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Review Article

New directions in childhood obesity treatment – A path forward or wishful thinking?

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BACKGROUND: The advent of highly effective pharmacotherapy that induces significant weight loss has revolutionized the treatment of obesity. Since 2020, these medications have been approved for use in children with obesity 12 years of age and older, and the American Academy of Pediatrics 2023 Clinical Practice Guidelines have endorsed their use.
SOURCES OF MATERIAL: Specifically, glucagon-like peptide 1 (GLP-1) agonists and similar related nutrient stimulated hormones induce weight loss of >15% of baseline body weight in clinical trials.
ABSTRACT OF FINDINGS: However, these benefits must be balanced with the known side effects and other potential unknown effects especially in growing children and adolescents. Moreover, barriers to access and long-term effects of these medications need to be addressed.
CONCLUSION: In this review, we discuss important considerations for the utilization of these newer weight loss agents in the rapidly evolving landscape of weight loss pharmacotherapy in children and adolescents.

Introduction and background: Past, present, and future

The application of pharmacologic interventions for obesity has exploded over the past few years with a significant spike in prescriptions for the highly effective glucagon-like peptide-1 receptor agonists (GLP-1RAs) such as semaglutide. This new generation of obesity medications has raised the bar for efficacy with clinical trials demonstrating an average of ∼12% decrease in body weight over placebo in adults (STEP)[1] and ∼19% decrease in body weight over placebo in adolescents (STEP TEENS).[2] Semaglutide was Food and Drug Administration (FDA) approved for the treatment of obesity in adults in June 2021 and subsequently for children ages 12 years and older in December 2022. Between 2020 and 2023 there was a remarkable 6-fold increase in the number of prescriptions for GLP-1RA in adolescents[3] in parallel with an 8-fold increase for adults.[4] Liraglutide was previously approved for the treatment of obesity in 2014 for adults and in 2020 for pediatric patients ages 12 and older after SCALE and SCALE Teens trials demonstrated clinical safety and efficacy.[5,6]

This swift evolution of novel treatment options comes to us in the context of a broad and gradual paradigm shift

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over the past several decades toward recognizing obesity as a chronic disease. Reframing obesity as a disease process and not as a lifestyle problem or failure of willpower, is foundational to this change in thinking. Adipose tissue is a key neuroendocrine organ that helps regulate appetite and energy storage in concert with other peripheral signals, such as insulin, which acts on the satiety centers within the hypothalamus.[7] Given obesity is driven largely by genetic and biological factors causing dysfunction of this system, biological interventions are accordingly appropriate and often necessary for clinically effective treatment.[8]

Almost 3 decades ago, the World Health Organization (WHO) published the WHO Consultation on Obesity in which obesity was recognized as a chronic disease albeit one described as "largely preventable through lifestyle strategies."[9] Over time we have moved toward a more comprehensive understanding of multifaceted biological, social, and psychological contributors to obesity. In 1998, the National Institutes of Health stated, "obesity is a complex, multifactorial chronic disease" and outlined multiple modalities for the treatment of obesity including behavioral approaches to influence dietary choices and physical activity, bariatric surgery, and pharmacotherapy.[10]

In 2007, the American Academy of Pediatrics (AAP) published a committee recommendation acknowledging the option to use pharmacotherapy to treat obesity but only in the context of tertiary care.[11] At that time, 2 agents were available to treat obesity: sibutramine, which was withdrawn from the market in 2010 after studies linked its use to adverse cardiovascular outcomes, and orlistat, which is now available over the counter but seldom utilized due to limited tolerability. In 2013 the American Medical Association recognized obesity as a disease and stated that doing so would “help change the way the medical community tackles this complex issue.”[12] Within this changing context, the fixed combination of phentermine-topiramate (Topamax tablets) extended release, which demonstrated about 10% reduction in body mass index (BMI) over placebo in clinical trials,[13] was FDA-approved for obesity in adults in 2012. The formulation was subsequently approved for children 12 years and older a decade later in June 2022.

In January 2023, in their first ever clinical practice guideline (CPG) on *treatment* of obesity in children and adolescents, the AAP provided guidance to pediatric health care providers (PHCPs) that pharmacotherapy to treat obesity *should* be offered as an adjunct to lifestyle interventions for children 12 years of age and older. Further, the CPG states that pharmacotherapy *may* be offered for children ages 8 to 11 years.[14]

With increasingly efficacious pharmacotherapeutic options already used in adults, such as the dual GLP-1/gastric inhibitory polypeptide (GIP) receptor agonist tirzepatide (a combination of 2 nutrient stimulated hormones),[15] not to mention even more mechanistically diverse options in the pipeline, the gap in options for intervention between lifestyle treatment and bariatric surgery is closing quickly. Novel, safe, and effective pharmacotherapies are expanding our repertoire to treat obesity and are paving a path forward.

Clinical approach to prescribing GLP-1RAs

Setting the stage for effective obesity care, regardless of the use of obesity pharmacotherapy, begins with establishing a nonstigmatizing clinical space free of judgement. Aligning goals and assessing motivation to change from the onset helps to prioritize a patient-centered approach. Prior to intervention, it is helpful to explain the spectrum of tools available to treat obesity to patients and their families. Clinicians should discuss chronicity of obesity care over the life course and strategies to support positive health outcomes which are sustainable over the long-term.[8]

Discussion of the multifactorial and chronic nature of obesity should occur during the first encounter with an emphasis on the role of biology and genetics in the development and perpetuation of the disease as well as acknowledgement of social, cultural, and environmental factors. We find it helpful to explain the roles of set point and metabolic adaptation to validate the significant challenges many families have already experienced in previous attempts at managing obesity with lifestyle interventions alone.[8]

To be clear, lifestyle modifications are at the foundation of obesity care, and we recommend communicating this to patients and their families. Utilization of pharmacotherapeutic and surgical interventions should not replace setting achievable and sustainable goals around nutrition and activity. Instead, lifestyle modifications should be used in tandem with other modalities. Indeed, many would argue that application of highly-effective medications requires even keener attention to nutrition and physical activity strategies to optimize body composition changes in the context of substantial weight loss[16] and to ensure adequate nutrient intake in the context of reduced appetite while taking obesity medications, particularly incretin-based therapies.[17]

The choice of a pharmacotherapeutic agent realistically begins with a conversation about accessibility based on the patient’s age. Although the FDA has approved GLP-1RA use for children 12 years and older for the treatment of obesity, recent clinical trial data for liraglutide have demonstrated safety and efficacy in children as young as 6 years old.[18,19] This potential expansion to younger children holds promise for broader GLP-1RA usage in pediatric obesity treatment in the future. In addition to age, cost and coverage of the medication can become another barrier to prescribing GLP-1RAs, which will be addressed below.

Newer GLP-1RAs offer the convenience of once weekly injections, which may improve compliance amongst those who struggle with daily medication administration. Pen devices which are easy to use also make dosing more convenient. Details on dosing, contraindications, and clinical pearls are in Table 1. Adolescents, in particular, have been shown to struggle with medication compliance, but many GLP-1RA trials conducted in this age group have shown excellent adherence to the injections.[20]

Table 1 FDA-approved GLP-1RAs for pediatric weight loss.[18]

	Liraglutide	Semaglutide
Brand name with FDA pediatric weight loss indication	Saxenda	Wegovy
Dosing	• Initial: 0.6 mg subQ daily • Second week: 1.2 mg subQ daily • Third week: 1.8 mg subQ daily • Fourth week: 2.4 mg subQ daily • Maintenance: 3 mg subQ daily	• Weeks 1-4: 0.25 mg subQ weekly • Weeks 5-8: 0.5 mg subQ weekly • Weeks 9-12: 1 mg subQ weekly • Weeks 13-16: 1.7 mg subQ weekly • Maintenance: 1.7 mg or 2.4 mg subQ weekly
Contraindications	• Pregnancy • Family history of medullary thyroid cancer • Multiple endocrine neoplasia type 2 • Hypersensitivity	• Pregnancy • Family history of medullary thyroid cancer • Multiple endocrine neoplasia type 2 • Hypersensitivity
Clinical pearls	• Discontinue if BMI has not decreased $\geq$ 1% from baseline after 12 wk on maintenance dose • If a dose is missed for $>$ 3 d, resume with a daily dose of 0.6 mg to minimize initiation reactions • Patients do not have to reach the 3 mg target dose to achieve weight loss	• Can decrease dose to 1.7 mg weekly for 4 extra weeks if 2.4 mg subQ dose is not tolerated • If 2 or more consecutive doses are missed, consider following the dose escalation schedule, which may reduce the occurrence of gastrointestinal symptoms associated with reinitiation of treatment

Abbreviations: BMI, body mass index; FDA, Food and Drug Administration; GLP-1RAs, glucagon-like peptide-1 receptor agonists; subQ, subcutaneous.

The 2023 AAP CPG states that obesity pharmacotherapy should be offered to adolescents 12 years and older with a BMI $\geq$95th percentile, according to medication indications.[14] Although BMI has its limitations in assessing true adiposity, it is a validated proxy measure of excess body fat and is used as a screening tool in the evaluation of obesity. Severe obesity is now divided into 2 categories based on BMI percentile using the age- and sex-specific Centers for Disease Control and Prevention (CDC) growth charts. Class II obesity denotes a BMI $\geq$120% to $<$140% of the 95th percentile or a BMI $\geq$ 35 kg/m^2 to $<$40 kg/m^2, whichever is lower based on age and sex. Class III obesity denotes $\geq$140% of the 95th percentile or BMI $\geq$ 40 kg/m^2, whichever is lower based on age and sex.[8,14] Patients with Class III obesity or rapid weight gain are particularly unlikely to achieve sufficient weight loss through lifestyle interventions alone. In these cases, GLP-1RAs have demonstrated significant efficacy, making them an optimal choice for achieving meaningful weight reduction and metabolic improvements.[8]

The presence of weight-related comorbidities, such as type 2 diabetes, metabolic liver disease, and cardiovascular disease, may further influence the decision to initiate GLP-1RA therapy in preference to other obesity medications. GLP-1RAs have long been used in the management of type 2 diabetes in both adults and children due to their ability to regulate blood glucose levels and to produce clinically sustainable weight loss in adults. Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), is another comorbidity that is improved with the use of GLP-1RAs in adults. Though current guidelines for the treatment of MASLD in children do not include pharmacotherapy, recent studies suggest GLP-1RAs may reduce hepatic steatosis and improve liver enzymes.[21] Similarly, while there is limited research on GLP-1RAs' effects on dyslipidemia, their mechanism of action suggests potential cardiometabolic benefits (see below), which may lead to further exploration of their use in the future.[22] Ultimately, GLP-1RAs provide an option to target multiple obesity-related comorbidities, making them an appealing choice for patients with complex metabolic profiles.

Effectiveness of GLP-1 receptor agonists

Two randomized controlled trials have been published detailing the safety and efficacy of GLP-1RAs for weight management in adolescents with obesity as adjunct to lifestyle modifications (Table 2). Liraglutide and semaglutide have both demonstrated to be superior to placebo with regards to lowering BMI.

The SCALE Teens trial was a phase 3 randomized, double-blind, placebo-controlled trial conducted between 2016-2019 in adolescents 12 to $<$18 years of age who were randomized to receive either liraglutide at 3.0 mg or placebo subcutaneously once daily, in addition to lifestyle therapy for 56 weeks.[6] Liraglutide demonstrated an estimated difference of –0.22 in BMI SD score from baseline to week 56, and this equated to an estimated decrease of 4.64% in BMI, along with an absolute and relative change in body weight of –4.5 kg and –5.01%, respectively, in the liraglutide group relative to placebo.[6] The proportion of participants in the liraglutide group who achieved a BMI reduction of at least 5% was 43.3% compared to 18.7% in the placebo group, and at least 10% BMI reduction was observed in 33% of partici-

Table 2 Summary of clinical trial findings.

Study	Medication	Study duration	Dose	Change in BMI (%)	Change in weight (%)
SCALE Teens	Liraglutide	56 wk	3 mg	−4.64	−5.01
STEP TEENS	Semaglutide	68 wk	2.4 mg	−16.7	−17.4
SCALE Kids	Liraglutide	56 wk	3 mg	−7.4	−8.4

Abbreviation: BMI, body mass index.

pants in the liraglutide group compared to 9% in the placebo group.[6]

The STEP TEENS trial evaluated the effectiveness of once weekly subcutaneous semaglutide in adolescents 12 years to <18 years of age with obesity in a randomized, double-blind, placebo-controlled trial. All participants received lifestyle intervention and were randomized to receive once weekly dosing of semaglutide 2.4 mg vs placebo for 68 weeks.[2] A greater reduction in BMI was observed in the semaglutide group with participants achieving a mean BMI change of −16.1% at 68 weeks compared to +0.6% with placebo.[2] At least 5% weight loss was achieved in 76% of participants in the semaglutide group vs 18% in the placebo group, and at least 10% and 15% weight loss was achieved in 62% and 53% of participants in the semaglutide group, respectively, compared to 8% and 5% in the placebo group.[2] The study also reported for the first time an improvement in weight-related quality of life with significant improvements in the Impact of Weight on Quality of Life (IWQOL)-Kids total score and the physical comfort domain score at week 68 in the semaglutide vs placebo groups.[2]

Moreover, in young children between the ages 6 to <12 years, liraglutide in conjunction with lifestyle intervention was shown to be more effective at reducing BMI compared to placebo plus lifestyle intervention in the SCALE Kids trial (Table 2). In this phase 3a trial, children randomized to receive daily liraglutide 3.0 mg or the maximum tolerated dose, showed a mean change in BMI of −5.8% compared to +1.6% in the placebo group with an estimated difference of −7.4 percentage points.[19] At least 5% reduction in BMI from baseline occurred in 46% of children in the liraglutide group compared to 9% in the placebo group, and 35% of the children had at least 10% reduction in BMI in the liraglutide group vs 4% in the placebo group.[19] After 56 weeks, the mean change in body weight compared to baseline was +1.6% with liraglutide compared to +10% with placebo for an estimated difference of –8.4 percentage points.[19] Therefore, while both groups gained weight, the liraglutide group gained significantly less weight over the study period. While these medications are being studied in younger children, there needs to be a balance between forging this new path and not assuming weight loss will be the same for all children.

Side effects and side benefits

As with all medications, GLP-1RAs have potential side effects. The most common are gastrointestinal (GI)-related events (including nausea, vomiting, and diarrhea) with a similar incidence in adults and children. In the SCALE Teens trial, GI events occurred in 64.8% of the liraglutide group vs 36.5% of the placebo group, and 10 out of 81 participants discontinued liraglutide due to GI events.[6] While in the STEP TEENS trial, GI events occurred in 62% of the semaglutide group vs 42% of the placebo group, and 3 out of 133 participants discontinued semaglutide due to GI events.[2] Most of these events occurred during the dose escalation period in both studies. The most common adverse events seen in clinical trials are summarized in Table 3. Other events with a known relationship to GLP-1RAs included acute cholecystitis, cholelithiasis, and pancreatitis, but all were rare occurrences with 0 to 5 participants having any adverse events during the study periods.[2,6] Moreover, growth, progression of bone age, and pubertal development were not different between the GLP-1RA and placebo groups in the SCALE Teens and STEP TEENS trials.[2,6] Nevertheless, exposures to the highest doses of GLP-1RAs have only been approximately 1 year in most studies, and longer term follow up and safety data are needed.

Table 3 Adverse events that occurred in ≥ 5% of participants in clinical trials.[2,6]

Liraglutide	Semaglutide
Nasopharyngitis	Nausea
Nausea	Vomiting
Headache	Diarrhea
Vomiting	Headache
Diarrhea	Abdominal pain
Oropharyngeal pain	COVID-19
Influenza	Nasopharyngitis
Gastroenteritis	Upper abdominal pain
Upper respiratory tract infection	Dizziness
Abdominal pain	Gastroenteritis
Pyrexia	Constipation
Dizziness	Decreased appetite

Additional concerns around increased psychiatric conditions such as depression, anxiety, and suicidal behaviors associated with the use of GLP-1RAs have become controversial as some studies in adults have shown an increased risk of these conditions[23] while others show no increased risk.[24,25] One retrospective cohort study, which included nearly 7000 adolescents – half of whom were treated with a GLP-RA – reported a 33% reduced risk of suicide ideation or attempts over 12 months of follow-up in the group receiving treatment.[26]

Finally, some retrospective data suggest an association between semaglutide and nonarteritic anterior ischemic optic neuropathy (NAION),[27] while other data have not demonstrated this association.[28] No pediatric data are available since NAION is a rare condition in children. More prospective long-term studies are needed to determine the impact of GLP-1RAs on psychiatric health and the risk of NAION in pediatric populations.

Benefits beyond weight loss

While the weight loss benefits of GLP-1RAs seem clear, newer weekly injectables (ie, semaglutide and tirzepatide) provide additional benefits above and beyond weight reduction. While data in children are lacking, evidence supporting the benefits of GLP-1 RAs in adults have lead to FDA approval for: (1) reduction of glucose in people with type 2 diabetes; (2) reduction in the risk of cardiovascular death, heart attack, and stroke in adults with cardiovascular disease and either obesity or overweight; (3) treatment of moderate to severe obstructive sleep apnea (OSA); (4) risk reduction of worsening kidney disease and cardiovascular death in adults with type 2 diabetes and chronic kidney disease.[29,30] Moreover in clinical trials GLP-1RAs have been shown to decrease the progression from prediabetes to diabetes[31] and to provide significant clinical benefit in patients with MASLD[21] and arthritis.[32] In addition to metabolic diseases, GLP-1RAs are being studied to treat addictive disorders and have shown promise in reducing the use of addictive drugs, alcohol, and tobacco.[33]

The SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) trial program enrolled >8000 adults with type 2 diabetes and demonstrated a glycated hemoglobin (HbA1c) reduction of 1.5% to 1.8% with semaglutide 1.0 mg vs <0.1 to 0.4% with placebo.[34] While in the SURPASS trial program, tirzepatide demonstrated mean reductions from baseline in HbA1c ranging from −1.87% to −2.59% vs 0.04% increase with placebo.[35] Clinical trials in youth with type 2 diabetes are ongoing as these medications are not yet approved in this population.

However, demonstrating cardiovascular benefit of any treatment in youth long term is difficult given the long term follow up that is necessary. While we cannot extrapolate from data in adults, the SELECT cardiovascular outcomes trial demonstrated a 20% reduction in major adverse cardiovascular events (MACE) in 8803 adults treated with semaglutide compared to 8801 adults receiving placebo; all had preexisting cardiovascular disease and overweight or obesity, but no diabetes.[36] Even more impressive, semaglutide reduced MACE in adults who were receiving a stable background of statins, antihypertensive agents, and other evidence-based medications for atherosclerotic disease. It remains to be seen what long term cardiovascular benefits can be achieved if GLP-1RAs are initiated at younger ages in children and adolescents.

Barriers to the use of GLP-1RAs

Despite the many benefits of GLP-1RAs, medical management of childhood obesity faces numerous challenges that can hinder the accessibility and effectiveness of interventions.

Insurance

While the use of pharmacotherapy for childhood obesity has been increasingly encouraged in clinical practice, particularly with the approval of newer medications like semaglutide and liraglutide, insurance coverage remains a major barrier to the widespread use of these medications. Some insurance policies hinder access to effective pharmacotherapy by excluding coverage entirely, exacerbating the challenges healthcare providers and families face in managing childhood obesity. While some weight-loss medications have been approved for use in children, insurance companies often have restrictive policies that only approve medications for adults or individuals who meet specific criteria.

As of August 2024, the annual Medicaid budget survey revealed that 17 states provide coverage for obesity pharmacotherapy while 4 states deny coverage of GLP-1RAs for weight loss.[37] Many insurance plans require children to have a BMI in the 95th percentile or higher, along with comorbidities like diabetes, before approving medication. However, this can delay intervention until obesity has already reached severe levels, making early and proactive treatment difficult. Some estimates show that 68% of the cost of obesity medications is paid by patients.[38] GLP-1RAs can be prohibitively expensive, costing nearly $1000 per month for families without comprehensive insurance coverage.[39] Even for those with coverage, out-of-pocket costs may still be significant, as insurance plans often classify these drugs under high-cost specialty medications. The financial burden of these medications can deter families from pursuing pharmacotherapy for weight loss, even if they are clinically indicated. Some health plans also limit initial coverage to a certain period or reverse coverage entirely due to high costs.[40] Coupled with the intermittent drug shortages, these pauses in care can limit drug effectiveness and the goals of achieving significant clinical weight loss.

Primary care constraints

While most pediatric primary care providers routinely screen for obesity, many often feel they lack the time and are uncomfortable with weight-related discussions to address it effectively.[41] Although the AAP provided evidence-based approaches to obesity management in their 2023 CPG, numerous questions remain around implementation, specifically in prescribing obesity pharmacotherapy (ie, who will benefit the most, when to initiate pharmacotherapy, for how long and at what dose medications should be continued).[14] Moreover, healthcare providers experience challenges with

time constraints during clinic visits, which limit effective management and counselling of patients with obesity. The target weight loss rate and the degree of weight loss while on obesity pharmacotherapy has not yet been determined, which can also be a deterrent to initiating these medications. Additional studies are needed to assess dose stabilization and de-escalation to limit excessive weight loss.[42]

Other factors

Obesity-related comorbidities such as hypertension, diabetes, and sleep apnea disproportionately affect ethnic minorities, and disparities remain in the access to quality care for obesity. For those who are prescribed obesity pharmacotherapy, race/ethnicity has been a determining factor in who is more likely to receive such treatment.[43] For example, a retrospective study reviewing electronic health records for children and adolescents with severe obesity showed that prescription incidence rates for obesity pharmacotherapy were lower in Hispanics/Latinos compared to non-Hispanic Whites within the first year of being followed in a pediatric weight management clinic. This study also revealed that obesity pharmacotherapy was prescribed 2.5 times more within the first year when an interpreter was utilized emphasizing this additional barrier in nonprimary English-speaking families.[44]

The lack of availability and accessibility of GLP-1RAs due to supply and cost have led to the use of unapproved compounded versions of these medications.[45] The FDA issued a warning outlining concerns with using unapproved GLP-1RAs that included dosing errors, significant adverse events, counterfeit versions of these medications, versions sold falsely for research purposes or not for human consumption, and illegal online sales.[46] Compared to adults, the number of available approved obesity pharmacotherapy options for children continue to be limited. More studies are needed in a diverse population of children with a variety of underlying medical conditions to mimic situations of care seen in the real world.

Conclusion

With the approval of highly effective medications such as GLP-1RAs, a new pathway has been opened to improve the overall health of children with obesity. While we are beginning to understand the impact of these medications on weight loss, there remains much more to learn about their long-term consequences and benefits in addition to weight loss. Medical management of childhood obesity is fraught with challenges, from biological factors and psychological barriers to socio-economic and systemic constraints. Effective treatment requires a comprehensive, multidisciplinary approach that addresses not only the physical aspects of obesity but also the social, emotional, and environmental factors that contribute to it. Overcoming these barriers will require concerted efforts from healthcare providers, researchers, policymakers, and families to create a more supportive and accessible framework for addressing this growing public health crisis. By continuing down a path that leads to combinations of improved medical treatments, better access to care, and effective prevention strategies, we can hope to reverse the tide of childhood obesity.

Ethical approval

Not applicable for this review paper.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work one author used ChatGPT in order to improve the cohesiveness and readability of one paragraph discussing obesity comorbidities in the Clinical Approach to Prescribing GLP-1RAs section. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication. No AI was used as a reference to generate any content.

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