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ADVANCES IN OBESITY PHARMACOTHERAPY: CURRENT STATE AND FUTURE PERSPECTIVES

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ABSTRACT

Introduction: Excessive body weight is a growing problem in Poland and worldwide. Adverse epidemiological trends necessitate the search for effective pharmacological therapies to support behavioral interventions in achieving sustainable therapeutic goals and reducing the risk of metabolic complications of obesity.
Material and Methodology: We reviewed the current medical literature and the results of phase 2 and 3 clinical trials (including the STEP, SURMOUNT, TRIUMPH, REDEFINE and ATTAIN programmes) regarding approved and experimental anti-obesity medications as part of this narrative review.
Results: The analysis shows the evolution of incretin-based therapies. In addition to approved GLP-1 receptor agonists (semaglutide) and dual GLP-1/GIP agonists (tirzepatide), the high efficacy of new molecules has been demonstrated: retatrutide (triple GLP-1/GIP/GCG agonist), survodutide, and cagrilintide/semaglutide combination therapy. Studies prove that new molecules enable significant weight reduction while offering beneficial cardiometabolic effects, including improved glycemic parameters, lipid profiles, and reduction of cardiovascular risk factors. New developmental directions include oral administration routes (orforglipron) and muscle-sparing drugs (bimagrumab).
Conclusions: Modern pharmacotherapy for obesity aims to achieve greater efficacy in weight reduction and maximize benefits in treating comorbidities. One of the developmental directions is improving adherence by introducing patient-friendly drug delivery forms. Overcoming therapeutic barriers, such as loss of lean body mass and preventing weight regain after treatment discontinuation, also remains a challenge.

KEYWORDS

Anti-obesity Pharmacotherapy, GLP-1 Receptor Agonists, GIP Receptor Agonists, Glucagon Receptor Agonists, Amylin Analogs, Body Composition, Weight Loss

CITATION

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1. Introduction

The World Health Organization (WHO) defines obesity as a chronic, relapsing disease conditioned by complex interactions of genetic, neurobiological, environmental, economic, and behavioral factors (World Health Organization, 2025). We know increasingly more about the pathogenesis of this condition; nevertheless, it is still diagnosed too late, as the majority of patients affected by it remain without appropriate treatment. This raises enormous concern, especially in the light of epidemiological studies which clearly indicate a constant increase in the prevalence of obesity in Poland (Bąk-Sosnowska et al., 2024).

In Poland, the scale of the problem remains significant. According to 2025 national public health data, 13.9% of Polish adults are already suffering from obesity, and 41.9% struggle with being overweight (World Obesity Federation, 2026). The systematic increase in the prevalence of excess body weight in recent years allows us to project a further deterioration in the health situation of the population. It is estimated that by 2035, the percentage of individuals suffering from obesity in Poland will increase to 33% (Bąk-Sosnowska et al., 2024).

This situation reflects global epidemiological trends. Worldwide, the prevalence of obesity among adults has more than doubled since 1990. In 2022, approximately one in eight people were living with this disease (World Health Organization, 2025). Data from 2022 indicate that excess body weight was present in 43% of adults worldwide, which translates to 2.5 billion people, of whom 890 million met the criteria for the diagnosis of obesity (Bąk-Sosnowska et al., 2024; World Health Organization, 2025). If the situation does not change, it is projected that by 2035 these values will increase to 4 billion people with overweight and 1.9 billion with obesity, respectively. Such a degree of prevalence currently allows obesity to be treated as a disease of a pandemic nature (Bąk-Sosnowska et al., 2024).

Obesity currently constitutes one of the main global health challenges (Pandey et al., 2025). Its occurrence translates into serious, negative health consequences, which lead not only to a significant deterioration in the overall quality of life of patients, but also to a shortening of their life expectancy. It is estimated that every year worldwide, over 2.5 million people die due to chronic conditions caused by or closely related to obesity (Bąk-Sosnowska et al., 2024).

The key risk factor in this case is the excessive accumulation of adipose tissue, in particular visceral adipose tissue, which drastically increases the probability of developing cardiovascular diseases and metabolic complications (Heymsfield et al., 2026a; Pandey et al., 2025). In its course, obesity predisposes to the occurrence of many comorbidities. These include primarily type 2 diabetes, carbohydrate metabolism disorders, arterial hypertension, atherogenic dyslipidaemia, atherosclerosis, and other cardiovascular complications. Furthermore, this disease leads to the development of metabolic dysfunction-associated steatotic liver disease, sleep apnoea syndrome, chronic kidney disease, fertility disorders, osteoarthritis of large joints, and also predisposes to certain malignant neoplasms (Bąk-Sosnowska et al., 2024).

The effective treatment of such a complex disease entity, however, remains exceptionally difficult. Weight loss achieved solely through lifestyle modification and habit change usually does not exceed 3–5% of the baseline value. While even such a small reduction brings noticeable health benefits, in the majority of patients, behavioural intervention proves to be insufficient for permanent weight normalisation and the minimisation of the long-term consequences of obesity (Bąk-Sosnowska et al., 2024). For this reason, pharmacotherapy becomes an essential tool. Despite the availability of effective therapies based on GLP-1 analogues, more effective solutions are being investigated. Therefore, the aim of this paper is to review the newest obesity therapies entering the market, taking into account their mechanism of action and clinical potential.

2. Methodology

This narrative review synthesises contemporary data on both approved and experimental anti-obesity pharmacotherapies.

We gathered relevant literature through a systematic search across PubMed, Google Scholar, and the ClinicalTrials.gov registry. The search logic relied on specific combinations of keywords rather than broad subject headings. These terms included: "obesity", "anti-obesity medications", "GLP-1 receptor agonists", "GIP", "glucagon receptor agonists", "semaglutide", "tirzepatide", "retatrutide", "survodutide", "cagrilintide", "orforglipron", and "bimagrumab". To supplement this data, we manually searched the official portals of major health authorities - specifically the WHO, the World Obesity Federation, and the Polish Society for the Treatment of Obesity - to collect the latest epidemiological statistics and clinical consensus papers.

The review focused on literature published up to April 2026, with a significant emphasis on clinical breakthroughs from the last decade (2015–2026). We specifically selected peer-reviewed original papers, focusing on phase 2 and phase 3 randomised controlled trials from major clinical programmes like STEP, SURMOUNT, TRIUMPH, REDEFINE and ATTAIN. Systematic reviews, meta-analyses, and official practice guidelines were also eligible. The final synthesis excludes papers focusing on obsolete treatments or those failing to report clear clinical endpoints. We restricted the language scope to English and Polish.

The extracted data were synthesised narratively, focusing on the mechanisms of action, clinical efficacy, primarily regarding the percentage of weight loss and cardiometabolic improvements, as well as the safety profiles of both approved and investigational drug molecules.

3. Diagnosis of obesity

The foundation of effective medical management is the early diagnosis of body weight disorders, based on objective anthropometric measurements performed routinely at least once a year (Bąk-Sosnowska et al., 2024).

The key screening test is the body mass index (BMI). A BMI value in the range of 25.0–29.9 kg/m² constitutes the criterion for the diagnosis of overweight, whereas a BMI ≥30 kg/m² allows for the diagnosis of obesity. Despite the common use of this index, its limitations must be remembered - it does not reflect the proportion between muscle and adipose tissue, nor the distribution of the latter in the body (Bąk-Sosnowska et al., 2024).

A significant complement to the BMI is the measurement of waist circumference, which is an indirect measure of the visceral distribution of adipose tissue and increased cardiometabolic risk. This examination is particularly recommended in individuals with overweight or class I obesity, because at a BMI ≥35 kg/m² (class II and III obesity) the risk of complications is already very high and this measurement usually does not provide additional diagnostic information. The measurement is taken in the mid-axillary line, halfway between the highest point of the iliac crest and the lowest point of the costal margin (Bąk-Sosnowska et al., 2024). According to the criteria of the International Diabetes Federation (IDF), abdominal obesity in Europeans is diagnosed at a waist circumference of ≥80 cm in women and ≥94 cm in men (International Diabetes Federation, 2006).

An additional parameter allowing for the assessment of adipose tissue distribution is the waist-to-hip ratio (WHR), calculated as the quotient of waist and hip circumference. Abdominal obesity is diagnosed when the WHR exceeds 0.85 in women and 0.9 in men. Both an elevated waist circumference and a high WHR index are closely correlated with an increased risk of developing metabolic complications and cardiovascular diseases (Bąk-Sosnowska et al., 2024).

4. Indications for pharmacological treatment

4.1. Criteria for initiating treatment

Pharmacological treatment can be used in patients for whom dietary and behavioural management have not achieved therapeutic goals, provided they meet specific clinical criteria. According to current indications, the following qualify for therapy:

- Adults with diagnosed obesity (BMI ≥30 kg/m²), for whom the body mass index alone constitutes a sufficient indication.
- Adults who are overweight (BMI 27.0–29.9 kg/m²) and who suffer from at least one weight-related disease (e.g., carbohydrate metabolism disorders, arterial hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease) (Bąk-Sosnowska et al., 2024).

4.2. Timing of treatment implementation

The decision to initiate pharmacotherapy is usually made when, after 3–6 months of lifestyle changes, the patient has not achieved a weight loss of ≥5% of the baseline value. Implementing treatment at an earlier stage may be considered. This particularly applies to patients whose medical history indicates the ineffectiveness of previous non-pharmacological interventions, and patients with coexisting conditions that significantly increase cardiovascular risk. In individuals with extreme obesity (class III, BMI ≥40 kg/m²), guidelines mandate striving for comprehensive treatment from the very beginning, taking into account both pharmacotherapy and the consideration of bariatric surgery (Bąk-Sosnowska et al., 2024).

4.3. Principles of drug selection

The decision to select a specific preparation is based on a thorough assessment of the patient's health status. In individuals with comorbidities, preference should be given to drugs for which beneficial metabolic effects and a positive impact on cardiovascular risk have been proven. In particular, when the primary goal of therapy is the reduction of this risk, the drugs of choice currently become semaglutide, the effectiveness of which was proven in the breakthrough SELECT trial (Lincoff et al., 2023), and tirzepatide, demonstrating significant clinical benefits in the SUMMIT trial (Packer et al., 2024). In the case of patients with low cardiometabolic risk, without significant burdens, all preparations available on the market are taken into consideration, guided primarily by their safety profile (Bąk-Sosnowska et al., 2024).

4.4. Comprehensiveness of treatment

The implementation of pharmacotherapy never exempts from the necessity of continuing comprehensive non-pharmacological therapy. Drugs should always be used in combination with a reduced-calorie diet and increased physical activity, and the doctor should verify adherence to these recommendations at every visit. Furthermore, pharmacotherapy plays an important role in surgical treatment - it should be considered during the period of preparing the patient for a bariatric procedure, and sometimes also after surgery, in order to inhibit weight regain (Bąk-Sosnowska et al., 2024).

5. Current state of knowledge: Registered drugs in the treatment of obesity

Orlistat

Among the drugs currently registered for the treatment of obesity by the European Medicines Agency (EMA), orlistat is the oldest (Bąk-Sosnowska et al., 2024). Its mechanism of action is exclusively peripheral in its nature. The drug does not affect the central regulation of hunger and satiety, but specifically inhibits the activity of gastric and pancreatic lipase (Bąk-Sosnowska et al., 2024; Fredrick et al., 2025). The preparation, taken orally with every meal containing fat, prevents the hydrolysis of triglycerides into free fatty acids, which significantly reduces their absorption and limits the number of assimilated calories. The effectiveness of this therapy is relatively low and allows for a reduction of 2.8% to 4.8% of total body weight compared to placebo (Fredrick et al., 2025). Additionally, the reduced absorption of fats is associated with the occurrence of bothersome adverse effects, such as fatty stools (steatorrhoea), abdominal pain, flatulence, and sudden faecal urgency. These side effects are difficult for patients to accept, which constitutes the main reason for discontinuing treatment, and this translates into the negligible use of orlistat in contemporary clinical practice (Bąk-Sosnowska et al., 2024; Fredrick et al., 2025).

Naltrexone/Bupropion

Another therapeutic option is an oral, daily-administered combination preparation containing naltrexone hydrochloride and bupropion hydrochloride. These are substances with a multidirectional, central mechanism of action. In the treatment of obesity, their combination exhibits a synergistic effect: bupropion increases the feeling of satiety effectively decreasing food intake, while naltrexone blocks the autoinhibition of this process, which potentiates the therapeutic effect. Furthermore, this combination affects the mesolimbic reward system, reducing the strong craving to consume specific foods, which makes this drug particularly useful in patients with binge eating episodes (Bąk-Sosnowska et al., 2024; Fredrick et al., 2025). Due to the pharmacological profile of bupropion, considering this therapy is also highly justified in patients with obesity who are addicted to tobacco (Bąk-Sosnowska et al., 2024). Clinical trials have demonstrated treatment effectiveness at the level of a 6.1% to 9.3% reduction in total body weight compared to placebo after 56 weeks. This therapy is, however, associated with a risk of adverse effects (including nausea, constipation, headaches, and dizziness). Moreover, the drug primarily improves the parameters of central obesity and LDL cholesterol concentration, without a demonstrated significant impact on other cardiovascular risk factors (Fredrick et al., 2025).

Phentermine/Topiramate

The combination preparation containing phentermine and topiramate, available as capsules for oral administration, has been authorised for marketing on the Polish market, even though the European Medicines Agency (EMA) twice rejected the application for its central registration (Bąk-Sosnowska et al., 2024). The mechanism of action is based on the synergy of both molecules: phentermine inhibits appetite through the stimulation of neurotransmitter release, whereas topiramate induces weight loss probably through the modulation of GABAergic neurotransmission in the hypothalamus. The use of this combination allows for a reduction of nearly 11% of total body weight compared to placebo after 56 weeks of treatment, which secondarily improves the lipid profile as well as glycaemic and blood pressure parameters. The limitation for the use of this drug remains adverse effects, such as paraesthesia, xerostomia, or constipation (Fredrick et al., 2025). Furthermore, the negative opinion of the EMA was dictated by concerns about the unknown impact of the preparation on the cardiovascular system during long-term use. Another factor was the lack of sufficient studies regarding the impact of the therapy on the cognitive functions of patients (Bąk-Sosnowska et al., 2024).

Liraglutide

It is the first analogue of human glucagon-like peptide-1 (GLP-1) registered for the treatment of obesity. It is administered subcutaneously once a day. The mechanism of action is based on the activation of GLP-1 receptors in the brain, which increases the feeling of satiety and inhibits hunger. Additionally, the preparation slows gastric emptying and regulates the secretion of insulin and glucagon. In the therapy of obesity, a dose of 3.0 mg is used, which is higher than in the treatment of type 2 diabetes (Bąk-Sosnowska et al., 2024).

The effectiveness of the drug was confirmed by the SCALE trial (n=3731), in which patients after 56 weeks achieved a mean body weight reduction of 8.4 kg (versus 2.8 kg in the placebo group). Over 63% of the subjects achieved a weight loss of at least 5%, and one in three by over 10%. The therapy was also associated with an improvement in blood pressure, lipid profile, and pancreatic beta-cell function, which significantly delayed the development of type 2 diabetes in individuals with prediabetes. An improvement in the quality of life in the area of physical fitness was also noted (Pi-Sunyer et al., 2015).

Adverse effects primarily included transient nausea and vomiting, occurring most frequently in the first 4–8 weeks of treatment (Pi-Sunyer et al., 2015). Of key importance are also the results of the LEADER trial, which proved that liraglutide in at-risk patients significantly reduces the incidence of cardiovascular deaths, myocardial infarctions, and strokes (Marso et al., 2016).

Semaglutide

This is another GLP-1 receptor agonist, initially registered for the treatment of type 2 diabetes. Structural modifications of the molecule allowed for the prolongation of its half-life in the body from approximately two minutes for the natural hormone to almost a week, which enables the administration of the drug in the form of a single subcutaneous injection once a week (Bąk-Sosnowska et al., 2024). This provides a significant convenience advantage over liraglutide, which requires once-daily subcutaneous injections (Rubino et al., 2022). In the therapy of obesity, the mechanism of action of semaglutide consists of mimicking physiological incretin processes and modulating neurotransmission in the centres responsible for appetite control (Bąk-Sosnowska et al., 2024). It is hypothesized that structural differences allow semaglutide to target a wider range of neuronal GLP-1 receptors in the central nervous system compared to liraglutide (Rubino et al., 2022). The drug intensifies and accelerates the feeling of satiety, simultaneously reducing physiological hunger and the appetite for high-fat foods (food cravings), which consequently leads to a more profound reduction in overall calorie intake (Bąk-Sosnowska et al., 2024; Rubino et al., 2022).

The effectiveness of the preparation was confirmed by the STEP clinical trial programme. In the STEP 1 trial (n=1961), after 68 weeks, a mean body weight reduction of 14.9% was achieved (versus 2.4% in the placebo group). As many as 86% of the subjects lost at least 5% of their weight, approximately half over 15%, and one third achieved a 20% reduction, which brings this effect close to the results of bariatric surgery. The therapy was accompanied by an improvement in cardiometabolic parameters, including a decrease in waist circumference, a drop in blood pressure, an improvement in the lipid profile, a lowering of the glycated haemoglobin level, and a reduction in inflammatory markers (C-reactive protein), as well as an improvement in the quality of life. In terms of safety, transient nausea and diarrhoea were most frequently noted, which for the majority of patients did not constitute an obstacle to continuing treatment (Wilding et al., 2021).

Significant data was provided by the STEP 8 trial (n=338), which was a direct comparison of semaglutide and liraglutide. The study demonstrates that semaglutide used once a week causes significantly

greater weight loss (15.8%) than daily injections of liraglutide (6.4%), which consolidated its position as a more effective tool in the pharmacotherapy of obesity (Rubino et al., 2022).

Beyond weight reduction itself, semaglutide exhibits a cardioprotective effect. Building on evidence demonstrating the benefits of this group of drugs in diabetes, the SELECT trial (n=17,604) was conducted to assess the impact of semaglutide on cardiovascular risk in individuals with overweight or obesity without diabetes. It was demonstrated that therapy lasting on average 33 months reduced the risk of major adverse cardiovascular events, such as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, by 20% relative to placebo. These results prove that this drug goes beyond the mere treatment of obesity, constituting a key element in lowering overall cardiovascular risk (Lincoff et al., 2023).

Tirzepatide

It is a representative of the incretin class of drugs, being a long-acting, dual agonist of the receptors for glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 (Bąk-Sosnowska et al., 2024). Appropriate structural modifications of the molecule ensured a half-life prolonged to five days, which enables the preparation to be administered subcutaneously once a week (Bąk-Sosnowska et al., 2024; Packer et al., 2024). The drug is characterised by an affinity for the GIP receptor comparable to the native hormone, whereas its action on the GLP-1 receptor is slightly weaker in relation to the natural ligand. The synergistic mechanism of action is based on the stimulation of receptors located in the central nervous system, which leads to an increase in the feeling of satiety and fullness with a concurrent decrease in the sensation of hunger and total energy intake. Furthermore, both types of receptors are expressed on pancreatic α and β endocrine cells, cardiomyocytes, endothelial cells, immune system leukocytes, as well as within the intestines and kidneys. Receptors for GIP are additionally located on adipocytes (Bąk-Sosnowska et al., 2024).

Data regarding the effectiveness of this dual mechanism of action were provided by the SURMOUNT-1 trial, encompassing patients with obesity without coexisting diabetes. A significant, dose-dependent reduction in body weight was demonstrated therein. After 72 weeks of therapy, the mean weight loss was 16% for the 5 mg dose, 21.4% for the 10 mg dose, and 22.5% for the 15 mg dose, versus 2.4% in the placebo group. Over one third of the subjects taking the 15 mg dose achieved a body weight reduction of at least 25%, which is a result comparable to the effects of bariatric surgery. The weight loss was accompanied by a beneficial change in body composition. The percentage reduction in adipose tissue was approximately three times greater than the loss of lean body mass. Moreover, a significant improvement in all measured cardiometabolic risk factors was noted, including a decrease in waist circumference, a drop in systolic and diastolic blood pressure, a lowering of fasting insulin concentration, optimisation of the lipid profile, and a decrease in aspartate aminotransferase (AST) level. Over 95% of patients with prediabetes achieved normoglycaemia at the end of the trial. In terms of safety, gastrointestinal symptoms were most frequently reported. They included nausea, diarrhoea, and constipation, which were of a mild or moderate, transient nature and occurred primarily during the dose escalation phase (Jastreboff et al., 2022).

Tirzepatide also demonstrates a significant impact on the cardiovascular system, which was proven in the SUMMIT trial (n=731) conducted among patients with obesity and heart failure with preserved ejection fraction. During an observation lasting on average 104 weeks, it was demonstrated that the treatment lowers the risk of the occurrence of a composite endpoint, comprising cardiovascular death or sudden exacerbation of heart failure, from 15.3% in the placebo group to 9.9% in the study group. The therapy was furthermore characterised by a statistically significant improvement in the health status and physical capacity of the patients, which confirms the beneficial cardiovascular effect of the drug in this group of patients (Packer et al., 2024).

6. Future directions and perspectives in the pharmacotherapy of obesity

6.1. Retatrutide: triple agonist of receptors for GIP, GLP-1, and glucagon

Retatrutide (LY3437943) constitutes the next step in the evolution of obesity pharmacotherapy. In contrast to dual agonists such as tirzepatide, this molecule is a triple agonist activating GIP, GLP-1, and glucagon (GCG) receptors (Jastreboff et al., 2023). This drug demonstrates balanced affinity for GLP-1 and glucagon receptors, being characterised simultaneously by a significantly stronger activation of the GIP receptor. Activation of the glucagon receptor increases the body's energy expenditure. This prevents the natural slowing of metabolism, which usually accompanies a lower calorie intake as a result of appetite inhibition. Preclinical data indicate that this mechanism is responsible for 30–35% of total body weight loss. Weight loss results mainly from the reduction of adipose tissue, with the preservation of muscle mass, which increases the lean-to-fat mass ratio (Coskun et al., 2022).

Structural modification through acylation with a 20-carbon fatty acid prolongs the half-life of retatrutide to approximately 6 days, enabling subcutaneous administration once a week (Coskun et al., 2022; Jastreboff et al., 2023). As demonstrated in phase 1 trials, body weight reduction and appetite decrease after a single dose persist for up to 43 days, yielding an effect comparable to four weeks of tirzepatide use (Coskun et al., 2022).

The clinical effectiveness of the preparation was assessed in a phase 2 trial involving 338 adults with obesity, without type 2 diabetes. After 48 weeks, a dose-dependent weight loss was noted: 8.7% – 1 mg, 17.1% – 4 mg, 22.8% – 8 mg, and 24.2% – 12 mg relative to 2.1% in the placebo group. A weight reduction of ≥5% was achieved by 100% of patients treated with 8 mg and 12 mg doses. In the 12 mg group, 93% of subjects lost ≥10% of their body weight, and 26% of patients lost ≥30%. Waist circumference was reduced by an average of 6.5–19.6 cm. The authors of the study furthermore noted that at week 48 of observation, the body weight reduction curve had not yet reached a plateau, which suggests the potential for further weight loss during longer therapy. The effectiveness of the drug is comparable to the results of bariatric surgery. A baseline BMI >35 and female sex predisposed to a greater weight reduction (Jastreboff et al., 2023).

Treatment with retatrutide is also associated with significant beneficial changes in cardiometabolic parameters. During the 48-week observation, an improvement was demonstrated in blood pressure control, glycated haemoglobin, fasting glucose and insulin concentrations, and lipid profile (except for high-density lipoprotein - HDL). In 72% of participants with prediabetes, normoglycaemia was achieved, compared to 22% in the placebo group. The drop in blood pressure allowed for the discontinuation of at least one hypotensive drug in 41% of patients from the 8 mg group and 30% from the 12 mg group. A general improvement in the patients' quality of life and physical fitness was also noted (Jastreboff et al., 2023).

In terms of safety, the profile of retatrutide remains consistent with other incretin therapies. Over the course of the phase 2 trial, mild to moderate gastrointestinal symptoms during dose escalation were most frequently reported. The use of a lower starting dose of 2 mg allowed for a partial limitation of their occurrence. A transient, dose-dependent increase in heart rate resulting from a positive chronotropic effect was observed, peaking at week 24. Episodes of arrhythmia were mostly mild or moderate (Jastreboff et al., 2023). Moreover, rare, transient laboratory abnormalities were observed, including an asymptomatic increase in the concentration of amylase, lipase, and alanine aminotransferase, as well as mild cutaneous hyperaesthesia. None of these events required therapy interruption (Coskun et al., 2022; Jastreboff et al., 2023).

Taking into account the results to date, retatrutide constitutes a highly promising therapeutic option in the treatment of obesity. As of May 2026, the scientific community awaits the publication of the results of the phase 3 trials of the TRIUMPH programme, which will definitively verify the safety profile and long-term effectiveness of this drug.

6.2. Survodutide: dual agonist of receptors for GLP-1 and glucagon

Survodutide (BI 456906) is a dual agonist of GLP-1 and glucagon receptors. In terms of structure, the molecule is based on the 29-amino-acid human glucagon peptide, in which purposeful amino acid substitutions prevent degradation, increase stability, and confer activity towards the GLP-1 receptor. The drug is characterised by an asymmetry of action, demonstrating a greater potency of activation towards the GLP-1 receptor compared to the glucagon receptor (le Roux et al., 2026). The dual mechanism of action causes specific benefits: while the GLP-1 component is primarily responsible for appetite inhibition, activation of the glucagon receptor, as suggested by preclinical data, increases the body's energy expenditure, stimulates lipolysis, and limits fat accumulation in organs (Kosiborod et al., 2024).

The effectiveness of survodutide in the treatment of obesity was assessed in a 46-week, multicentre phase 2 trial involving patients with excess body weight without coexisting diabetes. A dose-dependent weight reduction was observed, which in individuals using the highest dose of 4.8 mg averaged 14.9%, whereas in the control group it was merely 2.8% (le Roux et al., 2024). A parallel 48-week phase 2 trial demonstrated additional benefits of the drug in the context of liver diseases. Among adult patients with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis at the F1-F3 stage, the 4.8 mg dose led to histological improvement of MASH without worsening of fibrosis in 62% of subjects, while in the placebo group this percentage was 14%. Additionally, in the vast majority of treated patients, a reduction in liver fat content of at least 30% was noted (Sanyal et al., 2024).

Similar to other incretin-based therapies, the most frequently reported adverse effects in phase 2 trials were gastrointestinal complaints, primarily nausea, diarrhoea, and vomiting (le Roux et al., 2024; Sanyal et al., 2024). In accordance with the premises from clinical practice, the risk of their occurrence is mitigated by slow and gradual escalation of the drug dose (le Roux et al., 2026). A slight increase in heart rate was also found, by an average of 2.7 beats per minute, which constitutes a value close to the effect exerted by semaglutide (Kosiborod et al., 2024).

Currently, the safety and effectiveness profile of survodutide is being evaluated in extensive phase 3 programme; consequently, definitive results are not yet available. In the international SYNCHRONIZE-1 trial, with a planned 78-week observation period, the drug is administered to patients with obesity without type 2 diabetes. The baseline cohort of this trial is characterised by a large representation of men (41%). This fact is significant from a clinical point of view, because studies published to date indicate that men subjected to GLP-1 therapy may achieve a slightly smaller body weight reduction than women, but on the other hand, they less frequently report gastrointestinal adverse effects (le Roux et al., 2026).

For the assessment of long-term safety, of key importance is the ongoing SYNCHRONIZE-CVOT trial, which is to answer the question of whether the use of the dual agonist reduces the risk of morbidity and mortality in individuals of the highest cardiovascular risk. The primary endpoint in this trial is 5P-MACE. This is a five-point major adverse cardiovascular events index. It encompasses not only atherosclerosis-based complications but also incidents related to heart failure. Such an expansion was decided upon, taking into account the growing clinical significance of this disease as a major complication of obesity. Thanks to the inclusion in the trial of a group of patients with heart failure (NYHA class II-III), it was possible to assess the drug's impact on cardiovascular events and the alleviation of symptoms of the failure itself, regardless of the left ventricular ejection fraction (Kosiborod et al., 2024).

6.3. Cagrilintide: long-acting amylin analogue and its combination with semaglutide

Cagrilintide is a molecule being a long-acting amylin analogue. Under physiological conditions, amylin is a hormone secreted by pancreatic beta cells. It plays a role in appetite regulation by inducing a feeling of satiety, slowing the rate of gastric emptying, and also inhibiting the postprandial release of glucagon (Madsbad & Holst, 2025). In clinical trials, this drug was administered by subcutaneous injections, once a week (Enebo et al., 2021; Lau et al., 2021). This molecule is also being investigated in the form of the combination preparation CagriSema, which is a combination of cagrilintide with semaglutide (Madsbad & Holst, 2025).

In a phase 1b trial, the use of cagrilintide with semaglutide was evaluated (n=96). Participants were allocated to groups receiving weekly injections of cagrilintide in a dose range from 0.16 mg to 4.5 mg, or a placebo. Semaglutide at a fixed dose of 2.4 mg was administered concurrently to all. After 20 weeks, a distinct effect in the form of body weight reduction was noticed, amounting to 15.7% for the 1.2 mg dose, 17.1% for the 2.4 mg dose, and 15.4% following the administration of the highest dose of 4.5 mg. In the control group, which used a placebo with semaglutide, this loss amounted to 9.8% (Enebo et al., 2021).

The effectiveness of cagrilintide alone in patients with overweight and obesity was assessed in a multicentre phase 2 trial involving adults (n=706). Participants were allocated to groups receiving various doses of cagrilintide (from 0.3 to 4.5 mg), liraglutide at a dose of 3.0 mg, or a placebo. After 26 weeks of using the 4.5 mg dose of cagrilintide, a body weight decrease at the level of 10.8% was observed. For comparison, in the group using liraglutide, this loss was 9.0%, and in the placebo group 3.0% (Lau et al., 2021).

Another phase 2 trial investigated the action of combination therapy in patients with type 2 diabetes (n=92). For 32 weeks, participants took a combination of both drugs, semaglutide alone at a dose of 2.4 mg, or cagrilintide alone at a dose of 2.4 mg. The primary endpoint was the change in HbA1c level, and secondary endpoints included, among others, body weight change, fasting glycaemia, and continuous glucose monitoring (CGM) parameters. The combination therapy lowered HbA1c by 2.2 percentage points (p.p.) - more effectively

than cagrilintide alone (0.9 p.p.), but without statistical significance relative to semaglutide (1.8 p.p.). However, an advantage was noted in the matter of body weight reduction, which in the group receiving combination treatment decreased by 15.6%, versus 5.1% for semaglutide and 8.1% for cagrilintide. The therapy also improved the studied CGM parameters (Frias et al., 2023).

The potential of the combination of cagrilintide and semaglutide at target doses of 2.4 mg in adults with overweight or obesity was confirmed in a large phase 3 trial conducted within the REDEFINE 1 programme (n=3417). The effectiveness of the combination preparation was evaluated therein relative to monotherapy with both components and in relation to a placebo. The results after 68 weeks of therapy showed that the mean body weight decrease in the group using the CagriSema combination treatment was 20.4%, compared to a 3.0% decrease in the group receiving a placebo. Individuals receiving the combination preparation also significantly more often achieved the designated body weight reduction thresholds, i.e., a loss of over 5%, 20%, 25%, and 30% (Garvey et al., 2025).

In all aforementioned trial phases, it was demonstrated that cagrilintide-based therapies, both in monotherapy and in combination with semaglutide, are well tolerated. The reported adverse effects were, in the vast majority, of a mild to moderate nature. Gastrointestinal complaints definitely predominated, such as nausea, vomiting, diarrhoea, constipation, and abdominal pain (Enebo et al., 2021; Frias et al., 2023; Garvey et al., 2025; Lau et al., 2021).

6.4. Orforglipron: an oral, non-peptide GLP-1 receptor agonist

Orforglipron is a novel nonpeptide GLP-1 receptor agonist. As a partial agonist, it exerts a greater effect on G protein signalling pathway activation than on β-arrestin recruitment. Moreover, orforglipron demonstrates high selectivity for the GLP-1 receptor compared with other class B G protein-coupled receptors (Kawai et al., 2020).

Owing to its pharmacokinetic profile, orforglipron can be administered orally. Additionally, as a nonpeptide molecule, it does not require such stringent administration conditions as oral semaglutide (a peptide-based GLP-1 receptor agonist available as a tablet co-formulated with an absorption enhancer). Oral semaglutide must be administered at least 30 minutes before the first meal and taken with no more than 120 mL (4 ounces) of water to ensure adequate gastrointestinal absorption. However, this formulation of semaglutide has been approved solely for the treatment of type 2 diabetes mellitus (Kawai et al., 2020). The introduction of a novel molecule – orforglipron, which can be conveniently administered orally, may represent a significant benefit for patients and provide a new alternative to injectable GLP-1 receptor agonists for the treatment of obesity (Kawai et al., 2020; Wharton et al., 2023).

In a randomised, double-blind, phase 2 trial involving 272 participants living with obesity or overweight and at least one weight-related comorbidity (excluding diabetes mellitus), orforglipron was administered as a once-daily morning capsule, independent of food intake, for 36 weeks. Participants were randomly assigned to groups receiving placebo or orforglipron at doses of 12 mg, 24 mg, 36 mg, or 45 mg. In the orforglipron groups therapy was initiated at a dose of 2 mg or 3 mg and escalated to the full target dose over a maximum of 16 weeks (Wharton et al., 2023). At week 26, in the groups receiving 12 mg, 24 mg, 36 mg, and 45 mg, the change in body weight from baseline was –8.6%, –11.2%, –12.3%, and –12.6%, respectively, compared to 2.0% in placebo group. By the week 36, these reductions deepened to 9.4%, 12.5%, 13.5% and 14.7% across the orforglipron groups, versus 2.3% for placebo. After adjustment for placebo, a decrease in BMI ranging from 2.5 to 4.6 kg/m² and a change in waist circumference from –5.6 cm to –9.6 cm were observed in the orforglipron groups at week 36. The observed reduction in body weight was continuous and dose-dependent. Moreover, improvements in lipid profile and a reduction in systolic blood pressure relative to baseline were also observed (Wharton et al., 2023).

These findings were further supported by the ATTAIN phase 3 trial, which involved 3,127 patients. At week 72, changes in body weight in the groups receiving orforglipron at doses of 6 mg, 12 mg, and 36 mg, as well as placebo, were –7.5%, –8.4%, –11.2%, and –2.1%, respectively. In the 36 mg group 54.6% of participants achieved a body weight reduction of at least 10%, and 18.4% achieved a reduction of at least 20%. In this study a reduction in waist circumference, improvement in lipid profile, and a decrease in systolic blood pressure were also confirmed in patients receiving orforglipron compared with those in the placebo group (Wharton et al., 2025). Moreover, in the ATTAIN-2 trial, which evaluated individuals with overweight or obesity and comorbid type 2 diabetes mellitus, a positive effect of orforglipron on body weight reduction was also observed (Horn et al., 2026).

The most frequently reported adverse events across all dose groups were gastrointestinal events, including nausea, vomiting, diarrhea, and constipation. The phase 2 trial demonstrated that patients tolerated the treatment better when dose escalation to the full target dose was initiated from a lower starting dose and progressed more gradually (Wharton et al., 2023).

Additionally, a 2026 meta-analysis reported that orforglipron doses ≥12 mg were associated with increases in pancreatic enzyme levels (including amylase and lipase). However, these biochemical changes were not accompanied by an increased incidence of reported adverse events related to pancreatic enzyme elevations (Hageen et al., 2026).

6.5. Bimagrumab: a monoclonal antibody for body weight reduction with the preservation of muscle tissue

Bimagrumab is a human monoclonal antibody designed to bind to the myostatin/activin type II receptor (ActRII). By blocking myostatin and activin A from binding to ActRII, it inhibits their function as negative regulators of muscle growth. Bimagrumab has been primarily developed to increase skeletal muscle mass and counteract atrophy in cachectic settings (Lach-Trifilieff et al., 2014). However, other studies suggest that its effects extend beyond muscles, also involving adipose tissue. In animal studies, ActRII inhibition increased energy expenditure, enhanced mitochondrial function, and promoted thermogenesis in brown adipocytes (Fournier et al., 2012). In an early explorational human study, bimagrumab administration led to significant improvement in insulin sensitivity, reductions in fat body mass (FBM), and increases in lean body mass (LBM), compared to placebo (Garito et al., 2018).

While the most effective bimagrumab dosing regimen remains to be elucidated, examples from clinical trials include 10-30 mg/kg of body mass, administered intravenously once every 4 to 12 weeks (Heymsfield et al., 2021; Heymsfield et al., 2026b). An analysis of bimagrumab pharmacokinetics and pharmacodynamics revealed that subcutaneous dosing once weekly was comparable with monthly intravenous administration, highlighting the feasibility of this approach (Petricoul et al., 2023).

A phase 2 study including 507 participants with obesity assessed the effect of bimagrumab and semaglutide on body mass reduction. Both drugs were given alone or together, and compared to a placebo. Patients received intravenous bimagrumab 10 mg/kg or 30 mg/kg, every 12 weeks, or subcutaneous semaglutide 1.0 mg or 2.4 mg once a week, or combinations of these drugs. A lifestyle intervention, consisting of dietary counselling and encouragement of undertake physical activity, was also performed in all groups. At week 48, the least square mean reduction of body weight ranged from 5.6% to 8.6% with bimagrumab, 9.8% to 13.5% with semaglutide, and 12.0% to 16.4% with combination therapy, versus 3.5% with placebo. By this time, the proportion of participants achieving ≥15% weight loss was 23.3% in the bimagrumab group, 43.4% in the semaglutide group, and 63.9% in the high-dose combination group. Of note, bimagrumab preserved - or slightly increased - total LBM at week 48 (+1.0% to +1.1%), in contrast to semaglutide alone, which was associated with lean mass reductions of −4.7% to −6.9%; combination therapy showed intermediate effects (−0.8% to −2.3%) (Heymsfield et al., 2026b).

Another study was conducted with 75 participants with type 2 diabetes and a BMI between 28 and 40 kg/m². They were receiving 10 mg/kg bimagrumab intravenously or a placebo, every 4 weeks. All participants were encouraged to consume a calorie-restricted diet (-500 calories per day) and to be physically active. At 48 weeks, the experimental group demonstrated significant improvements compared to placebo, including greater reductions in body weight (-6.5% vs. -0.8%), FBM (-20.5% vs. -0.5%), and HbA1c (-0.76% vs. +0.04%), alongside an increase in LBM (+3.6% vs. -0.8%) (Heymsfield et al., 2021).

Across clinical trials, bimagrumab demonstrated an overall acceptable safety profile, with muscle spasms, diarrhea, and acne representing the most commonly reported adverse events (Garito et al., 2018; Heymsfield et al., 2021; Heymsfield et al., 2026b). In one study, muscle cramps and acne were reported as reasons for discontinuation of bimagrumab (Heymsfield et al., 2026b). Myalgia, muscle weakness, and musculoskeletal stiffness were among less frequent adverse events (Garito et al., 2018).

As of May 2026, bimagrumab remains an investigational drug that has not yet been approved for general use. Current evidence suggests that it may represent a promising strategy for preserving lean body mass during pharmacologically induced weight loss. Further clinical trials, including a recruiting study comparing bimagrumab with tirzepatide, both administered subcutaneously (Haines, 2026), are expected to provide additional insight into its safety and efficacy.

7. Discussion

New therapeutic options

The emergence of subsequent generations of drugs significantly broadens the possibilities of pharmacological management. Initially, this effectiveness was based on preparations such as orlistat or the combination of naltrexone with bupropion, which allow for a reduction of around 5–9% of total body weight (Fredrick et al., 2025). A change in treatment effectiveness was brought about by the registration of long-acting incretin receptor agonists. Semaglutide allows for a loss of nearly 15% of body weight (Wilding et al., 2021), whereas in the case of tirzepatide, this loss reaches 22.5% (Jastreboff et al., 2022). Concurrently, advanced clinical trials on new drugs are underway. These include the triple agonist retatrutide, the dual agonist survodutide, and the combination therapy of cagrilintide with semaglutide - CagriSema. The results of phase 2 and 3 trials indicate that these drugs enable a body weight loss at the level of 15% to 25% (Garvey et al., 2025; Jastreboff et al., 2023; le Roux et al., 2024). This effectiveness means that the achieved body weight reduction becomes comparable with the effects of bariatric surgery, which is directly suggested by the authors of the trials on tirzepatide and retatrutide (Jastreboff et al., 2022; Jastreboff et al., 2023).

Multidirectional action of obesity drugs

Currently, obesity drugs are considered not only as body weight-reducing preparations, but also as therapies for diseases coexisting with or caused by obesity. In the case of already registered drugs, we have strong clinical evidence of their benefits extending beyond body weight reduction itself. Data derived from the SELECT trial for semaglutide proved that concurrently with weight loss, there is a decrease in the risk of major adverse cardiovascular events by as much as 20% (Lincoff et al., 2023). Similar conclusions arise from the analysis of the SUMMIT trial, in which tirzepatide significantly lowered the risk of progression of heart failure with preserved ejection fraction (Packer et al., 2024). Following in the footsteps of these reports are research programmes for new, not yet registered molecules. The results of the phase 2 trials on survodutide indicate its enormous potential in reversing steatohepatitis (Sanyal et al., 2024). Large clinical trials also remain underway, such as the SYNCHRONIZE-CVOT trial which assesses the long-term cardiovascular safety of survodutide (Kosiborod et al., 2024). In turn, the definitive verification of the safety profile and long-term effectiveness of retatrutide is to be provided by the results of the TRIUMPH programme (Jastreboff et al., 2023).

The chronic nature of obesity

A key aspect of the pharmacotherapy of obesity is the issue of maintaining the reduced body weight in the event of continuing or interrupting treatment. This is confirmed by trials with a drug withdrawal phase. The STEP 4 trial assessed patients who, after a 20-week period of using semaglutide, achieved a mean body weight reduction of 10.6%. After this time, participants were randomly assigned to a group continuing therapy or a group that switched to placebo. During the subsequent 48 weeks of observation, in patients using placebo, a renewed increase in body weight by an average of 6.9% was noted, whereas in the group taking semaglutide, the weight loss deepened by a further 7.9% (Rubino et al., 2021). Convergent conclusions flow from the SURMOUNT-4 trial evaluating the use of tirzepatide. After a 36-week lead-in phase, patients achieved a mean body weight reduction at the level of 20.9%. Drug withdrawal and the switch to placebo resulted in the regain of as much as 14% of body weight over the next 52 weeks. In turn, in patients continuing pharmacotherapy with tirzepatide, body weight decreased by an additional 5.5%, which translated into a total loss of 25.3% from the beginning of the trial compared to merely 9.9% in the group that was switched to placebo after 36 weeks (Aronne et al., 2024).

The route of administration vs patient adherence - the potential of oral drugs and orforglipron

Clinical data from the STEP 4 and SURMOUNT-4 trials (Rubino et al., 2021; Aronne et al., 2024) highlight that obesity requires continuous treatment to prevent weight regain. Consequently, patient's adherence is a major factor in long-term therapeutic success. Despite the high efficacy of modern injectable incretin therapies, their subcutaneous route of administration is not always convenient for patients requiring lifelong therapy. Oral semaglutide was an important step forward in non-injectable treatment, but its peptide nature requires strict fasting and fluid limits after dosing (Kawai et al., 2020), which can be difficult for patients to incorporate into their daily routines.

Orforglipron offers new hope in overcoming these limitations. As a non-peptide small molecule, it provides a once-daily oral option that does not depend on food intake or strict water restrictions (Kawai et al., 2020; Wharton et al., 2023). The ATTAIN phase 3 trial showed that this formulation led to a clinically significant weight reduction of 11.2% at week 72, along with the improvement of cardiometabolic parameters, such as blood pressure and lipid profile (Wharton et al., 2025). Removing the need for injections and strict fasting rules could significantly enhance the acceptance of advanced obesity treatments in daily clinical practice. Better convenience generally translates to better adherence, which remains essential for sustaining weight loss and cardiovascular health in chronic obesity management.

Quality of weight loss and the prevention of sarcopenia - the role of bimagrumab

Weight loss achieved with advanced obesity pharmacotherapy reaches 15% to 25%, which is comparable to the effects of bariatric surgery (Jastreboff et al., 2022; Jastreboff et al., 2023)

Given such significant reductions, the quality of the lost body weight requires clinical attention. Although incretin therapies are highly effective in reducing overall body mass, they are associated with a concurrent decrease in lean tissue (Heymsfield et al., 2026b; Jastreboff et al., 2022). For instance, a phase 2 trial showed that semaglutide monotherapy resulted in a 4.7% to 6.9% reduction in lean body mass (Heymsfield et al., 2026b). As a result, such changes in body composition highlight the potential risk of sarcopenic obesity, which requires special consideration in elderly or frail individuals.

Bimagrumab regulates body weight through an entirely different pharmacological pathway. By targeting the ActRII receptor and blocking myostatin, it directly blocks the inhibitory signals that restrict muscle growth (Lach-Trifilieff et al., 2014). Clinical trials demonstrated the value of this mechanism: bimagrumab helped preserve or slightly increase lean body mass (+1.0% to +1.1%) while effectively reducing fat. Furthermore, combining bimagrumab with semaglutide led to a substantial total weight loss of up to 16.4%. Importantly, this combination successfully limited the muscle loss typically seen with incretin monotherapy, restricting the lean mass drop to merely 0.8%–2.3% (Heymsfield et al., 2026b). As obesity pharmacotherapy continues to advance, combining appetite-suppressing GLP-1 analogues with muscle-sparing agents may become an important clinical objective.

8. Conclusions

The clinical approach to obesity management has evolved significantly over recent years, marking a profound shift from low-efficacy treatments to advanced pharmacological therapies with results comparable to bariatric surgery. While non-pharmacological interventions, such as a healthy diet and physical activity, remain the foundation of therapy, modern medications act as pivotal tools that strongly support weight loss. Furthermore, the expanding range of available drugs allows for a highly personalised approach, enabling clinicians to adjust treatments to maximise individual patient benefits.

Despite the presence of highly effective pharmacological therapies on the market, modern medicine continues to search for new solutions in the treatment of obesity, which will be characterised by:

- Higher effectiveness, allowing for the achievement of an even greater reduction in total body weight in patients.
- A beneficial impact on the cardiovascular system and concurrent effectiveness in the treatment of diseases coexisting with or caused by obesity. Managing both obesity and its complications comprehensively with a single therapeutic agent represents a significant clinical advantage.
- A higher degree of adherence, thanks to the introduction of forms of administration more convenient for the patient (e.g., swapping injections for oral tablets).
- The ability to overcome key challenges brought about by the pharmacotherapy of obesity, which are the loss of lean body mass and sarcopenia. Shifting the focus towards qualitative weight loss, specifically targeting fat reduction while actively preserving lean tissue, is a remarkable advancement in modern pharmacotherapy.

While recent clinical trials indicate that many of these therapeutic barriers can now be successfully overcome, one fundamental obstacle remains. Due to the relapsing nature of the disease, the necessity for long-term, chronic therapy to prevent weight regain after treatment cessation continues to be a major challenge in contemporary obesity management.

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