NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

BORKOWSKI, Konrad, LEJA, Wiktoria, BŁASZCZAK, Maciej, LATALSKA, Katarzyna, SZCZUPAJ, Maciej, JANUSZCZAK, Radosław, PASTUSZEK, Andżelika, RUDNICKI, Jakub, ZJAWIONY, Julia, and ZULFIQAR, Zeeshan. GLP-1 Receptor Agonists in the Treatment of Obesity: A Narrative Review of Current Therapeutic Methods. Quality in Sport. 2026;55:71099. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.55.71099

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 20.04.2026. Revised: 30.04.2026. Accepted: 4.05.2026. Published: 10.05.2026.

GLP-1 Receptor Agonists in the Treatment of Obesity: A Narrative Review of Current Therapeutic Methods

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Abstract

Introduction. Obesity is now considered to be one of the largest public health challenges of the twenty-first century, with over one billion adults affected. With conventional treatments such as lifestyle modifications and bariatric surgery being either ineffective or unavailable to the majority of obese individuals, there is an urgency for the development of safe and effective pharmacologic therapies. GLP-1 receptor agonists have developed into a unique and highly successful class of drugs that produce clinically relevant weight loss in addition to improving cardiovascular and metabolic risk factors.

Aim of the Study. This review aims to provide a practical and inclusive summary of GLP-1 receptor agonist therapy in obesity, focusing on mechanism of action, currently approved agents, clinical effectiveness, safety profiles and next generation therapeutic approaches.

Methodology. A literature search was conducted in PubMed/MEDLINE and ClinicalTrials.gov, covering publications from 2015 to March 2026. Randomized controlled trials, systematic reviews, meta-analyses, and expert consensus papers were prioritized.

Conclusions. The GLP-1 receptor agonists represent a paradigm shift in the treatment of obesity, achieving weight reductions of up to 21%. Both medications also appear to reduce cardiovascular disease risk in non-diabetic populations. While gastrointestinal side effects are the most commonly reported adverse reactions associated with these medications they can be effectively managed. As with all chronic diseases, once these medications are discontinued, patients will experience weight gain which emphasizes the importance of providing long term treatment options. Next-generation agents, including retatrutide and the cagrilintide-semaglutide combination, show even greater weight-reducing potential. Ensuring equitable

access, long-term safety monitoring, and individualized treatment approaches remain the key challenges for the field.
Keywords: glucagon-like peptide-1 receptor agonists, obesity, semaglutide, tirzepatide, liraglutide, weight loss

1. Introduction

Obesity is today viewed as a chronic condition caused by a complex combination of factors that tend to recur and negatively affect health and health systems at both the level of the individual and society. As defined by the World Health Organization, obesity is considered to be a leading non-communicable disease. Due to its increasingly rapid spread globally, obesity has become an urgent concern for scientists, policymakers and other stakeholders. According to data provided by the NCD Risk Factor Collaboration, the combined prevalence of being overweight or obese reached 50 percent in adults throughout the world by 2022; there are over 1 billion people who are currently classified as obese - more than double the number of people classified as obese in 1990 [1]. This trend is also concerning in terms of young people (children and adolescents) and underscores the inter-generational aspects of this public health crisis. This is an especially pressing concern due to the many adverse effects that are associated with obesity such as an increased risk of developing type 2 diabetes mellitus, cardiovascular disease, certain types of cancer, obstructive sleep apnea, non-alcoholic fatty liver disease, osteoarthritis, and a decreased life expectancy, all of which represent an enormous strain on patients and healthcare systems.

Lifestyle intervention treatments primarily consisting of diet modification, increased physical activity, and behavioral counseling have traditionally formed the foundation of managing obesity. However, although these interventions may be successful in achieving clinically meaningful weight loss for a relatively brief period, they generally fail to promote long-term sustained weight loss. A variety of biological responses occur when attempting to lose weight including decreases in resting metabolic rate, increases in hormones that stimulate hunger and changes in gut microbiota all contribute to create a physiological environment that promotes

weight gain after initial weight loss. Bariatric surgery represents the most effective method for treating severe obesity through promoting durable weight loss and significant improvements in metabolism, however, the invasiveness of bariatric surgery, the inherent risks associated with surgical procedures and the limited availability limits the ability to use this approach as a viable option for the vast majority of those suffering from obesity.

Historically, pharmacologic treatments designed specifically for the treatment of obesity have had limited efficacy and serious safety issues related to their use. Several products marketed for obesity treatment were removed from use prior to the advent of glucagon-like peptide-1 (GLP-1) based treatments. The introduction of GLP-1 receptor agonists as anti-obesity drugs has dramatically altered this paradigm [2]. Initially developed as glucose lowering agents for the treatment of type 2 diabetes mellitus, GLP-1 receptor agonists produced substantial and sustained reductions in body weight. Consequently, investigators began exploring their potential as anti-obesity drugs and eventually received regulatory approval as dedicated obesity treatments.

GLP-1 is an incretin hormone released from intestinal L-cells in response to ingestion of nutrients. Its influence extends to multiple organs including the pancreas, brain, gastrointestinal tract, cardiovascular system and thus affects appetite regulation, insulin secretion and energy homeostasis [3]. GLP-1 offers a wide range of targets for pharmacologic manipulation, making it an appealing drug development candidate since therapeutic manipulation of its receptor could potentially induce beneficial effects simultaneously on multiple metabolic pathways. The pharmacologic properties of GLP-1 receptor agonists allow them to mimic the endogenous effects of GLP-1 while providing longer duration of action than that of the native hormone.

Since the approval of liraglutide for obesity treatment in 2014, considerable progress has occurred in the evolution of therapeutics available for the treatment of obesity. For example, semaglutide was originally developed as a weekly subcutaneously administered injection for type 2 diabetes mellitus; however subsequent trials have demonstrated remarkable effectiveness in facilitating weight loss through achieving mean weight losses of around 15% in clinical trials [4]. More recent evidence supporting additional advancements include results obtained from studies using tirzepatide - a dual GIP/GLP-1 receptor agonist that has facilitated weight loss comparable to that observed with bariatric surgery [5]; these findings have initiated increasing debate regarding whether GLP-1-based treatments should be re-established as a standard-of-care for obesity [2]. Furthermore, an increasing number of new generation multi-receptor

agonists and combination therapies are under development that will likely expand opportunities for pharmacologic weight loss beyond what we have seen to date.

Despite the impressive advancements made in GLP-1 receptor agonist therapy for obesity, several critical questions still exist relative to long-term safety profiles, treatment sustainability upon discontinuation, equity of access to these agents, cost-effectiveness analyses, and optimal placement within overall obesity management algorithms. Therefore, this narrative review aims to provide readers with a broad and clinically relevant overview of current state of affairs related to GLP-1 receptor agonist therapy for obesity; topics included in this review include mechanisms of action, approved agents, clinical efficacy, safety profiles, emerging therapeutic options.

2. Methodology

This article is a narrative review of the current literature on GLP-1 receptor agonists in the pharmacological management of obesity. A literature search was conducted using PubMed/MEDLINE and ClinicalTrials.gov databases. The search covered publications from January 2015 to March 2026, with particular emphasis on studies published between 2020 and 2026, given the rapid evolution of evidence in this field.

The search strategy used a combination of Medical Subject Headings (MeSH) terms and free-text keywords, including: “GLP-1 receptor agonists,” “glucagon-like peptide-1,” “obesity,” “overweight,” “semaglutide,” “liraglutide,” “tirzepatide,” “retatrutide,” “cagrilintide,” “weight loss,” “weight management,” “anti-obesity medication,” “pharmacotherapy,” “cardiometabolic outcomes,” and “incretin-based therapy.” Boolean operators (AND, OR) were applied to combine search terms across different domains. The review prioritized phase 2 and phase 3 randomized controlled trials (RCTs), landmark cardiovascular outcome studies, and recent systematic reviews and meta-analyses as primary sources of evidence; narrative reviews and expert consensus papers were also included where they provided relevant clinical context. Original studies were included if they enrolled adult patients (≥18 years) with overweight or obesity, reported clinically relevant outcomes such as change in body weight, metabolic parameters, or adverse effects, and were published in peer-reviewed journals in English. Original observational studies without a comparator group, studies focused exclusively on pediatric populations, and reports lacking adequate methodological detail were excluded. Reference lists of included articles were hand-searched to identify additional relevant

publications not captured by the primary electronic search. The final selection of studies was guided by clinical relevance, methodological rigor, and the currency of the evidence.

3. Results

3.1. Mechanism of Action of GLP-1 Receptor Agonists in the Regulation of Body Weight

GLP-1 is a 30 amino acid incretin peptide produced by the L-cells predominantly found in the distal small intestine and colon as an end product of proglucagon. Circulating GLP-1 has a very short half-life in normal physiological conditions of about 1 – 2 minutes, primarily because it is quickly degraded by DPP-4. Therefore, GLP-1 receptor agonist drugs are designed to be resistant to this enzymatic degradation so that there can be prolonged receptor activity that will support therapy [6].

Depending upon how they are chemically structured, GLP-1 receptor agonists could potentially be injected once per day, one time each week, or even orally one time per day with future developing oral formulations.

There are multiple effects to GLP-1 receptor agonists that contribute to weight loss including both central and peripheral mechanisms [7]. Central to its actions within the CNS is the expression of GLP-1 receptors in critical hypothalamic nuclei involved in energy homeostasis such as the arcuate nucleus, the paraventricular nucleus and the nucleus tractus solitarius located in the brain stem [8]. Upon activating these receptors, GLP-1 stimulates satiation signaling and inhibits orexigenic drive. Also suppressed are neuropeptide Y and agouti-related protein production, two important promoters of food intake. The combined outcome results in smaller meals, fewer meals and less calories consumed overall while no voluntary dietary restrictions are required of the patient.

In addition to its actions at the level of the hypothalamus, GLP-1 receptor agonists modulate the mesolimbic dopaminergic pathway that controls reward-based consumption behaviors [8]. Through reducing the hedonic desire to consume calorie dense, but typically palatable foods; GLP-1 receptor agonists decrease food cravings and induce changes in eating patterns that differ significantly from those induced by typical appetite suppressant medications. It is possible that much of the significant weight loss observed in clinical trials with GLP-1 receptor agonists results from decreased craving for high fat and high sugar containing foods reported by subjects undergoing treatment.

Additionally, at the peripheral level, GLP-1 receptor agonists directly affect function within the GI tract. Specifically, GLP-1 receptor agonists slow down the rate of gastric emptying [6], thereby increasing feelings of postprandial satisfaction. Further, delayed gastric emptying decreases postprandial blood glucose levels and induces early cessation of meal intake. Vagal afferent neurons providing connection between the stomach and the brainstem, transmit sensation of satiety secondary to activation of GLP-1 receptors, providing additional centrally mediated reductions in food intake [7]. Thus, the concurrent action across gut-brain signaling pathways provides a distinguishing characteristic between GLP-1 receptor agonists and previously used appetite suppressants that were mostly limited to a single mechanism of action.

Finally, GLP-1 receptor agonists produce some degree of alteration in energy expenditure. Although clearly secondary to the alterations in appetite that lead to reduced caloric intake, preclinical data suggest that activation of brown adipose tissue thermogenesis and alterations in hepatic lipid metabolism contribute to improvements in metabolic efficiency [6]. Furthermore, GLP-1 receptors have been identified in cardiac muscle cells, vascular cells and renal cells suggesting that many of the pleiotropic effects of these agents go well beyond established metabolic pathways. Ultimately, all of these mechanisms contribute to long-term negative energy balance, leading to progressive weight reduction over time.

3.2. Approved GLP-1 Receptor Agonists for Obesity Treatment: Liraglutide, Semaglutide, and Tirzepatide

At present, there are three agents approved by regulatory authorities in major markets for the treatment of obesity in adult populations. These include liraglutide, semaglutide, and tirzepatide. Each drug has a common basis through GLP-1 receptor activation; however, they demonstrate considerable differences in terms of molecular structure, receptor selectivity, dosing frequency, and clinical efficacy. Thus, the sequential evolution of these drugs illustrates the overall progression of incretin-based pharmacotherapy, where each successive generation builds upon the shortcomings of the previous generation.

Liraglutide is a long chain fatty acid-acylated GLP-1 analogue delivered as a subcutaneous injection on a once per day regimen. Approval for use in obesity management was based on the results of the SCALE Obesity & Prediabetes trial (Pi-Sunyer et al., 2015) - a randomized phase III trial evaluating over 3700 adults who had either overweight or obese BMI without type 2 diabetes [9]. Participants treated with 3mg liraglutide resulted in a median weight loss of about 8.4 % of initial weight after 56 weeks relative to 2.8 % in subjects treated with a placebo. A

statistically greater number of subjects treated with liraglutide achieved at least a 5% weight reduction, along with beneficial changes in blood pressure, glycemic markers, and lipid profiles [9]. Despite its proven efficacy, the need to administer it daily and the lower degree of weight loss when compared to later agents position liraglutide as a first-generation agent within this therapeutic class.

Semaglutide is a GLP-1 analogue that is structurally 94% similar to native GLP-1 and has been chemically altered to facilitate once-weekly subcutaneous delivery and longer duration of receptor binding. The pivotal phase III STEP 1 (Wilding et al., 2021) trial examined the safety and efficacy of weekly subcutaneous delivery of semaglutide to adults with a BMI $\geq$30 kg/m^2 or $\geq$27 kg/m^2 and at least one weight related comorbidity [10]. Following 68 weeks of treatment with semaglutide, subjects exhibited a mean weight loss of 14.9%, whereas subjects treated with a placebo exhibited a mean weight loss of 2.4%. More than one third of subjects treated with semaglutide lost at least 20% of their initial weight. The STEP 3 (Wadden et al., 2021) trial showed that delivering semaglutide concomitantly with intensive behavioral therapy generated even greater outcomes, with a mean weight loss of 16.0% [11]. Subjects exhibited improvements in waist circumference, blood pressure and quality of life assessments. Collectively, these data provide evidence that semaglutide constitutes a major advancement in the field of pharmacologic obesity treatments.

Tirzepatide is a qualitative leap forward in this therapeutic class. Tirzepatide is a dual GIP (glucose-dependent insulinotropic peptide) and GLP-1 receptor agonist administered by subcutaneous injection on a weekly basis. Through simultaneous stimulation of two complementary incretin receptors, tirzepatide creates synergy among appetite-suppressant activity, insulin secretion and energy homeostasis. The SURMOUNT-1 (Jastreboff et al., 2022) trial investigated the safety and efficacy of weekly subcutaneous delivery of tirzepatide at doses of 5, 10 and 15 mg to adults with obesity or being overweight [12]. Mean weight losses after 72 weeks were found to be 15.0%, 19.5% and 20.9% at doses of 5 mg, 10 mg and 15 mg respectively. Approximately 57% of subjects in the highest dose group achieved at least 20% weight loss – outcomes previously considered to be achievable solely through surgical intervention. Further, fasting glucose, HbA1c, blood pressure and triglyceride values were reduced by substantial amounts in all dosage groups. Importantly, these weight loss benefits were achieved while providing subjects with behavioral counseling, thereby highlighting the pharmaceutical potency of tirzepatide [12].

3.3. Clinical Efficacy: Weight Reduction, Metabolic and Cardiometabolic Outcomes

The clinical effectiveness of GLP-1 receptor agonist drugs extend far beyond mere weight loss. They show real-world improvements in all areas of metabolic and cardio-metabolic risks, which represent the most critical consequences of obesity.

One of the first large scale trials demonstrating the cardiovascular effectiveness of these medications was the SELECT (Lincoff et al., 2023) trial, a randomized, placebo controlled trial examining the safety and efficacy of weekly doses of 2.4mg semaglutide in approximately 17,600 adults who were obese/overweight and had established cardiovascular disease but no type 2 diabetes [13]. In a follow-up after approximately 34 months, participants receiving semaglutide experienced a 20% relative risk decrease in major adverse cardiovascular events (MACE) which included non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality. This was the first trial to demonstrate cardiovascular risk reduction with an anti-obesity medication in a non-diabetic population, establishing semaglutide as a cardioprotective agent beyond its weight-lowering effects [13]. In addition, it appears that the cardiovascular protection provided by semaglutide exceeded the protection expected solely from weight loss itself; thereby indicating possible direct vascular and anti-inflammatory effects resulting from the stimulation of GLP-1 receptors.

Long term data from the SURMOUNT-1 (Jastreboff et al., 2025) extension trial showed similar metabolic benefits of tirzepatide. Individuals who completed the longer term follow up period maintained significant weight loss while experiencing decreases in waist circumference, HbA1c, fasting plasma glucose, systolic blood pressure and triglycerides levels [14]. Additionally, a notable result was that the incidence of developing type 2 diabetes among those with prediabetes at baseline was dramatically reduced in the group receiving tirzepatide. This may indicate a "disease modifying" effect for tirzepatide independent of glucose lowering. This finding is important because prediabetes is common in obese populations.

Additional information regarding comparative efficacy between different GLP-1 receptor agonists has recently become available. For example, the STEP 8 (Rubino et al., 2022) trial evaluated the efficacy of once weekly semaglutide 2.4mg versus daily liraglutide 3.0mg for 68 weeks in adults who were obese/overweight without type 2 diabetes [15]. At the conclusion of this study, semaglutide produced significantly more mean weight loss (15.8% vs 6.4%), along with greater improvements in each cardiometabolic risk factor evaluated. Therefore, semaglutide is now considered superior to liraglutide for use in weight management in almost

every clinical setting due to its greater efficacy and the added convenience of once-weekly administration.

Emerging therapies with existing clinical trial data include the combination therapy CagriSema (a combination of cagrilintide and semaglutide). The REDEFINE 2 (Davies et al., 2025) trial assessed the efficacy of CagriSema in adults who were obese/overweight and had type 2 diabetes [16]. This combination produced clinically relevant improvements in body weight and glycemic control. Overall, the findings support the potential utility of dual action hormone replacement strategies in managing complex metabolic diseases [16]. The ability to simultaneously reduce both obesity and diabetes with a single agent may offer an attractive solution to the high percentage of patients diagnosed with both conditions.

Overall, there is substantial evidence that GLP-1 receptor agonists - especially their new and stronger versions - provide better body weight loss, improved glycemic control, lipid changes, blood pressure changes and cardiovascular outcomes than any other pharmaceutical agent previously approved for the treatment of obesity.

3.4. Safety Profile, Adverse Effects, and Patient Tolerability

GLP-1 receptor agonists generally are very well tolerated; however, they do have a unique side-effect profile that providers need to understand so that patients can achieve optimal outcomes and avoid premature discontinuation of a highly effective long-term therapy. Early adverse effects - if not recognized or managed by the provider - are one of the main reasons why patients discontinue what otherwise could be an extremely successful long-term therapy.

The most commonly occurring side effects in patients taking a GLP-1 receptor agonist include gastrointestinal adverse effects. Many patients report experiencing nausea, vomiting, diarrhea and constipation, especially during the dose escalation phase [17]. The majority of gastrointestinal adverse effects associated with GLP-1 receptor agonists are usually dose-related, transient, and mild-to-moderate in severity. Most gastrointestinal side effects are experienced by patients during the initial few weeks of treatment or after each dose increase. Gradually increasing the dose, which is now a standard part of the prescribed regimen for all approved agents, has dramatically reduced both the frequency and intensity of these adverse effects. Clinical recommendations suggest reducing the dose temporarily, consuming the medication with food, eating small, more frequent meals, avoiding fatty and fiber-rich foods, and maintaining adequate fluid intake to help alleviate gastrointestinal adverse effects and

manage gastrointestinal intolerance in clinical settings [18]. In most patients, these symptoms resolve within weeks without the need for discontinuation of the therapy.

Beyond gastrointestinal symptoms, several other adverse effects warrant attention. Rare cases of acute pancreatitis have been reported with GLP-1 receptor agonist use, and these agents are generally contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, based on preclinical evidence of thyroid C-cell stimulation in rodent models [19]. However, observational data in humans have not confirmed a significantly elevated risk of thyroid malignancy to date. Cholelithiasis and cholecystitis have been reported at higher rates in patients receiving these medications, likely related to the rapid weight loss they induce rather than a direct drug effect [19]. Hypoglycemia is not a primary concern when these agents are used as monotherapy in non-diabetic patients, given their glucose-dependent mechanism of insulin secretion stimulation.

Injection site reactions are relatively uncommon and rarely clinically significant. Rare reports of gastroparesis and severe gastrointestinal events, including ileus and bowel obstruction, have emerged from real-world pharmacovigilance data, necessitating ongoing observation [19]. Patients with pre-existing gastroparesis or significant gastrointestinal dysmotility should be assessed carefully before initiating therapy, as the gastric-emptying-delaying effects of these agents may elevate underlying conditions.

A clinically important consideration is the phenomenon of weight regain following treatment discontinuation. A systematic review and meta-analysis examining outcomes after cessation of GLP-1 receptor agonist therapy found that patients regained a substantial proportion of lost weight within months of stopping treatment, with near-complete weight recovery in some over longer follow-up [20]. This observation reinforces the concept of obesity as a chronic disease requiring sustained pharmacological intervention, analogous to the need for continuous antihypertensive or lipid-lowering therapy. It also underscores the importance of developing strategies to support long-term treatment adherence, including patient education on the chronic nature of the disease, affordable access to medication, and the possible use of lower maintenance doses to balance efficacy with tolerability.

3.5. Emerging Therapies and Future Directions: Next-Generation Agonists and Combination Approaches

The phenomenal success of semaglutide and tirzepatide has initiated a historic expansion of anti-obesity drug development pipeline. Many new drugs and combinations of drugs are now in the investigative phases of clinical studies. These new drugs represent a greater acknowledgment by the medical community that obesity should receive similar levels of pharmacologic innovation that has improved the treatment options for many chronic conditions like type 2 diabetes and heart failure.

Retatrutide is a triple hormone receptor agonist that acts on GLP-1, GIP and glucagon receptors. Glucagon receptor agonism will provide additional avenues for increasing energy expenditure through increased hepatic fatty acid oxidation and brown fat activation. Retatrutide produced dose dependent weight losses up to 24.2% of baseline body weight in a phase 2 randomized controlled trial study using the highest dose for 48 weeks. The results demonstrate the greatest amount of pharmacologically induced weight loss ever reported in a clinical study [21]. Nausea and vomiting were identified as the most common side effects with tolerability being generally consistent with that of the GLP-1 receptor agonist class. Additionally, a systematic review and meta-analysis of available phase 2 data confirm a positive efficacy and safety profile for retatrutide; providing strong support for advancing retatrutide to Phase 3 trials [22].

Combining cagrilintide, a long-acting amylin analogue, with semaglutide, provides another highly promising strategy. The combination of these two agents was assessed in the REDEFINE 1 (Garvey et al., 2025) trial conducted in overweight or obese adults without diabetes. Weight losses of approximately 22.7% were achieved at 68 weeks using CagriSema, which exceeded the weight losses achieved when either agent was administered alone [23]. Each component of this combination exerts unique mechanisms of action; semaglutide reduces appetite by activating GLP-1 receptors whereas cagrilintide activates amylin receptors located in the area postrema and hypothalamus to produce prolonged postprandial satiety, slow gastric emptying, reduce glucagon release and extend the duration of these responses [23]. The additive effect of combining these two neuroendocrine pathways demonstrates how complementary pathways can be combined to achieve meaningful enhancements in weight loss relative to what can be achieved by administering a single agent.

A large number of potential novel therapeutic targets are also being investigated. Examples include GLP-1/glucagon dual agonists, peptide YY analogs, FGF21 receptor agonists, and oral

forms of current GLP-1 receptor agonists [24]. Of particular note among non-peptide small molecule oral GLP-1 receptor agonists is their ability to greatly enhance access and patient compliance relative to injectable formulations. Enhanced compliance will allow for greater inclusion of certain demographics previously unable to access GLP-1 receptor agonists. While early-stage clinical trial data suggest promise for several of these compounds, longer term efficacy and safety have yet to be determined [24].

An important concept behind the design of next generation agents is the idea that obesity is influenced by a variety of hormones involved in the control of energy balance. Therefore, it is likely that future pharmacotherapies will involve combinations of agents that target each patient's unique metabolic phenotypes, comorbidities and treatment goals [24]. Pharmacogenomics, metabolomics and digital health tools may also become incorporated into obesity treatment so that patients with a high likelihood of responding to specific therapies can be identified.

4. Discussion

The emergence and rapid development of GLP-1 receptor agonist therapies presents a major shift in the field of obesity medicine over the last few decades. The drugs' multi-faceted mechanism of action, clinically relevant efficacy, and favorable safety profile have changed the landscape of a disease that has traditionally had very limited options for pharmacologic treatment. These treatments do not stop with weight loss; they also improve cardiovascular risk factors, glucose metabolism, and overall metabolic function. They are therefore truly disease modifying agents for what we refer to broadly as the cardiometabolic syndrome.

The progression from liraglutide to semaglutide and tirzepatide demonstrates a pattern of increasing efficacy in which each new agent provides greater weight loss than the previous agent, ultimately approaching the levels seen after bariatric surgery [5]. The dramatic improvement in efficacy achieved by the newer agents is prompting a reevaluation of how obesity should be classified and treated, including increased recognition that obesity should be viewed as a chronic relapsing medical illness requiring long term pharmacologic treatment [2]. The analogy to other chronic diseases - where pharmacotherapy is accepted as an indefinite intervention - is increasingly applied to obesity, and GLP-1 receptor agonists are at the forefront of this conceptual transformation.

The demonstration of reduced cardiovascular risk using semaglutide in the SELECT (Lincoff et al., 2023) trial has both important clinical and public health implications [13]. It is the first anti-obesity drug to show a reduction in major adverse cardiac events in a non-diabetic population. The findings from the trial extend the therapeutic rationale for use of GLP-1 receptor agonists beyond just managing obesity and into secondary cardiovascular prevention and are expected to significantly affect current practice, guideline recommendations, insurance coverage, and prescribing patterns among practicing cardiologists and endocrinologists caring for obese patients with related cardiovascular co-morbidity.

Although there have been numerous breakthroughs in obesity treatment, several limitations exist. Long term effectiveness of treatments has yet to be determined. In fact, available research demonstrates rapid regain of weight upon cessation of therapy; thus it appears possible that long term (potentially life-long) treatment is required to realize sustained benefits from obesity drugs [20]. These considerations create significant issues regarding cost and availability of these medications. As the cost of these medications is currently very high, many patients cannot afford the medication even if it was covered by insurance [25]. Thus, in addition to additional pharmaceutical developments, resolving systemic barriers (e.g., through regulatory actions, generic competition, etc.) will be similarly important.

As noted above, adherence and tolerance present challenges in real world settings. While gastrointestinal side effects typically can be managed by slowly increasing doses, this remains the most common reason for early termination of therapy in clinical practice [17]. Patient education on the structured approach to manage gastrointestinal side effects; follow-up visits during the initial dose titration period; and individualization of the therapeutic strategy are all crucial factors for success in treating obese individuals using GLP-1 receptor agonists [18]. Providing patients with proactive communication about the timing and methods for managing gastrointestinal side effects will likely help avoid premature discontinuation of therapy.

Newer generation agents (retatrutide, CagriSema, oral GLP-1 receptor agonists, etc.) being developed promise both increased efficacy and greater accessibility of pharmacologic obesity treatment options [26]. Pharmacologically induced weight loss of 25-30% could potentially place pharmacology in direct competition with bariatric surgery for obese patients who do not wish to or are incapable of undergoing bariatric surgery. However, it will be imperative that as development of new pharmacologic obesity treatment accelerates, similar vigilance will need to occur with respect to conducting long term safety surveillance.

It is unlikely that a sustainable model for obesity care will be created solely based on pharmacologic innovations. Rather, structural models designed to address food environment issues; physical activity infrastructure needs; social economic determinants of health; and educational requirements for healthcare providers are necessary complementary tools to pharmacologic treatment [27]. Additionally, as the number of pharmacologic options increases, it will be critical to provide robust long-term safety data for cardiovascular disease; cancer; kidney function; and musculoskeletal health so that informed decision-making regarding appropriate patient selection and risk assessment can take place [28]. Registries and studies utilizing real-world evidence will be vital for developing the needed data.

During the next few years, it is expected that combination pharmacotherapies targeting multiple receptor pathways will become the standard of care for obesity, much like combination drug regimens have become the norm for treating hypertension, hyperlipidemia, and type 2 diabetes [28]. The major hurdle will be translating these advances into equitable access and substantial health improvement across diverse patient populations [27].

5. Conclusions

The introduction of GLP-1 receptor agonists has significantly improved how clinicians treat obesity through the delivery of substantial and long-lasting reductions in body weight, as well as by improving both metabolic and cardiometabolic risk factors. Semaglutide’s demonstration of an improvement in cardiovascular risk within a non-diabetic population, and Tirzepatide's achievement of weight loss comparable to bariatric surgery, indicate that there is considerable additional therapeutic benefit available with this class of drugs. Furthermore, the developing pipeline of next generation agents, especially retatrutide and cagrilintide-semaglutide combination products, indicates that the full potential of this drug class has yet to be realized.

To move pharmacologic innovations toward betterment of the population level burden of obesity, it will be necessary to address issues associated with duration of therapy; weight regain after discontinuing therapy; tolerance of gastrointestinal side effects; costs; and equity of access. Safety over the long term, particularly derived from real world experience and post-marketing surveillance, will be critical to ensure that such therapies can be safely integrated into general clinical practices. Decisions regarding which type of GLP-1 receptor agonist to prescribe, at what dose, and which co-morbidities to manage on an individual basis will determine the optimal use of these therapies.

Additionally, continued advancements in our understanding of neuroendocrine regulation of energy balance may lead to further developments in personalizing treatments using multiple target pharmacologic strategies to achieve long lasting obesity remission in a greater number of individuals across a broader and more diverse patient population. GLP-1 receptor agonists are already foundational to the treatment of obesity; they are expected to become even more so in the future. The greatest challenge facing the field moving forward is ensuring that the benefits associated with GLP-1 receptor agonists are equitably available to all patients regardless of social economic status or geographic location.

Disclosure

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All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgements: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet*. 2024;403(10431):1027-1050. https://doi.org/10.1016/S0140-6736(23)02750-2

2. Kaplan JM, Zaman A, Abushamat LA. Curbing the Obesity Epidemic: Should GLP-1 Receptor Agonists Be the Standard of Care for Obesity?. *Curr Cardiol Rep*. 2024;26(9):1011-1019. https://doi.org/10.1007/s11886-024-02097-4

3. Zheng Z, Zong Y, Ma Y, et al. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Signal Transduct Target Ther*. 2024;9(1):234. Published 2024 Sep 18. https://doi.org/10.1038/s41392-024-01931-z

4. Popoviciu MS, Păduraru L, Yahya G, Metwally K, Cavalu S. Emerging Role of GLP-1 Agonists in Obesity: A Comprehensive Review of Randomised Controlled Trials. *Int J Mol Sci*. 2023;24(13):10449. Published 2023 Jun 21. https://doi.org/10.3390/ijms241310449

5. Alfaris N, Waldrop S, Johnson V, Boaventura B, Kendrick K, Stanford FC. GLP-1 single, dual, and triple receptor agonists for treating type 2 diabetes and obesity: a narrative review. *EClinicalMedicine*. 2024;75:102782. Published 2024 Aug 30. https://doi.org/10.1016/j.eclinm.2024.102782

6. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. *Mol Metab*. 2022;57:101351. https://doi.org/10.1016/j.molmet.2021.101351

7. Moiz A, Filion KB, Tsoukas MA, Yu OH, Peters TM, Eisenberg MJ. Mechanisms of GLP-1 Receptor Agonist-Induced Weight Loss: A Review of Central and Peripheral Pathways in Appetite and Energy Regulation. *Am J Med*. 2025;138(6):934-940. https://doi.org/10.1016/j.amjmed.2025.01.021

8. Jones LA, Brierley DI. GLP-1 and the Neurobiology of Eating Control: Recent Advances. *Endocrinology*. 2025;166(2):bqae167. https://doi.org/10.1210/endocr/bqae167

9. Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med*. 2015;373(1):11-22. https://doi.org/10.1056/NEJMoa1411892

10. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021;384(11):989-1002. https://doi.org/10.1056/NEJMoa2032183

11. Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. *JAMA*. 2021;325(14):1403-1413. https://doi.org/10.1001/jama.2021.1831

12. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022;387(3):205-216. https://doi.org/10.1056/NEJMoa2206038

13. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *N Engl J Med*. 2023;389(24):2221-2232. https://doi.org/10.1056/NEJMoa2307563

14. Jastreboff AM, le Roux CW, Stefanski A, et al. Tirzepatide for Obesity Treatment and Diabetes Prevention. *N Engl J Med*. 2025;392(10):958-971. https://doi.org/10.1056/NEJMoa2410819

15. Rubino DM, Greenway FL, Khalid U, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. *JAMA*. 2022;327(2):138-150. https://doi.org/10.1001/jama.2021.23619

16. Davies MJ, Bajaj HS, Broholm C, et al. Cagrilintide-Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes. *N Engl J Med*. 2025;393(7):648-659. https://doi.org/10.1056/NEJMoa2502082

17. Wharton S, Davies M, Dicker D, et al. Managing the gastrointestinal side effects of GLP-1 receptor agonists in obesity: recommendations for clinical practice. *Postgrad Med*. 2022;134(1):14-19. https://doi.org/10.1080/00325481.2021.2002616

18. Gorgojo-Martínez JJ, Mezquita-Raya P, Carretero-Gómez J, et al. Clinical Recommendations to Manage Gastrointestinal Adverse Events in Patients Treated with Glp-1 Receptor Agonists: A Multidisciplinary Expert Consensus. *J Clin Med*. 2022;12(1):145. Published 2022 Dec 24. https://doi.org/10.3390/jcm12010145

19. Jalleh RJ, Talley NJ, Horowitz M, Nauck MA. The science of safety: adverse effects of GLP-1 receptor agonists as glucose-lowering and obesity medications. *J Clin Invest*. 2026;136(4):e194740. Published 2026 Feb 16. https://doi.org/10.1172/JCI194740

20. Berg S, Stickle H, Rose SJ, Nemec EC. Discontinuing glucagon-like peptide-1 receptor agonists and body habitus: A systematic review and meta-analysis. *Obes Rev*. 2025;26(8):e13929. https://doi.org/10.1111/obr.13929

21. Jastreboff AM, Kaplan LM, Frías JP, et al. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. *N Engl J Med*. 2023;389(6):514-526. https://doi.org/10.1056/NEJMoa2301972

22. Abdrabou Abouelmagd A, Abdelrehim AM, Bashir MN, et al. Efficacy and safety of retatrutide, a novel GLP-1, GIP, and glucagon receptor agonist for obesity treatment: a systematic review and meta-analysis of randomized controlled trials. *Proc (Bayl Univ Med Cent)*. 2025;38(3):291-303. Published 2025 Feb 5. https://doi.org/10.1080/08998280.2025.2456441

23. Garvey WT, Blüher M, Osorto Contreras CK, et al. Coadministered Cagrilintide and Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2025;393(7):635-647. https://doi.org/10.1056/NEJMoa2502081

24. Melson E, Ashraf U, Papamargaritis D, Davies MJ. What is the pipeline for future medications for obesity?. *Int J Obes (Lond)*. 2025;49(3):433-451. https://doi.org/10.1038/s41366-024-01473-y

25. Moiz A, Filion KB, Tsoukas MA, Yu OHY, Peters TM, Eisenberg MJ. The expanding role of GLP-1 receptor agonists: a narrative review of current evidence and future directions. *EClinicalMedicine*. 2025;86:103363. Published 2025 Jul 17. https://doi.org/10.1016/j.eclinm.2025.103363

26. Fredrick TW, Camilleri M, Acosta A. Pharmacotherapy for Obesity: Recent Updates. *Clin Pharmacol*. 2025;17:305-327. Published 2025 Sep 19. https://doi.org/10.2147/CPAA.S497904

27. Manne-Goehler J, Teufel F, Venter WDF. GLP-1 Receptor Agonists and the Path to Sustainable Obesity Care. *JAMA Intern Med*. 2025;185(1):8-10. https://doi.org/10.1001/jamainternmed.2024.3579

28. Park C, Kim Y, Raygani S, Grunvald E. A glimpse into the pipeline of anti-obesity medication development: combining multiple receptor pathways. *Front Endocrinol (Lausanne)*. 2025;16:1630199. Published 2025 Sep 11. https://doi.org/10.3389/fendo.2025.1630199