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MINIREVIEWS

Current and forthcoming pharmacotherapies for adolescent obesity: Evidence-based review

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Abstract

The prevalence of adolescent obesity has increased substantially in recent decades. This disease affects more than 20% of young people. Obesity is associated with metabolic disorders and heart disease. Conservative treatments are not effective in severe obesity. Therefore, this minireview aims to compare and clarify the effectiveness of treatments. It also seeks to identify areas requiring attention to guide clinical practice and future research. A literature search was conducted in databases including PubMed and Scopus. The study focused on randomised trials and meta-analyses in patients aged 12 to 18 years and lasting more than 12 weeks. The results show an improvement induced by glucagon-like peptide 1 receptor agonists, such as semaglutide. Semaglutide reduces body mass index by 16.1%. It is more effective than liraglutide in improving insulin sensitivity. The use of these drugs faces challenges, such as cost. There are also social inequalities that affect health equity. Although no short-term safety issues have been reported, there is still little information available on Tirzepatide and CagriSema in adolescents, compared to their known effect on adults. Therefore, we conclude that semaglutide is the current gold standard, but that there is an urgent need for longer-term studies, comparative evaluations, and safety trials that include paediatric cohorts in order to ensure safe access to pharmacological innovations.

Key Words: Adolescent obesity; Pediatric obesity; Anti-obesity medications; Weight reduction; Adherence; Quality of life

Core Tip: This minireview demonstrates that current evidence confirms that lifestyle interventions are insufficient for severe cases, proposing pharmacotherapy as a clinical necessity, where glucagon-like peptide 1 receptor agonists, especially semaglutide, are positioned as the current standard of care; while critically evaluating the horizon of dual agonists and other combinations. The article identifies new structural barriers such as high costs, global shortages, and strict insurance requirements. It highlights the urgency of conducting new direct comparisons emphasizing the need to integrate data from ongoing Food and Drug Administration-mandated post-marketing surveillance and prospective registries to monitor outcomes in pubertal maturation, bone health, and neurobiological impact.

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INTRODUCTION

Obesity constitutes a global public health challenge, defined as a chronic multifactorial disease with severe multisystemic, psychosocial, and economic impacts[1,2]. The shift of this disease burden toward increasingly younger populations is indicative of widespread exposure to obesogenic environments from early life stages[3]. Clinically, this precipitates the premature onset of cardiometabolic complications, resulting in a probable reduction in healthy life expectancy[4,5]. According to the American Academy of Pediatrics (AAP), adolescent obesity is defined as a body mass index (BMI) greater than or equal to the 95th percentile in individuals aged 10 years to 19 years[6]. Under these criteria, prevalence has increased from 17.7% to 21.5% in the last decade, particularly affecting the 12-to-19-year age group[7]. This trend aligns with findings from the most recent Global Burden of Disease study, which revealed that adolescent obesity has tripled globally over the last 30 years. Furthermore, it is estimated that by 2050, obesity will surpass overweight in the majority of world regions[8]. The likelihood of such a scenario suggests that current preventive strategies have been and will remain insufficient to contain the crisis, creating a cycle of disease expansion in the face of ineffective public health measures. Although lifestyle modification regarding nutrition and physical activity remains the cornerstone of treatment, it primarily addresses the behavioral component of energy intake[2,6]. However, its efficacy is often limited by compensatory neurobiological mechanisms. This provides the rationale for pharmacotherapy, which, by targeting any level of the gut-brain axis, can overcome biological resistance and facilitate therapeutic success[9-11]. Given that puberty represents a critical window for physical, psychological, and sexual development, delaying effective treatment following lifestyle failure may contradict the principle of beneficence[12]. This is particularly relevant as recent evidence confirms that timely intervention reduces risk, morbidity, and mortality extending into early and late adulthood[13,14]. Nevertheless, the indication for pharmacotherapy must be grounded in the concept of "robust pharmacological therapy", defined by high-quality evidence derived from meta-analyses, systematic reviews, and pivotal clinical trials that demonstrate safety, sustained efficacy, and clinically relevant outcomes. Therefore, the objective of this article is to review the current and forthcoming pharmacotherapies for adolescent obesity in 2025.

METHODOLOGY

A narrative minireview was conducted to synthesize the current evidence on pharmacological interventions for adolescent obesity. A comprehensive literature search was conducted in PubMed and Scopus using combinations of keywords and Medical Subject Headings. A total of 82 eligible studies were included, comprising clinical trials, systematic reviews, meta-analyses, observational studies, relevant narrative reviews, and selected case reports published in English. Conference abstracts, editorials, and non-peer-reviewed sources were excluded, and no restrictions were applied regarding publication date in order to collect both fundamental and recent evidence. Articles were selected based on their relevance to real-world clinical challenges in the pharmacotherapeutic management of adolescent obesity, specifically focusing on the efficacy, safety profiles, and metabolic outcomes of Food and Drug Administration (FDA)-approved agents, with the aim of providing a practical framework for evidence-based weight management in routine pediatric practice.

ESTABLISHED CLINICAL EVIDENCE IN ADOLESCENTS

Glucagon-like peptide 1 receptor agonists

This class of drugs mimics the action of the endogenous incretin hormone glucagon-like peptide 1 (GLP-1), acting on specific receptors in the hypothalamus (mainly the dorsomedial nucleus) through a combination of peripheral effects (glycemic control and delayed gastric emptying) and central effects (hypothalamus and reward pathways), resulting in reduced food intake and increased satiety[15].

The first GLP-1 agonist approved by the FDA (2020) and the European Medicines Agency (2021) for weight management in adolescents is liraglutide. Its efficacy has been established in the SCALE Teens study (Satiety and Clinical Adiposity - Liraglutide Evidence in adolescents). The study included 251 adolescents with obesity who had not responded adequately to lifestyle therapy alone, which is established as fundamental in the treatment regimen for children and adolescents[16]. Participants treated with liraglutide showed a greater reduction in BMI and greater categorical weight loss compared to placebo[17]. More recent evidence shows that liraglutide remains effective in reducing BMI-standard deviation score in routine clinical practice[18]. Another point is that the safety profile was consistent with that in adults. Meta-analyses confirm that among GLP-1 agonists, liraglutide was more likely to cause nausea, vomiting, hypoglycemia, and, in particular, injection site reactions than placebo[19]. These events were mild to moderate in intensity and decreased over time. In addition, evidence confirmed that treatment with liraglutide did not alter linear growth velocity or pubertal progression (Tanner stages)[17].

On the other hand, semaglutide has been positioned as the most effective treatment for this population compared to other treatments[19]. The STEP Teen (Semaglutide Treatment Effect in People with obesity) trial showed that semaglutide achieved an average BMI reduction of 16.1%[20], which is unprecedented in pediatric pharmacotherapy and superior compared to liraglutide[21] (Figure 1). As with liraglutide, semaglutide also has cardiometabolic benefits with regulation of alanine transaminase, very-low-density lipoprotein and total cholesterol[22,23]. Also, there has been an improvement in insulin sensitivity, measured by a 35% reduction in homeostatic model assessment of insulin resistance[24]. Semaglutide is administered by weekly subcutaneous injection (unlike the daily administration required by liraglutide), which promotes adherence to treatment. Another aspect is the safety profile which was consistent with the GLP-1 class, with gastrointestinal effects being the most common, although a 4% rate of cholelithiasis was also observed[20]. However, the available evidence on long-term safety in adolescents remains limited, particularly in relation to the risks of cholelithiasis, pancreatitis, suicidal ideation, and eating disorders[25]. There are other agonists such as exenatide and dulaglutide that have been evaluated in adolescents. Dulaglutide plays a lesser role in reducing BMI in adolescents. However, its primary indication is the management of type 2 diabetes, rather than obesity[26]. There are also meta-analyses that demonstrate benefits in weight reduction with exenatide, but with much less potency[27]. Therefore, these drugs are reserved for contexts in which diabetic comorbidity is more prevalent.

Other classes

Phentermine/topiramate (PHEN/TPM) is an oral pharmacological option for the treatment of obesity. Although topiramate alone is not approved by the FDA for obesity management, the combination therapy has demonstrated clinically meaningful efficacy. In clinical trials, PHEN/TPM has been shown to reduce BMI by approximately 10.4% at higher doses[28]. The combination also promotes appetite suppression and increased satiety[29]. However, adverse effects such as paresthesia and dysgeusia may limit its use in some patients. In addition, the teratogenic potential of topiramate must be considered; therefore, appropriate pregnancy prevention strategies are required in female adolescents [30]. Orlistat was historically the only pharmacological option available for the treatment of obesity in adolescents. However, more recent clinical evidence has demonstrated only modest efficacy compared with newer anti-obesity medications[21].

Therapies for monogenic and syndromic obesity

The assessment of genetic causes of obesity (syndromic, monogenic, and polygenic) is critical, particularly in children presenting with extreme obesity before 5 years of age, severe hyperphagia, or a strong family history. For these specific phenotypes, precision medicine has introduced targeted pharmacotherapies[31]. Setmelanotide has emerged as an effective treatment for monogenic and syndromic forms of obesity. Unlike the previous ones we have discussed, this is a

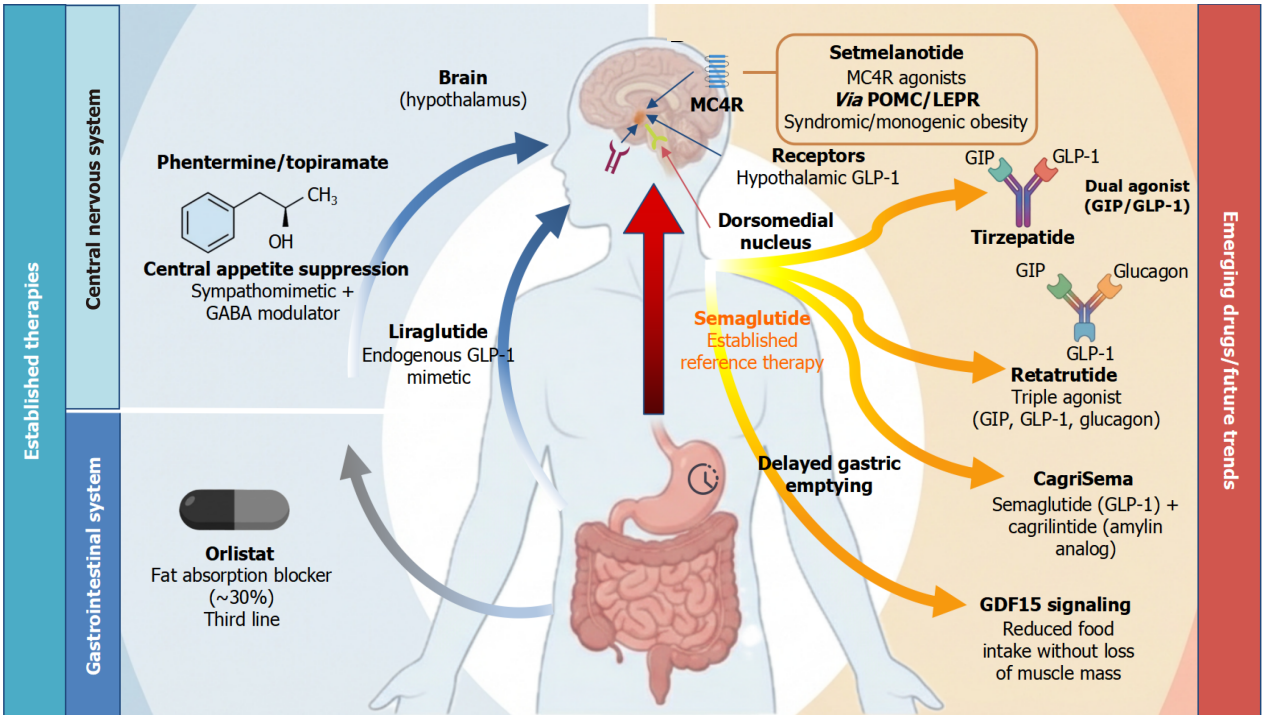

Figure 1 Current and emerging pharmacological landscape for adolescent obesity. The mechanisms of action of the reviewed therapies are presented. A: Established therapies. These include peripheral agents like orlistat, which inhibits gastric and pancreatic lipases to reduce fat absorption; central appetite suppressants such as phentermine/topiramate (acting *via* gamma-aminobutyric acid modulation and sympathomimetic pathways); and glucagon-like peptide-1 receptor agonists (liraglutide and semaglutide) that target the hypothalamus and dorsomedial nucleus to increase satiety while delaying gastric emptying. Setmelanotide is shown targeting the melanocortin 4 receptor pathway for specific monogenic obesity cases; B: Emerging drugs and future trends. This section details next-generation multi-agonists, including dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonists (tirzepatide) and triple glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1/glucagon agonists (retatrutide). It also highlights combination therapies like CagriSema (semaglutide and the amylin analog cagrilintide) and novel signaling pathways such as growth differentiation factor 15, aimed at reducing food intake while preserving lean muscle mass. GABA: Gamma-aminobutyric acid; MC4R: Melanocortin 4 receptor; POMC: Proopiomelanocortin; LEPR: Leptin receptor; GLP-1: Glucagon-like peptide-1; GIP: Glucose-dependent insulinotropic polypeptide; GDF15: Growth differentiation factor 15.

melanocortin-4 receptor agonist, which participates in appetite regulation through cyclic adenosine monophosphate-based signaling cascades[32]. The drug's efficacy had previously been established in proopiomelanocortin and leptin receptor deficiencies[33,34]. This demonstrated that the melanocortin 4 receptor pathway is a therapeutic target. More recently, research has been conducted that justifies its use in forms of obesity such as Bardet-Biedl syndrome, which is a rare hereditary disorder associated with hyperphagia and severe obesity[35]. When the drug is administered, significant weight loss has been demonstrated, with reductions in hunger severity/frequency scores[36]. On the other hand, the safety profile of this drug has been studied in several patients, in whom mostly mild or moderate effects have been found, the most common being skin hyperpigmentation and injection site reactions such as erythema, pruritus, and pain, in addition to gastrointestinal symptoms[37].

EMERGING AGENTS/IN DEVELOPMENT

Tirzepatide

The drug tirzepatide is an insulinotropic polypeptide [glucose-dependent insulinotropic polypeptide (GIP)] and a GLP-1 receptor agonist. The SURMOUNT-1 trial evaluated 2532 adult participants with obesity who were assigned to groups receiving different doses of tirzepatide. A reduction in body weight percentage directly proportional to the doses and a lower risk of progression to type 2 diabetes were observed compared to placebo[38-40]. On the other hand, treatment options for type 2 diabetes in adolescents are limited, so studies are needed to demonstrate the efficacy of tirzepatide in this population. The SURPASS-PEDS trial showed a median reduction of 2.23% in hemoglobin A1c compared to placebo, and there was also a reduction in BMI of between 7.4% and 11.2%, depending on the dose administered[41].

A recent study linked the use of tirzepatide with an increased risk of developing osteoporosis compared to other GLP-1 agonists. The most likely mechanism is the reflection of body weight reduction in bone mineral density, where lean mass is lost, which is related to osteoclast activity. Resorption prevails over bone formation, therefore increasing the risk of osteoporosis and fractures. Although the article mentions prevalence in young adults, it does not mention the inclusion of adolescents. However, it is known that lean mass loss in adolescents can be significantly risky for bone density, as they are in a period of acquiring maximum bone strength, and bone strength depends on muscle structure, making lean mass loss in adolescents risky[42-44].

Triple agonist/drug combinations

In an open-label, adult participants with obesity were evaluated after receiving retatrutide, a triple agonist of GIP, GLP-1, and glucagon receptors. Percentage weight reductions of up to more than 30% were observed with a 12 mg dose of retatrutide. In this trial, various adverse events were reported in more than 70% of participants who received the treatment, including nausea, vomiting, and constipation, occurring more frequently in participants who received retatrutide compared to placebo[45,46]. However, pediatric cohort studies are needed to clarify its efficacy and safety in this population[47].

The drug CagriSema is a combination of the GLP-1 receptor agonist semaglutide with the long-acting amylin analogue cagrilintide. A phase 2 trial showed clinical improvements in adults with type 2 diabetes, with reported improvements in glycemic control and body weight, where a greater reduction in hemoglobin A1c was found than with cagrilintide alone. Adverse events were reported less frequently by 68% of participants who received CagriSema, with gastrointestinal events being the most common. More studies are needed on the efficacy and safety of CagriSema in adolescents[48]. However, in a double-blind, placebo-controlled trial, adverse events were observed in adolescents, the most common being the same as in adults. Furthermore, no effect on pubertal development was found during the trial period[20].

Orforglipron, an oral GLP-1 receptor agonist, has been evaluated in a phase 2 trial involving adults with obesity or overweight without diabetes. In this study, the mean baseline body weight was 108.7 kg, and treatment resulted in a reduction of -9.4% to -14.7% in body weight at week 36. The most commonly reported adverse events were gastrointestinal in nature[49]. Another study conducted in patients with type 2 diabetes who were overweight or obese also demonstrated improvements in cardiometabolic parameters. Reductions in blood pressure and lipid profiles were observed compared with placebo, with decreases in blood pressure ranging from approximately -6.5 to -10.6 mmHg. Total cholesterol decreased by approximately -4.2% to -9.2%, while triglyceride levels decreased by -14.6%[20]. With regard to adolescents, dedicated clinical trials are still required to determine the tolerability, safety profile, and efficacy of orforglipron in this population[50].

Other pharmacological or non-traditional approaches

Currently, GLP-1 agonists have proven effective in treating obesity, but they have adverse effects such as diarrhea and constipation. Consequently, treatment options that do not cause recurrent side effects are needed. Recent studies indicate that the growth differentiation factor 15 signaling pathway is a promising option for the management of obesity, as it reduces food intake, leading to weight loss, and has minimal implications for muscle loss, making it ideal for those who cannot tolerate GLP-1. However, more studies are needed on its efficacy in children, as plasma growth differentiation factor 15 levels are different from those in adults. At the same time, precision medicine takes an individualized approach, covering preventive, diagnostic, and therapeutic measures, and seeks treatment efficacy by considering biological markers that can be used to predict the effectiveness of therapies[51-53]. Further information has been summarized in Figure 1.

COMPARISON OF EFFICACY AND SAFETY

We have found a limitation in the current literature, because of the scarcity of randomized clinical trials that compare head-to-head different anti-obesity drugs. Actually, most of the available evidence derives from placebo-controlled studies. Therefore, we considered recently published network meta-analyses that have synthesized both direct and indirect evidence.

When evaluating the magnitude of weight loss, weekly GLP-1 agonists are identified as the most potent interventions and are therefore considered the current pharmacological treatment. Specifically, semaglutide has shown the greatest reduction in BMI z-score in adolescents[20,22]. Compared to liraglutide, the latter is inferior in both weight loss and dosage preference[25]. However, as explained in the previous section, liraglutide achieves significant weight reduction compared to placebo, but the need for daily injections presents a barrier to long-term adherence.

With regard to PHEN/TPM, it is a competitive alternative in terms of efficacy, according to the latest research. In direct and indirect comparisons, PHEN/TPM demonstrated a greater reduction in BMI than liraglutide and, in some models, numerically close to semaglutide[21]. Orlistat, on the other hand, has been relegated to a third-line option. Its effectiveness in reducing BMI is modest, confirming its inferiority compared to other modern agents[54,55].

In terms of safety, GLP-1 agonists have the highest rate of gastrointestinal events, including nausea and vomiting[56]. However, semaglutide has a slightly higher tolerability profile in terms of severe discontinuation rates[19]. On the other hand, evidence also tells us that no significant association has been found between the use of GLP-1 receptor agonists and an increased risk of suicidal ideation or behavior in adolescents[57]. Further information has been summarized in Table 1 [17,20,24,28,32,35,58-66].

PHARMACOTHERAPY TRENDS AND BARRIERS

Prescription trends and market evolution

The pharmacological treatment of obesity in adolescents over the last 10 years has varied from minimal use to the integration of protocols into clinical practice. In 2023, AAP guidelines were published, and based on these, in 2024-2025, a large amount of information and evidence on their use was collected and consolidated. As a result, there has been an

Table 1 Comparative efficacy of pharmacotherapies for adolescent obesity, ranked by magnitude of body mass index reduction

Drug (class)	Mechanism of action	Efficacy (key data)	Additional comments and comparisons	Ref.
General obesity indications (ranked by potency)				
Semaglutide (GLP-1 agonist)	GLP-1 agonist (weekly). Increases satiety, reduces gastric emptying	BMI reduction: Approximately 16%-17% (*vs* placebo). Weight loss ≥ 5%: 73% of patients. Weight loss ≥ 20%: 37% of patients	Superior to liraglutide and exenatide in reducing BMI-SDS. Greater likelihood of achieving weight loss	[20,24]
Phentermine/topiramate (combination)	Sympathomimetic + GABA modulator. Central appetite suppression	BMI reduction: Approximately 10.4% (high dose *vs* placebo) to approximately 7.5% (real world). Weight loss ≥ 5%: Approximately 47% of patients	Efficacy comparable to semaglutide in some models, superior to liraglutide and orlistat. High-potency oral alternative, superior to Liraglutide, but with a higher safety monitoring burden	[28,58]
Liraglutide (GLP-1 agonist)	GLP-1 agonist (daily)	BMI-SDS reduction: -0.23 (*vs* placebo, common obesity), -0.34 (T2D). ≥ 5% BMI reduction: 43.3% of patients. ≥ 10% BMI reduction: 26.1%	Effective *vs* placebo, but inferior to semaglutide and Fen/Top in indirect comparisons. MD Weight: Approximately -5.6% *vs* placebo	[17,59,60]
Exenatide (GLP-1 RA)	GLP-1 agonist (weekly/daily)	BMI reduction: Between -1.1 and -1.7 points *vs* placebo. Main benefit in glycemic control	Inferior to semaglutide and liraglutide in terms of pure weight loss. Considered a second-line treatment	[61-63]
Orlistat (lipase inhibitor)	Blocks intestinal fat absorption (approximately 30%).	BMI reduction: -0.55 kg/m^2 *vs* placebo. No statistically significant difference between orlistat and placebo was also documented	Lower efficacy compared to all modern agents. High dropout rate. Recent meta-analyses show inconsistent short- and long-term results in BMI reduction	[64-66]
Precision medicine (genetic/syndromic indications)				
Setmelanotide (MC4R agonist)	MC4R agonist. Restores satiety pathway in genetic defects	POMC/LEPR deficiency: Massive reduction (approximately 42 points in BMI percentage of the 95th percentile). BBS: Moderate-high reduction (approximately 9.5% BMI)	Not comparable in general NMA. Exclusive gold standard for monogenic/syndromic obesity (BBS, POMC, LEPR). Key effect: Significant reduction in hunger score (hyperphagia) in > 60% of patients	[32,35]

GLP-1: Glucagon-like peptide-1; BMI: Body mass index; SDS: Standard deviation score; GABA: Gamma-aminobutyric acid; T2D: Type 2 diabetes; MD: Mean difference; RA: Receptor agonist; MC4R: Melanocortin 4 receptor; POMC: Proopiomelanocortin; LEPR: Leptin receptor; BBS: Bardet-Biedl syndrome; NMA: Network meta-analysis.

exponential increase in the use of GLP-1 receptor agonist molecules. Thanks to its superior efficacy, semaglutide has become the most widely used drug, compared to liraglutide, which is less effective in reducing BMI. In addition, the recent approval of a new dual GIP/GLP-1 agonist drug (tirzepatide) has changed expectations and the therapeutic horizon[66]. Much of the data collected in recent studies has demonstrated a radical change in medical behavior regarding obesity. It has gone from being addressed as a specific behavioral failure of the adolescent in question to a disease with a neurological and physiological component that requires comprehensive and early intervention to prevent and reduce widespread long-term complications[67].

Barriers to access, costs, and equity in health care

The gap between clinical need and actual effective access to medicines is critical. Among the main structural barriers are high costs and inconsistencies in health insurance reimbursement policies. These organizations often impose "prior authorization" criteria that require and prioritize months of behavioral therapy before covering new-generation drugs [68].

Due to global shortages, the immediate availability of these drugs has been compromised. This has created a secondary market of compounding pharmacies, with real risks and no safety regulations or clear standards. These limitations exacerbate the disparities already present in many Western societies: Adolescents belonging to ethnic minorities and low socioeconomic status who, sadly, experience substantial delays in starting treatment, as summarized in Table 2. The latter also have the highest rates of forced discontinuation, which exacerbates inequality in public health outcomes[69].

Psychosocial considerations, mental health, and ethical risk

Evidence from 2024 and 2025 indicates that the impact of these therapies goes beyond weight loss, with significant improvements in health-related quality of life and a considerable reduction in the internalization and relative impact of weight stigma[30]. However, the future is not all rosy, as there are still some gray areas to be clarified. The pharmacological management of obesity in adolescents still presents unique challenges. There is real and latent concern about the impact that rapid weight loss may have on developing body image, and whether it could mask or even exacerbate pre-existing eating disorders[70,71].

Table 2 Determinants of access, prescribing trends, and psychosocial challenges in the use of drugs for the treatment of obesity in the adolescent population: An analysis of the outlook for 2025[1]

Parameters	Current trend (2025)	Main barriers	Impact on equity/psychosocial	Ref.
Prescription	Shift from liraglutide to semaglutide and tirzepatide due to greater potency (BMI reduction > 15%)	Global supply shortages and clinical inertia in primary care	Preferential access in private sectors; gap in public health due to lack of stock	[6,67,68]
Economic access	Increased demand for health insurance coverage for new-generation drugs (arGLP-1)	High out-of-pocket costs and strict "prior authorization" requirements by insurers	Exclusion of adolescents from low socioeconomic status and ethnic minorities	[68,69]
Real use	Transition to digital care and telemedicine models for chronic disease management	Lack of specialists in pediatric obesity in rural or remote areas	Geographical inequality: "Medical deserts" in many communities and locations limit multidisciplinary follow-up	[68-70]
Psychosocial considerations	Reduction of weight stigma by validating the biological basis of treatment	Risk of off-label use driven by social media aesthetic standards	Possible exacerbation of eating disorders due to rapid weight loss	[70,71]

[1]This table summarizes the transition from treatment models based solely on lifestyle to the integration of molecules that serve as glucagon-like peptide-1 receptor agonists and dual agonists (glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1). It highlights the gap between the clinical efficacy of drugs such as semaglutide and tirzepatide and systemic barriers to coverage.
BMI: Body mass index; arGLP-1: Glucagon-like peptide-1 receptor agonists.

FUTURE DIRECTIONS

The emergence of GLP-1 receptor agonists as evidence-based pharmacotherapy for adolescent obesity represents a significant therapeutic advance, yet critical knowledge gaps persist across multiple domains that will shape the next decade of clinical practice and research. While short-term efficacy has been established through pivotal trials, the field now confronts fundamental questions about durability of effect, comparative effectiveness, optimal implementation strategies, and equitable access. This section synthesizes current evidence limitations and outlines priority research directions essential for responsible translation of pharmacotherapy into sustainable obesity management for adolescents.

Long-term efficacy and safety beyond two years

Current approvals for semaglutide and liraglutide rest on trials not exceeding 68 weeks[19], with post-treatment follow-up of 7-26 weeks showing early weight rebound signals. A five-year post-sleeve gastrectomy cohort demonstrated progressive GLP-1/GIP attenuation, with 23.5% requiring rescue semaglutide by year three[72], though this surgical context limits generalizability to primary pharmacotherapy. Critical outcomes remain unexamined: Linear growth velocity, peak bone mass accrual, pubertal maturation, and reproductive function during multi-year GLP-1 exposure. Ongoing trials of tirzepatide in adolescents will provide longer-term data in coming years. Given obesity's chronicity, surveillance registries tracking growth parameters, bone density, and reproductive health could bridge evidence gaps while extended trials mature.

Head-to-head comparative effectiveness studies

Direct comparative trials between GLP-1 receptor agonists in adolescents are absent, forcing reliance on network meta-analyses where semaglutide ranks first (surface under cumulative ranking > 98%)[21], yet certainty remains "very low" in substantial proportions of comparisons[73]. Real-world evidence from adult populations reveals discontinuation rates of 64.8% at 12 months among patients without type 2 diabetes[74], substantially higher than the 13.5% observed in the controlled environment of the STEP 8 trial[75]. This efficacy-effectiveness gap likely amplifies in adolescents given developmental factors affecting adherence. Priority research includes pragmatic trials comparing semaglutide *vs* liraglutide with discontinuation and quality of life as co-primary endpoints. Tirzepatide requires dedicated adolescent trials with direct comparisons to existing GLP-1 receptor agonists rather than perpetuating placebo-controlled designs that generate indirect evidence.

Pharmacokinetic optimization and novel formulations

Adolescent-specific pharmacokinetic characterization remains incomplete. Liraglutide has published population analysis identifying body weight, not age, as the primary covariate[74], while semaglutide pediatric data derive from modeling (steady-state 74.0 nmol/L at 2.4 mg) rather than direct measurement. Tirzepatide lacks any clinical data under 18 years, relying on physiologically-based modeling predicting 25%-50% dose reductions for younger adolescents. Oral formulations of semaglutide are under investigation and may improve treatment adherence[76]. Novel extended-interval formulations, including dual- and triple-agonist approaches, show promise in adult trials but require pediatric-specific evaluation[75]. Typical multi-year regulatory lags in pediatric drug approvals mean that current adolescents may not benefit from innovations in development during their critical treatment window[14].

Integrated care delivery model

Evidence supporting integrated multidisciplinary management, combining pharmacotherapy with intensive behavioral treatment, nutrition, and family engagement, derives almost entirely from lifestyle intervention implementation studies rather than from controlled comparisons against pharmacotherapy-alone strategies[2]. The nutrition counseling suite in GLP-1 therapy compares STEP-1 (semaglutide + general counseling) with STEP-3 (semaglutide + intensive intervention) and SURMOUNT-1/3 (tirzepatide with standard support *vs* after intensive intervention), suggesting possible added value of intensive programs, but without standardizing or quantitatively isolating the effect of behavioral "intensity"[76]. Specialty pharmacy integration models, such as the Vanderbilt model, have demonstrated the ability to improve access to and adherence to treatment through integrated workflows that manage prior authorizations and patient education[77]. Research priorities include pragmatic trials randomizing adolescents to integrated intensive treatment plus pharmacotherapy *vs* pharmacotherapy with standard counseling, and implementation science investigating barriers to evidence adoption across diverse settings, particularly rural communities lacking multidisciplinary obesity teams[2].

Health policy and equitable access

The 2023 AAP guideline recommending pharmacotherapy for adolescents aged 12 years and older[6] catalyzed increased prescribing between 2020 and 2023, yet fewer than 1% of eligible adolescents with obesity received pharmacological treatment, revealing a profound implementation-to-practice failure. Insurance coverage remains the primary barrier to access. State Medicaid and commercial insurers impose restrictive coverage policies, typically requiring elevated BMI thresholds (≥ 120% of the 95th percentile) plus multiple comorbidities[78]. Out-of-pocket costs exceeding 1000 dollars monthly create insurmountable barriers for many families, exacerbating disparities where adolescents from minority backgrounds, rural communities, and lower-income households face compounding obstacles to treatment initiation and continuity[79]. European Medicines Agency approval has not translated to systematic public financing, with most member states limiting coverage to exceptional cases. In middle- and low-income nations, GLP-1 receptor agonists remain effectively inaccessible outside private, out-of-pocket purchase. Policy research examining prior authorization reform, value-based contracting linking reimbursement to sustained weight loss outcomes, and mechanisms ensuring equitable geographic distribution of specialized obesity programs would complement clinical investigation[80].

Synthesis and priorities

These six domains converge on crosscutting themes: The necessity for longer follow-up beyond current efficacy endpoints, understanding real-world effectiveness separate from controlled trial efficacy, and addressing implementation barriers preventing evidence translation into equitable practice[81]. While awaiting long-term trials of sufficient duration, pragmatic registry studies could provide intermediate evidence on safety signals and comparative outcomes within diverse populations[39]. Stakeholder engagement with adolescents, families, and community health workers will prove critical for defining patient-centered outcomes that reflect lived experience with chronic disease[82]. Ultimately, future directions must balance scientific rigor with recognition that obesity requires sustained, multifaceted management, pharmacologic tools function optimally within comprehensive care ecosystems ensuring all adolescents benefit from therapeutic advances, regardless of insurance status, geography, or socioeconomic position.

CONCLUSION

By 2026, pharmacological therapies for adolescent obesity have reached unprecedented biological potency. The consolidation of semaglutide and the emergence of tirzepatide represent a major therapeutic advance, highlighting the limitations of lifestyle interventions alone and establishing pharmacotherapy as a key component of comprehensive obesity management.

However, this progress is accompanied by a challenging reality. While pharmacological innovation continues to advance toward next-generation agents such as the triple agonist retatrutide, real-world access to these therapies remains fragmented by socioeconomic barriers and systemic disparities. These limitations risk transforming new-generation anti-obesity medications into treatments accessible primarily to privileged populations, leaving the most affected groups with limited therapeutic options. From a clinical perspective, the challenge extends beyond prescribing medications to achieve BMI reduction. It also involves careful monitoring of potential long-term risks that remain uncertain, including pancreatic safety, effects on bone density, and the possible exacerbation of eating disorders within the context of rapid weight loss and aesthetic normalization.

In this context, the scientific community must actively integrate evidence emerging from prospective registries and mandated post-marketing surveillance studies to bridge the gap between clinical trial findings and real-world adolescent development. At the same time, public health policies must move beyond commercial enthusiasm to ensure equitable access and to limit cosmetic off-label use in a population that is still undergoing critical neurobiological development. Future research should therefore focus on addressing key knowledge gaps, particularly regarding the durability of treatment effects after discontinuation and the long-term consequences of chronic modulation of appetite and reward pathways in the adolescent brain.

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