Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

GLP-1 Agonists in Adolescent Obesity: A Narrative Review of Single, Dual, and Triple Agonists

Mahroz Abid[1], Khizer Sohail Sheikh[1], Muhammad Shahbaz Ahmad[2], Hongwei Jiang[1]

[1]Department of Metabolism and Endocrinology, Endocrine and Metabolic Disease Center, The First Affiliated Hospital and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, People's Republic of China; [2]Department of Internal Medicine, Lahore General Hospital, Ameer-Ud-Din Medical College, Lahore, Punjab, Pakistan

Correspondence: Hongwei Jiang, Department of Metabolism and Endocrinology, Endocrine and Metabolic Disease Center, The First Affiliated Hospital and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, People's Republic of China, Email jianghw@haust.edu.cn

Abstract: Adolescent obesity is an escalating global health concern associated with increased risks of cardiovascular disease, type 2 diabetes mellitus, and long-term metabolic complications. Although lifestyle interventions remain first-line therapy, their limited long-term effectiveness has led to increasing interest in pharmacological approaches. This narrative review evaluates the mechanisms, clinical efficacy, and safety of glucagon-like peptie-1 (GLP-1) receptor agonists, as well as emerging dual and triple incretin-based therapies, in the management of adolescent obesity. A literature search was conducted using PubMed and Scopus, focusing on clinical trials, systematic reviews, and real-world studies published between 2010 and 2024. Evidence from pediatric and adolescent populations was prioritized, while adult data were included where adolescent-specific evidence remains unavailable and are interpreted cautiously. Among single-agent therapies, GLP-1 receptor agonists have demonstrated clinically meaningful weight reduction and metabolic benefits in adolescents. In the STEP TEENS trial, once-weekly semaglutide resulted in approximately 16% mean body weight reduction over 68 weeks, while liraglutide produced more modest reductions. Dual agonists such as tirzepatide and emerging triple agonists, including retatrutide, have shown superior weight-loss efficacy in adult populations; however, pediatric data for these agents remain limited or unavailable. Across all incretin-based therapies, gastrointestinal adverse effects are the most commonly reported side effects. In conclusion, GLP-1 receptor agonists represent an effective pharmacological option for adolescents with obesity, while dual and triple incretin agonists offer promising future therapeutic potential. Nevertheless, the clinical application of multi-receptor agonists in adolescents requires caution, as long-term safety, developmental outcomes, and real-world adherence data in pediatric populations are still lacking. Further well-designed pediatric trials are essential before broader adoption can be recommended.

Keywords: GLP1, obesity, adolescents, GLP1 dual agonist, GLP1 triple agonist, diabetes

Introduction

The Growing Burden of Adolescent Obesity

With prevalence rates rising sharply over the past few decades, adolescent obesity has emerged as a major global public health challenge. Current estimates indicate that more than 20% of adolescents in the United States are affected by obesity, with similar trends observed worldwide.[1] The increasing burden of obesity during adolescence is of particular concern because excess weight gained during this critical developmental period frequently persists into adulthood, substantially increasing long-term morbidity and mortality.

Obesity in adolescents is associated with a wide range of metabolic and cardiovascular complications, including type 2 diabetes mellitus, hypertension, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), and early manifestations of cardiovascular disease.[2] These comorbidities, once considered conditions of adulthood, are now increasingly diagnosed in younger populations in parallel with rising obesity prevalence. In addition to physical health consequences, adolescent

https://doi.org/10.2147/DMSO.S566414
Received: 19 January 2026
Accepted: 17 March 2026
Published: 12 June 2026

Table 1 Prevalence of Adolescent Obesity Globally

Region	Prevalence (%)	Year
North America	20.5	2022
Europe	17.3	2022
Asia	12.1	2022
Africa	8.9	2022

obesity is strongly linked to psychological and emotional disorders, including anxiety, depression, low self-esteem, and impaired social functioning, which further complicate disease management and negatively influence long-term outcomes.[3]

Epidemiological data demonstrate a consistent upward trend in childhood and adolescent obesity. In the United States, obesity prevalence among children and adolescents aged 2 to 19 years increased from 17.7% in 2011–2012 to 21.5% in 2017–2020, underscoring the accelerating nature of this epidemic.[4] Global estimates also reveal substantial regional variation in adolescent obesity prevalence, reflecting differences in socioeconomic status, urbanization, dietary patterns, and physical activity levels (Table 1). These trends highlight the urgent need for effective, scalable, and evidence-based interventions tailored to adolescent populations.

Although lifestyle-based interventions, including dietary modification and increased physical activity, remain the cornerstone of obesity management, their long-term effectiveness in adolescents is often limited. Poor adherence, environmental influences, and complex neurohormonal mechanisms regulating appetite and energy balance frequently result in weight regain after initial success.[3] As a result, traditional behavioral approaches alone are often insufficient for adolescents with moderate-to-severe obesity or obesity-related complications.

Search Strategy and Study Selection

This narrative review was conducted to summarize and critically appraise current evidence on the use of glucagon-like peptide-1 (GLP-1) receptor agonists, dual incretin agonists, and triple receptor agonists in the management of obesity, with a particular focus on adolescent populations.

A comprehensive literature search was performed using electronic databases including PubMed, Scopus, and Google Scholar. Searches were conducted using combinations of keywords and Medical Subject Headings (MeSH) terms related to incretin-based therapies and obesity, including “GLP-1 receptor agonists”, “dual agonists”, “triple agonists”, “liraglutide”, “semaglutide”, “tirzepatide”, “mazdutide”, “retatrutide”, “adolescent obesity”, and “pediatric obesity”. Additional studies were identified through manual screening of reference lists from relevant review articles and clinical trial publications.

The review prioritized randomized controlled trials, Phase 2 and Phase 3 clinical trials, and high-quality observational studies published in peer-reviewed journals. Given the limited availability of pediatric data for dual and triple agonists, evidence from adult clinical trials was included where relevant to provide mechanistic insights and contextual understanding. However, findings derived from adult populations were interpreted cautiously, and distinctions between adolescent and adult evidence were explicitly acknowledged throughout the manuscript.

Studies were selected based on relevance to obesity treatment, clarity of reported outcomes, and applicability to metabolic and weight-related endpoints. No formal meta-analysis was conducted, and data were synthesized narratively to highlight trends in efficacy, safety, and mechanistic differences among single, dual, and triple incretin-based therapies.

Role of Pharmacotherapy in Adolescent Obesity

Over the past two decades, pharmacologic approaches to obesity treatment have evolved substantially. Earlier anti-obesity medications primarily targeted appetite suppression or fat absorption but were often limited by modest efficacy

and significant safety concerns, including cardiovascular and psychiatric adverse effects.[5] These limitations restricted their use, particularly in pediatric populations, where long-term safety is paramount.

In contrast, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as effective and comparatively safe therapeutic options for weight management. GLP-1RAs mimic endogenous incretin hormones that regulate insulin secretion, glucose homeostasis, gastric emptying, and appetite control. Although initially developed for the treatment of type 2 diabetes mellitus, these agents demonstrated clinically meaningful weight loss, leading to their approval for obesity management.[6]

In adolescents with obesity, first-generation GLP-1RAs such as liraglutide (Saxenda®) and semaglutide (Wegovy®) have shown significant reductions in body mass index (BMI) and improvements in metabolic parameters.[5] These findings have positioned GLP-1RAs as the most evidence-based pharmacologic option currently available for adolescent obesity. However, despite their effectiveness, weight loss responses to single-agent GLP-1RAs may plateau over time, reflecting adaptive physiological mechanisms that counteract sustained energy deficit.

The Evolution of GLP-1 Agonists: From Single to Multi-Receptor Therapies

To overcome the limitations of GLP-1 monotherapy, newer pharmacologic strategies have focused on multi-receptor incretin agonism. These next-generation agents simultaneously target GLP-1 receptors along with additional metabolic pathways, including glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors, to enhance weight loss and metabolic outcomes.[7]

Dual agonists such as tirzepatide (GLP-1/GIP) and mazdutide (GLP-1/glucagon), as well as triple agonists like retatrutide (GLP-1/GIP/glucagon), have demonstrated unprecedented weight loss and cardiometabolic benefits in adult clinical trials. By engaging complementary hormonal mechanisms, these agents aim to improve satiety, insulin sensitivity, fat oxidation, and energy expenditure beyond what is achievable with GLP-1 receptor activation alone.

However, it is important to emphasize that, at present, robust clinical evidence for dual and triple agonists is derived predominantly from adult populations. Pediatric and adolescent data for these agents remain limited or unavailable.[1] Consequently, while multi-receptor agonists represent a promising future direction in obesity pharmacotherapy, their application in adolescents must be interpreted cautiously, with careful consideration of developmental safety, long-term outcomes, and ethical implications of extrapolating adult data to younger populations.

Why Multi-Receptor Agonists Are a Game-Changer for Adolescent Obesity

Despite the success of GLP-1 monotherapy, dual and triple agonists offer significant advantages in obesity treatment by engaging multiple hormonal pathways. Multi-receptor agonists target complementary pathways to enhance appetite suppression, insulin secretion, fat oxidation, and energy expenditure compared to GLP-1 monotherapy (Table 2).

- Superior Weight Loss Outcomes: Multi-agonists provide greater weight reduction by targeting multiple hormonal pathways, improving satiety, glucose metabolism, and energy expenditure.

Table 2 Mechanisms of Action of GLP-1, GIP, and Glucagon Agonists

Mechanism	GLP-1 Agonists	Dual Agonists (GLP-1/GIP)	Dual Agonists (GLP/GCP)	Triple Agonists (GLP-1/GIP/Glucagon)
Appetite Suppression	High	High	High	Very High
Insulin Secretion	High	Very High	Moderate	Very High
Fat Oxidation	Low	Moderate	High	High
Energy Expenditure	Low	Moderate	High	High

Note: Values are synthesized from the mechanistic studies and pre-clinical/clinical data summarized in the review article and cited in the main text (see original manuscript for detailed references).

- Improved Glycemic Control: GIP receptor activation enhances insulin sensitivity, while glucagon receptor activation promotes fat oxidation, making these agents effective for adolescents with both obesity and insulin resistance.
- Enhanced Cardiometabolic Benefits: Studies suggest that multi-receptor agonists lower cardiovascular risk factors, including lipid profiles, blood pressure, and inflammation markers.[8]

Challenges and Considerations in Multi-Agonist Therapy

Despite their advantages, GLP-1-based therapies face several challenges in adolescent populations:

- Gastrointestinal Side Effects: Nausea, vomiting, diarrhea, and constipation are common adverse events, especially during dose escalation.
- Adherence Issues: Injectable formulations may be a barrier for some adolescents, necessitating the development of oral alternatives or combination therapies.
- Long-Term Safety Concerns: While short-term data are promising, the long-term impact of GLP-1, dual, and triple agonists on adolescent metabolic health remains unclear.[2]

Future Directions in Adolescent Obesity Treatment

As the obesity epidemic continues, future research should focus on:

- Long-term studies evaluating the safety and efficacy of GLP-1 multi-agonists in adolescents.
- Personalized medicine approaches, identifying which patients benefit most from single versus multi-receptor agonists.
- Comparative trials assessing GLP-1 monotherapy against dual and triple agonists in pediatric populations.
- Exploring combination therapies, integrating GLP-1 agonists with behavioral and lifestyle interventions for long-term success.

Mechanisms of GLP-1, Dual, and Triple Agonists in Adolescent Obesity

The development of glucagon-like peptide-1 receptor agonists (GLP-1RAs), followed by the emergence of dual and triple incretin-based therapies, has substantially expanded pharmacological options for the management of obesity. These agents target multiple metabolic pathways involved in appetite regulation, insulin secretion, glucose homeostasis, and energy expenditure, making them particularly relevant for adolescents with obesity and associated metabolic complications. GLP-1 receptor agonists mimic endogenous GLP-1 activity and are currently approved for the treatment of obesity and type 2 diabetes mellitus.

A clear understanding of the underlying mechanisms of these therapies is essential for evaluating both their efficacy and safety in adolescent populations, where long-term metabolic and developmental considerations are critical. This section provides a detailed overview of the physiological mechanisms of single GLP-1 receptor agonists, GLP-1/GIP dual agonists, and GLP-1/GIP/glucagon triple agonists, with emphasis on their effects on appetite control, glycemic regulation, and energy balance. Collectively, these agents promote weight loss primarily through appetite suppression, enhanced satiety, and delayed gastric emptying, while newer multi-receptor agonists further augment metabolic efficiency and energy expenditure.

GLP-1 Receptor Agonists: Single Agonists in Obesity Treatment

Role of GLP-1 in Energy and Glucose Homeostasis

Glucose-dependent insulinotropic polypeptide (GIP) is an incretin hormone secreted by enteroendocrine K cells in the proximal small intestine in response to nutrient ingestion. Together with GLP-1, GIP plays an important role in postprandial glucose regulation by enhancing glucose-dependent insulin secretion. While earlier studies suggested a diminished insulinotropic response to GIP in individuals with obesity and type 2 diabetes, more recent evidence indicates that pharmacologic GIP receptor activation can exert beneficial metabolic effects when combined with GLP-1 receptor agonism.

Activation of the GIP receptor contributes to metabolic regulation through several mechanisms. GIP enhances insulin secretion in a glucose-dependent manner, thereby supporting glycemic control while minimizing hypoglycemia risk. In addition, GIP signaling has been implicated in the regulation of lipid metabolism, with evidence suggesting a role in promoting lipid utilization and improving insulin sensitivity in metabolically active tissues. Furthermore, GIP receptor activation may modulate glucagon secretion in a context-dependent manner, suppressing glucagon during hyperglycemia while preserving counterregulatory responses during hypoglycemic states.

These complementary metabolic actions provide the mechanistic rationale for combining GIP receptor agonism with GLP-1 receptor activation. By targeting overlapping yet distinct hormonal pathways, dual incretin therapies aim to amplify weight loss, enhance insulin sensitivity, and improve overall metabolic outcomes beyond what is achievable with GLP-1 receptor agonists alone.

First-Generation GLP-1RAs: Liraglutide and Semaglutide

- Liraglutide (Saxenda®) was the first GLP-1RA approved for adolescent obesity. Clinical trials demonstrated a 4.3% BMI reduction over 56 weeks, but gastrointestinal side effects led to treatment discontinuation in some cases.[9]
- Semaglutide (Wegovy®) has emerged as a more effective alternative, with a 16.1% BMI reduction over 68 weeks, making it the most potent single GLP-1RA for adolescent obesity.

However, despite their benefits, single GLP-1RAs have limitations. Weight loss may plateau over time due to counter-regulatory hormonal mechanisms that resist further reductions. This has led to the development of multi-receptor agonists that target additional metabolic pathways.

Dual GLP-1/GIP Agonists: Expanding Incretin-Based Therapy

The Role of GIP in Metabolic Regulation

Glucose-dependent insulinotropic polypeptide (GIP) is another incretin hormone secreted by K cells in the small intestine in response to food intake. Historically, GIP was believed to have a minor role in glucose metabolism, but recent evidence suggests that it enhances insulin secretion and regulates lipid metabolism.

Key mechanisms of GIP receptor activation include:

- Amplifying insulin secretion in response to glucose.
- Promoting fat oxidation rather than storage in metabolically active tissues.
- Reducing glucagon secretion in hyperglycemic states, while promoting glucagon release when glucose levels are low.

Tirzepatide: The First GLP-1/GIP Dual Agonist

Tirzepatide is a dual incretin agonist that activates both the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors and was developed to enhance metabolic and weight-loss outcomes beyond those achieved with GLP-1 receptor agonists alone. By simultaneously engaging complementary incretin pathways, tirzepatide improves insulin sensitivity, glycemic control, and overall energy balance.[10]

In large adult randomized controlled trials, tirzepatide demonstrated substantial weight-loss efficacy, with mean body weight reductions of up to 20.9% over 72 weeks, surpassing outcomes observed with semaglutide monotherapy.[11] These findings underscore the potential of dual incretin agonism to achieve greater and more sustained weight reduction in individuals with obesity.

At present, clinical data evaluating tirzepatide in adolescent populations remain limited. While its superior efficacy in adults suggests potential relevance for adolescent obesity treatment, direct extrapolation to younger populations is not yet supported by robust pediatric evidence. Nevertheless, the dual mechanism of action of tirzepatide—combining GLP-1–mediated appetite suppression with GIP-driven improvements in insulin sensitivity and lipid metabolism—represents a promising therapeutic strategy that warrants further investigation in adolescent-specific clinical trials.[12]

Mazdutide: A Dual GLP-1/Glucagon Receptor Agonist with Promising Results

Mazdutide (IBI362) is a dual agonist that targets both the glucagon-like peptide-1 (GLP-1) receptor and the glucagon receptor, thereby combining appetite suppression with mechanisms aimed at increasing energy expenditure. By engaging these complementary pathways, mazdutide represents an alternative approach to incretin-based therapy beyond GLP-1 monotherapy.

Across seven randomized controlled trials involving approximately 680 adult participants, mazdutide demonstrated a mean weight loss of 6.22%, with non-diabetic individuals achieving reductions of up to 8.44% in body weight. In addition to weight reduction, treatment with mazdutide was associated with significant improvements in metabolic parameters, including reductions in glycated hemoglobin (HbA1c), fasting plasma glucose, blood pressure, and lipid profiles in individuals with type 2 diabetes mellitus.[13]

In these early-phase studies, mazdutide exhibited a favorable safety profile, with predominantly mild-to-moderate gastrointestinal adverse effects reported.[14] While these findings highlight the therapeutic potential of dual GLP-1/glucagon receptor agonism in adults, evidence in adolescent populations is currently lacking. Consequently, further clinical studies are required to evaluate the safety, tolerability, and efficacy of mazdutide in adolescents with obesity before its clinical application in this population can be considered.

Triple GLP-1/GIP/Glucagon Agonists

The Next Generation of Anti-Obesity Drugs.

The Role of Glucagon in Energy Expenditure

Unlike GLP-1 and GIP, which primarily promote energy storage and insulin release, glucagon is a catabolic hormone that mobilizes energy reserves. Glucagon:

- Stimulates hepatic glucose production during fasting states.
- Increases lipid oxidation, promoting fat breakdown rather than storage.
- Enhances thermogenesis by activating brown adipose tissue.[15]

By incorporating glucagon receptor activation into GLP-1/GIP-based therapies, researchers aim to counteract metabolic adaptation that limits weight loss over time.

Retatrutide: A Triple Agonist with Unprecedented Efficacy

Retatrutide (LY3437943) is a novel triple incretin agonist that simultaneously targets the glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors. By integrating the appetite-suppressive effects of GLP-1, the insulin-sensitizing properties of GIP, and the energy expenditure–enhancing actions of glucagon, retatrutide is designed to maximize weight loss and metabolic improvement through complementary hormonal pathways.

In phase 2 clinical trials conducted in adult populations, retatrutide demonstrated substantial weight-loss efficacy, with reported reductions of up to 24.2% over a 48-week treatment period. These outcomes exceed those observed with both single and dual incretin agonists, highlighting the potential metabolic advantages of triple receptor agonism. In addition to weight reduction, retatrutide has been associated with improvements in glycemic control and other cardiometabolic parameters in adults with obesity.

Despite these promising findings, it is important to emphasize that evidence supporting the use of retatrutide is currently limited to adult clinical trials. No robust pediatric or adolescent data are available to date. Consequently, while triple agonists represent an important advancement in obesity pharmacotherapy, their safety, tolerability, and long-term developmental effects in adolescents remain unknown. Further well-designed clinical trials in pediatric populations are essential before retatrutide can be considered a therapeutic option for adolescent obesity.

Comparative Efficacy of Single, Dual, and Triple Agonists

Weight Loss Outcomes

Comparative evaluation of single, dual, and triple incretin-based therapies suggests a stepwise increase in weight-loss efficacy with greater receptor engagement. However, these comparisons should be interpreted with caution, as the available data are derived from trials with heterogeneous study designs, durations, endpoints, and patient populations.

Among single GLP-1 receptor agonists, liraglutide has demonstrated modest efficacy, with an approximate 4.3% reduction in BMI over 56 weeks in adolescents with obesity.[16] Semaglutide has shown substantially greater effectiveness, achieving a mean BMI reduction of approximately 16.1% over 68 weeks in adolescent populations.[17]

In contrast, dual and triple agonists have primarily been evaluated in adult populations. Tirzepatide, a GLP-1/GIP dual agonist, has demonstrated mean body weight reductions of approximately 20.9% over 72 weeks in adults with obesity.[18] Mazdutide, a dual GLP-1/glucagon receptor agonist, has shown weight loss of up to 14.0% over 48 weeks at a 6 mg dose in Chinese adult populations, with pooled early-phase trials reporting reductions of up to 8.44%.[19,20] Retatrutide, a triple GLP-1/GIP/glucagon agonist, has demonstrated the greatest reported efficacy to date, with weight loss reaching approximately 24.2% in adult clinical trials.[21]

It is essential to emphasize that direct numerical comparisons across these agents are limited by differences in trial duration, baseline characteristics, and study populations. Consequently, efficacy rankings derived from these data should not be interpreted as definitive or predictive of outcomes in adolescent patients.

Mechanistic Advantages

Single GLP-1 receptor agonists primarily promote weight loss through appetite suppression and delayed gastric emptying, leading to reduced caloric intake. Dual incretin agonists extend these effects by enhancing insulin sensitivity and modulating lipid metabolism through complementary receptor activation.

Dual GLP-1/glucagon receptor agonists additionally engage pathways that increase energy expenditure and fat oxidation, potentially counteracting metabolic adaptations that limit sustained weight loss.[12] Triple agonists further integrate appetite suppression, insulin sensitization, and increased energy expenditure, theoretically offering the most comprehensive metabolic effects among incretin-based therapies.[13] However, the clinical relevance of these mechanistic advantages in adolescent populations remains uncertain due to the absence of robust pediatric data.

Challenges and Future Research Directions

Despite the demonstrated efficacy of GLP-1–based therapies, several challenges limit their widespread application in adolescent populations. Gastrointestinal adverse effects, including nausea, vomiting, diarrhea, and constipation, are commonly reported, particularly during dose escalation phases. These side effects may affect treatment adherence and long-term persistence.

Adherence represents an additional challenge, as most GLP-1–based therapies require injectable administration. This may pose practical and psychological barriers for adolescents, underscoring the need for alternative formulations, improved delivery systems, or combination treatment strategies.

Long-term safety remains a critical unresolved issue. The effects of chronic GLP-1 receptor agonist exposure during adolescence—a period of ongoing growth, neurodevelopment, and hormonal maturation—are not yet fully understood. Furthermore, limited data exist regarding long-term weight maintenance, treatment discontinuation, and weight regain following cessation of therapy. Addressing these gaps will require well-designed longitudinal studies and pediatric-specific clinical trials to establish the safety, durability, and optimal positioning of incretin-based therapies in adolescent obesity management.

Clinical Evidence on GLP-1, Dual, and Triple Agonists in Adolescents

The clinical evidence surrounding GLP-1RAs and their dual and triple agonist counterparts has grown significantly in recent years. Initially developed for T2DM, these drugs have proven to be highly effective in reducing body weight and improving metabolic health in adolescents with obesity.[11] This section provides an overview of clinical trials

investigating GLP-1RAs, dual GLP-1/GIP agonists, and triple GLP-1/GIP/glucagon agonists, with an emphasis on their efficacy, safety, and long-term implications.

Clinical Trials on GLP-1 Single Agonists

Liraglutide: The First GLP-1RA Approved for Adolescent Obesity

Liraglutide (Saxenda®) was the first glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for the management of obesity in adolescent populations. Its efficacy and safety were evaluated in a 56-week, randomized, placebo-controlled trial involving adolescents aged 12 to 18 years with obesity.[15]

- Participants: A total of 251 adolescents were enrolled and randomized to receive either liraglutide (3.0 mg once daily) or placebo.
- BMI Reduction: Participants receiving liraglutide achieved a mean BMI reduction of 4.3%, compared with a 0.3% reduction observed in the placebo group.
- Weight Loss: Adolescents treated with liraglutide experienced a mean body weight reduction of approximately 5 kg, whereas those in the placebo group lost an average of 0.5 kg.
- Metabolic Effects: Modest improvements in markers of glucose regulation and lipid profiles were reported.
- Limitations: Gastrointestinal adverse effects, particularly nausea and vomiting, were common and contributed to relatively high dropout rates.

Overall, liraglutide demonstrated statistically significant but moderate weight-loss efficacy in adolescents when compared with placebo. Findings from the pivotal New England Journal of Medicine trial confirmed a 4.3% reduction in BMI over 56 weeks, supporting its clinical effectiveness in this age group.[16] However, the burden of gastrointestinal side effects and challenges with long-term adherence limited its broader applicability and underscored the need for more effective and better-tolerated therapeutic alternatives.[3]

Semaglutide: A More Potent GLP-1RA for Weight Loss

Semaglutide (Wegovy®) has emerged as a more effective alternative to liraglutide for the treatment of adolescent obesity, demonstrating greater reductions in body weight and improvements in cardiometabolic parameters. Its efficacy was evaluated in a 68-week randomized, placebo-controlled trial (STEP TEENS) involving adolescents with obesity.

- Participants: A total of 201 adolescents aged 12–18 years were randomized to receive once-weekly semaglutide (2.4 mg) or placebo.
- BMI Reduction: Adolescents treated with semaglutide achieved a mean BMI reduction of 16.1%, compared with a 0.6% reduction in the placebo group.
- Weight Loss Achievement:
  - 73% of participants receiving semaglutide achieved at least a 5% reduction in body weight.
  - 53% achieved a weight reduction of ≥15%, compared with 5% in the placebo group.
  - 37% achieved ≥20% weight loss, indicating a magnitude of effect greater than that typically observed with earlier pharmacotherapies for obesity.

- Cardiometabolic Effects: Treatment with semaglutide was associated with reductions in waist circumference, glycated hemoglobin (HbA1c), and lipid levels.
- Safety and Tolerability: Gastrointestinal adverse effects, including nausea and vomiting, were commonly reported. However, discontinuation rates were lower than those observed with liraglutide, suggesting improved treatment tolerability.

Overall, semaglutide demonstrated substantially greater weight-loss efficacy than earlier GLP-1 receptor agonists in adolescent populations. While these findings support its clinical utility, gastrointestinal side effects remain a consideration, and long-term safety data in adolescents are still limited.

Clinical Trials on Dual GLP-1/GIP Agonists

Tirzepatide: Combining GLP-1 and GIP for Enhanced Weight Loss

Tirzepatide is a dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist developed to enhance weight loss beyond that achieved with GLP-1 receptor agonist monotherapy. Although pediatric clinical trials are currently lacking, substantial evidence from adult studies has demonstrated marked weight-loss efficacy.

In phase 3 adult clinical trials, most notably the SURMOUNT-1 study, tirzepatide produced significant and sustained reductions in body weight and metabolic parameters. The trial reported a mean weight loss of 20.9% over a 72-week treatment period, exceeding outcomes observed with semaglutide and positioning tirzepatide among the most effective pharmacologic treatments for obesity to date.[18] In addition to weight reduction, tirzepatide was associated with significant decreases in glycated hemoglobin (HbA1c), supporting its utility in individuals with obesity and insulin resistance.

While these findings highlight the therapeutic potential of dual incretin agonism, evidence for tirzepatide use in adolescent populations remains indirect. The absence of pediatric-specific clinical trials precludes definitive conclusions regarding its safety, efficacy, and tolerability in adolescents. Consequently, any consideration of tirzepatide for adolescent obesity management must be approached with caution, and its potential applicability remains speculative pending dedicated pediatric studies.[1] Unlike GLP-1 monotherapy, tirzepatide's additional GIP receptor activation may offer enhanced insulin sensitivity and lipid metabolism regulation; however, the clinical relevance of these effects in adolescents has yet to be established.

Mazdutide: A Dual GLP-1/Glucagon Receptor Agonist in Early Clinical Evidence

Mazdutide (IBI362) is a novel dual GLP-1 and glucagon receptor agonist designed to integrate appetite suppression with increased energy expenditure. Although its clinical development is still in early phases, available evidence from adult populations suggests favorable efficacy and tolerability profiles.

Pooled data from seven randomized controlled trials involving 680 adult participants demonstrated meaningful weight-loss outcomes, with non-diabetic individuals achieving reductions of up to 8.44% and diabetic participants achieving approximately 3.55% weight loss over a 24-week periods. Treatment with mazdutide was also associated with improvements in metabolic parameters, including reductions in HbA1c (−1.27%), fasting glucose levels, blood pressure, and lipid profiles, such as total cholesterol and triglycerides.[10]

Adverse events were predominantly mild to moderate gastrointestinal symptoms, including nausea, vomiting, and decreased appetite, with no significant increases in hypoglycemia or cardiovascular events reported. While pediatric data are currently unavailable, mazdutide's dual receptor mechanism and metabolic effects suggest potential future relevance for obesity treatment pipelines. Nevertheless, its role in adolescent obesity management remains theoretical and will require validation through appropriately designed pediatric clinical trials before clinical application can be considered.[11]

Clinical Trials on Triple GLP-1/GIP/Glucagon Agonists

Retatrutide: A Triple Agonist for Maximum Weight Loss

Retatrutide (LY3437943) is a triple incretin receptor agonist targeting the glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors, and is designed to maximize weight loss and metabolic improvement through complementary hormonal pathways. Its efficacy has been evaluated in adult populations, with a 48-week phase 2 clinical trial demonstrating substantial weight-loss outcomes.

- Weight Reduction:
  - A mean body weight reduction of 24.2% was observed, exceeding outcomes reported for both semaglutide and tirzepatide.
  - A total of 92% of participants achieved at least 5% weight loss, while 83% achieved reductions of ≥15% in body weight.
- Metabolic Effects:
  - Treatment was associated with improvements in fasting glucose levels and insulin sensitivity.
  - Favorable changes in lipid metabolism were observed, suggesting potential cardiometabolic benefits.

Despite these marked outcomes, it is important to emphasize that all available evidence for retatrutide is derived exclusively from adult clinical trials. Although its magnitude of effect has generated interest in its possible future role in adolescent obesity management, no pediatric-specific safety or efficacy data are currently available. Consequently, any potential application in adolescents remains speculative and requires confirmation through dedicated pediatric clinical trials.[13]

Triple agonists such as retatrutide introduce glucagon receptor activation, which may enhance fat oxidation and thermogenesis, thereby increasing energy expenditure and contributing to sustained weight loss. However, the long-term safety and developmental implications of glucagon receptor activation in adolescent populations remain uncertain.

Clinical trials of GLP-1–based therapies demonstrate a broad range of weight-reduction outcomes, as summarized in Table 3 and Figure 1. Liraglutide produced a mean weight loss of 4.3% after 56 weeks, whereas semaglutide achieved a substantially greater reduction of 16.1% over 68 weeks. Tirzepatide yielded the largest decrease among currently approved dual agonists, with an average weight loss of 20.9% at 72 weeks. Mazdutide resulted in a 14.0% weight reduction after 48 weeks at a 6 mg dose and an 8.44% reduction after 24 weeks in non-diabetic adults across two separate trials.[14,15] Retatrutide demonstrated the greatest reported efficacy among incretin-based therapies to date, with a mean weight reduction of 24.2% at 48 weeks.[22] These findings illustrate the progressive efficacy observed with increasing receptor engagement, while underscoring the need for cautious interpretation across heterogeneous study designs.

Safety and Tolerability of GLP-1-Based Therapies in Adolescents

Despite their effectiveness, GLP-1, dual, and triple agonists have side effects that require careful management:

Common Adverse Events

- Gastrointestinal Symptoms:
  - Nausea (42–61%).
  - Vomiting (22–36%).
  - Diarrhea (14–22%).

Table 3 Weight Reduction Outcomes in Clinical Trials

Treatment	% Weight Reduction (Weeks)
Liraglutide	4.3% (56 weeks)
Semaglutide	16.1% (68 weeks)
Tirzepatide	20.9% (72 weeks)
Mazdutide	14.0% (48 weeks, 6 mg dose) 8.44% (24 weeks, non-diabetic adults)[23,24]
Retatrutide	24.2% (48 weeks)

Note: Percent weight-reduction values are drawn from the pivotal clinical trials and phase 2/3 studies cited in the main manuscript (see references for detailed trial information, including sources[23] and[24] for Mazdutide).

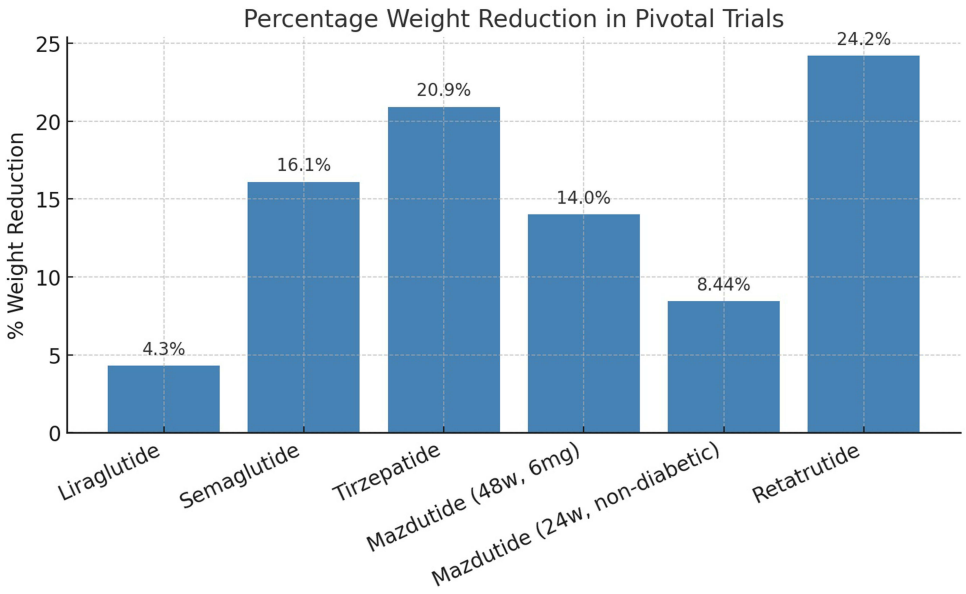

Figure 1 Proposed mechanisms of action of single, dual, and triple incretin-based agonists in obesity management. The figure illustrates hypothesized pathways through which GLP-1, GIP, and glucagon receptor activation may influence appetite regulation, insulin secretion, energy expenditure, and weight loss. These mechanisms are based on preclinical studies and adult clinical data, and their relevance to adolescent populations has not been fully established.

- Appetite Suppression: While beneficial for weight loss, excessive appetite suppression can lead to nutrient deficiencies.[3]
- Increased Heart Rate: Higher doses of GLP-1-based therapies have been linked to slight heart rate increases, warranting long-term monitoring.

Long-Term Safety Considerations

- Need for adolescent-specific trials: Most data come from adult studies, and pediatric safety remains underexplored.
- Exploring non-injectable formulations: Many adolescents prefer oral medications, driving research into oral GLP-1RA formulations.

Safety and Tolerability of GLP-1, Dual, and Triple Agonists in Adolescents

While GLP-1RAs and their dual and triple agonist counterparts have shown remarkable efficacy in weight loss and metabolic control, their safety and tolerability profiles remain key concerns, especially in adolescent populations. Since obesity pharmacotherapy in pediatric patients is relatively new, assessing potential risks and adverse effects is crucial to ensure long-term safety and adherence. This section reviews the side effects, risk factors, adherence challenges, and strategies to mitigate adverse effects associated with these therapies.

Common Adverse Effects of GLP-1-Based Therapies

Gastrointestinal (GI) Side Effects

Gastrointestinal discomfort is the most frequently reported side effect of GLP-1-based therapies, including single, dual, and triple agonists.

- Nausea: Experienced by 42–61% of patients, nausea is the leading cause of treatment discontinuation.[5]
- Vomiting: Reported in 22–36% of patients, especially in higher-dose regimens.[20]
- Diarrhea and Constipation: Affecting 14–22% of patients, these symptoms are dose-dependent but often improve over time.[3]

https://doi.org/10.2147/DMSO.S566414

Table 4 Common Side Effects of GLP-1-Based Therapies

Side Effect	GLP-1 (%)	Dual Agonists (%)	Triple Agonists (%)
Nausea	42	45	50
Vomiting	22	28	30
Diarrhea	14	18	22
Increased Heart Rate	3	5	7

Note: Percentages are approximate incidence rates from phase 2/3 clinical trials as cited in the main text (see References 2–5).

These adverse effects occur due to delayed gastric emptying, which prolongs satiety but can lead to discomfort.[24] The severity of symptoms varies between patients and is dose-dependent. Across pivotal trials, nausea occurred in 42% of participants on GLP-1 agonists, 45% on dual agonists, and 50% on triple agonists, with similar patterns for vomiting and diarrhea (Table 4 and Figure 2).

Strategies to Mitigate GI Side Effects

- Gradual dose escalation: Slowly increasing the dose over several weeks reduces the likelihood of severe nausea and vomiting.
- Taking medications with food: Some studies suggest that co-administering GLP-1RAs with meals can reduce nausea.
- Hydration and fiber intake: Encouraging fluid and fiber consumption may help alleviate constipation and diarrhea.

Cardiovascular Effects

GLP-1-based therapies have been associated with slight increases in heart rate, which may be a concern for adolescents with underlying cardiovascular conditions.[25]

- Semaglutide and liraglutide have shown a 3–4 bpm increase in resting heart rate in clinical trials.
- Tirzepatide and retatrutide may cause slightly higher increases, potentially due to their broader metabolic effects.

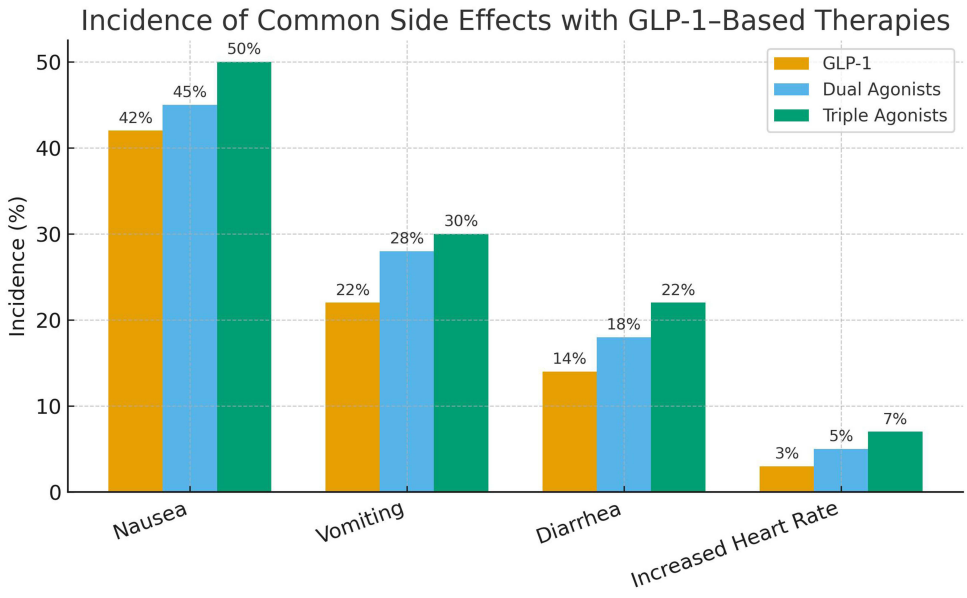

Figure 2 Reported weight-loss outcomes associated with GLP-1 receptor agonists and multi-receptor incretin therapies across selected clinical trials. The values presented are derived from independent studies with differing designs, durations, patient populations, and endpoints. Direct comparisons across agents should therefore be interpreted with caution. Data shown do not represent results from a single head-to-head comparative trial.

Clinical Implications

- While no major cardiovascular risks have been identified, monitoring heart rate and blood pressure is recommended for adolescents with pre-existing cardiovascular conditions.
- Recent reviews note the need for careful monitoring of cardiometabolic effects, particularly since long-term safety data in adolescents are still emerging.[14]

Gallbladder-Related Issues (Cholelithiasis)

Gallstone formation has been reported in patients using GLP-1RAs, particularly in those experiencing rapid weight loss.

- Liraglutide and semaglutide users exhibited higher rates of gallstone formation compared to placebo.[7]
- The risk is likely dose-dependent, with higher doses increasing bile saturation and slowing gallbladder motility.[1]

Preventive Strategies

- Slower weight loss rates may help mitigate gallstone formation.
- Bile acid supplements have been suggested for patients at high risk.

Long-Term Safety Considerations

Since GLP-1-based therapies are relatively new in pediatric populations, there are still limited long-term safety data available. Areas requiring further investigation include:

Effects on Growth and Development

Adolescence is a critical period for growth, and concerns exist regarding the long-term impact of GLP-1RAs on bone development and muscle mass.

- Preliminary studies indicate no significant negative impact on growth hormones, but more research is needed.
- Weight loss associated with GLP-1 agonists may lead to lean mass loss, which could be concerning for developing adolescents.

Recommendations for Monitoring Growth.

- Regular bone density and muscle mass assessments should be conducted in adolescents undergoing long-term treatment.[17]
- Combining pharmacotherapy with resistance training may help preserve lean body mass.

Psychological and Behavioral Considerations

Adolescents with obesity often face psychological distress, including depression, anxiety, and disordered eating behaviors.[3]

- GLP-1RAs have shown potential benefits in reducing emotional eating and food cravings, possibly improving mental well-being.[25]
- However, some patients experience increased anxiety related to appetite suppression and rapid weight loss.

Addressing Mental Health Concerns

- Integrating psychological support into obesity treatment plans can help manage emotional well-being.
- Close monitoring for disordered eating patterns is essential, especially in adolescents who may be vulnerable to unhealthy weight control behaviors.[1]

Adherence and Discontinuation Rates

Despite their proven efficacy, adherence to GLP-1, dual, and triple agonist therapies in adolescents remains a challenge due to side effects, injection-related concerns, and long-term commitment issues.

Factors Affecting Adherence

- Injection Aversion: Many adolescents struggle with weekly or daily injections, leading to treatment discontinuation.
- Side Effects: Gastrointestinal symptoms are the leading reason for non-adherence.
- Weight Loss Expectations: Unrealistic expectations about weight loss speed and sustainability may lead to frustration and early discontinuation.

Strategies to Improve Adherence

- Oral GLP-1 formulations are currently in development and may improve adherence in adolescents.
- Personalized dose adjustments based on tolerance levels can help mitigate severe side effect.
- Parental and psychological support play a crucial role in helping adolescents adhere to treatment.

Future Research Priorities in Safety and Tolerability

Despite the promising role of GLP-1-based therapies, several areas require further investigation to ensure their long-term safety in adolescents:

- Long-Term Metabolic Effects: Future studies should evaluate how sustained GLP-1RA use affects insulin sensitivity, lipid metabolism, and cardiovascular health over decades.
- Comparative Safety Studies: More research is needed to compare the safety profiles of single vs. multi-agonists in adolescents.
- Effects on Brain Development: Since GLP-1 receptors are expressed in the brain, there is interest in understanding their long-term impact on cognitive function and appetite regulation.
- Combination Therapies: Future clinical trials should explore whether combining GLP-1 agonists with other medications (eg, SGLT2 inhibitors or metformin) can enhance efficacy while reducing side effects.

Future Directions and Clinical Implications of GLP-1, Dual, and Triple Agonists in Adolescent Obesity

The use of GLP-1RAs and their dual and triple agonist counterparts has transformed obesity treatment, offering unprecedented weight loss and metabolic benefits. However, despite their proven efficacy, challenges remain in long-term safety, adherence, and accessibility for adolescents. As research progresses, personalized medicine approaches, novel drug formulations, and combination therapies will shape the future of obesity pharmacotherapy. This section explores potential future developments, research priorities, and clinical applications of GLP-1-based therapies for adolescent obesity.

Long-Term Safety and Efficacy in Adolescents

While short-term studies demonstrate the safety and effectiveness of GLP-1, dual, and triple agonists in adolescents, their long-term effects remain largely unknown.

Need for Long-Term Clinical Trials

Most trials evaluating liraglutide, semaglutide, tirzepatide, and retatrutide in adolescents have lasted 56–72 weeks, which may not be sufficient to assess long-term metabolic, cardiovascular, and developmental effects.[26]

- Future studies should track adolescent patients for at least 5–10 years to determine whether weight loss is sustainable and whether metabolic adaptations occur.

- Investigating cardiovascular health outcomes is critical, as weight loss may reduce long-term risks of hypertension, atherosclerosis, and insulin resistance.[12]
- Monitoring for endocrine effects: Given that adolescence is a critical period for growth and hormone regulation, it is essential to evaluate whether long-term GLP-1 therapy influences puberty, bone mineral density, or reproductive health.

Research Priorities for Long-Term Studies

- Establishing the long-term safety profile of GLP-1 and multi-receptor agonists in adolescents.
- Assessing adherence and weight regain trends after treatment discontinuation.
- Investigating the impact of long-term GLP-1 use on cardiovascular and endocrine health.

Personalized Medicine: Matching the Right Drug to the Right Patient

Not all adolescents respond equally to GLP-1-based therapies, highlighting the need for personalized treatment approaches.

Genetic and Metabolic Predictors of Treatment Response

- Some individuals exhibit greater weight loss and metabolic benefits with GLP-1 monotherapy, while others require dual or triple agonists to achieve similar effects.
- Genetic markers, gut microbiome composition, and baseline metabolic rate could help identify which patients benefit most from GLP-1, GLP-1/GIP, GLP-1/GCGR, or GLP-1/GIP/Glucagon agonists.
- Studies suggest that:
  - Patients with insulin resistance may respond better to GLP-1/GIP dual agonists (eg, tirzepatide).
  - Those with high lipid storage or hepatic steatosis may benefit more from GLP-1/GCGR agonists (eg, Mazdutide), due to enhanced fat oxidation and liver-fat reduction.[27]
  - Patients with more severe obesity and energy balance dysregulation may achieve better outcomes with triple agonists (eg, retatrutide).

The Role of Biomarkers in Predicting Outcomes

- HbA1c levels, fasting insulin, and lipid profiles may serve as biomarkers for predicting GLP-1RA treatment success.
- Future research should focus on identifying metabolic signatures that can guide drug selection for individualized obesity treatment.

Clinical Implications of Personalized Medicine

- More precise obesity treatment plans, reducing trial-and-error prescribing.
- Improved adherence, as patients are prescribed medications tailored to their specific metabolic profile.
- Better long-term weight loss outcomes, as therapies are matched to individual physiologic responses.[28]

Expanding the Use of GLP-1-Based Therapies Beyond Obesity

Although primarily used for obesity treatment, GLP-1 agonists and multi-receptor therapies may have broader applications in metabolic disease management.

Cardiovascular and Metabolic Benefits

- GLP-1 agonists reduce cardiovascular disease (CVD) risk factors, including hypertension, dyslipidemia, and systemic inflammation.[5]
- Retatrutide and tirzepatide have demonstrated significant improvements in lipid profiles and insulin sensitivity, making them valuable for adolescents at risk for metabolic syndrome.
- GLP-1RA therapy may also help prevent type 2 diabetes in obese adolescents, reducing the need for lifelong medication use.[12]

Table 5 Projected Growth of GLP-1-Based Therapies

Year	Estimated Number of Patients (Millions)
2022	5.4
2025	8.1
2030	12.3

Note: Estimated global patient numbers are drawn from market-analysis and epidemiologic projections discussed in the manuscript (see References 25–28 for the primary forecasting studies).

Treating Obesity-Related Comorbidities

- GLP-1 agonists show promise in treating NAFLD, a condition commonly seen in adolescents with obesity.
- Studies suggest potential applications for GLP-1RAs in reducing obstructive sleep apnea severity, particularly in adolescents with obesity and respiratory issues. Global utilization of GLP-1–based therapies is projected to rise from an estimated 5.4 million patients in 2022 to more than 12 million by 2030 (Table 5 and Figure 3).

Improving Adherence and Accessibility of GLP-1 Therapies in Adolescents

Despite their benefits, adherence challenges remain a major concern, particularly among adolescents who may struggle with long-term commitment to injectable medications.[29]

Addressing Injection Aversion

- Many adolescents prefer oral medications over injectables, leading to interest in developing oral formulations of GLP-1 agonists.
- Oral semaglutide has already been introduced for type 2 diabetes, and future research should explore oral formulations of dual and triple agonists.

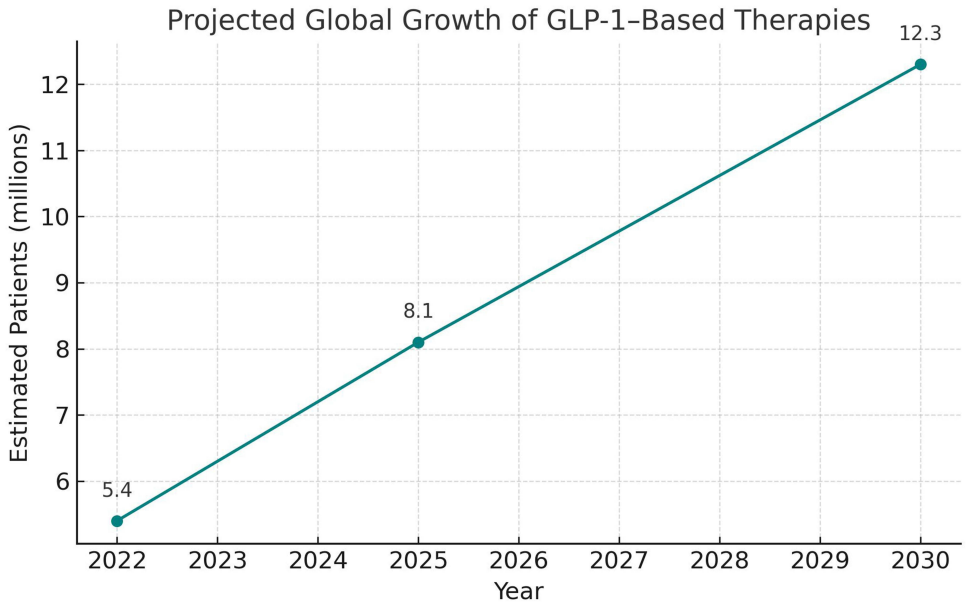

Figure 3 Developmental pipeline and projected clinical availability of incretin-based therapies for obesity. This figure represents developmental status and projected timelines rather than comparative clinical efficacy or treatment recommendations.

Enhancing Treatment Adherence

- Personalized support programs, digital tracking apps, and behavioral counseling could improve adherence.[19]
- Gradual dose escalation and managing expectations may help reduce early discontinuation due to side effects.[5]

Potential Strategies for Improving Access to GLP-1 Therapy

- Reducing treatment costs through insurance coverage expansion.
- Developing patient assistance programs for underprivileged adolescents.

Investigating Combination Therapies for Enhanced Outcomes

Given that obesity is a complex, multifactorial condition, combining GLP-1 agonists with other pharmacological agents may further improve treatment outcomes.

GLP-1 Agonists with SGLT-2 Inhibitors

- SGLT-2 inhibitors, used in diabetes treatment, may synergize with GLP-1 agonists to enhance weight loss and reduce cardiovascular risk.

GLP-1 Agonists with Behavioral Therapy

- Studies suggest that combining pharmacotherapy with structured lifestyle counseling leads to greater long-term success.

Lean Mass Preservation and Pubertal Development

It represent critical yet underexplored considerations in the pharmacological management of adolescent obesity. Rapid weight reduction induced by GLP-1–based therapies has been associated with proportional losses in fat-free mass in adult populations, raising concerns regarding potential impacts on skeletal muscle accrual during adolescence—a developmental period characterized by dynamic changes in body composition and linear growth. Given the role of insulin, growth hormone, and sex steroids in pubertal maturation, pharmacological modulation of appetite and energy balance during this window may theoretically influence musculoskeletal development, bone mineralization, and long-term metabolic health. However, current clinical trials of single, dual, and triple GLP-1 receptor agonists in adolescents provide insufficient data to adequately assess changes in lean mass trajectories or pubertal outcomes. Future studies should therefore incorporate standardized assessments of body composition, pubertal staging, and longitudinal growth parameters to ensure that weight-loss efficacy is not achieved at the expense of healthy developmental processes.

Conclusion

The development of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and their evolution into dual and triple receptor agonists represent an important advancement in the pharmacologic management of obesity. With the rising global prevalence of obesity among adolescents, lifestyle interventions alone are often insufficient to achieve sustained weight reduction and metabolic improvement. In this context, GLP-1–based pharmacotherapies have emerged as a valuable adjunct to lifestyle modification, with growing evidence supporting their role in improving weight-related and cardiometabolic outcomesThis review has examined the mechanisms of action, clinical efficacy, safety considerations, and future directions of GLP-1 single, dual, and triple agonists, with a focus on their potential relevance to adolescent obesity management.

Mechanisms of GLP-1, Dual, and Triple Agonists

GLP-1 receptor activation promotes appetite suppression, delayed gastric emptying, and improved insulin secretion, making it an established therapeutic target in obesity treatment. Dual GLP-1/GIP receptor agonists, such as tirzepatide, demonstrate enhanced metabolic effects in adult populations through improved insulin sensitivity and lipid metabolism. Dual GLP-1/glucagon receptor agonists, including mazdutide, integrate appetite suppression with increased energy

expenditure and fat oxidation, while triple GLP-1/GIP/glucagon agonists, such as retatrutide, further augment these mechanisms through multi-pathway receptor engagement.

Clinical Efficacy and Safety Considerations

Among adolescents, single GLP-1 receptor agonists—particularly liraglutide and semaglutide—have demonstrated clinically meaningful reductions in body mass index and improvements in cardiometabolic markers. In contrast, evidence supporting the use of dual and triple agonists is currently derived primarily from adult clinical trials. While these agents have demonstrated progressively greater weight-loss efficacy in adults, their safety, tolerability, and long-term effects in adolescent populations remain insufficiently characterized.

Across GLP-1–based therapies, gastrointestinal adverse effects remain the most commonly reported limitation. Additional concerns regarding cardiovascular effects, gallbladder disease, and potential long-term impacts on growth and development underscore the need for cautious interpretation of existing data in adolescents.

Implications for Clinical Practice and Future Research

At present, GLP-1 receptor agonists remain the primary evidence-supported pharmacologic option for adolescents with obesity. The integration of these therapies into clinical practice should emphasize individualized decision-making, close monitoring, and combination with behavioral and lifestyle interventions. While dual and triple agonists represent a promising area of pharmacologic innovation, their role in adolescent obesity management cannot be established without dedicated pediatric clinical trials.

Future research should prioritize long-term safety studies, real-world effectiveness analyses, and investigations into predictors of treatment response. Advances in pharmacogenomics and precision medicine may eventually refine patient selection; however, such approaches remain exploratory. Policy efforts should focus on improving access, affordability, and education surrounding obesity pharmacotherapy, while avoiding premature adoption of emerging agents in pediatric populations.

In conclusion, GLP-1–based therapies have expanded the therapeutic landscape of obesity management and offer meaningful benefits for adolescents when supported by appropriate evidence. Continued research, cautious clinical integration, and clear differentiation between adult and pediatric data will be essential to ensuring safe and effective use of these agents in adolescent obesity care.

Expert Opinion

GLP-1 receptor agonists, along with dual and triple agonists, have transformed the landscape of adolescent obesity treatment, offering an effective alternative to lifestyle interventions that often fail to produce long-term results. While liraglutide and semaglutide have laid the foundation for GLP-1-based therapies, the introduction of tirzepatide (GLP-1/GIP) and retatrutide (GLP-1/GIP/GCGR) has demonstrated the potential for even greater weight loss and metabolic improvements.[23]

Importantly, Mazdutide, a GLP-1/GCGR dual agonist, has shown promising outcomes in recent clinical trials, offering a unique mechanism that enhances fat oxidation, energy expenditure, and liver-fat reduction. With up to 14% weight loss over 48 weeks in Phase 3 trials and a favorable safety profile, it may represent an effective treatment option for adolescents, particularly those with lipid-driven metabolic disturbances.[30]

These advancements raise important questions about how multi-receptor agonists should be integrated into routine clinical care for adolescents and whether they could eventually replace more invasive treatments like bariatric surgery.

One of the biggest challenges in implementing GLP-1-based therapies is ensuring long-term adherence. Many adolescents struggle with injection-related discomfort, gastrointestinal side effects, and unrealistic expectations about weight loss timelines, leading to high discontinuation rates. Future research should focus on:

- Developing oral formulations.
- Improving patient education.
- Integrating behavioral support to enhance adherence.

Additionally, the high cost of these medications remains a major barrier, requiring policy changes to ensure broader insurance coverage and affordability.

Another key area for future investigation is personalized medicine. Not all adolescents respond equally to GLP-1 therapies, suggesting that genetic and metabolic profiling could help determine which patients benefit most from single, dual (GLP-1/GIP or GLP-1/GCGR), or triple agonists.

Moreover, the long-term effects of these treatments on adolescent growth, bone density, and cardiovascular health remain unclear, necessitating extended follow-up studies.

Overall, GLP-1, GLP-1/GIP, GLP-1/GCGR, and GLP-1/GIP/GCGR agonists are poised to become cornerstones of obesity treatment in adolescents. However, their integration into clinical practice must be strategic and personalized. Future efforts should prioritize patient stratification, cost reduction, accessibility, and robust safety monitoring to fully harness the benefits of these groundbreaking therapies.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analysed in this study. The material supporting the findings of this review is available from the cited sources.

Author Contributions

Mahroz Abid: Conceptualization, Formal Analysis, Data curation, Writing – review & editing, Visualization. Hongwei Jiang: Conceptualization, Writing – original draft, Writing – review & editing, Supervision. Muhammad Shahbaz Ahmad: Formal Analysis, Data curation, Writing – original draft, Visualization. Khizer Sohail Sheikh: Data curation, Writing – original draft, Writing – review & editing, Visualization. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No funding was received for this study.

Disclosure

The authors declare no competing interests.

References

1. Jakubowska A, le Roux CW, Viljoen A. The road towards triple agonists: glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide, and glucagon receptor – an update. *Endocrinol Metab*. 2024;39(1):12–22. doi:10.3803/EnM.2024.1942
2. 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. doi:10.1016/j.eclinm.2024.102782
3. Zhang X, Liu J, Ni Y, et al. Global prevalence of overweight and obesity in children and adolescents: a systematic review and meta-analysis. *JAMA Pediatr*. 2024;178(8):800–813. doi:10.1001/jamapediatrics.2024.1576
4. Fox CK, Barrientos-Pérez M, Bomberg EM, et al. Liraglutide for children 6 to <12 years of age with obesity—A randomized trial. *New Engl J Med*. 2024. doi:10.1056/NEJMoa2407379
5. Dauleh H, Pasha M, Gad H, et al. Single-center experience of using liraglutide in adolescents with obesity ± type 2 diabetes. *Cureus*. 2024;16(4):e58720. doi:10.7759/cureus.58720
6. Jastreboff AM, Kaplan LM, Frías JP, et al. Triple–hormone-receptor agonist retatrutide for obesity – a phase 2 trial. *New Engl J Med*. 2023;389(6):514–526. doi:10.1056/NEJMoa2301972
7. Hannon TS, Arslanian SA. Obesity in adolescents. *New Engl J Med*. 2023;389(3):251–261. doi:10.1056/NEJMcp2102062
8. Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: united States, 1963–1965 through 2017–2018. National Center for Health Statistics; 2020. Available from: https://www.cdc.gov/nchs/data/hestat/obesity-child-17-18/obesity-child-17-18.htm. Accessed May 18, 2026.
9. Kelly AS, Auerbach P. Glucagon-like peptide-1 agonists and pediatric obesity. *Pediatr Rev*. 2023;46(2):123–132. doi:10.1542/pir.2022-002873
10. Dickson SL, Shirazi RH, Hansson C, Bergquist F. GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. *Diabetes*. 2012;63(12):4186–4196. doi:10.2337/db13-1688
11. Williams DL, Nagaoka A, Kitami A, Mitsuhashi T, Hayakawa Y, Kobayashi M. Effects of GLP-1 on appetite and weight. *Front Neurosci*. 2014;8:91. doi:10.3389/fnins.2014.00091

12. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2020;43(2):487–493. doi:10.2337/dci19-0066
13. Cleveland Clinic. GLP-1 agonists: what they are, how they work & side effects. Cleveland Clinic; 2023. Available from: https://my.clevelandclinic.org/health/treatments/13901-glp-1-agonists. Accessed May 18, 2026.
14. Holst JJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Physiol Rev*. 2018;98(3):1405–1436. doi:10.1152/physrev.00034.2017
15. Mayo Clinic. Diabetes drugs and weight loss. Mayo Clinic; 2023. Available from: https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/expert-answers/byetta/faq-20057955. Accessed May 18, 2026.
16. ElSayed NA, Aleppo G, Aroda VR; American Diabetes Association. 9. pharmacologic approaches to glycemic treatment: standards of care in diabetes—2023. *Diabetes Care*. 2023;46(Suppl. 1):S140–S157. doi:10.2337/dc23-S009
17. American Journal of Medicine. Mechanisms of GLP-1 receptor agonist-induced weight loss. *Am J Med*. 2025;138:934–40.
18. Weghuber D, Barrett T, Barrientos-Pérez M, et al; STEP TEENS Investigators. Once-weekly semaglutide in adolescents with obesity. *New Engl J Med*. 2022;387(24):2245–2257. doi:10.1056/NEJMoa2208601
19. Anderson SL, Greenway FL, Fujioka K. Characterizing GLP-1 receptor agonist use in preadolescent and adolescent populations. *JAMA Network Open*. 2023;6(9):e2333648. doi:10.1001/jamanetworkopen.2023.33648
20. StatPearls. *GLP-1 Receptor Agonists in the Management of Type 2 Diabetes and Obesity*. StatPearls Publishing; 2023.
21. Kelly AS, Armstrong SC, Michalsky MP, Fox CK. Obesity in adolescents: a review. *JAMA*. 2024;332(9):738–748. doi:10.1001/jama.2024.11809
22. Eli Lilly and Company. Tirzepatide reduced sleep apnea severity by up to nearly two-thirds in adults with obstructive sleep apnea (OSA) and obesity. *PR Newswire*. 2024. Available from https://www.prnewswire.com/news-releases/tirzepatide-reduced-sleep-apnea-severity-by-up-to-nearly-two-thirds-in-adults-with-obstructive-sleep-apnea-osa-and-obesity-302118929.html. Accessed May 18, 2026.
23. Nalisa DL, Cuboia N, Dyab E, et al. Efficacy and safety of Mazdutide on weight loss among diabetic and non-diabetic patients: a systematic review and meta-analysis of randomized controlled trials. *Front Endocrinol*. 2024;15:1309118. doi:10.3389/fendo.2024.1309118
24. Ji L, Jiang H, Bi Y, et al. Once-weekly mazdutide in Chinese adults with obesity or overweight. *New Engl J Med*. 2025;392(22):2215–2225. doi:10.1056/NEJMoa2411528
25. Kelly AS, Auerbach P, Barrientos-Pérez M, et al; CARTA Study Group. A randomized, controlled trial of liraglutide for adolescents with obesity. *N Engl J Med*. 2020;382(22):2117–2128. doi:10.1056/NEJMoa1916038
26. Jastreboff AM, Aronne LJ, Ahmad NN, et al; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205–216. doi:10.1056/NEJMoa2206038
27. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of tirzepatide (dual GIP/GLP-1 agonist) in type 2 diabetes. *N Engl J Med*. 2021;385(6):503–515. doi:10.1056/NEJMoa2107519
28. Taweesedt PT, Orakpo N, Pelayo R. Pharmacological management of sleep apnea and obesity, a new frontier. *J Clin Sleep Med*. 2025. doi:10.5664/jcsm.11798
29. Sanyaolu A, Okorie C, Qi X, Locke J, Rehman S. Childhood and adolescent obesity in the United States: a public health concern. *Glob Pediatr Health*. 2019;6:1–11. doi:10.1177/2333794X19891305
30. Urva S, Coskun T, Loh MT, et al. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial. *Lancet*. 2022;400(10365):1869–1881. doi:10.1016/S0140-6736(22)02033-5