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GLP-1 RECEPTOR AGONISTS IN PEDIATRIC OBESITY: EVIDENCE, KNOWLEDGE GAPS, AND CLINICAL IMPLICATIONS

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ABSTRACT

BACKGROUND

The increasing prevalence of obesity in children and adolescents represents a major public health concern associated with metabolic, cardiovascular, and psychosocial complications. Lifestyle interventions remain the cornerstone of management but are often insufficient in severe obesity or after inadequate response to behavioral and nutritional strategies.

AIMS

To evaluate current evidence on the efficacy and safety of GLP 1 receptor agonists in pediatric obesity, to analyze their mechanisms of action, to review clinical recommendations and regulatory status, and to identify knowledge gaps, ethical considerations, and future research priorities.

METHODS

This narrative review was based on a structured, non systematic literature search in PubMed MEDLINE, Scopus, Embase, Web of Science, and the Cochrane Library for publications from 2010 to 2025. Regulatory documents and clinical guidelines were also reviewed. Of 289 identified publications, 29 sources were included after predefined selection criteria were applied. The analysis focused on pediatric studies reporting efficacy and safety outcomes, with emphasis on randomized controlled trials. No quantitative synthesis was performed.

RESULTS

GLP 1 receptor agonists demonstrate clinically meaningful reductions in body weight and body mass index predominantly in adolescents with obesity under controlled study conditions with intensive monitoring. In the STEP TEENS trial, semaglutide was associated with a mean BMI reduction of 16.1 percent, with 73 percent of participants achieving at least a 5 percent reduction. Liraglutide showed a smaller effect, with a mean BMI reduction of 5.8 percent and 46 percent of patients achieving at least a 5 percent reduction. Semaglutide showed the greatest BMI reduction, whereas liraglutide had the most established pediatric evidence base. These differences are based on separate studies with heterogeneous designs and without direct comparative trials. Exenatide

demonstrated moderate efficacy, whereas dulaglutide lacked convincing evidence for weight reduction outside type 2 diabetes. Data on tirzepatide in pediatric populations remained insufficient to define its clinical role. Gastrointestinal adverse events were frequent, reaching up to 62 percent of patients, and may affect adherence. Long term safety remained uncertain, particularly regarding growth, pubertal development, bone metabolism, and neuropsychological outcomes. Evidence was limited by short follow up, small sample sizes, heterogeneous study designs, and partial extrapolation from adult populations.

CONCLUSIONS

GLP 1 receptor agonists may be considered for selected adolescents with severe obesity, particularly in the presence of metabolic complications such as insulin resistance or type 2 diabetes and after insufficient response to intensive lifestyle interventions. They should not be used as first line therapy and require careful patient selection, clinical monitoring, and integration into a comprehensive treatment strategy. Regulatory approvals remain limited, especially for younger children. Current evidence is derived from selected adolescent populations under controlled conditions and short term outcomes, which limits generalizability to routine practice. Ethical considerations include pharmacotherapy in a developing population, the need for informed family involvement, and potential effects on body image and treatment expectations. Further research is needed to clarify long term safety, durability of effect, and predictors of response.

Keywords: pediatric obesity, GLP 1 receptor agonists, semaglutide, liraglutide, dulaglutide, tirzepatide, safety, ethics, pediatric pharmacotherapy

INTRODUCTION

Pediatric obesity is defined as excessive accumulation of adipose tissue associated with adverse health outcomes and disturbances in physical and psychosocial development. In children and adolescents, diagnosis is based on body mass index interpreted using age specific and sex specific percentile charts, with obesity defined as values above the 95th percentile. [1,2]

Childhood obesity represents a major and rapidly increasing global health problem associated with early onset of metabolic, cardiovascular, and psychosocial complications. [2,6,10] Despite the implementation of lifestyle interventions, their long term effectiveness remains limited, particularly in severe obesity. [2,3,28,47] In this context, pharmacotherapy, especially glucagon like peptide 1 receptor agonists, has emerged as a promising therapeutic option. [5,10,28,44]

The scientific novelty of this review lies in the integration of recent pediatric clinical trial data with a critical evaluation of developmental safety, durability of treatment effects after discontinuation, and the positioning of GLP 1 receptor agonists within current clinical and regulatory frameworks. [5,9,21,22] Particular attention is given to newly available evidence from recent trials and emerging therapies, as well as to the discrepancy between expanding clinical use and the limited long term data in pediatric populations. [5,7,9,13,21,22]

Pediatric obesity is a chronic multifactorial disease resulting from interactions among genetic, hormonal, environmental, and behavioral factors that influence energy balance and metabolic regulation. Environmental and behavioral determinants, including dietary patterns, physical inactivity, and psychosocial factors, play a central role in disease development and progression. [2,3,10] At the pathophysiological level, obesity is associated with dysregulation of central appetite control, impaired satiety signaling, insulin resistance, and alterations in gut hormone secretion, including incretin pathways. [2,37,39] These mechanisms contribute to persistent positive energy balance and reduced responsiveness to behavioral interventions. [2,3,37]

This pathophysiological background provides a rationale for the use of glucagon like peptide 1 receptor agonists. By enhancing glucose dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and acting on central pathways regulating appetite and satiety, these agents directly target key mechanisms involved in the development and maintenance of obesity. [37,38,39,48] Their effects on neuroendocrine regulation and energy intake are particularly relevant in pediatric patients, in whom disturbances of appetite control and eating behavior play a central role. [2,3,37,38]

The clinical consequences of pediatric obesity include early development of type 2 diabetes, hypertension, nonalcoholic fatty liver disease, metabolic syndrome, and dyslipidemia, leading to increased morbidity and long term health risks. [2,3,6,10,49] Earlier onset of obesity is associated with reduced effectiveness of non pharmacological interventions, which supports the need for adjunctive pharmacotherapy in selected patients. [2,3,28,47] GLP 1 receptor agonists, initially developed for type 2 diabetes, have demonstrated significant weight reducing effects and are now approved for use in specific pediatric populations. [5,11,12,28]

Despite the growing number of publications on GLP 1 receptor agonists in pediatric obesity, existing reviews remain limited in several key aspects. [5,9,19,20,21,22] Available evidence is fragmented, with most analyses focusing on individual agents or extrapolating data from adult populations rather than providing an integrated evaluation specific to children and adolescents. [5,19,20,22] There is insufficient synthesis of recent clinical trial data, particularly studies published in 2024 and 2025 and emerging therapies such as tirzepatide. [5,7,9,13,14,21] In addition, current reviews do not adequately address long term safety, including effects on growth, pubertal development, and metabolic regulation, nor do they systematically evaluate the persistence of treatment effects after discontinuation. [5,9,21,23,24,25,27] The integration of clinical efficacy, regulatory status, and real world applicability remains incomplete. [5,20,21,22,28] Ethical and socio clinical implications of early pharmacological intervention in pediatric populations are also underrepresented. [3,28,47] These limitations indicate the need for a focused and updated synthesis of evidence that critically integrates efficacy, safety, developmental considerations, and clinical applicability of GLP 1 receptor agonists in children and adolescents. [5,9,21,22]

In this paper, we present the current state of knowledge on this topic, while highlighting remaining gaps and uncertainties requiring further research. The aim of this study is to evaluate the current evidence on the efficacy and safety of GLP 1 receptor agonists in the treatment of obesity in children and adolescents.

The specific research objectives are:

1. to analyze mechanisms of action of GLP 1 receptor agonists relevant to pediatric populations;
2. to assess clinical trial evidence regarding efficacy and safety;
3. to review current clinical recommendations and regulatory status;
4. to identify knowledge gaps and future research priorities;
5. to discuss ethical and socio-clinical implications of pharmacotherapy in children and adolescents.

METHODS

REVIEW CHARACTERISTICS

This study was designed as a narrative review conducted in accordance with the principles of Narrative Evidence Synthesis and the SANRA recommendations. The objective was to summarize and critically interpret available evidence on the efficacy, safety, and clinical use of glucagon like peptide 1 receptor agonists in pediatric obesity.

LITERATURE SEARCH STRATEGY

A structured, non systematic literature search was performed in PubMed MEDLINE, Scopus, Embase, Web of Science, and the Cochrane Library. Additional sources included regulatory documents from the European Medicines Agency and the U.S. Food and Drug Administration, as well as reports from the American Academy of Pediatrics and the World Health Organization. The search covered publications from January 2010 to October 2025. Conference materials from the Endocrine Society and selected preprints from bioRxiv and medRxiv were also screened where relevant.

KEYWORDS AND SEARCH LOGIC

The search was conducted using predefined search terms: GLP 1 receptor agonist OR liraglutide OR semaglutide OR exenatide AND pediatric obesity OR childhood obesity OR adolescent obesity AND clinical trial OR randomized OR meta analysis OR systematic review.

For Polish language sources, equivalent terms were applied.

INCLUSION CRITERIA

The review considered randomized clinical trials and controlled studies in individuals aged up to 18 years, systematic reviews and meta analyses, pharmacotherapy registries, and regulatory documents reporting pediatric data. Studies addressing efficacy, safety, metabolic outcomes, growth, or pubertal development were included.

EXCLUSION CRITERIA

Preclinical studies, studies limited to adult populations, and publications without primary or synthesized clinical data were excluded. Conference abstracts without sufficient data and non English or non Polish publications were not included.

DATA SELECTION AND SYNTHESIS PROCEDURE

A total of 289 publications were initially identified. After removal of duplicates and application of the inclusion criteria, 29 sources were included in the final analysis, comprising 8 randomized clinical trials, 4 meta analyses and systematic reviews, 3 regulatory documents, and 14 narrative and expert review publications. Narrative and expert reviews were used to support contextual interpretation of clinical findings and were not treated as primary evidence. Systematic reviews and meta analyses were used for contextual interpretation of evidence and not as primary data sources.

Data on efficacy, safety, and developmental outcomes were synthesized descriptively, with emphasis on methodological, clinical, and population differences across studies. A thematic approach was applied, grouping results by type of GLP 1 receptor agonist and by clinical parameters assessed. No formal systematic review methodology or quantitative meta analysis was performed, and the findings should be interpreted within the limits of a narrative synthesis.

RESULTS

MECHANISM OF ACTION OF GLP-1 ANALOGUES

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) exert their effects through activation of the GLP-1 receptor, which is present both in the peripheral gastrointestinal system and in the central nervous system. Following administration, these agents stimulate insulin secretion in a glucose-dependent manner and inhibit glucagon secretion, thereby improving glycemic control and reducing the risk of hyperglycemia. A key mechanism underlying the effectiveness of GLP-1RAs in obesity treatment is appetite suppression and increased satiety, mediated through their action on hypothalamic centers involved in the regulation of hunger. Additionally, these medications delay gastric emptying, which slows the absorption of nutrients and reduces postprandial glucose excursions. Central effects include modulation of neurotransmitter pathways (including dopaminergic and serotonergic pathways), resulting in a reduction in behaviors associated with excessive food intake. [7–8] GLP-1RAs also exert beneficial effects on metabolic parameters: they improve insulin sensitivity, reduce body weight, BMI, waist circumference, and systolic blood pressure, without significantly affecting

lipid profiles or fasting glucose levels in pediatric populations without diabetes. Clinical trials have demonstrated that the weight-reducing effect is more pronounced in children and adolescents with obesity than in patients with type 2 diabetes. The most common adverse effects result from the mechanism of action of GLP-1RAs and involve gastrointestinal symptoms (nausea, vomiting, diarrhea), which are usually mild and transient. These effects stem from delayed gastric emptying. [9–10] In summary, the mechanism of action of GLP-1 analogues includes central and peripheral regulation of appetite, delayed gastric emptying, improved glycemic control, and beneficial metabolic effects, making them an effective tool in the treatment of obesity in children and adolescents.

LIRAGLUTIDE (SAXENDA)

Evidence for the efficacy and safety of liraglutide (Saxenda) in the treatment of obesity in children and adolescents comes primarily from a randomized, controlled clinical trial in adolescents aged 12–17 years (Kelly et al., NEJM 2020), which demonstrated a significant reduction in BMI and body weight compared with placebo, with an acceptable adverse-event profile. The most common adverse effects included gastrointestinal symptoms (nausea, vomiting, diarrhea); sporadic episodes of hypoglycemia, isolated cases of pancreatitis, and increases in resting heart rate were also reported. [11] The study by Fox et al. (NEJM 2025) was a multicenter, double-blind, placebo-controlled, randomized trial involving children aged 6–11 years with obesity (BMI ≥95th percentile according to CDC). Participants were randomized in a 2:1 ratio to receive either liraglutide (up to 3.0 mg/day) or placebo. Both groups concurrently participated in an intensive lifestyle-intervention program. The primary endpoint was the percentage change in BMI after 56 weeks of treatment. Results showed an average BMI change of −5.8% in the liraglutide group vs. +1.6% in the placebo group (difference −7.4 percentage points; 95% CI, −11.6 to −3.2; P<0.001). A BMI reduction of ≥5% was achieved by 46% of children treated with liraglutide compared with 9% in the placebo group (OR 6.3; 95% CI, 1.4–28.8; P=0.02). The therapeutic effect was also reflected in reductions in body weight and improvements in selected metabolic parameters. The most common adverse effects were gastrointestinal (nausea, vomiting, diarrhea), typically mild and transient. Serious adverse events occurred in 12% of children in the liraglutide group and 8% in the placebo group, with no significant differences regarding effects on growth, pubertal development, or safety parameters. This study provides evidence supporting the efficacy and safety of liraglutide as an adjunct treatment for obesity in children aged 6–11 years. However, at present liraglutide is not approved by the FDA or EMA for use in this age group. According to current regulatory approvals, liraglutide (Saxenda) is authorized by both the FDA and EMA only for adolescents ≥12 years of age with obesity, as an adjunct to lifestyle intervention. The findings of Fox et al. may form the basis for future changes in regulatory indications and clinical guidelines, but currently the use of liraglutide in children <12 years remains off-label. [7]

SEMAGLUTIDE (WEGOVY / OZEMPIC)

The long-term efficacy and safety of semaglutide in treating obesity among adolescents aged 12–17 years have been evaluated in the STEP TEENS trial (Weghuber et al., NEJM 2022) and in recent meta-analyses including 18 studies with a total of 1,400 children and adolescents aged 6–17 years. Semaglutide administered at a dose of 2.4 mg subcutaneously once weekly for 68 weeks produces a mean BMI reduction of −16.1% from baseline, corresponding to a placebo-adjusted effect of −16.7 percentage points (95% CI, −20.3 to −13.2; p<0.001). Weight reduction reached −14.7% (placebo-adjusted −17.4 percentage points), 73% of participants achieved a ≥5% reduction in BMI, and 62% achieved ≥10% weight loss. [13–14] These effects are substantially greater than those observed with other anti-obesity medications used in pediatric populations. Semaglutide significantly reduces waist circumference (by a mean of −12.7 cm) and improves metabolic parameters, lowering HbA1c (−0.4 percentage points), total cholesterol, LDL, VLDL, triglycerides, and ALT. The effect on systolic blood pressure is modest (mean reduction −2.7 mmHg). [13] The most common adverse events are gastrointestinal symptoms—nausea, vomiting, diarrhea—reported in 62% vs. 42% in the placebo group, typically mild and transient. Cholelithiasis occurs in approximately 4% of treated individuals. The rate of serious adverse events is similar to placebo (11% vs. 9%). No new safety signals or adverse effects on growth or pubertal development have been observed. 13–14]. Semaglutide is currently approved for the treatment of obesity in adolescents ≥12 years as an adjunct to lifestyle intervention. [15] All studies emphasize the necessity of concurrent intensive behavioral therapy. In summary, semaglutide demonstrates high efficacy in reducing body weight, improves metabolic parameters, and has an acceptable safety profile consistent with observations in adults.

TIRZEPATIDE (MOUNJARO / ZEPBOUND – GIP + GLP-1 AGONIST)

No large randomized clinical trials have yet evaluated the efficacy and safety of tirzepatide for the treatment of primary obesity in children or adolescents. Available evidence comes from studies in youth with type 2 diabetes (SURPASS-PEDS), post hoc analyses of adults with early-onset obesity, case reports, and ongoing trials (SURMOUNT-ADOLESCENTS-2). In the SURPASS-PEDS trial, tirzepatide in adolescents with type 2 diabetes led to significant weight reduction (8–14% after 52 weeks) and improvements in metabolic parameters, with a safety profile similar to adults (most commonly gastrointestinal symptoms). [16] However, the pathophysiology and metabolic course of primary pediatric obesity differ from type 2 diabetes, limiting extrapolation to non-diabetic populations. Post hoc analyses of the SURMOUNT-1, -3, and -4 trials in adults with early-onset obesity found that weight-loss effects and metabolic improvements were similar regardless of age of onset, but these analyses did not include children or adolescents. [17] Data from adult studies (SURMOUNT-1, -2, -3, -4) consistently show high efficacy of tirzepatide (15–20% weight loss after 72 weeks) with a favorable safety profile (primarily mild gastrointestinal symptoms). [18] Nevertheless, these findings cannot be directly applied to pediatric populations due to developmental, metabolic, and long-term safety differences. Currently, tirzepatide is not approved for obesity treatment in children or adolescents by either the FDA or EMA. The Obesity Society does not recommend tirzepatide for this population outside clinical trials. [19] Ongoing studies (SURMOUNT-ADOLESCENTS-2) may provide future evidence necessary to assess its efficacy and safety in primary pediatric obesity. In summary, tirzepatide use for primary obesity in children and adolescents is not recommended outside clinical research due to insufficient evidence and important physiological differences compared with adults and youth with type 2 diabetes.

DULAGLUTIDE (TRULICITY) – GLP-1 AGONIST

Dulaglutide is not approved by the FDA or EMA for the treatment of primary obesity in children or adolescents. Its authorization is

limited to the treatment of type 2 diabetes in patients aged ≥10 years. [1]

In the AWARD-PEDS trial (Arslanian et al., *NEJM* 2022), dulaglutide (0.75 mg and 1.5 mg once weekly) significantly improved glycemic control in adolescents with type 2 diabetes but did not reduce BMI or body weight, even with long-term use. [20] The safety profile was consistent with adults, with gastrointestinal symptoms being the most common adverse events. Post hoc analyses (2023) confirmed the lack of clinically meaningful effects on body weight in adolescents with type 2 diabetes and found no evidence supporting its use for primary obesity. [20] Unlike liraglutide and semaglutide, dulaglutide does not produce weight-loss benefits in pediatric populations without diabetes. [5] Preliminary reports from the ongoing trial NCT06122334 (Eli Lilly) and presentations from the ADA 2025 conference showed no significant reductions in BMI or body weight among youth with primary obesity treated with dulaglutide; however, the trial is ongoing and final efficacy results are not yet available. In summary, dulaglutide is not recommended or approved for the treatment of primary obesity in children and adolescents. Its use should remain limited to its approved indication (type 2 diabetes ≥10 years), and other GLP-1RAs with demonstrated efficacy are preferred for obesity management.

EXENATIDE AND OTHER GLP-1 AGONISTS

Exenatide and other GLP-1 receptor agonists show moderate efficacy in treating obesity in children and adolescents, leading to reductions in BMI, body weight, and waist circumference. Meta-analyses show that exenatide reduces BMI by approximately −1.1 units (95% CI −1.91 to −0.31) and body weight by −0.6% (95% CI −0.93 to −0.27) compared with placebo - effects smaller than those of semaglutide or liraglutide. [21–23] The most common adverse events across all GLP-1RAs, including exenatide, are gastrointestinal symptoms - nausea, vomiting, diarrhea, abdominal pain. The risk of nausea is more than double that of placebo (RR 2.11; 95% CI 1.44–3.09), though most symptoms are mild and transient. No significant increase in risks of depression, suicidal ideation, or severe metabolic disturbances has been found in short-term studies. [5] Exenatide is not approved by the FDA or EMA for obesity treatment in children or adolescents; its authorization covers only type 2 diabetes in youth aged 10–17 years. [6] In summary, exenatide shows moderate efficacy in reducing BMI in pediatric obesity but lacks regulatory approval for this indication, and its adverse-event profile is typical for the GLP-1RA class.

META-ANALYSES AND SYSTEMATIC REVIEWS (2023–2025)

Recent meta-analyses and systematic reviews published between 2023 and 2025 confirm that GLP-1 receptor agonists (liraglutide, semaglutide, exenatide, tirzepatide) are effective in treating obesity in pediatric populations, reducing BMI, body weight, and improving selected metabolic parameters. [5, 10, 12, 23–25]

Semaglutide shows the greatest efficacy (mean BMI reduction −16.7% at 68 weeks), followed by liraglutide (−4.6% at 56 weeks), exenatide (−2.3% at 24 weeks), while dulaglutide and tirzepatide do not demonstrate significant BMI reductions in pediatric populations without type 2 diabetes. Benefits are most pronounced in adolescents ≥12 years, but improvements are also observed in children aged 6–12 years. [24] Regarding metabolic parameters, GLP-1RAs improve glycemia (HbA1c, fasting glucose), reduce systolic blood pressure, decrease waist circumference, and improve insulin-resistance markers (HOMA-IR). Effects on lipid profiles are small or clinically insignificant. [5,10,7,23–25] The most common adverse events are gastrointestinal symptoms (nausea, vomiting, diarrhea; prevalence 18–24%), typically mild and self-limited. [5,10,12,23–26] No significant increases in risks of depression, suicidal thoughts, severe metabolic complications, or hepatobiliary disorders have been observed compared with placebo.[5] Dulaglutide and tirzepatide are currently not approved for obesity treatment in children or adolescents, and their use should remain limited to clinical trials.

A summary of the efficacy and safety profiles of individual GLP-1 receptor agonists in pediatric populations is presented in Table 1.

Table 1. Efficacy and safety profile of GLP-1 receptor agonists in pediatric obesity (clinical perspective)

Drug	Pediatric Approval	Population	Mean BMI Reduction	Proportion achieving ≥5% BMI reduction	Safety Profile	Age Restrictions	Clinical Interpretation
Liraglutide	**FDA/EMA approved ≥12 years**	**Obesity**	**−4–6%**	**~46%**	**Gastrointestinal symptoms (nausea, vomiting, diarrhea), generally mild**	**≥12 years**	**Moderate efficacy with the most established pediatric evidence**
Semaglutide	**FDA/EMA approved ≥12 years**	**Obesity**	**−16.1%**	**~73%**	**Gastrointestinal symptoms (up to 62%), cholelithiasis (~4%)**	**≥12 years**	**Highest efficacy among available agents; limited long-term pediatric data**

Dulaglutide	**Approved ≥10 years (T2D only)**	**Type 2 diabetes**	**No significant BMI reduction**	**Not applicable**	**Gastrointestinal symptoms; safety profile consistent with adults**	**≥10 years**	**Not effective for weight reduction in pediatric obesity**
Exenatide	**Not approved for obesity**	**Obesity (investigational)**	**~−1.1 BMI units**	**Not available**	**Gastrointestinal symptoms; generally mild**	**Not approved**	**Moderate efficacy; limited evidence and no regulatory approval**
Tirzepatide	**Not approved**	**Type 2 diabetes (pediatric data)**	**Insufficient data**	**Not available**	**Gastrointestinal symptoms; data extrapolated from adults**	**Not approved**	**Promising agent, but insufficient pediatric evidence**

Note: Data are derived from separate clinical trials with heterogeneous designs, populations, durations, and endpoints. Therefore, results are not directly comparable and should not be interpreted as a hierarchy of efficacy.

EFFECTIVENESS

RCTs indicate that in adolescents with obesity, semaglutide and liraglutide can lead to significant reductions in BMI and body weight compared to placebo, often exceeding the effects observed with behavioral interventions alone. In the semaglutide trial, a large proportion of patients achieved a ≥10% reduction in body weight, which is clinically significant in the pediatric population and may translate into improvements in metabolic risk factors. Nevertheless, these effects need to be evaluated in the context of maintaining the results after discontinuation of the drug—some evidence from the adult population suggests weight regain after stopping therapy, indicating that GLP-1 RAs may require long-term use or integration with sustained lifestyle changes.

SAFETY AND ADVERSE EFFECT PROFILES

Contraindications for GLP-1 RA Use

Absolute contraindications:

- Personal or family history of medullary thyroid carcinoma (MTC) – potential activation of GLP-1 receptors in cancer cells. [11, 25, 27, 29]
- Multiple Endocrine Neoplasia type 2 – increased risk of C-cell tumors. [11, 25, 27]
- Hypersensitivity to any component of the preparation – particularly concerning anaphylactic reactions, angioedema, or severe skin reactions. [11, 12, 29]
- Pregnancy and breastfeeding. [11, 16, 28]

Relative contraindications:

- Severe gastroparesis and post-gastric surgery conditions. One of the mechanisms of GLP-1 analogs is delayed gastric emptying, which can exacerbate gastroparesis symptoms. [5, 8, 17, 20, 28]
- History of or active pancreatitis. Currently, no pediatric data are available; however, if such an adverse event occurs, the drug should be discontinued immediately. [5, 11, 12, 19, 21]
- Severe diabetic retinopathy. Rapid improvement in glycemic control may temporarily worsen retinopathy symptoms. [12, 17, 21]
- Severe psychiatric disorders, particularly suicide risk. Patients with a history of depression should be closely monitored. [7, 8, 28]
- Liver and kidney diseases. Cases of acute liver and kidney injury have been reported in adolescents treated with liraglutide, so monitoring biochemical markers of organ damage is essential. [5, 7, 9, 11, 12, 20]

Drug Interactions

The most significant drug interactions of GLP-1 analogs are related to their mechanism of action, which delays gastric emptying and can impair the absorption of orally administered medications. This is particularly important for drugs with a narrow therapeutic index, such as antiepileptics, contraceptives, anticoagulants, and immunosuppressants. In these cases, special caution is required when initiating GLP-1 analogs. In most cases, dose adjustments have not been shown to be necessary. [5, 12, 18] Another group requiring careful monitoring includes children with type 2 diabetes who are treated simultaneously with a GLP-1 analog and sulfonylurea derivatives or insulin. In this group, due to the risk of hypoglycemia, frequent monitoring of the glycemic profile is recommended, and dose adjustments should be considered based on the results. [3, 5, 17, 19] During therapy, no significant interactions have been observed with lipid-lowering or antihypertensive drugs; however, data in the pediatric population are limited. [5, 20]

Short-term Adverse Effects

The most commonly reported adverse effects are gastrointestinal symptoms (nausea, vomiting, constipation, abdominal pain), which are usually mild to moderate and transient in most cases. Hypoglycemia occurs less frequently in patients without diabetes, but the risk increases when used concomitantly with hypoglycemic agents.

Impact on Growth and Pubertal Development

A key consideration is the potential impact of therapy on linear growth and pubertal development. Current studies have not demonstrated clear adverse effects on growth velocity or the onset of puberty; however, most studies have limited observation periods and relatively small patient populations. Therefore, longer-term monitoring and registries are necessary to evaluate the impact of treatment on these parameters.

Bone Health

Rapid weight loss in adolescents, whose bone growth and modeling are active, may lead to reduced bone mineral density (BMD) and increased fracture risk. Weight loss, especially rapid loss (≥14% over a few months), is associated with increased bone turnover, predominance of resorption over formation, and decreased BMD, particularly in mechanically stressed sites (femoral neck, spine). [27–28]

This effect is particularly pronounced during puberty, when bones grow intensively and underweight may permanently impair peak bone mass. GLP-1 receptor agonists (GLP-1 RAs), such as liraglutide and semaglutide, cause significant weight loss, but their impact on bone health in young patients remains unclear. Clinical studies have shown a slight decrease in BMD and an increase in bone resorption markers while maintaining a neutral or non-significant effect on fracture risk. [27–28] This effect correlates with the magnitude and rate of weight loss, rather than a direct pharmacologic effect of the drug. In animal models, liraglutide has shown beneficial effects on bone material properties, but at doses higher than those used in humans. [27, 30] Long-term pediatric data on the effects of GLP-1 RAs on growth, puberty, and bone microarchitecture are lacking. It is recommended that future GLP-1 RA studies in adolescents include assessment of bone mineral density via DEXA, bone turnover markers, and follow-up over more than two years, as only long-term, prospective analyses can evaluate the durability of effects, fracture risk, and impact on peak bone mass. To minimize bone mass loss, it is emphasized that GLP-1 RA therapy should be combined with a resistance exercise program and nutritional monitoring to reduce bone mass loss.

Other Risks and Long-term Uncertainties

The long-term risks and uncertainties associated with GLP-1 receptor agonist use in children primarily include unknown effects on the nervous, hormonal, and reproductive systems, the potential occurrence of rare adverse events, and the consequences of therapy discontinuation, such as rebound weight gain observed in adults. Observed adverse effects mainly involve the gastrointestinal tract (nausea, vomiting, diarrhea). More serious events, such as cholecystitis, pancreatitis, myopathies, or severe dehydration, have also been reported. Short-term pediatric studies have not shown a significant increase in the risk of depression, suicidal thoughts, or hepatobiliary disorders; however, the observation period was limited to 0.5–1 year. [5, 9, 22] The impact on the nervous and hormonal systems remains unclear. Animal studies suggest potential neuroprotective and mood-modulating effects, but long-term data in children are lacking. After discontinuation of GLP-1 RAs, most adults regain a substantial portion of lost body weight, which may also apply to adolescents, although long-term data in this group are lacking. The potential development of eating disorders, particularly during adolescence, requires careful attention. Due to the limited duration of clinical observations, there is an urgent need for long-term observational studies and registries monitoring the effects of GLP-1 RA therapy in children, including impacts on neurohormonal development, bone health, the risk of rare adverse events, and the durability of treatment effects.

ETHICAL AND SOCIO-LEGAL CONSIDERATIONS

Consent, Autonomy, and Family Involvement

Pharmacotherapy in children requires particular ethical caution. It is essential to involve parents or guardians in the process, obtain informed consent, and secure the child's assent whenever possible. This should be an ongoing cycle including education of both the family and the child about the diagnosis, available treatment options, potential benefits, risks, alternatives, and the monitoring plan. Weighing the benefits and risks of pharmacotherapy and considering the impact of treatment on the child's quality of life is crucial. Therapeutic decisions must be made transparently, considering the individual needs, values, and expectations of both the family and the child. Adequate time should be provided for education, discussion, and consideration of all possible treatment options, and consent should be regularly updated throughout therapy. [31]

Medicalization of Obesity and Stigmatization

Widespread use of weight-loss medications in adolescents may influence the perception of obesity solely as a medical problem, potentially overlooking environmental and social determinants. This can both reduce stigmatization (through treatment) and paradoxically create new pressures regarding body image. Ethical considerations should account for sociocultural impacts and the potential pressure on adolescents to use medication.

Availability, Costs, and Equity

Modern therapies are often expensive, and access can be uneven. From a health equity perspective, it is important to consider whether widespread introduction of GLP-1 RAs could exacerbate existing disparities in care for children with obesity.

Advertising, Market Pressure, and Deprescription

The rapid expansion of the anti-obesity drug market carries the risk of off-label promotion or marketing misuse. Evidence-based, transparent communication and oversight of commercial practices are essential.

CLINICAL RECOMMENDATIONS AND SOCIETY POSITIONS

Current positions of specialist medical societies emphasize that a comprehensive medical assessment should include not only the identification of metabolic complications but also psychosocial evaluation, consideration of the child's and family's preferences and values, as well as environmental and socioeconomic factors. Risk assessment algorithms and obesity severity classification tools are recommended, including screening instruments for depression, sleep disorders, and metabolic complications. Guidelines recommend that behavioral and psychological interventions - particularly multicomponent family-based programs - should form the foundation of treatment, with implementation individualized and conducted through shared decision-making with the family.

Pharmacotherapy and surgical interventions are recommended only as adjunct options when lifestyle interventions are insufficient, and decisions regarding their use should follow a shared decision-making model, taking into account availability, acceptability, and patient preferences. Initiation of pharmacotherapy should be cautious, preceded by detailed family education, informed consent, and regular monitoring of efficacy and safety. Treatment should be delivered within a multidisciplinary team model, involving a dietitian, psychologist, physical activity specialist, and physician. Regular assessment of the child's and family's quality of life is also essential. All recommendations stress that pharmacotherapy should be reserved for cases of severe obesity or when intensive lifestyle interventions fail, and its implementation requires dedicated monitoring, assessment of adverse effects, and close collaboration with the family. [32–33]

Key randomized and controlled clinical trials evaluating GLP-1 receptor agonists in pediatric populations are summarized in Table 2.

Table 2. Randomized and controlled clinical trials of GLP-1 receptor agonists in pediatric populations (heterogeneous study designs)

1. **Population with obesity**

Study (Year)	Drug	Population	Sample Size (N)	Study Design	Duration	Primary Outcome	BMI Effect	Key Safety Findings
Kelly et al. (2020)	Liraglutide	Adolescents with obesity (12–17 years)	251	Randomized, double-blind, placebo-controlled trial	56 weeks	Change in BMI	−4.6%	Gastrointestinal symptoms, generally mild
Weghuber et al. (2022)	Semaglutide	Adolescents with obesity (12–17 years)	201	Randomized, double-blind, placebo-controlled trial	68 weeks	Change in BMI	−16.1%	Gastrointestinal symptoms (up to 62%), cholelithiasis (~4%)

2. **Population with type 2 diabetes**

Study (Year)	Drug	Population	Sample Size (N)	Study Design	Duration	Primary Outcome	BMI Effect	Key Safety Findings
Arslanian et al. (2022)	Dulaglutide	Youth with type 2 diabetes	154	Randomized, double-blind, placebo-controlled trial	26 weeks	HbA1c reduction	No significant change	Gastrointestinal symptoms
Danne et al. (2019)	Liraglutide	Youth with type 2 diabetes	135	Randomized, controlled trial	26 weeks	HbA1c reduction	Minimal	Gastrointestinal symptoms

The included studies are heterogeneous in terms of study design, duration, patient populations, and study conditions. Therefore, their results are not directly comparable and should not be interpreted as a hierarchy of efficacy.

KNOWLEDGE GAPS AND RESEARCH PRIORITIES

Based on the literature review, the following key gaps and research areas have been identified:

- **Long-term safety (5–10 years of follow-up):** impact on growth, puberty, bone health, reproductive function, and neurocognitive development.
- **Discontinuation effects and maintenance strategies:** can combined behavioral programs sustain benefits after therapy cessation?
- **Response biomarkers:** identification of predictors of good response (genetic, metabolic, behavioral).
- **Head-to-head comparisons:** semaglutide vs. liraglutide vs. other GLP-1 RAs in children.
- **Cost-effectiveness and quality of life impact:** economic analyses, patient-reported outcomes (PROs).
- **Studies in younger children**: current data mainly involve children aged ≥12 years; studies in younger children are limited and require separate risk-benefit evaluation.

PRACTICAL IMPLICATIONS FOR CLINICIANS

GLP-1 RA pharmacotherapy should be considered only as part of a comprehensive therapeutic program, including nutritional interventions, physical activity, and psychological support. Decisions regarding initiation should be individualized, taking into account the degree of obesity, presence of comorbidities, patient and family motivation, and availability of monitoring. Monitoring should include adverse effects (especially gastrointestinal), growth and pubertal parameters, bone health (as indicated), metabolic parameters, and quality-of-life measures. Before initiating therapy, potential scenarios after drug discontinuation and a long-term support plan should be discussed.

DISCUSSION

Available data indicate clinical efficacy and acceptable short-term safety of GLP-1 receptor agonists in children and adolescents with obesity, although the evidence base remains heterogeneous. [5,19,20,21,22] These effects should be interpreted with caution, as most studies were conducted under controlled conditions with intensive monitoring and patient support.

GLP-1 receptor agonists regulate appetite through central mechanisms, enhance satiety, delay gastric emptying, and modulate glucose-dependent insulin secretion. [37,38,39] These effects are pathophysiologically relevant in the pediatric population, although reliable data on long-term effects on growth and pubertal development are lacking. [5,9,21,22] This mechanism of action explains the observed reductions in body weight and body mass index reported in clinical studies. [5,12,21] In clinical practice, the magnitude of effect may vary depending on baseline obesity severity, presence of insulin resistance, and adherence to lifestyle interventions.

Clinical studies show that the greatest reduction in body weight is achieved with semaglutide, while liraglutide has the most established evidence base in adolescents. [5,12,21] In the STEP TEENS trial, semaglutide was associated with a mean reduction in BMI of 16.1 percent from baseline, with a placebo-adjusted difference of 16.7 percentage points; 73 percent of participants achieved at least a 5 percent reduction in BMI, and 62 percent achieved at least a 10 percent reduction in body weight. [12] Liraglutide demonstrated a smaller but clinically meaningful effect: in children aged 6 to 11 years, the mean change in BMI was a decrease of 5.8 percent compared to an increase of 1.6 percent with placebo, and a reduction of at least 5 percent in BMI was achieved in 46 percent of patients versus 9 percent in the control group. [7] Exenatide demonstrates a moderate effect, with a reduction in BMI of approximately 1.1 units, whereas dulaglutide does not demonstrate a clinically meaningful effect on body weight in the absence of type 2 diabetes. [17,18,20] Data on tirzepatide in pediatric populations remain limited and are largely derived from studies in adolescents with type 2 diabetes or from adult populations. [13,14,15] Direct comparisons between agents are lacking, and differences in efficacy are based on separate studies with heterogeneous designs. Most studies have short-term follow-up periods, and extrapolation from adult populations is limited. [5,19,22]

The safety profile is characterized predominantly by gastrointestinal adverse events, which are generally transient. [5,9,19,21] In the semaglutide trial, gastrointestinal symptoms were reported in 62 percent of patients compared to 42 percent in the placebo group, while serious adverse events occurred in 11 percent versus 9 percent, respectively. [12] In liraglutide-treated children aged 6 to 11 years, serious adverse events were observed in 12 percent of patients compared to 8 percent in the placebo group. [7] This frequency of adverse events may limit treatment adherence and requires gradual dose titration and clinical monitoring. Important uncertainties remain regarding long-term effects on bone metabolism, reproductive function, and neuropsychological development. [24,25,27]

In clinical practice, these agents should be used only as part of a comprehensive treatment strategy. [3,28,47] Their use is justified primarily in adolescents with severe obesity or in cases of insufficient response to intensive lifestyle interventions. [3,28] Pharmacotherapy should not be considered a first-line approach and requires prior evaluation of behavioral and nutritional strategies. Treatment decisions should involve careful patient selection, assessment of comorbidities, and informed involvement of the family. Weight regain after discontinuation remains a clinically relevant concern, indicating the need for long-term follow-up and sustained lifestyle support. [31,32,33]

Regulatory limitations reflect the incompleteness of the current evidence base. Approval applies to a limited number of agents and age groups, while data for younger children are lacking. [11,28] This requires cautious use, particularly outside approved indications.

Key gaps include the absence of long-term data, limited evidence on outcomes after treatment discontinuation, lack of predictors of response, and the scarcity of direct comparative studies. [5,9,21,22] In clinical practice, these limitations limit the ability to individualize treatment and to select the most appropriate agent.

This analysis has limitations. Available studies are characterized by small sample sizes and short duration of follow-up. A substantial proportion of data is extrapolated from adult populations. There is substantial heterogeneity in study design and endpoints, and direct comparative studies as well as data for younger age groups are lacking. The long-term impact of therapy on growth, pubertal development, and metabolic regulation remains insufficiently studied, limiting confidence in long-term safety.

In summary, GLP-1 receptor agonists demonstrate clinically meaningful efficacy with acceptable short-term safety in adolescents with obesity, but their use should be selective and accompanied by careful clinical monitoring, taking into account long-term risks and the current limitations of the evidence base. [5,12,21]

CONCLUSIONS

GLP 1 receptor agonists demonstrate clinically meaningful reductions in body weight and body mass index in adolescents with obesity in randomized controlled studies; however, these results are derived from selected populations under intensive monitoring and require cautious interpretation in routine clinical practice. The magnitude of effect varies depending on baseline obesity severity, insulin resistance, and adherence to non pharmacological interventions.

Semaglutide shows the greatest reduction in body mass index, whereas liraglutide has the most established evidence base in adolescents. These differences are based on separate studies without direct comparisons and in the context of heterogeneous designs, which precludes interpretation as a definitive hierarchy of efficacy. Exenatide demonstrates a moderate effect, dulaglutide lacks evidence for weight reduction outside type 2 diabetes, and data on tirzepatide in pediatric populations remain insufficient.

The safety profile is dominated by frequent gastrointestinal adverse events that may reduce adherence. Long term safety remains uncertain, particularly regarding bone metabolism, reproductive function, and neuropsychological development.

GLP 1 receptor agonists should not be used as first line therapy and may be considered only within a comprehensive treatment strategy in adolescents with severe obesity or insufficient response to intensive lifestyle interventions. Their use requires careful patient selection, monitoring, and informed family involvement. Weight regain after discontinuation remains a significant limitation.

Current evidence is limited by small sample sizes, short follow up, heterogeneous study designs, and partial extrapolation from adult populations. Regulatory approvals remain restricted by age and indication.

Thus, despite demonstrated short term efficacy, the use of GLP 1 receptor agonists in children and adolescents requires strict clinical control and careful consideration of the limitations of the evidence base and long term uncertainties.

DISCLOSURE

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

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