OPTIONS AND LIMITATIONS OF OBESITY TREATMENT WITH GLP-1 RECEPTOR AGONISTS

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Introduction *Obesity constitutes a chronic, relapsing disease characterized by a complex pathophysiology and significant cardiometabolic consequences. Despite sustained emphasis on lifestyle interventions, long-term weight reduction remains inadequate in the majority of patients. Advances in the understanding of the incretin system have led to an expansion of therapeutic options to include glucagon-like peptide-1 (GLP-1) receptor agonists, which exert their effects through both central and peripheral mechanisms regulating energy homeostasis.*

Objective *The aim of this article is to provide a systematic evaluation of the mechanisms of action, clinical efficacy, safety profile, and limitations associated with the use of GLP-1 receptor agonists in the treatment of obesity, within the context of current therapeutic guidelines.*

Methods *This study is designed as a narrative review of the literature, with a focus on randomized controlled trials, meta-analyses, and recommendations issued by professional societies over the past decade.*

Results *GLP-1 receptor agonists have been shown to induce statistically significant reductions in body weight compared with placebo, with mean weight loss ranging from approximately 8% to 15%, depending on the specific agent and dosing regimen. In addition to weight reduction, the treatment is associated with improvements in the glycemic control, lipid parameters, and blood pressure. Certain agents have also demonstrated favourable effects on the cardiovascular outcomes. However, the therapy is commonly associated with gastrointestinal adverse events. Key limitations include limited economic accessibility, the necessity for long-term administration, and a propensity for weight regain following the treatment discontinuation.*

Conclusion *GLP-1 receptor agonists represent a significant advancement in the pharmacological management of obesity and reflect the contemporary understanding of obesity as a biologically mediated chronic disease. Notwithstanding their demonstrated efficacy, their use necessitates careful, individualized assessment of the benefit–risk profile and should be integrated into a comprehensive, long-term management strategy.*

Key words: obesity, GLP-1 receptor agonists, pharmacotherapy, incretins, weight reduction, cardiometabolic risk

Introduction

Obesity represents one of the most significant challenges in contemporary public health due to its increasing prevalence, chronic nature, and strong association with increased morbidity and mortality. According to the data from the World Health Organization (WHO), the global prevalence of obesity has more than tripled since 1975 and currently affects over 650 million adults worldwide [40]. In the European region, obesity is among the most important risk factors for non-communicable diseases, with its prevalence in the adult population exceeding 20% in many countries and demonstrating a steadily increasing trend [42]. Epidemiological studies further indicate that obesity significantly increases the risk of developing type 2 diabetes mellitus, cardiovascular diseases, non-alcoholic steatosis of the liver, certain malignancies, and premature mortality [39].

At present, obesity is unequivocally defined as a chronic, relapsing disease with a complex etiopathogenesis that requires a long-term therapeutic approach. This concept is supported by the professional organizations, including the European Association for the Study of Obesity (EASO) and the American Association of Clinical Endocrinology (AACE), which emphasize the biological basis of the disease and the need for its systematic treatment [11]. Obesity is not merely a consequence of excessive caloric intake but rather the result of complex dysregulation of neuroendocrine mechanisms governing energy balance, involving both central and peripheral control of appetite, satiety, and energy expenditure [13].

The regulation of energy homeostasis is mediated by a complex interplay between the central nervous system, particularly the hypothalamus, and peripheral signals originating from the gastrointestinal tract, pancreas, and adipose tissue. The key regulatory hormones include leptin, insulin, ghrelin, and incretin hormones, including glucagon-like peptide-1 (GLP-1), which modulate hunger, satiety, and metabolic processes [22]. In obesity, these regulatory mechanisms become disrupted, including the development of leptin and insulin resistance, chronic low-grade inflammation, and alterations in neuronal circuits regulating food intake, thereby promoting the persistence of increased body weight [24, 10].

Lifestyle interventions, including caloric restriction, increased physical activity, and behavioural modification, remain the cornerstone of the obesity treatment. However, despite their fundamental importance, their long-term effectiveness remains limited. Weight reduction is frequently accompanied by compensatory adaptive mechanisms, including increased appetite, reduced energy expenditure, and hormonal changes that promote weight regain [33]. These biological adaptations represent a major barrier to achieving and maintaining long-term weight loss and underscore the need for pharmacological therapeutic strategies.

Pharmacotherapy for obesity has undergone significant progress in recent years as a result of improved understanding of neuroendocrine mechanisms regulating energy homeostasis. Historically available agents were limited by either modest efficacy or unfavourable safety profiles, which restricted their clinical use. The introduction of GLP-1 receptor agonists represents a major therapeutic advancement, as these agents target the central mechanisms regulating appetite while simultaneously improving metabolic parameters [3, 9].

The incretin system plays a key role in the regulation of glucose metabolism and energy balance. GLP-1 is a physiological hormone produced by enteroendocrine L-cells of the small intestine, which, in addition to stimulating insulin secretion, also affects the central mechanisms of appetite regulation, slows gastric emptying, and reduces energy intake [9]. Pharmacological activation of GLP-1 receptors therefore represents a rational therapeutic approach based on targeting fundamental pathophysiological mechanisms of obesity.

The aim of this article is to systematically review current knowledge on the mechanism of action of GLP-1 receptor agonists, to analyze their clinical efficacy and safety profile, and to critically discuss their opportunities and limitations in the treatment of obesity within the context of current clinical practice.

Methods

This narrative review was based on a structured literature search conducted in PubMed, Embase, and Web of Science for articles published up to March 2026. Eligible studies included randomized controlled trials, observational studies, systematic reviews, and meta-analyses relevant to the clinical efficacy, safety, and cardiovascular effects of GLP-1 receptor agonists. Preference was given to large clinical trials, high-quality meta-analyses, and guideline documents.

Diagnosis of Obesity and Assessment of Cardiovascular Risk

In the context of obesity management, accurate identification of the patients with increased cardiometabolic risk plays a crucial role. Although the body mass index (BMI) is traditionally used to provide a basic assessment of the degree of obesity, it does not adequately reflect the distribution of adipose tissue, which is of fundamental importance for the development of metabolic complications. In this regard, the anthropometric indicators of central obesity, such as waist circumference and waist-to-height ratio, have gained an increasing importance.

As demonstrated in a study conducted in a the population of young Slovak women, these parameters represent reliable tools for estimating visceral adipose tissue and identifying individuals at increased cardiometabolic risk, with waist-to-height ratio and waist circumference showing the highest diagnostic accuracy [34]. A notable finding is the presence of increased visceral adiposity even in a young, apparently healthy population, highlighting the need for early screening and preventive interventions.

These findings have important clinical implications, as they enable earlier identification of at-risk individuals and the timely initiation of targeted therapeutic strategies. In this context, the pharmacological treatment of obesity, including GLP-1 receptor agonists, may be viewed not only as a tool for reducing body weight but also for decreasing visceral adiposity and overall cardiometabolic risk. The integration of simple anthropometric measures into routine clinical practice may therefore significantly contribute to optimizing patient selection for modern pharmacotherapy.

Pharmacological Treatment of Obesity Using GLP-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) is an incretin hormone produced by enteroendocrine L-cells, primarily in the ileum and colon, in response to the nutrient stimulation, particularly carbohydrates and lipids. Following secretion, GLP-1 acts through both the paracrine and endocrine mechanisms and is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), which determines its short plasma half-life [7]. Just, these properties have led to the development of stable GLP-1 analogues, which are currently used as effective pharmacological agents in the treatment of obesity.

Mechanism of Action of GLP-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent a pharmacological class with well-established effects on glucose homeostasis, energy balance, and body weight regulation. Their actions are mediated through activation of GLP-1 receptors expressed in both the central nervous system and peripheral tissues. Their mechanisms are complex and involve interactions between neuroendocrine and metabolic pathways.

Central Effects

GLP-1 receptor agonists influence the central regulation of food intake and energy balance through GLP-1 receptors localized in the hypothalamus and brainstem, including the arcuate nucleus, paraventricular nucleus, and ventromedial nucleus [12]. Activation of these receptors:

- enhances the activity of anorexigenic neurons (e.g., POMC/CART) while inhibiting orexigenic signaling pathways (NPY/AgRP), thereby suppressing appetite and reducing energy intake;
- modulates neurotransmitter systems involved in satiety and reward processing, including serotonergic and dopaminergic pathways;
- contributes to the weight reduction independently of its glucose-lowering effects [23,14].

Peripheral Effects

Peripheral mechanisms of GLP-1 receptor agonists involve actions on the gastrointestinal tract, pancreas, and other organs. At the pancreatic level, GLP-1 RAs enhance glucose-dependent insulin secretion and suppress glucagon secretion, leading to improved postprandial glycemic control. This effect underlies their established role in the treatment of type 2 diabetes mellitus.

Gastrointestinal effects include delayed gastric motility and gastric emptying, thereby prolonging satiety and reducing the rate of postprandial glucose absorption. Additional peripheral effects of GLP-1 RAs may include improvement of insulin sensitivity in peripheral tissues, reduction of fat mass, and modulation of lipid metabolism [31].

Table 1 Systematic overview of the effects of GLP-1 receptor agonists on target tissues [27]

Target Organ/Tissue	GLP-1 Effect
Pancreas (β- cells)	Stimulates insulin secretion
Pancreas (β- cells)	Promotes proliferation and reduces apoptosis
Pancreas (α-cells)	Inhibits glucagon secretion
Brain (hypothalamus and brainstem)	Increases satiety → reduces food intake
Brain	Supports cognitive function and modulates mood (mechanisms under investigation)
Gastrointestinal tract (GIT)	Slows gastrointestinal motility → prolongs satiety and reduces postprandial glycemia

Effect on Energy Intake

GLP-1 receptor agonists reduce food intake through complex central actions on the structures of the central nervous system that regulate energy homeostasis, hunger, and satiety. Their effects are mediated via activation of GLP-1 receptors localized primarily in the hypothalamus, brain stem, and mesolimbic system, with these mechanisms acting synergistically to produce an overall reduction in energy intake [27].

A key role is played by the hypothalamus, particularly the arcuate nucleus, where GLP-1 receptor agonists modulate the activity of neuronal populations responsible for appetite regulation. Specifically, they activate anorexigenic neurons producing proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which promote satiety, while simultaneously inhibiting orexigenic neurons producing neuropeptide Y (NPY) and agouti-related peptide (AgRP), which stimulate food intake. This mechanism shifts the balance toward reduced appetite and lower energy intake [14].

The brain stem, particularly the nucleus tractus solitarius, also plays an important role as an integrative centre for afferent signals from the gastrointestinal tract. GLP-1 receptor agonists enhance vagal afferent signalling associated with gastric distension and the presence of nutrients in the digestive tract, thereby promoting earlier onset of satiety during meals. This mechanism is closely linked to their peripheral effects, particularly delayed gastric emptying, which prolongs satiety and secondarily increases afferent signaling to the central nervous system [31].

In addition to homeostatic regulation of food intake, GLP-1 receptor agonists also influence the hedonic aspects of eating through their action on the mesolimbic dopaminergic system, including the ventral tegmental area and nucleus accumbens. In these regions, they reduce dopaminergic responses to food-related stimuli, leading to attenuation of the reward effect of food and decreased preference for energy-dense foods. This mechanism explains why patients treated with GLP-1 receptor agonists frequently report reduced cravings for high-calorie foods and a lower incidence of binge eating episodes [16].

Overall, the effect of GLP-1 receptor agonists results from synergistic actions at multiple levels of food intake regulation, including modulation of hypothalamic centres of hunger and satiety, enhancement of afferent gastrointestinal signalling, and influence on central reward pathways. These mechanisms lead to reduced caloric intake, earlier onset of satiety, and prolonged satiety, which clinically manifest as significant weight reduction.

Effect on Metabolism

One of the most important effects of GLP-1 receptor agonists is their impact on glucose homeostasis. These agents enhance glucose-dependent insulin secretion from pancreatic β-cells while simultaneously inhibiting glucagon secretion from α-cells, resulting in a reduction in blood glucose levels without a significant risk of hypoglycemia [38]. In addition, they delay gastric emptying, thereby reducing postprandial glycaemic excursions. Long-term administration of GLP-1 receptor agonists is also associated with improved insulin sensitivity, contributing to overall metabolic control [38].

In terms of energy metabolism, GLP-1 receptor agonists induce a negative energy balance primarily through reduction of caloric intake. In addition to central appetite suppression, there is evidence suggesting a modest increase in energy expenditure; however, this effect appears less pronounced and its clinical significance remains a subject of ongoing debate [6,2]. Weight reduction is accompanied by a decrease in visceral adiposity, which is closely linked to metabolic risk.

GLP-1 receptor agonists also exert favourable effects on lipid metabolism. Clinical studies have demonstrated reductions in triglyceride and low-density lipoprotein (LDL) cholesterol levels, along with increases in high-density lipoprotein (HDL) cholesterol, thereby improving the overall atherogenic profile [38]. This effect is partly mediated by weight reduction, but also by direct actions of GLP-1 on lipid metabolism in the liver and adipose tissue.

An important aspect is their effect on the cardiovascular system. GLP-1 receptor agonists lead to modest reductions in systolic blood pressure and exhibit potential antiatherosclerotic and anti-inflammatory properties. Large cardiovascular outcome trials have demonstrated a reduction in major adverse cardiovascular events in the patients with type 2 diabetes mellitus, indicating benefits beyond glycemic control [38].

At the level of adipose tissue, GLP-1 receptor agonists improve the adipocyte metabolic activity and reduce chronic low-grade inflammation characteristic of obesity. Some experimental studies also suggest a potential influence on adipocyte differentiation and redistribution of

adipose tissue toward less metabolically harmful depots [17].

Overall, it can be concluded that GLP-1 receptor agonists affect the metabolism through coordinated actions across multiple organ systems. Their effects result in improved glycaemic control, reduction in body weight, optimization of lipid profile, and reduction of cardiovascular risk. These properties position them among key agents in contemporary cardiometabolic therapy.

GLP-1 Receptor Agonists and Atherosclerosis

Beyond their effects on weight reduction and glycaemic control, GLP-1 receptor agonists have demonstrated significant cardiovascular benefits, including a potential role in atherosclerosis modulation.

Large cardiovascular outcome trials have shown that GLP-1 receptor agonists reduce major adverse cardiovascular events (MACE), such as myocardial infarction, stroke, and cardiovascular mortality [19,20]. These effects likely extend beyond metabolic improvements, suggesting direct vascular mechanisms.

GLP-1 receptor activation is associated with improved endothelial function, reduced inflammation, and attenuation of oxidative stress, all of which are key processes in atherogenesis [23,29]. In addition, these agents favourably influence traditional cardiovascular risk factors, including body weight, blood pressure, and lipid profile [13].

Overall, GLP-1 receptor agonists may contribute not only to metabolic control but also to the prevention and progression of atherosclerotic cardiovascular disease.

Overview of GLP-1 Receptor Agonists Used in the Treatment of Obesity: Which Agent to Choose and When?

Currently, the most clinically relevant agents for the treatment of obesity include liraglutide, semaglutide, and tirzepatide, which differ in their pharmacokinetic profiles, efficacy, and clinical applications. Liraglutide is a long-acting GLP-1 analogue administered once daily. In the randomized SCALE trial, it achieved a mean body weight reduction of approximately 5 - 8 % after 56 weeks of treatment [20]. Its mechanism of action includes stimulation of glucose-dependent insulin secretion, inhibition of glucagon release, and central appetite suppression [3, 31]. Liraglutide is particularly suitable for the patients with mild to moderate obesity or for those requiring gradual dose titration to improve tolerability [9].

Semaglutide represents a second-generation GLP-1 receptor agonist with an extended half-life, allowing for once-weekly administration. In the STEP 1 trial, treatment with semaglutide (2.4 mg weekly) resulted in a mean body weight reduction of 14.9 % compared with 2.4 % in the placebo group [3]. Semaglutide exerts a more pronounced effect on the central appetite regulation and leads to significant reductions in visceral adiposity and improvements in insulin sensitivity [19, 31]. Additionally, it has demonstrated cardiovascular benefits in the patients at high risk [25]. Its clinical use is particularly relevant in the patients with moderate to severe obesity, prediabetes, or type 2 diabetes mellitus, as well as in those with elevated cardiometabolic risk [25].

Tirzepatide represents a novel class of agents with dual agonistic activity at receptors for glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). This dual mechanism enhances the incretin effect, resulting in greater reductions in both glycated haemoglobin (HbA1c) and body weight [20]. In the SURPASS-2 trial, tirzepatide demonstrated superiority over semaglutide in reducing both HbA1c and body weight in the patients with type 2 diabetes mellitus. Body weight reduction ranged from approximately 11 % to 13 %, depending on the dose, while the reduction in HbA1c was more pronounced than with semaglutide [3].

In additional studies within the SURPASS program, weight reductions of approximately 15 - 20 % were observed, approaching the efficacy of bariatric interventions [9]. From a clinical perspective, tirzepatide represents a promising therapeutic option, particularly for patients with type 2 diabetes mellitus and obesity, where comprehensive metabolic intervention is required.

Table 2 Rational selection of GLP-1 receptor agonists in the treatment of obesity [3, 20, 25]

Parameter	Tirzepatide	Semaglutid	Liraglutide
Mechanism of action	Dual GIP + GLP-1 receptor agonist	Selective GLP-1 receptor agonist	Selective GLP-1 receptor agonist
Administration	Once weekly, s.c.	Once weekly, s.c.	Once daily, s.c.
HbA1c reduction	↓↓↓	↓↓	↓
Body weight reduction	↓↓↓ (≈15–22%)	↓↓ (≈10–15%)	↓ (≈5–8%)
Proportion of fat mass loss	High	Moderate	Moderate
Effect on lean mass	Lowest relative reduction	Moderate reduction	Moderate reduction
Effect on appetite	Very pronounced	Pronounced	Moderate
Cardiovascular benefit	Probable (ongoing studies)	Demonstrated (CVOT)	Demonstrated (CVOT)
Hypoglycemia	Low risk (without insulin/SU)	Low	Low
Indication	Type 2 diabetes + obesity	Type 2 diabetes, obesity	Type 2 diabetes, obesity

Clinical Efficacy and Systemic Benefits of GLP-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent an established therapeutic strategy in the management of type 2 diabetes mellitus and obesity, with effects extending beyond glycaemic control to encompass a broad spectrum of metabolic, cardiovascular, and systemic processes. Weight reduction is predominantly attributable to the loss of adipose tissue, although a proportion of lean body mass reduction is also observed, reflecting the physiological response to the negative energy balance.

The metabolic effects of GLP-1 RAs are complex and include improvement in the glycaemic control through the glucose-dependent stimulation of insulin secretion and suppression of glucagon, resulting in the significant reductions in HbA1c without an increased risk of hypoglycaemia. Concurrently, favourable changes in the lipid profile are observed, characterized by reductions in triglycerides and low-density lipoprotein (LDL) cholesterol and modest increases in high-density lipoprotein (HDL) cholesterol. Additionally, a reduction in systolic blood pressure has been documented, likely resulting from a combination of weight loss, improved endothelial function, and natriuretic effects [19]. These changes contribute to an overall improvement in the cardiometabolic risk profile.

Cardiovascular benefits of GLP-1 RAs have been unequivocally demonstrated in large randomized cardiovascular outcome trials (CVOTs). Liraglutide in the LEADER trial and semaglutide in the SUSTAIN-6 trial both showed significant reductions in major adverse cardiovascular events (MACE), including cardiovascular mortality, non-fatal myocardial infarction, and stroke [20, 27]. The mechanisms underlying these benefits are multifactorial and include not only improvements in traditional risk factors but also direct anti-atherosclerotic, anti-inflammatory, and endothelial-protective effects.

Beyond cardiometabolic outcomes, GLP-1 RAs have shown relevance in reproductive health, particularly in the women with polycystic ovary syndrome (PCOS), where they improve insulin resistance, reduce hyperandrogenism, and restore ovulatory cycles, thereby secondarily enhancing fertility. These effects are primarily mediated through the weight reduction and improvements in metabolic milieu [19]. In the context of oncological considerations, current evidence does not demonstrate an increased risk of most malignancies associated with GLP-1 RA therapy; on the contrary, there are indications of a potential protective effect, likely mediated through reductions in obesity, insulin resistance, and chronic inflammation, although further research is required in this area [16].

Additional important systemic benefits include improvement of non-alcoholic fatty liver disease (NAFLD), with reductions in hepatic steatosis and inflammation, as well as renoprotective effects characterized by slowing the progression of diabetic nephropathy. Experimental and clinical studies also suggest potential neuroprotective effects of GLP-1 RAs, which may be relevant in the context of neurodegenerative disorders. Overall, GLP-1 RAs can be considered a pleiotropic therapeutic class with broad systemic effects that extend beyond traditional metabolic indications and significantly contribute to reductions in morbidity and mortality in the patients with metabolic diseases.

Safety and Adverse Effects of GLP-1 Receptor Agonists

GLP-1 receptor agonists are predominantly associated with gastrointestinal (GI) adverse effects, which represent the most commonly reported events during treatment. The underlying mechanisms include delayed gastric motility, activation of central anorexigenic pathways, and modulation of vagal signalling, leading to the symptoms such as nausea, vomiting, and diarrhea [1, 43].

- **Nausea:** The most common gastrointestinal symptom associated with GLP-1 therapy, with an incidence significantly higher than with placebo. In most patients, symptoms diminish over time during dose titration and continued treatment [1].
- **Vomiting:** Occurs secondary to nausea and delayed gastric emptying; typically mild, transient, and rarely necessitates treatment discontinuation [1,8].
- **Diarrhoea:** Related to modulation of intestinal secretory activity and motility; may range from mild to moderate severity and, in cases of persistent dehydration, may have metabolic consequences [43].

These gastrointestinal adverse effects are generally dose-dependent and most frequently occur during treatment initiation or dose escalation. Gradual dose titration reduces both the frequency and severity of these effects and is considered the standard clinical approach for minimizing gastrointestinal intolerance [1,43].

Less Common Adverse Effects

Although less frequent, certain clinically relevant complications require particular attention:

- **Pancreatitis:** Multiple controlled studies and meta-analyses suggest that GLP-1 receptor agonists are not significantly associated with an increased relative risk of acute pancreatitis compared with placebo; however, sporadic cases have been reported in post-marketing surveillance [8]. Clinical vigilance is recommended in the presence of acute abdominal symptoms, severe nausea, persistent vomiting, or significant abdominal pain.
- **Cholelithiasis:** Rapid weight loss induced by GLP-1 therapy may secondarily increase the risk of gallstone formation. Cholelithiasis and complicated biliary disease have been reported in some large clinical trials involving incretin-based therapies [8].

These less common adverse effects require clinical monitoring, particularly in the patients with a predisposition to pancreatic or biliary disease.

Contraindications

GLP-1 receptor agonists have specific contraindications arising from their pharmacodynamic properties and safety profiles:

- Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2) – animal studies have demonstrated an increased risk of thyroid C-cell tumors; therefore, these agents are contraindicated in patients with these conditions [31].
- Pregnancy and breastfeeding – due to the lack of adequate and well-controlled studies in pregnant women, GLP-1 receptor agonists are not recommended during pregnancy and lactation [31].
- Hypersensitivity to the drug or its excipients represents an absolute contraindication due to the risk of allergic reactions.
- Acute pancreatitis or severe gastrointestinal disorders are considered relative contraindications due to the potential for condition exacerbation.

A thorough medical history and careful assessment of risk factors are essential prior to initiation of therapy in order to minimize the risk of serious complications.

Limitations of Treatment with GLP-1 Receptor Agonists

Treatment with GLP-1 receptor agonists represents a significant advancement in the management of obesity and type 2 diabetes mellitus. However, despite their proven efficacy, several important limitations affect their long-term effectiveness, accessibility, and sustainability in clinical practice.

Economic Accessibility

The financial burden represents one of the major limiting factors in the use of GLP-1 receptor agonists. These therapies are costly and are often indicated for long-term use, leading to cumulative expenses over time. In many healthcare systems, the access is restricted by reimbursement policies, resulting in selective availability for patients.

Real-world data suggest that high cost, combined with insufficient insurance coverage, is among the main reasons for premature treatment discontinuation. It is estimated that approximately 50% of patients discontinue therapy within 12 months, with financial burden being a dominant contributing factor [27].

From a healthcare system perspective, the widespread use of GLP-1 receptor agonists raises questions regarding cost-effectiveness, particularly in the indication of obesity without diabetes, where long-term administration is required to maintain therapeutic benefits. This supports the concept of obesity treatment as a chronic therapy requiring sustained financial investment.

Economic analyses indicate that these agents are generally less cost-effective compared with other interventions (e.g., bariatric surgery or lifestyle modification), particularly in the treatment of obesity without diabetes [5].

Patient Adherence

Adherence and treatment persistence are critical determinants of real-world clinical effectiveness. While randomized clinical trials demonstrate high adherence rates, real-world data are considerably less favourable. Observational studies indicate that treatment persistence is approximately 46 % at 6 months and declines to around 32 % at 12 months. Adequate adherence (proportion of days covered ≥ 80%) is achieved by only about 27 % of patients [21].

These findings confirm that the majority of patients do not adhere optimally to therapy, resulting in reduced therapeutic benefit. Even in controlled multidisciplinary programs, median persistence remains approximately 10.7 months [35].

The main factors contributing to the poor adherence include gastrointestinal adverse effects, high treatment cost, the requirement for long-term therapy, and psychological and behavioural factors. Poor adherence has significant clinical implications, as the efficacy of GLP-1 receptor agonists is directly dependent on treatment continuity.

Weight Regain after Treatment Discontinuation

One of the most significant limitations is the tendency for weight regain following treatment discontinuation. This phenomenon reflects underlying biological mechanisms regulating energy balance, which favour a return to baseline body weight.

Data from clinical trials and meta-analyses indicate that:

- patients may regain up to 64 % of lost weight within one year after discontinuation [36];
- in some cases, body weight returns to baseline within 10 - 20 months [35];
- average weight regain may reach approximately 0.8 kg per month [26];
- total regain may reach approximately 9.9 kg within the first year after treatment cessation [26].

Meta-analytic data further confirm that weight regain is consistent across different GLP-1 receptor agonists, although its magnitude may vary depending on the specific agent [38].

From a clinical perspective, it is important to note that weight regain is accompanied by deterioration in metabolic parameters (glycaemia, lipid profile, blood pressure), indicating reversibility of the therapeutic effect [18].

These findings support the conceptualization of obesity as a chronic disease requiring long-term pharmacological intervention. They also highlight the importance of combining pharmacotherapy with behavioural and lifestyle interventions to minimize the rebound effect.

Controversies and Unresolved Questions

Despite the substantial clinical benefits of GLP-1 receptor agonists, several important controversies and unresolved questions remain.

One of the key issues is the heterogeneity of treatment response. Not all patients achieve clinically meaningful weight loss, and a subset of individuals can be classified as “non-responders.” The mechanisms underlying this variability are not fully understood but may involve gene-

tic factors, differences in central appetite regulation, and behavioural components [23, 29].

Another area of ongoing discussion concerns the differences between pharmacological classes, particularly between traditional GLP-1 receptor agonists and newer dual or multi-agonists (e.g., GLP-1/GIP receptor agonists). While dual agonists appear to provide superior weight loss outcomes, their long-term safety profile, tolerability, and cost-effectiveness remain subjects of active investigation [9, 15].

There is also uncertainty regarding the optimal duration of therapy. Current evidence suggests that discontinuation leads to weight regain; however, the long-term implications of lifelong pharmacological treatment are not fully established, including potential metabolic adaptation and long-term safety [26, 31].

Furthermore, the role of GLP-1 receptor agonists in different patient populations (e.g., individuals without diabetes, elderly patients, or those with psychiatric comorbidities) requires further clarification, as most clinical trials include selected populations that may not fully reflect real-world diversity [11, 17].

Finally, questions remain about the integration of pharmacotherapy with lifestyle and behavioural interventions, including how to optimize long-term adherence and whether combination approaches can mitigate weight regain after treatment discontinuation [13, 16].

Position of GLP-1 Receptor Agonists in Current Guidelines

GLP-1 receptor agonists currently represent one of the most important pharmacological options in the treatment of obesity and type 2 diabetes mellitus. Their position within clinical guidelines has evolved significantly in recent years, primarily due to the growing body of evidence supporting their efficacy in weight reduction and their beneficial effects on the cardiometabolic risk factors. This development also reflects a paradigm shift in the understanding of obesity as a chronic, multifactorial, and relapsing disease requiring long-term management.

Indication criteria for initiating GLP-1 receptor agonists are relatively consistent across major regulatory authorities and professional societies. The primary parameter remains body mass index (BMI), supplemented by the presence of obesity-related comorbidities. Pharmacological treatment is indicated in the patients with BMI $\geq$ 30 kg/m², or in those with BMI $\geq$ 27 kg/m² in the presence of comorbidities such as arterial hypertension, dyslipidemia, type 2 diabetes mellitus, or obstructive sleep apnea syndrome [41].

Current recommendations from the international professional societies reflect the growing importance of GLP-1 receptor agonists in the obesity management. The 2025 World Health Organization guidelines explicitly state that GLP-1 receptor agonists may be used as long-term pharmacological therapy in the adults with obesity, provided they are combined with the lifestyle and behavioural interventions [28, 41].

Similarly, the Endocrine Society emphasizes that pharmacotherapy for obesity, including GLP-1 receptor agonists, should be considered in the patients who have not achieved adequate weight reduction through non-pharmacological measures [17].

European recommendations, particularly those of the European Association for the Study of Obesity, highlight that newer GLP-1 receptor agonists, such as semaglutide and tirzepatide, achieve significantly greater weight reduction compared with earlier pharmacological options [4].

Discussion

Treatment with GLP-1 receptor agonists represents a significant advancement in the management of obesity and type 2 diabetes mellitus. The results from large randomized clinical trials consistently demonstrate their high efficacy in reducing body weight, as well as their favourable effects on cardiometabolic parameters. At the same time, however, the implementation of these agents in real-world clinical practice raises several questions that require critical interpretation of the available evidence.

Interpretation of Results

Available clinical evidence indicates that GLP-1 receptor agonists lead to significant reductions in body weight, which, in the case of modern agents such as semaglutide or tirzepatide, reach approximately 10 - 20 % of baseline body weight. This effect has been confirmed in randomized trials and meta-analyses demonstrating substantially greater efficacy compared with older pharmacological options [32].

However, interpretation of these findings must take into account the differences between randomized clinical trial settings and real-world clinical practice. Clinical trials are characterized by high adherence, intensive patient monitoring, and strict inclusion criteria, which may lead to an overestimation of treatment effects compared with routine practice. Real-world data indicate lower treatment persistence and higher rates of early discontinuation, which may significantly reduce the overall therapeutic benefit [21].

A crucial aspect of interpretation is the fact that the effect of GLP-1 agonists is largely dependent on the continuity of treatment. Following discontinuation, gradual weight regain occurs, as demonstrated in extension phases of the STEP trials, where patients regained a substantial proportion of lost weight after cessation of semaglutide therapy [30].

From a clinical perspective, GLP-1 receptor agonists represent an important therapeutic tool, particularly in the patients with elevated cardiometabolic risk. Weight reduction exceeding 10% is associated with significant improvements in glycaemic control, lipid profile, and blood pressure, as confirmed by the multiple clinical studies [43]. Furthermore, their impact on the cardiovascular risk is of particular relevance. Some clinical trials have demonstrated reductions in major adverse cardiovascular events, suggesting that the benefits of GLP-1 receptor agonists extend beyond weight reduction and encompass broader cardiometabolic effects [20, 25].

On the other hand, their clinical benefit is limited by the need for long-term administration. Available evidence indicates that discontinuation of therapy leads to the gradual weight regain, underscoring the chronic nature of obesity and the need for continuous pharmacological intervention [30].

Comparison with Other Treatment Modalities

Compared with non-pharmacological interventions, such as dietary and behavioural measures, GLP-1 receptor agonists demonstrate substantially greater efficacy in the weight reduction. While lifestyle interventions alone typically result in weight loss of approximately 3 - 7 %, treatment with GLP-1 receptor agonists may achieve reductions exceeding 10 - 15 % [32].

In comparison with other pharmacological options, GLP-1 receptor agonists represent the most effective currently available treatment for obesity. Meta-analyses confirm that their efficacy is significantly greater than that of older anti-obesity agents, such as orlistat or combination pharmacotherapies [21].

The most pronounced difference, however, is observed when compared with bariatric surgery, which remains the most effective treatment modality for obesity. Surgical interventions typically result in weight reductions of 25 - 35 % and provide more durable long-term effects with lower rates of weight regain. GLP-1 receptor agonists may therefore be considered an intermediate option between conservative and surgical treatment, with the advantages of non-invasiveness and broader applicability [29].

Limitations of Available Data

Interpretation of the available evidence is limited by several factors. Most randomized clinical trials have relatively short durations, typically 1 - 2 years, which limits the ability to assess long-term sustainability of treatment effects and safety profiles [32]. Another limitation is the selection of patients in clinical trials, which does not fully reflect the heterogeneity of the real-world population. The patients enrolled in trials often demonstrate higher motivation and better adherence, which may lead to an overestimation of treatment efficacy compared with routine clinical practice [21].

A further important limitation is the relatively limited amount of data on long-term outcomes following treatment discontinuation.

Conclusion

Treatment with GLP-1 receptor agonists represents a significant advancement in the management of obesity and type 2 diabetes mellitus, with available evidence consistently demonstrating high efficacy in weight reduction and improvement of cardiometabolic parameters. The results from randomized clinical trials and meta-analyses indicate that modern agents within this class can achieve body weight reductions exceeding 10 - 15 %, which is clinically meaningful and associated with reduced risk of both the cardiovascular and metabolic complications [3, 32].

From a therapeutic perspective, GLP-1 receptor agonists currently represent the most effective pharmacological option available for the treatment of obesity. Their effects are comprehensive and extend beyond weight reduction to include improvements in glycaemic control, lipid profile, and blood pressure, as well as potential cardioprotective effects [20, 27]. This pleiotropic profile supports their integration into the broader framework of cardiometabolic therapy.

From a clinical standpoint, GLP-1 receptor agonists have important implications for everyday practice. They represent an effective therapeutic option, particularly for the patients with obesity and associated comorbidities, allowing for clinically meaningful improvements in health status without the need for invasive intervention. However, it is essential to emphasize that their efficacy depends on long-term administration and adequate patient adherence. Following the treatment discontinuation, gradual weight regain occurs, highlighting the chronic nature of obesity and the need for continuous therapeutic strategies [18, 30].

Despite their substantial benefits, certain limitations remain that affect their broader implementation in clinical practice. The most important include high economic costs, lower patient adherence in real-world settings, and the lack of long-term data on sustainability and safety. These factors underscore the need for individualized treatment approaches and the integration of pharmacotherapy into comprehensive obesity management.

From the perspective of future research, it is essential to focus on the long-term follow-up of patients in order to better understand the durability of treatment effects and safety profiles. Further important areas include the development of strategies to prevent weight regain after treatment discontinuation, as well as the optimization of combined therapeutic approaches incorporating pharmacological, behavioural, and, where appropriate, surgical interventions. Promising directions also include the development of novel agents with greater efficacy and improved safety profiles, as well as the identification of biomarkers to enable personalized treatment strategies.

In conclusion, GLP-1 receptor agonists represent a significant therapeutic tool in the treatment of obesity; however, their optimal use requires a comprehensive, long-term, and individualized approach that takes into account the biological, clinical, and socioeconomic aspects of the disease.

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https://doi.org/10.33542/ATE2026-12-6

The author declares no conflict of interest.

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