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MODERN GLP-1 BASED PHARMACOTHERAPY FOR SEVERE ADOLESCENT OBESITY: CLINICAL PROMISE, SAFETY CONCERNS, AND ETHICAL CHALLENGES

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ABSTRACT

Childhood obesity is an emerging worldwide health crisis, which has far-reaching harmful impacts on the health and development of affected adolescents (Hesketh et al., 2024; Li et al., 2024; Marcus et al., 2022). Innovative therapies such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown great promise as pharmacological intervention, with substantive clinical benefit to the population. This review provides a detailed synthesis of GLP-1RAs from the perspectives of their pharmacological mechanisms, clinical potential in adolescents, safety profiles and associated ethical and social considerations. The pharmacological rationale for GLP-1RAs is due to their ability to mimic the effect of endogenous GLP-1, a hormone which plays an important role in maintaining glucose homeostasis and in regulating appetite (Moiz et al., 2025; Muzurović et al., 2022). These agents promote glucose-dependent insulin secretion, reduce glucagon release and also slow gastric emptying, thereby attenuating glycaemic excursions after a meal and promoting satiety (Alharbi, 2025; Drucker, 2021; Shah & Vella, 2014). Importantly, GLP-1RAs also activate receptors in the central nervous system to reduce hunger and food intake, which result in weight loss of significant and sustained magnitude (Dailey & Moran, 2013; Hayes, 2012; Moiz et al., 2025). This multifaceted mechanism is the basis of their efficacy to treat both type 2 diabetes and obesity. Within the adolescent age group, GLP-1RAs have shown significant clinical potential especially with liraglutide and semaglutide.Liraglutide, approved for people aged 12-17 years, has led to better body mass index (BMI) z-score and clinically significant reduction in weight compared with placebo (Berman et al., 2023; Jensterle & Janež, 2021). Semaglutide, which is approved for adolescents 12+ years, continues to push the efficacy bar and confirmatory trials have reported mean BMI reductions of over 16% with a high prevalence of participants achieving significant weight loss (Weghuber, Barrett, et al., 2023; Weghuber, Kelly, et al., 2023). Beyond reducing weight, GLP-1RAs improve key metabolic markers - triglycerides, total cholesterol, HbA1c and systolic blood pressure - which reduces the risk of cardiovascular and type 2 diabetes in the long term (Silvia et al., 2021; Weghuber, Barrett, et al., 2023; Weghuber, Kelly, et al., 2023). Moreover, these medications improve weight-related quality of life, especially the physical comfort, which addresses the psychological burden of obesity in youth (Weghuber, Barrett, et al., 2023; Weghuber, Kelly, et al., 2023).

Despite their efficacy, GLP-1RAs are a unique category of pharmacologic agents with regard to safety profile that requires close scrutiny. Frequently encountered adverse events are gastrointestinal in nature - nausea, vomiting, diarrhoea and constipation - generally being mild, transient and amenable to dose titration (Santos & Castro, 2025; Silvia et al., 2021). More serious issues include proven risks of cholelithiasis and acute pancreatitis, as seen in some trials (Weghuber et al., 2022; Woronow et al., 2022). A black box warning (defined by FDA) is used to alert clinicians to the potential risk of thyroid C-cells tumours, such as medullary thyroid carcinoma, based on rodent studies, and therefore require contraindication in certain clinical situations (Bezin et al., 2022; Kelly & Sipos, 2024; Pasternak et al., 2024).Long-term data on the effect of GLP-1RA on adolescent growth, pubertal development and neuropsychiatric outcomes (including suicidal ideation) are still sparse and the need for continued, rigorous surveillance (Bartkoski et al., 2025; Cooper et al., 2023).
Ethical and societal considerations are very important when incorporating GLP-1RAs into the care of adolescents. Challenges include the need for truly informed consent, and respect for adolescent autonomy, in particular because of the chronic nature of therapy (Turhal & Bağlam, 2025; Viner et al., 2020). Dramatic increases in cost and poor insurance coverage create important equity issues, which may serve to exacerbate health disparities (Berman et al., 2023; Wright et al., 2023). Societal stigma against obesity and the potential for reinforcing a "weight-normative" paradigm or misuse for cosmetic purposes also need to be watched out for (Button et al., 2025; Cominato et al., 2021; Floegel-Shetty, 2023). A holistic approach that goes beyond simply reducing weight to include but is not limited to metabolic health, psychological wellbeing, and quality of life is crucial to ethical and effective practice. In conclusion, GLP-1RAs have been shown to be a transformational approach in the management of severe obesity in adolescents, but their introduction into the clinic will need to be accompanied by a commitment to long-term safety studies and equitable and patient-centred care.

KEYWORDS

Obesity, Glucagon-like Peptide-1 receptor agonists, Personalized Therapy, Childhood Obesity

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Introduction

Childhood obesity has become a widespread worldwide health disaster that poses significant threats to the immediate and long-term health and development processes of affected adolescents (Hesketh et al., 2024; Li et al., 2024; Marcus et al., 2022). The prevalence of obesity has risen alarmingly throughout the world, and projections suggest that the prevalence of obesity will continue to increase in all populations, thereby raising the urgent need for effective interventions (Kerr et al., 2025; Zhang et al., 2024). Against this background, modern Glucagon-like Peptide-1 receptor agonists (GLP-1RAs) have taken the therapeutic world by storm, offering themselves as highly promising pharmacological interventions that bring significant clinical benefits to this vulnerable demographic. This review systematically examines the role of GLP-1RAs in the setting of severe adolescent obesity, carefully reviewing the intricate pharmacological actions of these agents, describing how these drugs act in intricate ways to modulate appetite, restore glucose homeostasis and regulate energy balance in order to produce clinically relevant weight loss.Furthermore, this synthesis provides critical appraisal of their amazing clinical promise and strong evidence of efficacy in adolescents, their profound effect on weight reduction, cardiometabolic health improvement, and overall quality of life. Simultaneously, a critical review of the safety profile and possible long-term risks of GLP-1RAs is presented, including common gastrointestinal side effects, the risk of cholelithiasis and rare, but serious concerns including thyroid C-cell tumours. Lastly, the review explores the complex ethical and social considerations present in the integration of GLP-1RAs in adolescent care (i.e., issues regarding informed consent, equitable access, societal perceptions of obesity and body image, and so on). By providing this balanced view of GLP-1RAs, the review aims to add to the understanding of GLP-1RAs as an evolving, transformative therapeutic approach to treating severe obesity in adolescents.

Childhood Obesity: Epidemiology, Determinants, and Health Consequences

Childhood obesity represents one of the most urgent and complex global public health challenges of the twenty-first century with a prevalence that has been rapidly increasing in both developed and developing territories and therefore poses significant risks to the immediate and long-term health and developmental trajectory of affected individuals (Hesketh et al., 2024; Li et al., 2024; Marcus et al., 2022). The world over, the picture is equally alarming, as the prevalence of overweight and obesity in children and adolescents has doubled between 1990 and 2021, which means that more than 100 million children are living with obesity today (Kerr et al., 2025; Marcus et al., 2022; Zhang et al., 2024). Projections for 2050 predict the further increase of rates of obesity in all populations and regions, making coordinated and strong public health interventions a pressing need to address this crisis (Kerr et al., 2025). Although the overall prevalence of obesity among children and adolescents is about 8.5% on average, there is a wide range of prevalence rates, from negligible percentages in some areas to nearly 30% in others, with higher prevalence rates being common in countries with higher Human Development Index scores and higher average incomes (Zhang et al., 2024). This continued rise, especially evident in the low and middle income countries, indicates a widespread shift to a chronic positive energy balance worldwide with substantial associated health, economic and societal burdens (Ali et al., 2024; Blaauwendraad et al., 2024; Gao et al., 2023; Li et al., 2024).

The etiology of childhood obesity is highly multifactorial, emerging from a complex and dynamic interaction between genetic predispositions, physiological mechanisms, individual behaviours, psychosocial factors and ubiquitous environmental determinants that are accumulated throughout the life course starting from conception (Hesketh et al., 2024; Mohamed et al., 2022; Wójcik et al., 2023). Genetic factors are a large contributor to obesity susceptibility; twin studies have found that heritability can explain between 40-80 per cent of the variance in obesity - and this heritable component is often multiplied within an obesogenic home environment (Hüls et al., 2021; Vourdoumpa et al., 2023). However, genetic predispositions act in a non-deterministic way, and comparatively, in combination with lifestyle and environmental exposures, this implies that obesogenic environments can 'trigger' genetic susceptibilities (Vourdoumpa et al., 2023; Wang, 2021). Parental body-mass index (BMI) helps identify a strong predictor of childhood obesity to highlight the genetic contribution (Zembura et al., 2023). In addition to the role of genetics, there are also a myriad of modifiable and non-modifiable determinants of the increasing prevalence Non-modifiable elements consist of genetic syndromes, endocrine disorders and certain medical conditions (Zembura et al., 2023). Critically, modifiable factors are the best targets for intervention, including unhealthy dietary behaviours (e.g., excessive consumption of sugar sweetened beverages, fast eating speed) and insufficient physical activity, increased sedentary behaviours (e.g. extended screen time) and insufficient sleep duration (Jiang et al., 2025; Mohamed et al., 2022; Šket et al., 2024; Wang, 2021). The "first 1000 days" of life from conception to a child's second birthday represents a particularly consequential period of development during which early life exposures have a lasting impact on long term health outcomes (Blaauwendraad et al., 2024; Maccarini et al., 2025). Maternal factors during pregnancy - including nutrition, psychosocial stress and exposure to environmental pollutants - may epigenetically modulate the programming of the fetus, shaping the metabolic pathways of the child and future risk of obesity (Maccarini et al., 2025; Panera et al., 2022). Moreover, family-level factors such as overweight/obesity of parents and residence in urban areas are found to be salient factors (Jiang et al., 2025). More general socioeconomic and environmental factors such as agricultural policy, urban land use planning and aggressive marketing of unhealthy foods interact to create an "obesogenic environment" that encourages weight gain (Mazza et al., 2025; Saliba & Cuschieri, 2021; Šket et al., 2024; Wang, 2021). Socioeconomic status, parental education, and neighbourhood characteristics have also been found to be major risk factors, often resulting in distrust of expensive food, or limited access to environments favourable for healthy lifestyle (Mazza et al., 2025; Šket et al., 2024).

The health consequences of childhood obesity are extensive, engaging virtually every physiological system and significantly increasing the risk of chronic disease and anticipating a reduced life expectancy (Calcaterra & Zuccotti, 2022; Marcus et al., 2022; Pacocha et al., 2024). Even before adulthood, almost every organ system can be affected negatively (Marcus et al., 2022). In the short term, there are cardiometabolic risk factors, such as hypertension, dyslipidaemia and early signs of cardiovascular dysfunction, that are common in children with obesity (Calcaterra & Zuccotti, 2022; Tully et al., 2022). Type 2 diabetes mellitus is increasingly being diagnosed in adolescents and young adults who were obese as children, and often presents with a more aggressive course and more morbidity and mortality compared with adult-onset disease (Marcus et al., 2022). Additional common complications include non-alcoholic fatty liver disease, obstructive sleep apnoea and polycystic ovary syndrome (Denova-Gutiérrez et al., 2022; Vajravelu et al., 2023). Furthermore,

childhood obesity is closely interrelated with chronic low grade systemic inflammation, which can already be measured in preschool children and is responsible for a higher long term risk for a variety of severe diseases, including autoimmune diseases such as multiple sclerosis, Crohn's disease and type-1 diabetes (Marcus et al., 2022). In addition to the physical consequences, obese children often face serious psychological problems such as depression, anxiety, low self-esteem, and behavioural disorders (Calcaterra & Zuccotti, 2022; Mohamed et al., 2022; Tully et al., 2022). These psychosocial burdens may affect quality of life, interferes with educational attainment and puts pressure on social relations (Denova-Gutiérrez et al., 2022; Mohamed et al., 2022; Vajravelu et al., 2023). Weight-related stigma and bullying are widespread problems amongst adolescents with obesity, and they may worsen weight gain and further negatively affect psychological health (Tully et al., 2022; Vajravelu et al., 2023). The maintenance of obesity from childhood into adulthood is frequent, which results in long-lasting cardiovascular risk factors and increased vulnerability to premature death(Mohamed et al., 2022; Pacocha et al., 2024; Saliba & Cuschieri, 2021). Excess body mass has been definitively established as a leading modifiable risk factor for mortality and disability-adjusted life-years globally, with obesity being recognised as a complex chronic disease which produces immediate impacts on physical and mental health, manifesting serious dysfunction well before adulthood (Kerr et al., 2025). The economic implications are equally staggering with the global cost of obesity estimated in the trillions of U.S. dollars, taking into account direct healthcare costs, loss of productive life as well as societal costs (Ling et al., 2022; Mazza et al., 2025; Segal et al., 2020). Stabilizing obesity prevalence may bring in significant annual worldwide savings that support the immense societal and economic advantages of effective prevention and management strategies (Mazza et al., 2025). Consequently, tackling childhood obesity is not only an imperative from a medical perspective but a key public health and economic concern that requires comprehensive, interdisciplinary and sustained action at the global level (Denova-Gutiérrez et al., 2022; Šket et al., 2024; Tully et al., 2022).

Pharmacological Mechanism and Rationale GLP-1

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are one of the pillars of the treatment of metabolic disease, due to their multifaceted pharmacological actions. These agents mimic the endogenous GLP-1 and stimulate glucose-dependent insulin secretion and reduce glucagon secretion, which improves glycaemic control. Simultaneusly, they slow gastric emptying, enhance satiety and influence the central nervous system pathways to reduce appetite and caloric intake, thereby resulting in significant weight loss(Moiz et al., 2025; Muzurović et al., 2022)The synergistic effect on glucose homeostasis and energy balance provides a strong rationale for the therapeutic efficacy of the GLP-1RAs in type 2 diabetes mellitus and obesity (Drucker, 2021).

The pharmacological mechanism and rationale behind glucagon-like peptide-1 receptor agonists (GLP-1RAs) is based on their ability to mimic and enhance the physiological actions of the natural incretin hormone GLP-1 secreted by intestinal L-cells that is predominantly released in response to nutrient ingestion (Pabreja et al., 2013; Shah & Vella, 2014). Native GLP-1 has a very short half-life because it is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) (Sfairopoulos et al., 2018). GLP-1RAs are synthetic analogues of GLP-1 that have been designed to be protected from degradation by DPP-4 to extend their circulation time and therapeutic effect and allow convenient once-daily or once-weekly administration depending on their particular pharmacokinetic profile (Jacobsen et al., 2015; Sfairopoulos et al., 2018). This prolonged action is a basic pharmacologic benefit that ensures the prolonged activation of GLP-1 receptors in different tissues.

The basic mechanisms of GLP-1RAs have profound actions on glucose homeostasis and energy balance through peripheral and central pathways. The GLP-1RAs in the pancreas selectively promote glucose-dependent insulin secretion from the beta cells (Drucker, 2021; Moiz et al., 2025). This glucose dependency ensures that insulin release is initiated when needed and this decreases the risk of hypoglycaemia (a very common side effect of insulin secretagogues) greatly; a common issue with conventional insulin secretagogues (Andreasen et al., 2021). At the same time, GLP-1RAs reduce glucagon secretion from alpha cells, especially in situations of hyperglycaemia, which further reduces hepatic gluconeogenesis and enhances glycaemic control (Drucker, 2021; Moiz et al., 2025).

In addition to these direct actions on the pancreas, GLP-1RAs have far-reaching effects on the gastrointestinal system. They slow down gastric emptying, which slows the absorption of nutrients and reduces postprandial glucose excursions (Alharbi, 2025; Pabreja et al., 2013; Shah & Vella, 2014). This physiological delay also supports the development of a greater feeling of fullness and satiety, which is an important factor in the reduction of overall caloric intake and weight loss (Dailey & Moran, 2013; Moiz et al., 2025; Pabreja et al., 2013).

In addition, central nervous system pathways are a key determinant of the therapeutic effect of GLP-1RAs.GLP-1 receptors are ubiquitously expressed in the brain, including in the regions of the brain involved in appetite regulation, such as the hypothalamus, brainstem and reward circuitry, including the nucleus accumbens and ventral tegmental area (Hayes, 2012; Muzurović et al., 2022; Shah & Vella, 2014; Suter et al., 2025). Activation of these central receptors by GLP-1RAs suppresses hunger sensations, food cravings, and the brain's reward responses to food to achieve a sustained and appreciable reduction in caloric intake and body weight (Alharbi, 2025; Dailey & Moran, 2013; Moiz et al., 2025; Suter et al., 2025). The communication between the gut and the brain, facilitated in part by the vagal afferent nerves that express GLP-1 receptors, plays a role in the latter, and signals from the periphery combine with signals processed centrally about hunger and satiety (Alharbi, 2025; Hayes, 2012; Pabreja et al., 2013).

At a cellular and molecular level the interaction of GLP-1RAs with GLP-1 receptors sets a cascade of intracellular signaling events in motion. This is mainly because of an activation of adenylate cyclase which results in an increase of cyclic adenosine monophosphate (cAMP) within the cell (Muzurović et al., 2022). Elevated cAMP levels in turn activate protein kinase A and other pathways such as protein kinase C, mitogen-activated protein kinase, extracellular signal-regulated kinase 1/2 (ERK1/2) and AMP activated protein kinase (AL-Noshokaty et al., 2025; Bu et al., 2024). These complex signaling pathways are the mediators of the diverse biological responses such as enhanced transcription of insulin genes, beta-cell proliferation, inhibition of apoptosis and modulation of neuronal activity (AL-Noshokaty et al., 2025; Hayes, 2012; Muzurović et al., 2022).

Beyond their well-established roles in glucose control and weight loss, GLP-1RAs exhibit a wide range of "beyond pancreatic" effects, which are a huge contribution to their clinical rationale (Zhao et al., 2021). These include cardiovascular benefits such as enhanced endothelial function, lessened inflammation, reduced atherosclerotic plaque formation and positive results in cardiovascular function such as blood pressure and cardiac function (Alharbi, 2025; Suter et al., 2025). Some GLP-1RA have shown a reduction in major adverse cardiovascular events in patients with type 2 diabetes and established cardiovascular disease (Andreasen et al., 2021). Furthermore, they show neuroprotective effects, including a reduction in neuroinflammation and neurotoxicity as well as potential effects on neurodegenerative diseases, such as Alzheimer's and Parkinson's (Alharbi, 2025; Bu et al., 2024; Suter et al., 2025; Zhao et al., 2021). They are also involved in the regulation of metabolism, specifically by improving lipid profiles (reducing triglycerides and low-density lipoprotein cholesterol), reducing inflammation in adipose tissues and reducing ectopic fat deposits (Bu et al., 2024; Moiz et al., 2025). Renal benefits including improvements in indicators of kidney function have also been observed (Andreasen et al., 2021). This broad range of positive effects brings out the wide-ranging metabolic and systemic improvements that GLP-1RA therapy provides (Wilbon & Kolonin, 2023; Zhao et al., 2021).

The clinical rationale for GLP-1 based pharmacotherapy is therefore very sound and extensive. For type 2 diabetes, they provide good glucose lowering, with a low risk of hypoglycemia and often cause weight loss, which is beneficial given the high co-morbidity of diabetes and obesity (Andreasen et al., 2021; Drucker, 2021). In the case of obesity, therefore, they can be a powerful tool when it comes to controlling weight by targeting key physiological pathways through the regulation of appetite and metabolism, resulting in clinically significant and sustained weight loss (Moiz et al., 2025; Tamayo-Trujillo et al., 2024). This is especially important in a population such as adolescents with severe obesity where there were previously few effective pharmacological options. The wide variety of different GLP-1RAs available, which are distinguished by their pharmacokinetic properties (e.g., short-acting versus long-acting) offers the possibility of personalised treatment strategies depending on the individual patient's needs, glucose profiles and tolerability (Kalra et al., 2021; Miñambres & Pérez, 2017; Tahrani et al., 2016). The further development of this class of agents, which includes the development of dual and triple co-agonists which target GLP-1 and other incretin pathways such as GIP and glucagon, promises even more efficacy and metabolic flexibility in the future (Alharbi, 2025; Först et al., 2025; Moiz et al., 2025). In summary, GLP-1RAs are a sophisticated and effective approach to pharmacological treatment that makes use of natural physiologic processes to address the complex pathophysiology of metabolic diseases (Holst, 2024).

Clinical Promise – Efficacy in the Adolescent Population

The clinical potential of GLP-1RAs in the management of severe adolescent obesity is being supported by an increasing body of sound scientific evidence. These agents show a significant level of efficacy in key areas such as weight management, metabolic health improvement and general quality of life enhancement. GLP-1RAs have proven to be game-changing pharmacological interventions that offer a much-needed therapeutic bridge between traditional lifestyle changes and more invasive treatment options to a historically underserved demographic in terms of effective medical interventions. The strong efficacy of GLP-1RAs in adolescents is deeply connected with their multifaceted mechanism of action, which goes beyond glucose homeostasis to have a profound effect on energy balance and the complex regulation of appetite(Moiz et al., 2025; Muzurović et al., 2022).By physiologically mimicking endogenous GLP-1, such agents greatly enhance glucose-dependent insulin secretion and simultaneously block inappropriate glucagon release to provide for superior glycemic control. In addition to this, they cause a significant delay in the gastric emptying process, which actively promotes longer satiety, they also critically modulate pathways in the central nervous system that reduce appetite and subsequent caloric intake (Alharbi, 2025; Drucker, 2021; Moiz et al., 2025; Shah & Vella, 2014). This extensive physiological modulation, through peripheral and central pathways, leads to significant and sustained weight loss that forms the basic foundation for their clinical value in helping to meet the urgent public health challenge of adolescent obesity

In the field of weight management, both liraglutide and semaglutide have received important regulatory approvals and have been shown to have amazing efficacy in carefully designed clinical trials in adolescents. Liraglutide was exceptionally the first GLP-1RA that received approval by the US Food and Drug Administration for people aged 12-17 years with obesity. This approval was based on compelling evidence from pivotal trials, which showed that it is statistically superior to placebo in causing reductions in BMI z-score(Berman et al., 2023; Jensterle & Janež, 2021). For example, a seminal study done on 251 adolescents showed that liraglutide used at a dose of 3.0 mg daily led to a statistically superior change in BMI z-score from baseline at 56 weeks with an estimated treatment difference of -0.22 ($p=0.002$). Furthermore, 43.3% of participants treated with liraglutide had a BMI reduction of at least 5% compared with 18.7% of the placebo group. 26.1% had a BMI reduction of at least 10% (Berman et al., 2023). These strong results are also supported by real world data, which consistently show that liraglutide is effective and safe in achieving significant reductions in adiposity including BMI, BMI z-score, body weight and waist, height ratio in children and adolescents with severe obesity in routine clinical settings. Importantly, these improvements in anthropometric parameters were usually noted within 6 months of starting treatment and were durably maintained up to 12 months in those who continued to adhere to treatment (Cominato et al., 2025).

Semaglutide, a recently approved once weekly GLP-1RA has shown a clear improvement in the efficacy of weight loss in adolescents. A pivotal double blind, randomised, placebo controlled trial enrolled adolescents aged 12 to under 18 years with obesity or overweight and associated comorbidities (Weghuber et al., 2022). This is a landmark study that reported an average body mass index (BMI) reduction of -16.1% among the semaglutide group vs. a 0.6% increase among the placebo group with an estimated difference in treatment of -16.7 percentage points (Weghuber et al., 2023). In addition, 73 percent of the participants in the semaglutide arm had clinically significant weight loss (of at least 5 percent) by week 68, a clinically significant difference compared with 18 percent in the placebo group(Weghuber et al., 2023). These results, which are so compelling, illuminate the therapeutic effect of Isemaglutide on weight loss in this susceptible population.

In addition to weight loss, GL P-1RAs have beneficial effects on various aspects of the metabolism. Semaglutide administration has been linked to improvements in triglyceride and total cholesterol concentrations (except HDL) and a significant reduction in systolic blood pressure (Weghuber et al., 2023). Even though some meta analysis studies have shown variable improvements in lipid profile, consistent lowering of glycated haemoglobin A1c (HbA1c), as well as systolic blood pressure, are often observed, reinforcing the metabolic benefits (Silvia et al., 2021). These metabolic ameliorations are vital in the mitigation of long term health consequences of pediatric obesity, which include progression to type 2 diabetes and increased susceptibility to cardiovascular disease (Marcus et al., 2022). The inherent ability of GLP - 1RAs to ameliorate these biomarkers therefore highlights their multifaceted role not only in the treatment of obesity as an isolated condition, but also in the proactive prevention and comprehensive management of its associated chronic health conditions..

Furthermore, the clinical promise of GLP-1RAs doesn't end with improving treatment of obesity in adolescents. Clinical data, especially from rigorous trials of semaglutide, strongly imply a measurable improvement in the quality of life related to weight, especially the physical comfort category (Weghuber et al.,

2023). This witnessed enhancement can translate into increased ease of movement, decreased physical discomfort and higher ability to engage actively in different physical and social activities (Weghuber et al., 2023). This particular aspect of GLP-1RA efficacy is extremely useful, as it directly addresses the lived experience and subjective well-being of adolescents with obesity, and helps to create a greater sense of well-being, promote positive body image, and potentially better adherence to treatment regimens and engagement in positive lifestyle changes (Vajravelu et al., 2023). This particular aspect of GLP-1RA efficacy is extremely useful, as it directly addresses the lived experience and subjective well-being of adolescents with obesity, and helps to create a greater sense of well-being, promote positive body image, and potentially better adherence to treatment regimens and engagement in positive lifestyle changes (Berman et al., 2023).

Safety Profile and Long-Term Risks

The The safety profile and long-term risks of GLP-1RAs in the adolescent population needs to be carefully considered, despite the proven efficacy of GLP-1RAs in weight management and metabolic improvement. While these medications are considered to be well-selling and tolerated generally, increasing utilisation of them requires and necessitates a thorough understanding of the potential adverse events, especially considering the critical time of growth and development in children and adolescents(Cooper et al., 2023). The most common adverse events are gastrointestinal, which is consistent with the GLP-1RA mechanism of action that involves delayed gastric emptying (Santos & Castro, 2025; Silvia et al., 2021). Nausea is often reported and occurs when initiating the treatment, with patients usually adapting to the treatment over time (Silvia et al., 2021), other frequently reported gastrointestinal symptoms include vomiting, diarrhoea and constipation (Santos & Castro, 2025). Although the incidence of gastrointestinal adverse events is generally higher in groups treated with GLP-1RAs than in placebo groups, these events are generally mild to moderate and are rarely the reason for permanent treatment discontinuation based on information from semaglutide trials in adolescents (Weghuber, Barrett, et al., 2023; Weghuber, Kelly, et al., 2023). Comprehensive patient education and slow increase in dosage remains an important strategy to control these transient effects. In addition to gastrointestinal symptoms, the risks of pancreatic and gallbladder are significant issues. Although acute pancreatitis is uncommon it has been reported with GLP-1RA use in adults. In trials in adolescents, occurrences of cholelithiasis (gallstones) have been observed and one of the key semaglutide trials found a 4% incidence in the active treatment arm compared to zero in placebo surveillance of the Adverse Event Reporting System by the US FDA is ongoing to identify and track cases of acute cholecystitis associated with GLP-1RA products (Weghuber et al., 2022; Woronow et al., 2022). Long-term data about these events related to the pancreas and gallbladder in adolescents is still lacking, and more research is needed to determine the full implications of these events (Bensignor et al., 2024). A critical safety consideration with a black box warning for GLP-1RAs is the possibility of thyroid C-cell tumours with a particular type, medullary thyroid carcinoma of the thyroid gland, which was first discovered in rodent studies (Pasternak et al., 2024). For this reason, GLP-1RAs are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia type 2 (Kelly & Sipos, 2024; Pasternak et al., 2024). While it is unclear whether findings in rodents can be extrapolated to humans, some research in adults has shown an elevated risk of all thyroid cancer and medullary thyroid carcinoma after 1-3 years of GLP-1RA treatment, although other studies have shown conflicting findings regarding differentiated thyroid cancer (Bezin et al., 2022; Kelly & Sipos, 2024). For adolescents, strong and ongoing vigilance, as well as additional research, is of the utmost importance to elucidate any long-term oncological risks (Balachandra et al., 2025; Kelly & Sipos, 2024). The effects of GLP-1RAs on growth and pubertal development in adolescents is another important area of exploration, as medications that have a profound effect on body weight and metabolic pathways during critical time periods of development could have a potential effect on growth hormones (Cooper et al., 2023). Although a semaglutide trial lasting 68 weeks did not show any negative effects on growth or pubertal development, the long-term data on these all-important aspects in adolescents are so far limited (Bensignor et al., 2024; O'Connor et al., 2024; Weghuber, Barrett, et al., 2023; Weghuber, Kelly, et al., 2023). This calls for the need for longer term follow up studies to ensure the benefits of weight loss are not inadvertently affecting normal physiological development and addresses the call to investigate "unintended consequences" in this age group (Cooper et al., 2023). Neuropsychiatric considerations have also become an area of concern; post-marketing surveillance reports have reported possible psychiatric side effects such as insomnia, anxiety, nervousness and depressive symptoms, the European Medicines Agency reporting cases of depression, self-injury and suicidal ideation. Although adverse event reporting systems are inherently limited by underreporting and bias, preventing definite causality, one study found a significant association between GLP-1RA treatment

and increased risk of psychiatric disorders, major depression, anxiety and suicidal behaviour in adult patients with obesity (Kornelius et al., 2024). On the other hand, GLP-1RAs are also being investigated for their potential neuroprotective and psychotropic effects for mental health conditions (Valenta et al., 2024). his complex dynamic requires careful clinical observation for the development or worsening of neuropsychiatric symptoms, particularly in adolescents in whom mental health problems are common, with long term data on suicidal ideation being scarce in this particular age group (Bartkoski et al., 2025; Bensignor et al., 2024). Overall while the general safety profile of GLP-1RAs in adolescents seems to be similar to in adults, with tolerable gastrointestinal side effects, the long-term effects on growth and development and the more rare events such as pancreatitis, cholelithiasis and potential thyroid C-cell tumours require constant and intensive investigation (Jensterle & Janež, 2021; Weghuber, Barrett, et al., 2023; Weghuber, Kelly, et al., 2023). The reassurance that there are no "new safety concerns" in the short to medium term trials needs to be balanced with the fact that the studies are limited in duration (some involving follow-up for no longer than 17 months), given the chronic nature of the treatment of obesity, and the possibility of weight regain on discontinuation the importance of comprehensive long-term safety data in the adolescent population (Bensignor et al., 2024; O'Connor et al., 2024; Weghuber, Barrett, et al., 2023; Weghuber, Kelly, et al., 2023). The clinical utility of GLP-1RAs in the management of severe adolescent obesity must always be carefully considered against a determination to fully characterise and address these changing safety considerations (Cooper et al., 2023; Stefater-Richards et al., 2025).

Ethical and Social Considerations

The use of GLP-1-based pharmacotherapy in adolescents with severe obesity is a complex interweaving of ethical and social issues characterized prominently by the issues of informed consent and respect for adolescent autonomy during a critical time of development. A large social challenge exists due to the high cost of these medications and often limited insurance coverage that can heighten the already present health inequities and limit access to vulnerable populations (Berman et al., 2023; Wright et al., 2023).Furthermore, societal perceptions of obesity, and body image and stigma are critical, the over-reliance on using BMI as a sole measure of eligibility for medication runs the risk of reinforcing a 'weight-normative' approach and detracts from holistic improvements in health, and may also encourage disordered eating behaviours or misuse due to external pressures (Button et al., 2025; Cominato et al., 2021; Floegel-Shetty, 2023). The prevalence of public awareness and media coverage of these drugs also leads to concerns about unsupervised acquisition and use of these drugs by adolescents, especially those vulnerable to body image concerns (Cooper et al., 2023). Finally, because obesity treatment is long term, careful consideration must be given to adherence, degree of monitoring for "unintended consequences" on growth and neurodevelopment, as well as defining treatment success, not simply weight loss, but stable improvements in metabolic health, maintaining psychological well-being, and overall quality of life (Bartkoski et al., 2025; Cooper et al., 2023).

Conclusions

GLP-1RAs are a truly revolutionary development in the therapeutic arena of severe obesity in adolescents with immense clinical potential based on their multifaceted pharmacological effects that effectively target appetite regulation, restore glucose homeostasis and regulate overall energy balance (Alharbi, 2025; Moiz et al., 2025; Weghuber et al., 2023). Clinical trials have shown conclusively their amazing efficacy, with agents like semaglutide leading to substantial weight loss, notable improvement in cardiometabolic health markers (including blood pressure and HbA1c) and an improved quality of life, especially in terms of physical comfort, for adolescents stricken with obesity (Silvia et al., 2021; Weghuber, Barrett, et al., 2023; Weghuber, Kelly, et al., 2023). These benefits highlight their potential to reduce the immediate and long-term health consequences related to the obesity of children and therefore offer a vital intervention in a group with limited effective treatment options.

However, the wide scale use of GLP-1RAs requires careful and continuous consideration of the safety profile and any long-term risks. While generally well tolerated, and the majority of adverse events are transient gastrointestinal issues such as nausea and vomiting, more serious issues, such as cholelithiasis and acute pancreatitis, have been reported (Santos & Castro, 2025; Weghuber et al., 2022; Woronow et al., 2022). The black-box warning of the risk of medullary thyroid carcinoma, extrapolated from rodent studies, requires careful screening of patients as well as the need for more human data, especially in the adolescent population (Bezin et al., 2022; Kelly & Sipos, 2024; Pasternak et al., 2024). Critical gaps in the knowledge of the long-term effects on growth and puberty, and neuropsychiatry, including suicidal thoughts, remain, and rigorous

and extended surveillance studies are needed to fully characterize and address these possible "unintended consequences" (Bartkoski et al., 2025; Bensignor et al., 2024; Cooper et al., 2023).

Beyond the clinical field, there are very great ethical and social challenges to be navigated. Ensuring truly informed consent and respecting the evolution of autonomy of adolescent in long term treatment decisions is paramount (Turhal & Bağlam, 2025; Viner et al., 2020). This expense of such therapies and frequently-limited access to them through insurance imposes deep concerns about equity and threaten to deepen existing health disparities while limiting access to those population that are socioeconomically vulnerable youth (Berman et al., 2023; Wright et al., 2023). Moreover, the cultural stigma of obesity in society together with the media's depiction of these drugs may inadvertently promote a "weight-normative" strategy, which may lead to disordered eating habits or misuse within a population already vulnerable to body image pressures (Button et al., 2025; Cominato et al., 2021; Floegel-Shetty, 2023). Therefore, in order for GLP-1RAs to be successfully and responsibly incorporated into adolescent obesity care, a holistic, patient-centered approach to care that prioritizes the attainment of comprehensive health outcomes (e.g., metabolic improvement, psychological well-being, and overall quality of life) rather than mere weight reduction is necessary. Continuous and transparent research in long-term safety, as well as more focused efforts to ensure equitable access and work against societal biases that prevent effective and compassionate care for adolescents with obesity, is essential.

Discussion

GLP-1RAs hold great clinical potential in the management of severe obesity in adolescents, showing effective weight loss, improved cardiometabolic outcomes and a better quality of life (Silvia et al., 2021; Weghuber, Barrett, et al., 2023; Weghuber, Kelly, et al., 2023). One such drug, semaglutide, has achieved significant reductions in BMI as well as physical comfort (Weghuber, Barrett, et al., 2023; Weghuber, Kelly, et al., 2023).

However, safety and ethical issues are important. Common gastrointestinal side effects are usually mild in nature but there are risks of cholelithiasis and acute pancreatitis (Santos & Castro, 2025; Weghuber et al., 2022; Woronow et al., 2022). A black box warning for potential thyroid C- cell tumors requires careful screening(Kelly & Sipos, 2024; Pasternak et al., 2024).Long-term data concerning growth, puberty and neuropsychiatric consequences, including suicidal ideation are limited so far, and long-term monitoring is required (Bartkoski et al., 2025; Bensignor et al., 2024; Cooper et al., 2023).

Ethical issues are concerned with informed consent and fair access because of high cost and insurance (Berman et al., 2023; Wright et al., 2023). Tackling stigma in society and avoiding abuse for cosmetic purposes are also important. A holistic approach that is patient centered and focuses on overall well-being rather than just on weight loss is important.

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