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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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INCRETIN-BASED PHARMACOTHERAPY FOR OBESITY: A COMPARATIVE NARRATIVE REVIEW OF GLP-1, DUAL AND TRIPLE AGONISTS AND COMBINATION THERAPIES

Łukasz Krzystek *(Corresponding Author, Email: lukasz_krzystek@wp.pl)*
Pomeranian Medical University, Szczecin, Poland
ORCID ID: 0009-0001-1988-0402

Karolina Buć
Pomeranian Medical University, Szczecin, Poland
ORCID ID: 0009-0000-8491-7200

Paweł Buć
Pomeranian Medical University, Szczecin, Poland
ORCID ID: 0009-0001-1533-6610

Michał Mazurek
University Teaching Hospital named after F. Chopin, Rzeszów, Poland
ORCID ID: 0009-0005-7111-2397

Jagoda Józefczyk
Pomeranian Medical University, Szczecin, Poland
ORCID ID: 0009-0007-5235-2074

Konrad Zieliński
Pomeranian Medical University, Szczecin, Poland
ORCID ID: 0009-0005-3652-592X

Karolina Ganczar
University Teaching Hospital named after F. Chopin, Rzeszów, Poland
ORCID ID: 0009-0003-8152-8076

Stanisław Jurkowski
Pomeranian Medical University, Szczecin, Poland
ORCID ID: 0009-0005-9715-8385

Marianna Rudzińska
Pomeranian Medical University, Szczecin, Poland
ORCID ID: 0009-0002-9622-7439

Mikołaj Zalewski
Pomeranian Medical University, Szczecin, Poland
ORCID ID: 0009-0002-7803-6145

ABSTRACT

Background: Incretin-based pharmacotherapy has emerged as a central component in modern obesity management. Recent developments include ont only GLP-1 receptor agosnists byt albo dual GIP/GLP-1 agonists, triple multi-rceptor agnosits and combination regimens integrating complementary hormonal pathways.
Aim: The narrative review provides a comparative analysis of current incretin-based therapies for obesity, summarizing clinical evidence on their efficacy, safety and mechanisms of action.
Methods: A structured literature search was conducted using PubMed, Scopus and Web of Science. The review included randomized controlled trials, original research articles, meta-analyses and selected narrative reviews addressing GLP-1 receptor agonists, dual GIP/GLP-1 agonists, triple agonists and combination therapies. Case reports, small uncontrolled studies and non-peer-reviewed sources were excluded.
Results: GLP-1 receptor agonists, such as liraglutide and semaglutide, demonstrate consistent weight-reducing effects and metabolic benefits. Dual agonists, particularly tirzepatide, show enhanced efficacy, likely due to synergistic modulation of GIP and GLP-1 pathways. Triple receptor agonists, such as retatrutide, achieve the most pronounced reductions in body weight reported to date in pharmacotherapy. Combination therapy with semaglutide and cagrilintide provides clinically meaningful weight loss comparable to multi-receptor agonists. Across therapeutic classes, gastrointestinal adverse events remain the most common limitation.
Conclusions: Incretin-based therapies represent a rapidly evolving field, with multi-receptor agonists and combination approaches offering the strongest therapeutic potential. Long-term studies are required to evaluate durability of outcomes and to better define patient phenotypes best suited for specific treatment strategies.

KEYWORDS

Obesity, Incretin System, GLP-1 Receptor Agonists, Tirzepatide, Dual Agonists, Triple Agonists, Cagrilintide, Combination Therapy

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Introduction

Obesity is a chronic, multifactorial metabolic disease whose prevalence continues to rise and which represents one of the most significant global public health challenges of the modern era. According to the World Health Organization (WHO), the worldwide increase in overweight and obesity has been observed across virtually all regions, regardless of economic development level. This trend is evident not only among adults but also among children and adolescents, reflecting widespread and progressive disruptions in population- level energy balance. WHO defines obesity as a body mass index (BMI) of 30kg/m2 or higher, indicating excessive adipose tissue accumulation associated with increased health risk (World Health Organization, 2025). This epidemiological shift highlights the complex interplay of social, environmental, behavioural and biological factors contributing to the development of obesity.

Obesity is associated with a significantly increased risk of numerous metabolic and cardiovascular complications, including type 2 diabetes, hypertension, dyslipidaemia, atherosclerotic cardiovascular disease and non-alcoholic fatty liver disease (Sinha et al., 2023). It also adversely affects respiratory, musculoskeletal and reproductive health. The psychosocial consequences of obesity are equally important- infividuals living with obesity frequently experience stigma, reduced self-esteem, social marginalisation and depressive symptoms, all of which further impair quality of life and may hinder treatment adherence (Sinha et al., 2023).

Although lifestyle-based interventions such as dietary modification, increased physical activity and behavioural therapy remain the foundation of obesity treatment, maintaining long-term weight reduction is challenging for most patients. Physiological adaptations, including increased appetite, neurohormonal changes

and reduced energy expenditure following weight loss, contribute to weight regain (Htike et al., 2017). For many years, available pharmacotherapies offered only modest efficacy or were associated with safety concerns, underscoring the nned for more effective and safer therapeutic options (Davies et al., 2015; O'Neil et al., 2018; Pi-Sunyer et al., 2015; Wadden et al., 2013).

A major breakthrough in obesity treatment came with the introduction of incretin-based therapies. Gut-derived hormones such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) play essential roles in the regulation of glucose and energy homeostasis by enhancing glucose-dependent insulin secretion, suppressing glucagon release, slowing gastric emptying and modulating central appetite-regulating pathways (Knudsen & Lau, 2019; J. Lau et al., 2015; Montanya & Sesti, 2009). Advances in peptide engineering have enabled the development of stable, long-acting incretin analogues capable of harnessing these physiological mechanisms in the treatment of obesity and metabolic disease.

In recent years, incretin- based pharmacotherapy has evolved rapidly – from classic GLP-1 receptor agonists to multi- receptor agents targeting both GLP-1 and GIP receptors and further to novel triple agonists incorporating glucagon receptor activation (Jastreboff et al., 2023; Mu et al., 2024; Rubino et al., 2022; Sanyal et al., 2024). This multi- hormonal modulation allows for therapeutic effects that extend beyond those achievable with single-target-agents-affecting not only appetite regulation but also lipid metabolism, energy expenditure and liver function, thereby significantly expanding the potential scope of treatment.

The growing global burden of obesity, the limitations of traditional therapeutic approaches and the rapid development of modern incretin- based medications highlight the necessity of thoroughly evaluating their role in contemporary obesity management. Understanding their mechanisms of action, therapeutic potential and positioning within current treatment strategies is essential for optimising clinical care.

The aim of this review is to summarise current knowledge on incretin- based pharmacotherapy for obesity, with a particular focus on GLP-1 receptor agonists, dual GLP-1/GIP agonists, triple agonists and combination therapies, as well as to discuss their mechanisms of action and their significance within modern therapeutic frameworks.

Search Strategy

This review was conducted according to the principles of a narrative literature review, complemented by elements of a scoping approach. The literuature search was performed in the databases PubMed, Scopus and Web of Science. Additionally, documents published by international health organizations were considered, with particular attention to reports from the World Health Organization (World Health Organization, 2025).

The search strategy employed combinations of keywords and theirs synonyms including:

- obesity, overweight, metabolic disease,
- GLP-1 receptor agonist, liraglutide, semaglutide,
- GIP, dual agonist, tirzepatide,
- triple agonist, retatrutide,
- CagriSema, cagrilintide, amylin analogue,
- incretin therapy, multihormonal therapy, energy balance

Boolean operators (AND/OR) were used and filters were applied to restrict results to human studies and full-text articles available in English.

Inclusion criteria were as follows:

- original clinical studies investigating pharmacotherapy based on GLP-1 receptor agonists, dual GLP-1/GIP agonists, triple GLP-1/GIP/glucagon agonists and combination therapies involving amylin analogues,
- randomised clinical trials (RCTs), phase 2 and phase 3 studies, observational studies, and long-term follow-up analyses,
- review articles, meta- analyses and conceptual papers discussing incretin biology and mechanisms of action of incretin- based,
- publications on the epidemiology and pathophysiology of obesity, including current reports from the World Health Organization and relevant narrative reviews.

The exclusion criteria included:

- animal studies and preclinical models,
- conference abstracts without full text,
- publications in languages other than English,
- articles not relevant to obesity or incretin- based pharmacotherapy.

Given the objectives of this paper and the rapidly evolving landscape of metabolic pharmacotherapy, a narrative literature review approach was adopted, supplemented by elements of a scoping review. This allowed for:

- a broad discussion of the mechanisms of action of various incretin- based therapies,
- analysis of key clinical trials evaluating GLP-1 agonists, dual agonists, triple agonists and combination therapies,
- comparison of efficacy and safety across classes of incretin- based treatments,
- presentation of emerging therapeutic strategies in obesity management.

This review was not designed as a systematic review and no formal risk of bias assessment was performed. Priority was given to randomised trials, high-quality studies and the most recent publications relevant to current clinical practice.

GLP-1 Receptor Agonists

GLP-1 receptor agonists represent one of the key pharmacological classes currently used in the treatment of overweight and obesity. Their mechanism of action is based on the enhancement of the physiological effects of endogenous GLP-1, including modulation of postprandial glucose metabolism, glucose- dependent stimulation of insulin secretion, inhibition of glucagon release and interactions with central pathways regulating appetite (Knudsen & Lau, 2019; Montanya & Sesti, 2009). Contemporary GLP-1 analogues demonstrate increased resistance to enzymatic degradation by dipeptidyl peptidase-4 (DDP-4) and prolonged half-life, enabling once- daily or once- weekly dosing (Knudsen & Lau, 2019).

Studies evaluating the effects of GLP-1 receptor agonists have shown that these agents influence feeding behaviour by reducing appetite, increasing satiety and modifying the brain's response to food- related cues. These effects include decreased activity of orexigenic neuronal pathways and altered signaling within hypothalamic structure (Rubino et al., 2022). This contributes to a reduction in daily energy intake, which forms an important mechanism underlying weight loss observed during GLP-1 based therapy (Montanya & Sesti, 2009). In addition to their central effects, GLP-1 receptor agonists delay gastric empyting, which influences the rate of glucose absorption and plays a role in modulating the postrprandial metabolic response (J. Lau et al., 2015).

The efficacy of liraglutide in weight reduction and weight maintenance has been demonstrated in the SCALE Maintenance trial, which showed that, following an initial low-calorie diet-induced weight loss, continued treatment with liraglutide supported weight stabilization and facilitated additional weight reduction (Wadden et al., 2013). In paralel with changes in body weight, improvements in several parameters related to glucose metabolism were also observed, highlighting the broader metabolic benefits of liraglutide beyond weight control.

The introduction of long-acting agents, such as once-weekly semaglutide, enabled assessment of their efficacy in various populations with overweight and obesity. In a study including a broad population of individuals with obesity, semaglutide therapy resulted in substantial weight reduction and improvements in metabolic parameters (Jastreboff et al., 2023). Observed outcomes included changes in fasting and postprandial glucose, insulin resistance and appetite control, the latter associated with central nervous system activity (Rubino et al., 2022).

Additional studies have shown that GLP-1 receptor agonists exert beneficial effects on cardiometabolic risk markers, including reductions in body weight, improvements in glycaemic control and favourable changes in lipid parameters, findings also reflected in the STEP 7 trial (Mu et al., 2024). These mechanisms have been observed in both physiological models and clinical analyses involving individuals treated with GLP-1 receptor agonists. Pharmacological studies further demonstrated that activation of the GLP-1 receptor affect pancreatic and gastrointestinal function, as highlighted in pharmacodynamic characterizations of this drug class (Knudsen & Lau, 2019).

The safety profile of GLP-1 receptor agonists has beed evaluated extensively in clinical trials. The most frequently reported adverse events include gastrointestinal symptoms such as nausea, vomiting and diarrhea, which generally occur during the initial phase of therapy and tend to diminish with continued use (Jastreboff et al., 2023; Wadden et al., 2013). These adverse events correspond to the expected mechanism of action involving delayed gastriv emptying and gastrointestinal modulation (J. Lau et al., 2015). The risk of severe hypoglycemia has beed assessed as low, attributed to the glucose-dependent stimulation of insulin secretion characteristic of GLP-1 receptor activation (Knudsen & Lau, 2019). Long-term studies have also demonstrated good treatment tolerability and stable pharmacological effect during prolonged therapy (Jastreboff et al., 2023).

Tirzepatide (Dual GIP/GLP-1 Receptor Agonist)

Tirzepatide is a dual GIP/GLP-1 receptor agonist whose pharmacological action is based on the simultaneous activation of receptors for glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1. This mechanism includes glucose-dependent stimulation of insulin secretion, inhibition of postprandial glucagon release and effect on appetite regulation through modulation of gut-pancreas signaling and central pathways involved in the control of food intake (Knudsen & Lau, 2019; Montanya & Sesti, 2009). Tirzepatide has an extended half-life, allowing once-weekly administration and maintaining stable metabolic activity.

The efficacy of tirzepatide in the treatment of obesity was evaluated in the randomized SURMOUNT-1 trial, which assessed once-weekly doses of 5mg, 10mg and 15mg in individuals with overweight or obesity without type 2 diabetes (Jastreboff et al., 2022). Significant weight reduction was observed across all tirzepatide groups, with a dose-dependent effect. A decrease in daily energy intake was also reported, consistent with the drug's impact on satiety and appetite regulation.

In the analysis of metabolic parameters, improvements were observed in fasting glucose, postprandial glucose, and insulin resistance during tirzepatide treatment, reflecting its influence on postprandial hormonal responses involving modulation of GIP and GLP-1 signaling (Jastreboff et al., 2022). The study also described changes in blood pressure and lipid profile, including reductions in systolic and diastolic blood pressure and decreases in total cholesterol, LDL cholesterol and triglucerides, accompanied by an increase in HDL cholesterol during treatment (Jastreboff et al., 2022). These changes were observed throughout the 72-week treatment period.

The most commonly reported adverse events duting tirzepatide therapy were gastrointestinal symptoms such as nausea, vomiting and diarrhea, typically of mild to moderate intensity and occurring mainly during the dose-escalation phase (Jastreboff et al., 2022). Occasional cases of constipation, dyspepsia and decreased appetite were also noted. The risk of hypoglycemia in individuals without diabetes remained low, in line with the glucose-dependent pharmacological mechanism (Knudsen & Lau, 2019). The study confirmed good long-term tolerability of treatment and did not identify safety signals limiting the use of the drug in individuals without type 2 diabestes (Jastreboff et al., 2022).

Retatrutide (Triple Agonist)

Ratatrutide is a triple GLP-1/GIP/glucagon receptor agonist whose pharmacological activity involves simultaneous activation of metabolic pathways regulated by these three postprandial hormones. This mechanism includes modulation of glucose-dependent insulin secretion, regulation of glucagon levels, appetite control and effects on metabolic processes related to substrate utilization (Sanyal et al., 2024). The drug has an extended half-life, allowing once-weekly administration.

The efficacy of retatrutide was evaluated in a randomized, placebo-controlled phase 2 clinical trial that included individuals with obesity or overweight and assessed once-weekly doses ranging from 1mg to 12mg (Sanyal et al., 2024). During the 48-week treatment period, substantial weight reduction was observed across all retatrutide dose groups, with the greatest reductions documented at higher doses. Weight loss progressed throughout the full duration of therapy, and a significantly higher proportion of participants achived at least 15% and at least 20% weight reduction compared with placebo.

In the analysis of metabolic outcomes, improvements were observed in fasting glucose, postprandial glucose regulation and indices resistance (Sanyal et al., 2024). Favorable changes in lipid parameters were also reported, including reductions in total cholesterol, LDL cholesterol and triglycerides, accomapnied by increased in HDL cholesterol. A tendency toward reductions in both systolic and diastolic blood pressure was noted, and these changes were maintained throughout the 48-week treatment period.

The most commonly reported adverse events during retatrutide therapy were gastrointestinal symptoms, including nausea, vomiting, diarrhea and constipation, occurring primarily during the dose-escalation phase and typically presenting with mild to moderate intensity (Sanyal et al., 2024). Occasional events included increased appetite, dyspepsia and dizziness. Transient increases in heart rate were also noted in a subset of participants. The risk of hypoglycemia in individuals without diabetes remained low. Overall tolerability was favorable, with a low rate treatment discontinuation due to adverse events (Sanyal et al., 2024).

Cagrilintide and Cagrisema Combination Therapy

Cagrilintide is a long-acting amylin analogue with demonstrated effects on appetite suppression, delayed gastric emptying and modulation of postprandial metabolic signals involved in body-weight regulation. The efficacy and safety of cagrilintide monotherapy were evaluated in a phase 2 randomized trial conducted in individuals with overweight or obesity, assessing once-weekly doses ranging from 0,16mg to 4,5mg (D. C. W. Lau et al., 2021). During the 26-week treatment period, a progressive, dose-dependent reduction in body weight was observed, with the greatest decreases occurring in the higher-dose groups. The study also reported reductions in daily energy intake and improvements in metabolic parameters related to postprandial glucose regulation.

The efficacy of combination therapy with semaglutide and cagrilintide has been assessed in several randomized clinical trials. In a phase 2 study including individuals with type 2 diabetes, co-administration of cagrilintide and semaglutide resulted in a greater reduction in body weight compared with semaglutide monotherapy (Frias et al., 2023). Improvements in fasting glucose, measures of glycemic control and reductions in energy intake were also observed during treatment with the combination regimen. These metabolic changes were consistent with the appetite-modulating effects reported in the study population.

In the REDEFINE 1 trial, which evaluated adults with obesity without type 2 diabetes, combination therapy with cagrilintide and semaglutide produced substantial weight reductions over a 68-week treatment period (Garvey et al., 2025). A high proportion of participants achieved at least 15% and at least 20% weight loss, with progressive reductions observed throughout the entire study duration. Improvements in metabolic parameters were also reported, including reductions in systolic and diastolic blood pressure and improvements in lipid profile, such as decreases ion total cholesterol, LDL cholesterol and triglycerides, accomplanied by increases in HDL cholesterol.

In the REDEFINE 2 trial, conducted in adults with overweight or obesity and type 2 diabetes, once-weekly cagrilintide-semaglutide producted substantial and clinically meaningful reductions in body weight, together with improvements in glycaemic control and other cardiometabolic markers (Davies et al., 2025). These effects were maintained throughout the treatment period. The overall pattern of weight loss and metabolic responses was broadly consistent with findings from REDEFINE 1, although the magnitude of glycaemic improvements reflected the presence of type 2 diabetes in the study population.

The most commonly reported adverse events in trials evaluating cagrilintide monotherapy and combination therapy were gastrointestinal symptoms, including nausea, vomiting, diarrhea and constipation, typically of mild to moderate intensity and occurring mainly during the dose-escalation phase (Davies et al., 2025; Frias et al., 2023; Garvey et al., 2025; D. C. W. Lau et al., 2021). Occasional reports of dyspepsia, reduced appetite and transient increases in heart rate were noted. Overall, the combination therapy demonsrated good tolerability, with a low rate of treatment discontinuation due to adverse events.

Discussion

Findings from clinical trials included in this review indicate that various classes of incretin-based therapies differ substantially in the magnitude of weight reduction and the range of metabolic improvements achieved. Glucagon-like peptide-1 receptor agonists such as lir**a**glutide and semaglutide remain the foundation of contemporary pharmacotherapy for obesity, with their efficacy confirmed in large-scale clinical programs including SCALE trials for liraglutide and the STEP program for semaglutide (Knudsen & Lau, 2019; J. Lau et al., 2015; Montanya & Sesti, 2009; Rubino et al., 2022; Wadden et al., 2013).

The introduction of the dual GIP/GLP-1 receptor agonist tirzepatide represented a notable therapeutic advancement. In the SURMOUNT clinical program, tirzepatide produced large and clinically meaningful reductions in body weight and improvements in metabolic across multiple populations (Aronne et al., 2024; Garvey et al., 2023; Jastreboff et al., 2023). These findings highlight the potential contribution of GIP signalling to appetite regulation, energy homeostasis and metabolic control.

Triple-receptor agonists, such as retatrutide, have achieved the highest levels of weight reduction observed to date in pharmacological obesity treatment. In the phase 2 obesity trial, ratatrutide produced exceptionally large reductions in body weight, accompanied by improvements in cardiometabolic markers. Mechanistic analyses from this trial suggest that glucagon receptor activation may contribute to enhanced energy expenditure and increased reliance on lipid-derived fuels (Jastreboff et al., 2023).

Combination therapies have emerged as an alternative strategy to broaden hormonal modulation. The combination of semaglutide with the amylin analogue cagrilintide (CagriSema) has demonstrated substantial and clinically meaningful reductions in body weight across multiple clinical trials, with efficacy approaching

that observed for multi-receptor agonists. Evidence from phase 2 studies and subsequent phase 3 findings indicates that this dual-hormone approach targets complementary metabolic pathways, producing additive effects on appetite regulation, energy intake and body-weight reduction (Davies et al., 2025; Frias et al., 2023; Garvey et al., 2025; D. C. W. Lau et al., 2021).

Incretin-based therapies are associated with characteristic adverse effects, most commonly gastrointestinal symptoms such as nausea, vomiting and diarrhea. These reactions may impede titration to full therapeutic doses and contribute to treatment discontinuation, as reported in studies involving GLP-1 receptor agonists (Rubino et al., 2022; Wadden et al., 2013). Across clinical trials, including REDEFINE 2, gastrointestinal symptoms were the most frequently observed adverse events with cagrilintide-semaglutide, occurring predominantly during dose escalation and typically presenting with mild to moderate severity(Davies et al., 2025). A similar tolerability pattern has been documented for other multi-hormonal agents, including tirzepatide and ratatrutide, in which nausea, vomiting and diarrhoea were likewise the most common early-treatment adverse events (Jastreboff et al., 2022; Sanyal et al., 2024). Although generally transient and manageable, these effects highlight the importance of graduał dose titration and ongoing monitoring of gastrointestinal tolerability in clinical pracitce.

Another consideration is the small but measurable increase in heart rate observed in trials of several multi-receptor agonists. Increases in heart rate have been consistently reported for tirzepatide and retatrutide, although the clinical significance of this effect remains uncertain (Jastreboff et al., 2022; Sanyal et al., 2024). These changes are typically modest and transient, but they highlight the need for continued cardiovascular monitoring during treatment. Findings from clinical trials included in this review indicate that incretin-based therapies produce substantial weight loss and metabolic improvements. However, long-term data evaluating the durability of these effects remain limited. While the SCALE and STEP programmes have demonstrated sustained weight reduction during the treatment period, both trials highlight the need for extended follow-up to better understand weight trajectories after treatment discontinuation (Rubino et al., 2022; Wadden et al., 2013). These gaps underscore the importance of longer monitoring periods in future clinical studies.

Conclusions

Incretin-based therapies represent a major advancement in the pharmacological treatment of obesity, with efficacy increasing alongside broader hormonal modulation. Multi-receptor agonists and combination regimens demonstrate the greatest potentian for weight reduction while maintaininig and acceptable safety profile.

Key limitations include gastrointestinal adverse effects and the current lack of long-term data on durabilioty of treatment outcomes. Futeute research should focus on evaluating long-term effectiveness, identifying patient phenotypes that respond optimally to specify therapeutic classes and comparing monotherapy with combination approaches in more clinically diverse populations.

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