treatment of obesity. <https://vial.com/updates/pr/vial-initiates-phase-1-trial-of-vial-inhbe-an-inhbe-activin-e-sirna-for-the-treatment-of-obesity/> (2025).
320. Wave Life Sciences. News release. Wave Life Sciences announces positive interim data from phase 1 INLIGHT trial of WVE-007 (INHBE) for obesity; single dose resulted in improvement in body composition with fat loss similar to GLP-1 at three months without muscle loss. [wavelifesciences.com https://ir.wavelifesciences.com/news-releases/news-release-details/wave-life-sciences-announces-positive-interim-data-phase-1](https://ir.wavelifesciences.com/news-releases/news-release-details/wave-life-sciences-announces-positive-interim-data-phase-1) (2025).
321. Arrowhead Pharmaceuticals, Inc. news release. Arrowhead Pharmaceuticals requests regulatory clearance to initiate phase 1/2a study of ARO-ALK7 for the treatment of obesity. [arrowheadpharma.com https://arrowheadpharma.com/en-us/newsroom/arrowhead-pharmaceuticals-requests-regulatory-clearance-initiate](https://arrowheadpharma.com/en-us/newsroom/arrowhead-pharmaceuticals-requests-regulatory-clearance-initiate) (2024).
322. Holst, J. J. & Rosenkilde, M. M. GIP as a therapeutic target in diabetes and obesity: insight from incretin co-agonists. *J. Clin. Endocrinol. Metab.* **105**, e2710–e2716 (2020).
323. Heymsfield, S. B. et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA* **282**, 1568–1575 (1999).
324. Flier, J. S. & Maratos-Flier, E. Leptin's physiologic role: does the emperor of energy balance have no clothes? *Cell Metab.* **26**, 24–26 (2017).
325. Wade, K. H. et al. Loss-of-function mutations in the melanocortin 4 receptor in a UK birth cohort. *Nat. Med.* **27**, 1088–1096 (2021).
326. Farooqi, I. S. et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *N. Engl. J. Med.* **356**, 237–247 (2007).
327. Krishna, R. et al. Potent and selective agonism of the melanocortin receptor 4 with MK-0493 does not induce weight loss in obese human subjects: energy intake predicts lack of weight loss efficacy. *Clin. Pharmacol. Ther.* **86**, 659–666 (2009).
328. Chami, N. et al. Genetic subtyping of obesity reveals biological insights into the uncoupling of adiposity from its cardiometabolic comorbidities. *Nat. Med.* **31**, 3801–3812 (2025).
329. Su, Q. J. et al. Genetic predictors of GLP1 receptor agonist weight loss and side effects. *Nature* <https://doi.org/10.1038/s41586-026-10330-z> (2026).
330. Cifuentes, L. et al. Genetic and physiological insights into satiety variability predict responses to obesity treatment. *Cell Metab.* **37**, 1655–1666.e5 (2025).
331. Maretty, L. et al. Proteomic changes upon treatment with semaglutide in individuals with obesity. *Nat. Med.* **31**, 267–277 (2025).
332. Finan, B. et al. Targeted estrogen delivery reverses the metabolic syndrome. *Nat. Med.* **18**, 1847–1856 (2012).
333. Coupland, C. et al. Estrogenic activity of E2-conjugated GLP-1 is mediated by intracellular endolysosomal acidification and estrone metabolism. *Mol. Metab.* **96**, 102136 (2025).
334. Quarta, C. et al. Molecular integration of incretin and glucocorticoid action reverses immunometabolic dysfunction and obesity. *Cell Metab.* **26**, 620–632.e6 (2017).
335. Décarie-Spain, L. et al. GLP-1/dexamethasone inhibits food reward without inducing mood and memory deficits in mice. *Neuropharmacology* **151**, 55–63 (2019).
336. Quarta, C. et al. GLP-1-mediated delivery of tesaglitazar improves obesity and glucose metabolism in male mice. *Nat. Metab.* **4**, 1071–1083 (2022).
337. Petersen, J. et al. GLP-1-directed NMDA receptor antagonism for obesity treatment. *Nature* **629**, 1133–1141 (2024).
338. Åmmälä, C. et al. Targeted delivery of antisense oligonucleotides to pancreatic β-cells. *Sci. Adv.* **4**, eaat3386 (2018).
339. Knerr, L. et al. Glucagon like peptide 1 receptor agonists for targeted delivery of antisense oligonucleotides to pancreatic beta cell. *J. Am. Chem. Soc.* **143**, 3416–3429 (2021).
340. Zhu, L. et al. Conjugation with glucagon like peptide-1 enables targeted protein degradation. *Bioorg Chem.* **141**, 106908 (2023).
341. Finan, B. et al. Chemical hybridization of glucagon and thyroid hormone optimizes therapeutic impact for metabolic disease. *Cell* **167**, 843–857.e14 (2016).
342. Wittrisch, S. et al. NPY1R-targeted peptide-mediated delivery of a dual PPARα/γ agonist to adipocytes enhances adipogenesis and prevents diabetes progression. *Mol. Metab.* **31**, 163–180 (2020).
343. Khan, S. S., Ndumele, C. E. & Kazi, D. S. Discontinuation of glucagon-like peptide-1 receptor agonists. *JAMA* **333**, 113–114 (2025).
- This article reports that fewer than 50% of patients remain on GLP1-based therapy 1 year after initiation.**
344. Do, D. et al. GLP-1 receptor agonist discontinuation among patients with obesity and/or type 2 diabetes. *JAMA Netw. Open* **7**, e2413172 (2024).
345. Ladebo, L. et al. Real-world use of semaglutide for weight management: patient characteristics and dose titration—a Danish cohort study. *Diabetes Care* **47**, 1834–1837 (2024).
346. Thomsen, R. W., Mailhac, A., Løhde, J. B. & Pottegård, A. Real-world evidence on the utilization, clinical and comparative effectiveness, and adverse effects of newer GLP-1RA-based weight-loss therapies. *Diabetes Obes. Metab.* **27** (Suppl. 2), 66–88 (2025).
347. Almoħaileb, F. I., le Roux, C. W. & Crotty, M. Why do patients with obesity discontinue glucagon-like peptide 1 analogues? *Diabetes Obes. Metab.* **27**, 5342–5345 (2025).
348. Gasoyan, H. et al. Reasons for discontinuation of obesity pharmacotherapy with semaglutide or Tirzepatide in clinical practice. *Obesity* <https://doi.org/10.1002/oby.70058> (2025).
349. Paddu, N. U., Lawrence, B., Wong, S., Poon, S. J. & Srivastava, G. Weight maintenance on cost-effective antiobesity medications after 1 year of GLP-1 receptor agonist therapy: a real-world study. *Obesity* **32**, 2255–2263 (2024).
350. Astbury, N. M. et al. A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss. *Obes. Rev.* **20**, 569–587 (2019).
351. Vaz, C. L., Carnes, N., Pousti, B., Zhao, H. & Williams, K. J. A randomized controlled trial of an innovative, user-friendly, interactive smartphone app-based lifestyle intervention for weight loss. *Obes. Sci. Pract.* **7**, 555–568 (2021).
352. Gemesi, K. et al. Efficacy of an app-based multimodal lifestyle intervention on body weight in persons with obesity: results from a randomized controlled trial. *Int. J. Obes.* **48**, 118–126 (2024).
353. Elmendorf, A. J., Douros, J. D., Knerr, P. J. & Flak, J. N. Improving incretin-mediated body weight loss via energy expenditure. *Trends Endocrinol. Metab.* <https://doi.org/10.1016/j.tem.2025.12.004> (2026).
354. Christoffersen, B. Ø et al. Beyond appetite regulation: targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss. *Obesity* **30**, 841–857 (2022).

355. Kleinert, M. et al. Glucagon regulation of energy expenditure. *Int. J. Mol. Sci.* **20**, 5407 (2019).
356. Axelrod, C. L. et al. BAM15-mediated mitochondrial uncoupling protects against obesity and improves glycemic control. *EMBO Mol. Med.* **12**, e12088 (2020).
357. Perry, R. J., Zhang, D., Zhang, X.-M., Boyer, J. L. & Shulman, G. I. Controlled-release mitochondrial protonophore reverses diabetes and steatohepatitis in rats. *Science* **347**, 1253–1256 (2015).
358. Motso, A. et al. GRK-biased adrenergic agonists for the treatment of type 2 diabetes and obesity. *Cell* **188**, 5142–5156.e23 (2025).
359. Sharma, A. K., Khandelwal, R. & Wolfrum, C. Futile cycles: emerging utility from apparent futility. *Cell Metab.* **36**, 1184–1203 (2024).
360. Geng, L., Lam, K. S. L. & Xu, A. The therapeutic potential of FGF21 in metabolic diseases: from bench to clinic. *Nat. Rev. Endocrinol.* **16**, 654–667 (2020).
361. Yeo, G. S. H. et al. The melanocortin pathway and energy homeostasis: from discovery to obesity therapy. *Mol. Metab.* **48**, 101206 (2021).
362. Sass, F. et al. NK2R control of energy expenditure and feeding to treat metabolic diseases. *Nature* **635**, 987–1000 (2024).
363. Watanabe, M. et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature* **439**, 484–489 (2006).
364. Poret, J. M. et al. 2180-LB: Bimagramab augments metabolic rate to improve incretin-induced weight loss in obese mice. *Diabetes* **74** (Suppl. 1), 2180-LB (2025).
365. Feetham, C. H. et al. Analog of prolactin-releasing peptide reduces body weight primarily through sustained fatty acid oxidation rather than hypophagia. *Cell Metab.* **38**, 100–114 (2026).
366. Song, J. et al. Predictive factors of response to liraglutide in patients with type 2 diabetes mellitus and metabolic syndrome. *Front. Endocrinol.* **15**, 1449558 (2024).
367. Nathan, B. M. et al. Predictors of weight-loss response with glucagon-like peptide-1 receptor agonist treatment among adolescents with severe obesity. *Clin. Obes.* **6**, 73–78 (2016).
368. German, J. et al. Association between plausible genetic factors and weight loss from GLP1-RA and bariatric surgery. *Nat. Med.* **31**, 2269–2276 (2025).
369. Dent, R., McPherson, R. & Harper, M.-E. Factors affecting weight loss variability in obesity. *Metabolism* **113**, 154388 (2020).
370. Segal, J. B. et al. Assessing heterogeneity of treatment effect in real-world data. *Ann. Intern. Med.* **176**, 536–544 (2023).
371. West, S. et al. Weight regain after cessation of medication for weight management: systematic review and meta-analysis. *BMJ* **392**, e085304 (2026).
372. Rosenbaum, M., Murphy, E. M., Heymsfield, S. B., Matthews, D. E. & Leibel, R. L. Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J. Clin. Endocrinol. Metab.* **87**, 2391–2394 (2002).
373. Clemmensen, C. et al. GLP-1/glucagon coagonism restores leptin responsiveness in obese mice chronically maintained on an obesogenic diet. *Diabetes* **63**, 1422–1427 (2014).
374. Müller, T. D. et al. Restoration of leptin responsiveness in diet-induced obese mice using an optimized leptin analog in combination with exendin-4 or FGF21. *J. Pept. Sci.* **18**, 383–393 (2012).
375. Quarta, C., Sánchez-Garrido, M. A., Tschöp, M. H. & Clemmensen, C. Renaissance of leptin for obesity therapy. *Diabetologia* **59**, 920–927 (2016).
376. Ge, X. et al. LEAP2 is an endogenous antagonist of the ghrelin receptor. *Cell Metab.* **27**, 461–469.e6 (2018).
377. Holm, S. K., Johansen, V. B. I. & Clemmensen, C. LEAP2 as a therapeutic target in obesity and cardiometabolic disorders. *Rev. Endocr. Metab. Disord.* <https://doi.org/10.1007/s11154-025-10007-4> (2025).
378. Holm, S. K. et al. Sustained weight loss with combined LEAP2 and semaglutide treatment in mice. *Diabetes* **74**, 2089–2100 (2025).
379. Fenselau, H. et al. A rapidly acting glutamatergic ARC→PVH satiety circuit postsynaptically regulated by α -MSH. *Nat. Neurosci.* **20**, 42–51 (2017).
380. Liu, T. et al. Fasting activation of AgRP neurons requires NMDA receptors and involves spinogenesis and increased excitatory tone. *Neuron* **73**, 511–522 (2012).
381. Brennan, B. P. et al. Memantine in the treatment of binge eating disorder: an open-label, prospective trial. *Int. J. Eat. Disord.* **41**, 520–526 (2008).
382. Schaefer, M., Leopold, K., Hinzpeter, A., Heinz, A. & Krebs, M. Memantine-associated reversal of clozapine-induced weight gain. *Pharmacopsychiatry* **40**, 149–151 (2007).
383. Rosenbaum, M. I., Clemmensen, L. S., Bredt, D. S., Bettler, B. & Strömgaard, K. Targeting receptor complexes: a new dimension in drug discovery. *Nat. Rev. Drug Discov.* **19**, 884–901 (2020).
384. Fadahunsi, N. et al. Targeting postsynaptic glutamate receptor scaffolding proteins PSD-95 and PICK1 for obesity treatment. *Sci. Adv.* **10**, eadg2636 (2024).
385. Structure Therapeutics. Press release. Structure Therapeutics announces initiation of phase 1 clinical study of oral small molecule amylin receptor agonist ACCG-2671 for the treatment of obesity. <https://ir.structuretx.com/news-releases/news-release-details/structure-therapeutics-announces-initiation-phase-1-clinical/> (2025).
386. Terns Pharmaceuticals, Inc. News release. Terns Pharmaceuticals reports topline 12-week data from its phase 2 trial evaluating oral GLP-1 receptor agonist TERN-601 in obesity. <https://ir.ternspharma.com/news-releases/news-release-details/terns-pharmaceuticals-reports-topline-12-week-data-its-phase-2/> (2025).
387. Sattar, N. et al. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. *Nat. Med.* **28**, 591–598 (2022).
388. Malhotra, A. et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N. Engl. J. Med.* **391**, 1193–1205 (2024).
- This article demonstrates that tirzepatide treatment markedly improves symptoms of obstructive sleep apnoea in people with obesity and obstructive sleep apnoea.**
389. Eli Lilly & Co. News release. Lilly's Taltz (ixekizumab) and Zepbound (tirzepatide) used together delivered superior efficacy in first-of-its-kind phase 3b trial for adults with active psoriatic arthritis and obesity or overweight. <https://investor.lilly.com/news-releases/news-release-details/lillys-taltz-ixekizumab-and-zepbound-tirzepatide-used-together> (2026).
390. Strohl, W. R. Fusion proteins for half-life extension of biologics as a strategy to make biobetters. *BioDrugs* **29**, 215–239 (2015).
391. Kurtzhals, P. et al. Albumin binding of insulins acylated with fatty acids: characterization of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect in vivo. *Biochem. J.* **312**, 725–731 (1995).
392. Havelund, S. et al. The mechanism of protraction of insulin detemir, a long-acting, acylated analog of human insulin. *Pharm. Res.* **21**, 1498–1504 (2004).
393. Markussen, J. et al. Soluble, fatty acid acylated insulins bind to albumin and show protracted action in pigs. *Diabetologia* **39**, 281–288 (1996).
394. Myers, S. R. et al. Acylation of human insulin with palmitic acid extends the time action of human insulin in diabetic dogs. *Diabetes* **46**, 637–642 (1997).
395. Jonassen, I. et al. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. *Pharm. Res.* **29**, 2104–2114 (2012).
396. Pyzik, M., Kozičky, L. K., Gandhi, A. K. & Blumberg, R. S. The therapeutic age of the neonatal Fc receptor. *Nat. Rev. Immunol.* **23**, 415–432 (2023).
397. Duivelshof, B. L. et al. Therapeutic Fc-fusion proteins: current analytical strategies. *J. Sep. Sci.* **44**, 35–62 (2021).
398. Martins, J. P., Kennedy, P. J., Santos, H. A., Barrias, C. & Sarmento, B. A comprehensive review of the neonatal Fc receptor and its application in drug delivery. *Pharmacol. Ther.* **161**, 22–39 (2016).
399. Rath, T. et al. Fc-fusion proteins and FcRn: structural insights for longer-lasting and more effective therapeutics. *Crit. Rev. Biotechnol.* **35**, 235–254 (2015).
400. Zaykov, A. N. et al. Toward once-monthly insulin therapy via synergy in two pharmacokinetic protractors: Fc-conjugation and fatty acid acylation. *RSC Chem. Biol.* **5**, 763–775 (2024).
401. Reusch, J. et al. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. *Diabetes Obes. Metab.* **16**, 1257–1264 (2014).
402. Ghetie, V. et al. Increasing the serum persistence of an IgG fragment by random mutagenesis. *Nat. Biotechnol.* **15**, 637–640 (1997).
403. Vaccaro, C., Zhou, J., Ober, R. J. & Ward, E. S. Engineering the Fc region of immunoglobulin G to modulate in vivo antibody levels. *Nat. Biotechnol.* **23**, 1283–1288 (2005).
404. Andersen, J. T. et al. Extending serum half-life of albumin by engineering neonatal Fc receptor (FcRn) binding. *J. Biol. Chem.* **289**, 13492–13502 (2014).
405. Douros, J. D., Mokrosinski, J. & Finan, B. The GLP-1R as a model for understanding and exploiting biased agonism in next-generation medicines. *J. Endocrinol.* **261**, e230226 (2024).
406. Jones, B. et al. Targeting GLP-1 receptor trafficking to improve agonist efficacy. *Nat. Commun.* **9**, 1602 (2018).
407. Zaimia, N. et al. GLP-1 and GIP receptors signal through distinct β -arrestin 2-dependent pathways to regulate pancreatic β cell function. *Cell Rep.* **42**, 113326 (2023).
408. Chen, K. et al. Tail engagement of arrestin at the glucagon receptor. *Nature* **620**, 904–910 (2023).
409. Rammanan, C. J., Edgerton, D. S., Kraft, G. & Cherrington, A. D. Physiologic action of glucagon on liver glucose metabolism. *Diabetes Obes. Metab.* **13** (Suppl 1), 118–125 (2011).
410. Killion, E. A. et al. Chronic glucose-dependent insulinotropic polypeptide receptor (GIPR) agonism desensitizes adipocyte GIPR activity mimicking functional GIPR antagonism. *Nat. Commun.* **11**, 4981 (2020).
411. Davies, I. et al. Chronic GIPR agonism results in pancreatic islet GIPR functional desensitisation. *Mol. Metab.* **92**, 102094 (2025).

Acknowledgements

V.B.I.J. is supported by a Novo Nordisk Foundation Center for Basic Metabolic Research International PhD Fellowship. T.D.M. receives funding from the European Research Council (ERC-CoG Trusted no.101044445), the German Research Foundation (DFG TRR296, TRR152, SFB1123 and GRK 2816/1) and the German Center for Diabetes Research (DZD e.V.). Financial support to C.C. was provided through the Novo Nordisk Foundation (NNF22OC0073778 and NNF24OC0089508). The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent Research Center, based at the University of Copenhagen, Denmark, and partially funded by an unconditional donation from the Novo Nordisk Foundation (www.cbmr.ku.dk) (NNF23SA0084103).

Author contributions

J.P. and C.C. conceptualized, researched, wrote, contributed to figure preparation and edited the manuscript. V.B.I.J. contributed to editing and preparation of figures and manuscript. B.F. and T.D.M. contributed to writing and editing. All authors approved the final version of the manuscript.

Review article

Competing interests

C.C. and J.P. are co-founders of Ousia Pharma, a biotech company developing therapeutics for the treatment of obesity. C.C. and J.P. are co-founders of Heureka Therapeutics, a biotech company developing therapeutics for the treatment of metabolic liver disease. C.C. has received speaking fees from Novo Nordisk. B.F. is a shareholder and former employee of Novo Nordisk. B.F. is an employee of Eli Lilly and Company and may hold stock. T.D.M. receives funding from Novo Nordisk and has received speaking fees from Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Merck, AstraZeneca, Mercodia and Berlin Chemie AG. T.D.M. further holds stocks from Novo Nordisk and Eli Lilly. V.B.I.J. declares no competing interests.

Additional information

Peer review information *Nature Reviews Drug Discovery* thanks Michael Nauck, Stefan Trapp and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Related links

ClinicalTrials.gov: <https://clinicaltrials.gov/>

© Springer Nature Limited 2026