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EMERGING PHARMACOLOGICAL STRATEGIES IN OBESITY: FROM GLP-1 AGONISTS THROUGH TRIPLE INCRETIN THERAPY TO AMYLIN ANALOGS – NARRATIVE REVIEW

Dagmara Laufer[1], Olga Klimczak[1],
Filip Chodań[1], Estera Sośniecka[1],
Adam Miler[1], Krystian Domeracki[1]

[1] Medical University of Silesia, Katowice, Poland

krystiandomeracki5@icloud.com

ABSTRACT

Background

Obesity is one of the most prevalent chronic diseases and a growing public health burden, resulting from complex interactions between genetic, environmental, and neuroendocrine mechanisms that regulate energy homeostasis. Because lifestyle modifications alone frequently fail to maintain long-term weight reduction, modern pharmacotherapy targeting physiological pathways of appetite and metabolism has become an essential component of care.

Aim

This review aims to summarize the evolution of pharmacological treatments for obesity, with particular emphasis on established GLP-1 receptor agonists and emerging strategies, including dual and triple incretin receptor agonism and amylin-based therapies. It critically evaluates their efficacy, safety, current limitations, and potential future role in chronic obesity management.

Materials and Methods

PubMed, Google Scholar, and ClinicalTrials.gov were searched for English language sources from January 2010 to September 2026. The final search was conducted on 15th of September 2026. Earlier landmark and mechanistic sources were considered. The synthesis included 61 publications and registry records; preclinical evidence informed mechanisms only.

Results

Incretin-based and multi-receptor therapies have demonstrated substantial body weight reductions in clinical trials. GLP-1 receptor agonists, including liraglutide and semaglutide, reduce body weight, with cardiovascular benefits demonstrated in specific patient populations. Dual receptor agonists, including tirzepatide, mazdutide, and survodutide, and the triple receptor agonist retatrutide have also demonstrated substantial weight reductions. Retatrutide produced a mean weight reduction of 24.2% at the highest dose after 48 weeks in a phase II trial. Selected agents have shown improvements in hepatic steatosis or MASH, depending on the therapy and study population. Cagrilintide and its combination with semaglutide (CagriSema) have demonstrated weight reduction in clinical trials. The most common adverse events were gastrointestinal, generally mild to moderate, with frequency influenced by dose and dose escalation.

Conclusions

The pharmacological treatment of obesity has transitioned toward targeted, mechanism-based modulation of neuroendocrine pathways, demonstrating high clinical efficacy. Because treatment discontinuation frequently leads to weight regain, obesity requires sustained, chronic pharmacological management. Future therapeutic selection

should be highly individualized, expanding beyond body mass index (BMI) alone to consider specific metabolic phenotypes and associated comorbidities.

Keywords: obesity, pharmacotherapy, GLP-1 receptor agonists, dual agonists, triple agonists, amylin analogues.

INTRODUCTION

Obesity has become one of the most prevalent chronic diseases worldwide and represents a major and continuously increasing public health burden. Its prevalence has risen markedly over recent decades across almost all regions of the world and across both adult and pediatric populations. A large pooled analysis of 3663 population-based studies including more than 222 million participants demonstrated a substantial increase in obesity prevalence between 1990 and 2022, with obesity now exceeding underweight in most countries [1]. Rather than being regarded simply as a consequence of excessive caloric intake or insufficient physical activity, obesity is increasingly recognized as a chronic, relapsing, and multifactorial disease, resulting from interactions between genetic susceptibility, environmental and socioeconomic factors, behavior, and complex neuroendocrine mechanisms regulating energy homeostasis [2,3]. In clinical practice, obesity is most commonly classified using body mass index (BMI), calculated as body weight in kilograms divided by height in meters squared. In adults, obesity is conventionally defined as a BMI ≥30 kg/m^2 and further categorized as class I (30.0-34.9 kg/m^2), class II (35.0-39.9 kg/m^2), and class III (≥40 kg/m^2) [3]. However, BMI does not directly assess body composition or fat distribution and should therefore be interpreted alongside clinical assessment. Measures such as waist circumference and waist-to-height ratio provide additional information regarding central adiposity and cardiometabolic risk, while methods including dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis can be used for more detailed assessment of body composition [3,4]. The clinical significance of obesity extends far beyond excess body weight. It is strongly associated with type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular disease, obstructive sleep apnea, osteoarthritis, and several malignancies [3,5]. The relationship with T2DM is particularly important, as visceral and ectopic adiposity promote insulin resistance through increased free fatty acid availability, adipokine dysregulation, chronic low-grade inflammation, and impaired insulin signaling. Progressive β-cell dysfunction may subsequently lead to persistent hyperglycemia and T2DM [6].

Similar metabolic disturbances contribute to MASLD and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH). Insulin resistance and excessive fatty acid delivery promote hepatic lipid accumulation, while lipotoxicity, oxidative stress, and inflammation contribute to hepatocellular injury and progression toward fibrosis and cirrhosis [7]. Obesity also contributes to cardiovascular disease through hypertension, dyslipidemia, insulin resistance, systemic inflammation, endothelial dysfunction, and structural and functional cardiac abnormalities [8]. These closely interconnected complications emphasize the need for therapies capable of addressing both excess adiposity and its metabolic consequences.

Lifestyle modification, including dietary intervention, physical activity, and behavioral therapy, remains fundamental to obesity management. However, lifestyle intervention alone often produces weight loss that is difficult to maintain over time. Weight reduction activates compensatory mechanisms, including increased hunger and reduced energy expenditure, that favor restoration of lost body weight [9,10]. These physiological adaptations help explain the frequent occurrence of weight regain and further support the concept of obesity as a chronic disease requiring sustained management rather than a temporary behavioral intervention. Pharmacological treatment of obesity has undergone substantial evolution. Earlier agents primarily targeted central sympathomimetic or serotonergic pathways, but several were limited by modest efficacy, poor tolerability, or serious adverse effects. Subsequently introduced therapies, including orlistat and naltrexone/bupropion, provided additional options for long-term weight management but remained limited by efficacy or tolerability in some patients [11]. The introduction of GLP-1 receptor agonists marked a major transition toward pharmacological modulation of physiological pathways controlling appetite and metabolism. This approach subsequently expanded to dual-target therapies, particularly combined GIP/GLP-1 receptor agonism, and more recently to triple GIP/GLP-1/glucagon receptor agonists, reflecting growing interest in simultaneously targeting complementary metabolic pathways [12]. In parallel, renewed interest in amylin signaling has stimulated the development of long-acting amylin analogues and incretin-amylin combinations, further broadening the range of potential pharmacological strategies [13,14].

Despite these advances, important therapeutic challenges remain. Response to anti-obesity medications varies between individuals, gastrointestinal adverse effects may limit incretin-based treatment, and long-term therapy is generally required to maintain weight reduction. Discontinuation can be followed by weight regain as physiological mechanisms defending body weight re-emerge. Cost, accessibility, long-term tolerability, and the predominance of injectable formulations remain additional barriers and

have stimulated the development of more effective, better tolerated, and orally administered therapies.

Important uncertainties also remain regarding the relative clinical value of established and emerging treatments. Differences in study populations, diabetes status, treatment duration, dosing regimens, and outcome assessment limit comparisons across clinical trials. For several investigational agents, direct comparative evidence and long-term data on safety, maintenance of weight reduction, and effects on obesity-related complications remain limited. These uncertainties complicate the interpretation of differences in reported weight reductions and the assessment of the potential role of newer therapies in individualized obesity management.

AIM

To critically summarize the mechanisms of action, clinical efficacy, safety, and potential role of established and emerging pharmacological therapies in long-term obesity management.

Objectives

1. To describe the mechanisms of action of the therapies considered in this review.
2. To summarize evidence on weight reduction, metabolic outcomes, outcomes related to obesity-associated comorbidities, safety, and maintenance of weight reduction.
3. To identify limitations of the available evidence and directions for future research.

MATERIALS AND METHODS

This narrative literature review was conducted to identify current evidence on established and emerging pharmacological strategies for obesity. Publications from January 2010 to September 2026 were searched in PubMed and Google Scholar, while ClinicalTrials.gov was used to identify ongoing and recently completed clinical trials. The final search was performed on 15th of September 2026. Earlier publications were considered when they provided fundamental information on appetite regulation, energy homeostasis, or mechanisms relevant to contemporary anti-obesity therapies.

The PubMed search combined obesity-related terms with therapeutic targets, drug classes, and individual agents using the following strategy: ("obesity" OR "overweight") AND ("pharmacotherapy" OR "anti-obesity medication" OR "GLP-1" OR "GLP-1 receptor agonist" OR semaglutide OR liraglutide OR GIP OR tirzepatide OR "dual agonist" OR glucagon OR "triple agonist" OR retatrutide OR amylin OR "amylin analogue" OR cagrilintide OR CagriSema OR amycretin OR PYY OR leptin OR ghrelin OR orforglipron). Google Scholar searches were performed using combinations of the terms obesity, overweight, GLP-1 receptor agonist, semaglutide, liraglutide, GIP, tirzepatide, glucagon, retatrutide, amylin, cagrilintide, CagriSema, amycretin, PYY, leptin, ghrelin, and orforglipron, together with clinical trial, efficacy, safety, adverse events, and treatment outcomes. ClinicalTrials.gov was searched using the terms obesity and overweight in combination with semaglutide, liraglutide, tirzepatide, retatrutide, cagrilintide, CagriSema, amycretin, and orforglipron to identify completed, ongoing, and recently reported clinical trials and to determine the current clinical development status of the investigated therapies.

Eligible sources included randomized controlled trials, prospective and observational clinical studies, systematic reviews, relevant narrative reviews, meta-analyses, clinical guidelines, and relevant trial registry records addressing the mechanisms, efficacy, safety, or clinical development of pharmacological therapies for obesity. Preclinical studies were considered only when they provided relevant mechanistic information. Studies focusing exclusively on bariatric or endoscopic procedures or non-pharmacological interventions were excluded, as were duplicate reports, conference abstracts without full-text publications, non-English-language articles, and publications without relevant clinical or mechanistic information.

Titles and abstracts were initially screened for relevance, followed by full-text assessment of potentially eligible publications. Extracted information included the mechanism of action, study design and phase, patient population, treatment regimen, clinical efficacy, safety, and regulatory status. Primary reports of pivotal clinical trials were prioritized for efficacy and safety assessment, whereas review articles were mainly used for mechanistic and contextual information.

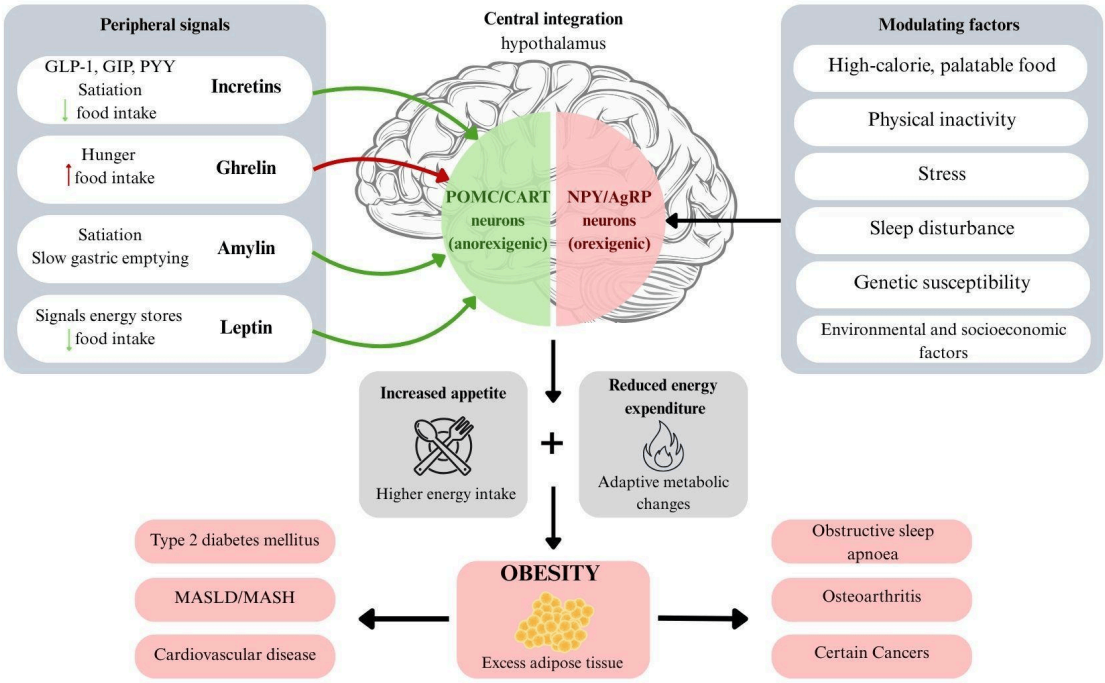
Overall, 61 publications and clinical trial registry records were included in the final narrative synthesis. As this was a narrative review, literature selection followed a structured but non-systematic approach, and no formal risk-of-bias assessment was performed.

RESULTS

Pathophysiology of obesity

Body-weight regulation is controlled by a complex neuroendocrine network integrating peripheral signals with central pathways regulating hunger, satiety, and energy expenditure. The hypothalamus, particularly the arcuate nucleus, plays a central role in this process. Orexigenic neurons expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) promote food intake, whereas pro-opiomelanocortin (POMC) neurons exert anorexigenic effects through the melanocortin system [15,16]. These neuronal populations receive hormonal and nutritional signals originating from the gastrointestinal tract, pancreas, and adipose tissue, allowing peripheral energy status to influence feeding behavior. Several of these peripheral signals have become important pharmacological targets. Glucagon-like peptide-1 (GLP-1) promotes glucose-dependent insulin secretion, delays gastric emptying, and reduces food intake through peripheral and central mechanisms, while glucose-dependent insulinotropic polypeptide (GIP) enhances glucose-dependent insulin secretion and contributes to the regulation of energy metabolism [15,17]. Glucagon increases hepatic glucose production but may also influence satiety and energy expenditure, providing a rationale for its incorporation into multi-receptor agonists [17]. Other signals include PYY, which promotes postprandial satiety; ghrelin, which stimulates hunger; and leptin, an adipose-derived signal involved in long-term energy homeostasis, although common obesity is typically associated with reduced responsiveness to its anorexigenic effects [15,18]. Amylin, cosecreted with insulin by pancreatic β cells, promotes satiation, delays gastric emptying, and suppresses postprandial glucagon secretion, making the amylin pathway another important target for emerging anti-obesity therapies [13]. The principal central and peripheral mechanisms regulating appetite and body weight and their relationship with obesity are summarized in Figure 1.

Figure 1. Neuroendocrine regulation of energy homeostasis, therapeutic targets, and obesity-related complications (created by authors)



Single-receptor agonists

Liraglutide

Liraglutide is an approved GLP-1 receptor agonist exhibiting 97% homology to the natural hormone, which significantly improves glycemic control and induces weight loss in patients with obesity [19,20,21]. The pivotal 56-week SCALE trial demonstrated that liraglutide-treated patients lost an average of 8.4 kg (8.0% of baseline weight) compared to 2.8 kg (2.6%) in the placebo group, with 63.2% of individuals in the active treatment arm achieving a weight loss of ≥ 5%—significantly outperforming the 27.1% observed in the placebo group—while 33.1% achieved a greater than 10% reduction compared to just 10.6% on placebo, all accompanied by a marked 8.2 cm mean reduction in waist circumference that significantly surpassed the changes recorded in the placebo group [20]. Early clinical response is a robust predictor of long-term success; patients losing ≥4% of their weight at 16 weeks achieved an impressive 10.8% (non-diabetics) and 8.5% (diabetics) total weight reduction at 56 weeks. Conversely, non-responders in the same study achieved only a 3.0% and 3.1% reduction, respectively [22]. Efficacy extends to adolescents aged 12 to <18 years, where 56 weeks of therapy led to a decrease of 0.22 points in the BMI standard-deviation score relative to placebo. In this younger cohort, 43.3% of participants achieved a ≥ 5% decrease in BMI [23]. Beyond weight management, liraglutide provides crucial cardioprotective benefits in type 2 diabetes, notably reducing the risk of cardiovascular death by 22% (hazard ratio

0.78) and all-cause mortality by 15% (hazard ratio 0.85) [24]. In a phase 2 trial directly comparing incretin therapies, individuals receiving 3.0 mg of liraglutide for 52 weeks achieved an estimated mean weight reduction of 7.8%, whereas once-weekly alternatives like semaglutide demonstrated a statistically greater efficacy, yielding weight losses ranging from 11.2% up to 13.8% depending on the dosage [21].

Semaglutide

Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has demonstrated substantial weight-loss efficacy across the STEP clinical trial programme. In the foundational STEP 1 trial involving 1,961 adults without diabetes, once-weekly semaglutide 2.4 mg yielded a mean body weight reduction of 14.9% after 68 weeks, compared with just 2.4% for placebo. This equated to an absolute average weight loss of 15.3 kg and a waist circumference decrease of 13.54 cm. Furthermore, the intervention drove significant clinical milestones: 86.4%, 69.1%, and 50.5% of treated patients achieved weight reductions of at least 5%, 10%, and 15%, respectively, vastly outperforming the placebo group [25]. The clinical benefits of semaglutide extend seamlessly to diverse patient populations. In the STEP 2 trial targeting patients with type 2 diabetes, the 2.4 mg dose produced a 9.6% mean weight reduction over 68 weeks, with nearly 69% of participants achieving at least a 5% weight loss [26]. Efficacy was similarly evident in adolescents; the STEP TEENS trial reported a 16.1% reduction in BMI for the treatment group—contrasting with a 0.6% increase in the placebo arm—and enabled 73% of adolescent participants to reach the ≥5% weight-loss threshold [27]. Finally, the STEP programme highlights both the need of sustained therapy and the potential of dose escalation. The STEP 4 trial underscored the importance of continuous treatment: participants who lost 10.6% of their body weight during a 20-week lead-in period achieved a total estimated weight reduction of 17.4% over 68 weeks if treatment was maintained, whereas those switched to placebo regained 6.9% of their weight [28]. More recently, the STEP UP trial indicated that escalating the once-weekly dose to 7.2 mg further enhanced efficacy, resulting in a mean weight reduction of 18.7% after 72 weeks, compared with 15.6% for the standard 2.4 mg dose and 3.9% for placebo [29]. In addition to subcutaneous administration, semaglutide can also be administered orally and has demonstrated satisfactory weight-loss outcomes [30,31]. Oral semaglutide at a dose of 14 mg reduced participants' body weight by 5.7% and significantly decreased waist circumference by 5.5 cm [30]. Treatment with oral semaglutide 50 mg resulted in a mean body weight reduction of 15.1%, compared with 2.4% in the placebo group. Additionally, 85% of participants achieved a weight loss of ≥5% (versus 26% for placebo), and 34% achieved a reduction of ≥20% (versus 3% for placebo) [31].

Orforglipron and Danuglipron

Recent advancements in obesity and diabetes pharmacotherapy include the development of oral, small-molecule GLP-1 receptor agonists - orforglipron and danuglipron. Orforglipron reduced glycated hemoglobin by up to 1.48 percentage points and body weight by 7.6% at 40 weeks in patients with type 2 diabetes [33]. In adults with obesity, once-daily orforglipron at a dose of 36 mg resulted in an 11.2% mean body weight reduction at 72 weeks, alongside improvements in cardiometabolic parameters such as waist circumference, blood pressure, and lipid profiles [32]. The phase 3b ATTAIN-MAINTAIN trial highlighted its efficacy in weight loss maintenance, as participants transitioning from injectable tirzepatide or semaglutide to orforglipron successfully maintained 74.7% and 79.3% of their initial weight reduction after 52 weeks, respectively [34]. Similarly evaluated for weight reduction in adult patients, danuglipron represents another option within this class of oral small-molecule agents [35,36]. In a 12-week phase 2 study, participants with obesity receiving danuglipron 200 mg twice daily achieved an observed mean weight reduction of 7.17 kg, compared with a 0.30 kg reduction in the placebo group [35]. A subsequent phase 2b trial demonstrated that 26 to 32 weeks of danuglipron treatment in adults with obesity resulted in placebo-adjusted least squares mean body weight reductions ranging from 5.0% to 12.9% across different dose-escalation regimens. In this trial, up to 88% of participants receiving the 200 mg dose (with a 4-week escalation interval) achieved a weight reduction of at least 5% [36].

Dual-target therapies

A significant advancement in obesity pharmacotherapy involves dual-targeted agents that simultaneously modulate two distinct receptor pathways, prominently featuring the GLP-1 and GIP agonist tirzepatide, alongside the GLP-1 and glucagon agonists mazdutide, survodutide, and pemvidutide. Furthermore, this innovative landscape includes MariTide—a unique molecule combining GLP-1 agonism with GIP antagonism—and CagriSema, a synergistic co-formulation targeting both GLP-1 and amylin receptors.

Tirzepatide

Tirzepatide is a once-weekly subcutaneous dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist that has demonstrated profound efficacy in the treatment of obesity. By acting synergistically on appetite regulation and metabolic function, it facilitates substantial weight reduction across diverse

patient populations. In the landmark SURMOUNT-1 trial involving adults with obesity or overweight without diabetes, tirzepatide provided sustained weight reductions, with the 15-mg dose resulting in a mean percentage change in weight of -20.9% (95% CI, -21.8 to -19.9) at week 72 [37]. The efficacy of this pharmacological intervention is also high and consistent across different demographic groups; for example, clinical trials confirm that in Chinese adults with obesity or overweight, the 15-mg dose led to a mean body weight reduction of -17.5% (95% CI, -19.7 to -15.3%) at week 52 [38]. The SURMOUNT-2 trial demonstrated that in adults with obesity and type 2 diabetes, the least-squares mean change in body weight at week 72 was -14.7% for the 15-mg dose [39]. Similarly, the SURPASS-5 trial, which evaluated patients with type 2 diabetes inadequately controlled on titrated insulin glargine, showed that the addition of tirzepatide yielded a mean body weight change of -8.8 kg (95% CI, -10.0 to -7.7) at 40 weeks for the 15-mg group [40]. Tirzepatide also exerts a therapeutic impact on other severe obesity-related comorbidities. The SURMOUNT-OSA trial evaluated patients with moderate-to-severe obstructive sleep apnea and obesity, revealing a mean percent change in body weight of -17.7% in Trial 1 for the treatment-regimen estimated at week 52 [41]. Crucially, obesity is a chronic disease requiring long-term management, and the SURMOUNT-4 trial highlighted the need of continued pharmacotherapy to prevent weight regain. After an initial 36-week lead-in period where participants achieved a 20.9% weight reduction, those who were randomized to switch to a placebo experienced a 14.0% (95% CI, 12.8 to 15.2) weight regain by week 88, whereas participants continuing on tirzepatide experienced an additional -5.5% (95% CI, -6.8 to -4.2) weight reduction [42].

Mazdutide

Mazdutide, an oxyntomodulin-analogue dual glucagon receptor (GCGR)/glucagon-like peptide-1 receptor (GLP-1R) agonist, has demonstrated substantial, dose-dependent efficacy in reducing body weight across multiple Chinese phase 2/3 trials. In the pivotal phase 3 GLORY-1 trial conducted specifically in adults with obesity or overweight, once-weekly mazdutide produced a least-squares mean body-weight reduction at week 32 of −10.09% (95% CI, −11.15 to −9.04) with the 4-mg dose and −12.55% (95% CI, −13.64 to −11.45) with the 6-mg dose, versus only 0.45% with placebo, with 73.9% and 82.0% of participants achieving ≥5% weight loss compared with 10.5% on placebo. These effects were sustained and even amplified through week 48, at which point 35.7% (4 mg) and 49.5% (6 mg) of participants had lost ≥15% of baseline body weight versus 2.0% with placebo [43]. In patients with type 2 diabetes, mazdutide also produced clinically meaningful weight loss as a secondary benefit, with the DREAMS-1

phase 3 trial reporting a −5.61% and −7.81% change in body weight for the 4-mg and 6-mg doses, respectively, versus −1.26% for placebo, and 48.8%/64.0% of participants reaching ≥5% weight loss versus 6.6% on placebo [44]. Earlier phase 2 data in patients with type 2 diabetes corroborated this weight-lowering effect, showing percent body-weight reductions ranging from −4.1% to −7.1% across mazdutide doses compared with −1.4% with placebo, with up to 57.1% of mazdutide-treated participants achieving ≥5% weight loss versus 9.8% with placebo [45].

Survodutide

Survodutide, a glucagon and glucagon-like peptide-1 (GLP-1) receptor dual agonist, demonstrates substantial efficacy in the pharmacological management of obesity by simultaneously reducing energy intake and increasing energy expenditure [46,47]. Clinical evidence indicates that the drug induces significant, dose-dependent reductions in body weight across different patient populations. In a phase 2 dose-finding trial involving adults with overweight or obesity without diabetes, patients receiving 4.8 mg of survodutide achieved a mean body weight reduction of 14.9% (95% CI: -16.9 to -13.0) over 46 weeks, compared to a 2.8% reduction in the placebo group [47]. Furthermore, a phase 3 trial evaluating adults with obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) corroborated these potent anti-obesity effects. In this phase 3 study, patients administered 6.0 mg of survodutide for 48 weeks experienced a mean body weight reduction of 12.2%, representing an estimated treatment difference of -11.2% (95% CI: -13.4 to -9.0) relative to placebo [46].

Pemvidutide

Pemvidutide, another GLP-1 and glucagon dual receptor agonist, has demonstrated clinical efficacy in reducing both body weight and liver fat in patients with metabolic dysfunction-associated steatohepatitis (MASH) and steatotic liver disease (MASLD) [48,49]. In a 24-week phase 2b trial involving patients with biopsy-confirmed MASH, 1.8 mg of pemvidutide led to MASH resolution without worsening of fibrosis in 52% of patients, yielding a significant treatment difference of 32% (95% CI: 19 to 46) compared to placebo [48]. Similarly, a 12-week study demonstrated that the 1.8 mg dose of pemvidutide achieved a robust 68.5% relative reduction in magnetic resonance imaging-assessed liver fat content among patients with MASLD. Beyond hepatic improvements, pemvidutide administration consistently induced body weight reductions, reaching a 4.3% decrease after 12 weeks without the need for dose titration [49]. Pemvidutide shows promising therapeutic potential; however, further clinical studies are needed to establish its efficacy and safety.

AMG 133

AMG 133 is an investigational hybrid molecule that combines a GIP receptor antagonist with GLP-1 receptor agonists to effectively promote weight loss. Thanks to its long half-life, it allows for less frequent, monthly dosing and is currently being evaluated in advanced clinical trials [50].

CagriSema

CagriSema (a combination of cagrilintide and semaglutide) has demonstrated efficacy as an anti-obesity medication, significantly outperforming both placebo and semaglutide monotherapy [51,52]. In a large-scale randomized trial involving 3,417 participants, those receiving CagriSema achieved an estimated mean body weight reduction of 20.4% from baseline to week 68, which was 17.3 percentage points greater than the 3.0% reduction observed in the placebo group [52]. Furthermore, a systematic review and meta-analysis highlighted its superiority over active comparators, showing that CagriSema led to a 9.07% greater mean percentage weight loss (an absolute difference of 9.11 kg) compared to semaglutide 2.4 mg over a 20- to 32-week period. However, this enhanced efficacy is associated with an increased risk of gastrointestinal adverse events, which affected 79.6% of users, compared to 39.9% on placebo [51].

Triple-receptor agonists

Retatrutide

Retatrutide is an innovative, single-molecule triple agonist of the glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors, which suppresses appetite and increases the body's energy expenditure. This preparation, administered subcutaneously once a week, currently represents one of the most promising investigational drugs in the context of obesity and metabolic disease therapy [53]. In a 48-week phase 2 clinical trial, patients with obesity receiving the highest dose of 12 mg achieved an average body weight reduction of 24.2 percent, while the 8 mg dose resulted in a 22.8 percent decrease, which exceeded the 2.1 percent result observed in the placebo group. In the same study, 100 percent of participants treated with the 8 mg and 12 mg doses reduced their initial body weight by at least 5 percent, and 83 percent of subjects on the highest dose lost 15 percent or more of their weight [54]. The efficacy of retatrutide in weight reduction is also confirmed by a comprehensive meta-analysis involving 878 patients from three randomized con-

trolled trials, which demonstrated an overall mean difference in weight loss of -14.33 percent in favor of the retatrutide-treated groups compared to placebo [55]. This drug also demonstrates powerful effects in populations with harder-to-treat comorbidities, as evidenced in a study involving patients with obesity and type 2 diabetes, where the 12 mg dose led to a 16.94 percent weight loss after 36 weeks of therapy, outperforming both placebo with a 3.00 percent decrease and dulaglutide with a 2.02 percent result [56]. In the same group of patients with diabetes, results in body composition improvement were additionally observed, where a specialized subanalysis utilizing DXA scans revealed a reduction in total fat mass of 26.1 percent for the 8 mg dose and 23.2 percent for the 12 mg dose after 36 weeks, exceeding the mere 4.5 percent placebo effect more than fivefold [57]. In turn, in a study of patients with obesity and metabolic dysfunction-associated steatotic liver disease (MASLD), retatrutide demonstrated the ability to reduce the volume of visceral adipose tissue, which was reduced by as much as 48.3 percent at the highest tested dose. In the same subgroup of patients, liver defatting was noted, achieving a relative liver fat reduction of 82.4 percent after 24 weeks, and after 48 weeks, as many as 93 percent of patients on the 12 mg dose experienced complete resolution of organ steatosis [58].

Amylin analogues

Cagrilintide

Cagrilintide is a long-acting amylin analogue designed to help manage body weight by inducing satiety and delaying gastric emptying [59]. A 26-week phase 2 clinical trial evaluated the effects of ascending once-weekly doses of cagrilintide in participants with overweight or obesity without diabetes. The mean body weight reduction showed a dose-dependent response, ranging from 6.0% (for the 0.3 mg dose) to 10.8% (for the 4.5 mg dose) after 26 weeks. Specifically, the weight reduction achieved with the highest 4.5 mg dose reached 10.8% (11.5 kg), which significantly outperformed the placebo group, where the decrease was limited to 3.0% (3.3 kg) [60]. Furthermore, building on the dual combination therapy strategies mentioned above, it is increasingly being investigated and co-administered in combination regimens alongside semaglutide (CagriSema) to achieve even greater, synergistic weight-loss benefits. To illustrate the rationale behind combining these two drugs, it is worth citing a study where the mean body weight reduction from baseline to week 32 reached 15.6% in the CagriSema group, compared to 5.1% in the semaglutide group and 8.1% in the cagrilintide group [59].

Petrelintide

Petrelintide is another long-acting, acylated analogue of human amylin currently being developed for chronic weight management. The reported phase I studies have demonstrated favourable tolerability for petrelintide, featuring a low incidence of mostly mild gastrointestinal adverse events, while producing noticeable weight reductions [61]. However, as clinical data on this agent remain relatively limited, future investigations building upon the initial phase I findings must focus on robustly demonstrating its therapeutic efficacy in the treatment of obesity.

Safety

Modern pharmacotherapy for obesity, encompassing GLP-1, GIP, and glucagon receptor agonists and co-agonists, demonstrates a generally acceptable safety profile across various agents. The predominant adverse events are gastrointestinal in nature, typically mild to moderate in severity, and frequently dose dependent or related to the titration schedule. The frequency of gastrointestinal adverse events varied across studies, with reported symptoms including nausea, diarrhea, vomiting, and constipation [19,42,43,48,56,59]. In trials evaluating CagriSema, a combination of semaglutide and cagrilintide, gastrointestinal events occurred in 58% of participants, compared to 32% for semaglutide alone and 33% for cagrilintide alone [59]. Similarly, tirzepatide demonstrated an 81.0% adverse event rate during the 36 week initial phase, predominantly characterized by nausea in 35.5% and diarrhea in 21.1% of patients. During the subsequent double blind phase, diarrhea affected 10.7% of the tirzepatide cohort versus 4.8% receiving placebo [42]. Mazdutide exhibited dose dependent gastrointestinal effects, with nausea reported in 32.5% of individuals receiving the 4 mg dose and 50.5% of those on the 6 mg dose, contrasting with 5.9% in the placebo group. Diarrhea was noted in 35.0% and 38.6% of the 4 mg and 6 mg mazdutide groups, respectively, while vomiting occurred in 26.1% and 43.1% [43]. Pemvidutide trials revealed gastrointestinal complaints in 46% of patients overall, with nausea affecting 22% of the 1.2 mg group and 41% of the 1.8 mg group, while diarrhea was observed in 10% and 21% of these groups, respectively [48]. Retatrutide therapy resulted in gastrointestinal events in 35% of patients overall, with a clear dose titration correlation. The incidence ranged from 13% in the stable 0.5 mg cohort to 50% among individuals rapidly titrated to an 8 mg dose [56]. Furthermore, specific agents in this class exhibit a propensity to stimulate the cardiovascular system, manifesting as an elevated heart rate. Patients receiving mazdutide experienced a mean heart rate increase not exceeding 4.6 beats per minute at the peak of the titration phase, with sinus tachycardia recorded in 2.0%

of the 4 mg group and 4.5% of the 6 mg group [43]. Despite the high frequency of mild to moderate side effects, complete treatment discontinuation due to adverse events remains generally low, and severe complications such as level 2 or 3 hypoglycemia are exceptionally rare [19,42,43,48]. Discontinuation rates attributed to adverse events were reported at 13% for the CagriSema cohort, 7.0% during the initial phase for tirzepatide, and 1.5% for the 4 mg mazdutide group [42,43,59]. Pemvidutide demonstrated very low discontinuation rates of 0% for the 1.2 mg dose and 1% for the 1.8 mg dose [48]. The incidence of serious adverse events across these therapies was consistently minimal, ranging from 0% for CagriSema, to between 2.0% and 3.0% for tirzepatide, approximately 2% to 4% for pemvidutide, and 4.0% to 5.9% for mazdutide. Crucially, the reviewed literature consistently emphasized a complete absence of fatalities directly linked to the investigated drugs and no instances of severe hypoglycemia [19,43,48,56,59]. Table 1 summarizes the mechanisms of action, effects on body weight, and adverse events of the therapies discussed in this review.

Table 1. Overview of Established and Investigational Pharmacological Therapies for Obesity

DRUG NAME	MECHANISM OF ACTION	FDA APPROVED	EFFECT ON WEIGHT	ADVERSE EFFECTS
Liraglutide	GLP-1 receptor agonist	Yes	The 56-week trial demonstrated an average weight loss- 8.0% of baseline weight, with 63.2% of patients achieving ≥5% weight loss and 33.1% losing >10% of their initial weight. This was accompanied by a mean reduction in waist circumference of 8.2 cm [20].	Serious adverse events were reported in 4% of individuals on liraglutide, compared to 5% to 13% of those on semaglutide [21].
Semaglutide	GLP-1 receptor agonist	Yes	In the 68-week STEP 1 trial, a weekly 2.4 mg dose reduced mean body weight by 14.9% (15.3 kg) and waist circumference by 13.5 cm, with 86.4%, 69.1%, and 50.5% of patients achieving reductions of ≥5%, ≥10%, and ≥15%, respectively [25].	The proportion of participants experiencing at least one adverse event was 85% in the liraglutide 3.0 mg group, while it ranged from 90% to 96% across the various semaglutide groups. Discontinuation due to adverse events was 9% for the liraglutide group. For semaglutide, the discontinuation rate ranged from 4% at lower doses to 17% at higher doses [26].
Orforglipron	Oral small-molecule GLP-1 receptor agonist	No	Dose of 36 mg resulted in an 11.2% mean body weight reduction at 40 weeks, alongside improvements in cardiometabolic parameters [33].	Permanent discontinuation of treatment occurred in 4.4 to 7.8% of participants receiving orforglipron and 1.4% (placebo) [33].
Danuglipron	Oral small-molecule GLP-1 receptor agonist	No	In 12-week study participants receiving danuglipron 200 mg twice daily achieved mean weight reduction of 7.17 kg, compared with a 0.30 kg in the placebo group [35].	In addition to typical GI adverse events, hypoglycemia occurred in 7.3% of subjects in the type 2 diabetes (T2D) group concurrently treated with metformin [35].
Tirzepatide	Dual GLP-1 and GIP receptor agonist	Yes	15 mg of tirzepatide reduced mean body weight by 20.9% at 72 weeks in non-diabetic adults with obesity [37].	Cholecystitis was reported more frequently in the tirzepatide groups than in the placebo group, although the incidences were low (≤0.6%) [37].
Mazdutide	Dual GLP-1 and Glucagon receptor agonist	No	Weekly mazdutide (4 mg and 6 mg) reduced mean body weight by 10.09% and 12.55% at 32 weeks in adults with obesity, compared to 0.45% with placebo [43].	Sinus tachycardia occurred in 2.0% and 4.5% of participants in the 4-mg and 6-mg mazdutide groups, versus 2.9% on placebo [43].

Survodutide	Dual GLP-1 and Glucagon receptor agonist	No	Patients receiving 4.8 mg of survodutide achieved a mean body weight reduction of 14.9% over 46 weeks, compared to a 2.8% in the placebo group [47].	At week 46, survodutide increased mean heart rate by 2.7 bpm versus 0.1 bpm for placebo [47].
Pemvidutide	Dual GLP-1 and Glucagon receptor agonist	No	1.8 mg dose reduced body weight by 4.3% after 12 weeks [49].	Only mild gastrointestinal adverse events were observed, with no significant changes in heart rate [49].
MariTide (AMG 133)	GLP-1 receptor agonist and GIP receptor antagonist	No	Further clinical trials are warranted to fully establish the safety and efficacy of this drug	-
CagriSema (Semaglutide + Cagrilintide)	GLP-1 receptor agonist and long-acting Amylin analog	No	In a 3,417-participant trial, CagriSema reduced mean body weight by 20.4% at 68 weeks, compared to 3.0% with placebo [52].	Aside from gastrointestinal adverse events, no others were reported.
Retatrutide	Triple GLP-1, GIP, and Glucagon receptor agonist	No	In a 48-week phase 2 trial, the 12-mg and 8-mg doses reduced mean body weight by 24.2% and 22.8%, respectively, compared to 2.1% with placebo in patients with obesity [54].	Mild elevations in heart rate, along with isolated instances of mild-to-moderate arrhythmias, were noted in a few patients [54].
Petrelintide	Long-acting Amylin analog	No	After 16 weeks, the 4.8-mg dose achieved a mean body weight reduction of 8.6%, compared to 1.7% in the placebo group [61].	Mild to moderate gastrointestinal adverse events [61].
Cagrilintide	Long-acting Amylin analog	No	In a 26-week trial, once-weekly cagrilintide produced dose-dependent weight reductions ranging from 6.0% (0.3 mg) to 10.8% (4.5 mg), significantly outperforming the 3.0% reduction seen with placebo [60].	Mild gastrointestinal adverse events occurred, with no significant differences in blood pressure or pulse rate [60].

DISCUSSION

The development of modern anti-obesity medications reflects a broader change in the understanding of obesity from a condition attributed predominantly to excess energy intake toward a chronic disease regulated by complex neuroendocrine and metabolic mechanisms. The clinical efficacy of GLP-1 receptor agonists and subsequent multi-receptor therapies supports the relevance of the gut-brain and pancreatic hormonal pathways described in the pathophysiology of obesity. The progression from liraglutide to semaglutide illustrates the substantial therapeutic gains achievable within a

single hormonal pathway: while liraglutide established GLP-1 receptor agonism as an effective strategy for chronic weight management, semaglutide achieved considerably greater weight reduction with once-weekly administration [20,21,25]. Furthermore, the additional efficacy observed with semaglutide 7.2 mg in STEP UP suggest that the therapeutic potential of GLP-1 receptor agonism may not yet be fully realized at established doses [29]. These findings are relevant when interpreting newer multi-receptor therapies, since greater efficacy cannot automatically be attributed to engagement of additional receptors but also on factors such as pharmacokinetics, receptor potency, molecular design, dosing, treatment duration and patient characteristics remain important determinants of clinical response [43,47,48].

Nevertheless, the results obtained with tirzepatide provide strong clinical support for combining complementary hormonal signals. Dual GIP/GLP-1 receptor agonism produced substantial weight reduction across several populations, including individuals without diabetes, patients with T2DM, and those with obesity-related obstructive sleep apnea [37-41]. This is particularly relevant given the initially uncertain role of GIP in obesity pharmacotherapy. The efficacy of tirzepatide demonstrates that GIP receptor activation can enhance a pharmacological strategy centred on GLP-1 signaling, although the precise contribution of each receptor to weight reduction remains difficult to determine clinically. The development of AMG 133 makes this question even more interesting, as this agent combines GLP-1 receptor agonism with GIP receptor antagonism rather than agonism [50]. The investigation of apparently opposing approaches to GIP signaling illustrates that the physiological effects of this pathway are more complex than a simple distinction between receptor activation and inhibition. Clinical efficacy may depend on the interaction between GIP signaling and other metabolic pathways rather than on the isolated direction of GIP receptor modulation.

The addition of glucagon receptor agonism represents another important extension of this multi-pathway strategy. In isolation, glucagon might appear counterintuitive as a treatment component because of its ability to increase hepatic glucose production. However, its effects on energy expenditure, lipid metabolism and food intake provide a rationale for combining glucagon signaling with the insulinotropic and appetite-reducing effects of incretin agonists. The weight reductions observed with mazdutide and survodutide support the feasibility of this approach [43–47]. Importantly, the potential value of glucagon-containing therapies may extend beyond the magnitude of weight loss. Survodutide and pemvidutide have demonstrated effects in metabolic liver disease, while retatrutide produced marked reductions in hepatic and visceral fat [46,48,49,58]. Given the close relationship between obesity, ectopic adiposity and

MASLD described earlier, these effects may be particularly relevant in patients in whom hepatic disease constitutes a major component of the obesity phenotype.

Triple GLP-1/GIP/glucagon receptor agonism extends this concept further. The magnitude of weight reduction observed with retatrutide in phase II studies indicates that simultaneous engagement of three metabolic pathways can produce a particularly strong treatment effect [54–56]. However, the additional findings regarding body composition may be equally important. Reductions in total fat mass, visceral adipose tissue and hepatic fat suggest that the metabolic consequences of treatment cannot be fully represented by changes in total body weight [57,58]. This is particularly relevant given the limitations of BMI discussed earlier. If therapies differ in their effects on visceral, hepatic and subcutaneous adiposity, similar reductions in body weight or BMI could potentially be associated with different metabolic consequences. Future studies incorporating body composition and ectopic fat measurements may therefore provide clinically relevant information beyond conventional weight-based endpoints.

The reviewed evidence also supports the importance of amylin as a therapeutic pathway independent of classical incretin signaling. Cagrilintide produced clinically meaningful weight reduction as monotherapy, consistent with the physiological role of amylin in satiation and gastric emptying [59,60]. More importantly, the greater efficacy observed when cagrilintide was combined with semaglutide suggests that simultaneous modulation of GLP-1 and amylin signaling may produce complementary effects on appetite regulation [51,52,59]. This strategy differs conceptually from incorporating additional receptor activity into a single co-agonist. Rather than increasing the number of targets within the incretin–glucagon system, CagriSema combines two separate hormonal pathways involved in satiation. The development of petrelintide indicates continued interest in this approach, although its clinical evidence remains preliminary [61]. These findings suggest that future improvements in efficacy may arise both from multi-receptor molecules and from combinations targeting physiologically distinct systems.

An important question is whether progressively greater percentage weight loss should remain the principal measure used to compare these therapies. Weight reduction is clearly clinically relevant and is associated with improvement in many obesity-related complications. However, the multisystem consequences of obesity make it unlikely that a single weight-based endpoint will fully characterize therapeutic benefit. The reviewed studies already demonstrate divergence in the types of additional benefits observed. Tirzepatide has shown clinically relevant effects in obstructive sleep apnea, glucagon-containing agonists have demonstrated substantial effects on hepatic

steatosis and MASH, and liraglutide has established cardiovascular benefit in patients with T2DM [24,41,46,48,49]. As increasingly effective treatments become available, their effects on cardiovascular disease, glycemic control, liver disease, sleep apnea, physical function and other complications may become more important in distinguishing between agents that all produce substantial weight reduction.

This issue is also relevant to differences between patients with and without T2DM. Across both semaglutide and tirzepatide trials, weight reduction was consistently smaller in participants with T2DM than in corresponding populations without diabetes [25,26,37,39]. The same general pattern is apparent with several emerging therapies. Although the mechanisms underlying this difference are not fully established, altered insulin sensitivity, β-cell function, concomitant medications and differences in metabolic phenotype may contribute. This finding emphasizes that obesity is biologically heterogeneous and that efficacy observed in one population should not be assumed to apply uniformly to another. It also suggests that future pharmacotherapy may increasingly be selected according to metabolic phenotype and associated disease rather than according to BMI alone.

Interindividual variability is equally important within apparently similar populations. Even highly effective therapies produce a wide distribution of responses, and mean weight reduction may conceal patients with minimal response as well as those achieving considerably greater weight loss. The liraglutide studies demonstrate that early treatment response can predict longer-term efficacy, with substantially greater weight reduction among individuals reaching the early-response threshold [22]. This raises the possibility that treatment could increasingly incorporate early assessment of therapeutic response rather than relying on prolonged exposure to an ineffective agent. As the number of available mechanisms increases, identifying predictors of response to GLP-1, GIP, glucagon or amylin-based treatment could become particularly valuable. At present, however, reliable biomarkers capable of guiding such selection remain lacking.

The findings observed following treatment withdrawal or transition to placebo further support the concept of obesity as a chronic, relapsing disease characterized by biological defense of body weight. In STEP 4 and SURMOUNT-4, withdrawal was followed by substantial weight regain, whereas continued treatment maintained or further increased weight reduction [28,42]. Pharmacotherapy therefore appears to control rather than permanently eliminate the biological mechanisms promoting weight regain. This distinction has important implications for how efficacy is interpreted:

achieving substantial weight reduction during the first year of treatment does not necessarily establish that the effect can be maintained after therapy is discontinued.

The requirement for prolonged treatment makes the route of administration and treatment burden increasingly relevant. The development of oral semaglutide demonstrates that peptide-based GLP-1 receptor agonism can achieve substantial efficacy without subcutaneous administration, while orforglipron and danuglipron extend this approach to non-peptide small molecules [30–36]. Oral therapy may be attractive to patients reluctant to initiate injections and could potentially broaden treatment uptake. However, an oral formulation should not automatically be assumed to improve adherence. Once-daily treatment may be less convenient for some patients than a once-weekly injection, and adherence under trial conditions may not reflect long-term persistence in routine clinical practice. The potential role of oral agents in maintaining weight loss following injectable treatment, as investigated with orforglipron, introduces an additional strategy in which route and intensity of therapy could potentially change over the course of treatment [34].

The requirement for chronic exposure also increases the importance of safety and tolerability. Gastrointestinal adverse events remain the most consistent limitation across GLP-1 receptor agonists, dual and triple agonists, and incretin–amylin combinations. Their dose-dependent nature is particularly relevant as drug development increasingly aims to maximize weight reduction through higher doses or broader receptor activation. The relationship between titration and adverse events observed with several agents suggests that maximal pharmacological potency may not always correspond to the most clinically useful regimen. A treatment capable of greater average weight reduction may offer limited additional benefit if adverse effects prevent a substantial proportion of patients from reaching or maintaining the effective dose [19,42,43,48,56,59].

The safety implications of newer receptor combinations also require longer observation. Increases in heart rate reported with some glucagon-containing agonists warrant continued evaluation, particularly because obesity itself is strongly associated with cardiovascular disease. Although serious adverse events and severe hypoglycemia have generally been uncommon in the available studies, absence of a safety signal in relatively short clinical trials cannot establish long-term safety. This is particularly relevant for retatrutide, pemvidutide, petrelintide and other investigational agents for which cumulative exposure remains substantially smaller than for liraglutide or semaglutide. As pharmacotherapy moves toward chronic or potentially lifelong admin-

istration, rare adverse events and effects of prolonged multi-receptor stimulation become increasingly relevant [19,43,48,56,59].

Limitations

This narrative review has several limitations. The search was restricted to PubMed, Google Scholar, and ClinicalTrials.gov and to English-language sources. The structured but non-systematic selection of publications may have introduced selection bias, and no formal risk-of-bias assessment was performed.

Comparisons between therapies are limited by differences in study populations, diabetes status, treatment duration, dose-escalation protocols, and methods used to estimate treatment effects. Evidence also varies in maturity, with established therapies supported by extensive phase III programmes and some investigational agents supported mainly by phase I or II studies. Direct comparisons remain limited, and long-term evidence on maintenance of weight reduction, safety, and obesity-related clinical outcomes is uneven across therapies. Consequently, differences in weight reduction reported in separate trials should not be interpreted as definitive evidence of one treatment's superiority over another.

CONCLUSIONS

The pharmacological treatment of obesity has undergone substantial development, shifting from agents with relatively modest efficacy toward therapies that directly target physiological pathways involved in appetite, satiation, glucose metabolism, and energy homeostasis. GLP-1 receptor agonism has established the clinical value of targeting these mechanisms, while the subsequent development of dual and triple receptor agonists, amylin analogues, and combination therapies has considerably expanded the range of potential therapeutic strategies. Clinical trials have demonstrated substantial weight reduction with newer pharmacological agents, with these effects maintained during continued treatment over the respective study follow-up periods.

The clinical value of these therapies should not be assessed exclusively according to the magnitude of body-weight reduction. Obesity is a heterogeneous multisystem disease, and treatment should ultimately aim to improve obesity-related complications in addition to reducing body weight. Emerging evidence of effects on glycemic control, cardiovascular outcomes, obstructive sleep apnea, hepatic steatosis, MASH, visceral

adiposity, and body composition indicates that individual therapies may differ in their broader metabolic effects. These differences may become increasingly relevant as multiple agents capable of producing substantial weight reduction become available.

Despite considerable progress, several challenges remain. Gastrointestinal adverse events continue to represent the principal tolerability limitation of most incretin- and amylin-based therapies, while the long-term safety of newer multi-receptor agonists remains to be established. Weight regain following treatment withdrawal further indicates that pharmacological control of obesity generally requires sustained therapy, consistent with its chronic and relapsing nature. The limited duration of follow-up in studies of emerging agents and the lack of sufficient direct comparisons between treatments constrain the assessment of their long-term safety and relative clinical benefits. Longer follow-up and further evaluation of cardiovascular and metabolic outcomes will therefore be necessary to define their relative roles in clinical practice.

Future research should prioritize the identification of predictors of treatment response, clarification of optimal treatment duration and maintenance strategies, and assessment of long-term safety. Given the heterogeneity of obesity and the differences in the metabolic effects of available therapies, treatment selection should integrate individual metabolic characteristics and comorbidities with demonstrated efficacy, safety, tolerability, route of administration, accessibility, and patient preferences. Such an approach may facilitate more individualized treatment strategies and support the comprehensive long-term management of obesity.

DISCLOSURE

Author Contributions

Conceptualization: Dagmara Laufer, Krystian Domeracki, Olga Klimczak

Methodology: Dagmara Laufer, Estera Sośniecka, Olga Klimczak.

Formal analysis: Krystian Domeracki, Dagmara Laufer.

Investigation and data collection: Krystian Domeracki, Olga Klimczak, Adam Miler, Estera Sośniecka.

Writing, original draft preparation: Olga Klimczak, Krystian Domeracki, Filip Chodań, Dagmara Laufer, Adam Miler.

Writing, review and editing: Dagmara Laufer, Estera Sośniecka, Adam Miler.

Supervision: Dagmara Laufer.

All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare no conflict of interest.

Use of Artificial Intelligence

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