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Second Generation Anti-Obesity Medications

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Abstract

Purpose of Review This review aims to synthesize recent advancements in the pharmacological management of pediatric obesity, highlighting second generation anti-obesity medications and focusing on their efficacy, safety and impact on metabolic outcomes in children and adolescents.

Recent Findings Significant progress has been made in the treatment of pediatric obesity through the introduction of second-generation anti-obesity medications. These have shown promising results in reducing body mass index (BMI) in adolescents. They represent a shift towards more, mechanistic approaches in treating pediatric obesity and producing effect sizes that were previously not possible with available pharmacotherapy. Also, the newer medications have more pleiotropic benefits.

Summary Pediatric obesity treatment is witnessing significant evolution with the introduction of second-generation anti-obesity medications and novel therapeutic strategies. As the field progresses, more effective, personalized, and safer treatment options promise to enhance the quality of life and health outcomes for children and adolescents struggling with obesity. The integration of these advanced pharmacotherapies into ongoing lifestyle interventions represents a key factor in the holistic and effective approach to managing this complex and increasingly prevalent condition.

Keywords Pediatric · Adolescent · Obesity · Medical · Treatment · FDA

Introduction

Pediatric obesity remains a substantial and growing global health challenge. According to the World Health Organization, in 2022, over 390 million children and adolescents aged 5–19 years had overweight or obesity [1–6]. Studies have shown that children who have obesity are more likely to have obesity as adults, increasing the chances of life-limiting obesity related complications, such as Type 2 diabetes mellitus (T2D), cardiovascular morbidity, and cancer [7–10]. Further, the multifaceted impact of pediatric obesity extends beyond the individual, affecting families, healthcare systems, and societies due to the increased healthcare costs and reduced quality of life [11]. Despite these extensive implications, pediatric obesity remains underdiagnosed, and there is a lack of access to effective, evidence-based treatments [12].

Traditionally, pediatric obesity management has rested solely on dietary changes, increased physical activity, and behavior modifications [13–15]. For a minority of individuals, lifestyle modifications alone are sufficient to achieve significant or lasting weight reduction. However, the effectiveness of lifestyle modification is limited for majority of patients, due to issues with adherence, the chronic nature of lifestyle habits, and the complex etiology of obesity which involves an interplay of genetic, metabolic, psychosocial, and environmental influence. Recent years have witnessed a paradigm shift in the approach to managing pediatric obesity, marked by an increased emphasis on integrating pharmacotherapy as an adjunct to lifestyle modifications to enhance treatment outcomes [16]. This shift highlights the acceptance of obesity as a chronic disease of the adipose tissue that leads to overeating, rather than a simple result of overeating, fundamentally changing the treatment approach [17]. Pharmacological treatments target the underlying biological pathways responsible for the altered energy balance

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in obesity [18]. The consideration to use anti-obesity medication is also supported by the latest American Academy of Pediatrics (AAP) statement that emphasizes the need for aggressive management and early introduction of pharmacotherapy when indicated [13].

Initially, FDA-approved pediatric anti-obesity drugs such as Orlistat and Sibutramine were limited by their modest efficacy and prevalent side effects [19]. In response to this, second-generation anti-obesity medications have been developed and have improved safety profiles, enhanced efficacy, and a more targeted effect on the biological pathways altered in obesity [20, 21]. These newer medications specifically target pathways involved in appetite regulation, energy balance, or metabolic function, producing effective weight loss. The introduction of these medications marks a significant evolution in the pharmacological management of pediatric obesity, potentially transforming treatment paradigms and offering renewed hope to patients and their families. Henceforth, this review aims to offer highlights of the recently approved second generation pediatric anti-obesity medications (Table 1).

Second-Generation Anti-Obesity Medications: An Overview

The second-generation anti-obesity agents involve glucagon like Glucagon-like peptide-1 (GLP-1) receptor agonists, melanocortin 4 receptor (MC4R) agonists, Phentermine/Topiramate (Qsymia) and the combined GLP-1 & glucose-dependent insulinotropic polypeptide (GIP) receptor agonists (Tirzepatide) that operate through distinct mechanisms. Here, we delve into their mechanism of action, clinical efficacy, metabolic effects, safety profile and discuss their use along with the challenges in pediatric age group.

Table 1 Summary of FDA approved second generation anti-obesity medications

Medication	Dose	Contraindications	Common side effects	FDA approved indication (years)
LIRAGLUTIDE (Saxenda)	0.6 mg subQ daily and titrate up by 0.6 mg every 1–2 weeks to 3 mg subQ daily (or highest tolerated dose)	Pregnancy, Personal or family h/o Medullary thyroid cancer or type 2 multiple endocrine neoplasia	GI side effects: nausea, vomiting, gall stones Headache, fatigue Hypoglycemia risk in those on insulinotropic medications.	12+
SEMAGLUTIDE (Wegovy)	0.25 mg subQ weekly and titrate up every 4 weeks to 2.4 mg (or highest tolerated dose)	Pregnancy, Personal or family h/o Medullary thyroid cancer or type 2 multiple endocrine neoplasia	GI side effects: nausea, vomiting, gall stones, Headache, fatigue Hypoglycemia risk in those on insulinotropic medications.	12+
SETMELANOTIDE (Imcivree)	*Age 6–12 years*: Start at 1 mg subQ once daily x 2 weeks and then increase up to 3 mg subQ daily as tolerated. *Age ≥ 12 years*: Start at 2 mg subQ once daily x 2 weeks and then increase up to 3 mg subQ daily as tolerated	Severe renal disease. Use with caution in patients with history of depression and suicidal ideation	Injection site reactions, skin hyperpigmentation, nausea, vomiting, abdominal pain, spontaneous penile erection, depression	6+
PHENTERMINE AND TOPIRAMATE EXTENDED-RELEASE (Qsymia)	Starting dose: 3.75 mg/23 mg for 1 week then increase to 7.5 mg/46 mg. Highest dose studied in Pediatric age 15 mg/92 mg oral daily in the morning	History of cardiovascular disease or congenital heart disease, During or within 14 days following use of monoamine oxidase inhibitors, Uncontrolled hyperthyroidism, Glaucoma, Agitated state, History of drug abuse, pregnancy	Increase heart rate, blood pressure, dry mouth, insomnia, constipation, worsening anxiety	12+

SubQ: Subcutaneous; GI: Gastrointestinal

Mechanism of Action

GLP-1 Receptor Agonists

GLP-1 receptor agonists approved in pediatric population include Liraglutide and Semaglutide [20, 22]. GLP-1 is a hormone predominantly secreted by the L cells of the small intestine after meals and centrally in the nucleus tractus solitarius (NTS) [23]. GLP-1 receptor agonists mimic the natural action of GLP-1 by binding to its receptors located on pancreatic beta cells, brain, gastrointestinal tract, and heart [24]. This interaction triggers a cascade of biochemical reactions crucial for appetite regulation and glucose control. Upon binding to its receptors on pancreatic beta cells, GLP-1 enhances glucose stimulated insulin secretion [25]. GLP-1 receptor agonists also inhibit the secretion of glucagon, thus reducing hepatic glucose output, further aiding in glucose control [25]. These agonists slow gastric emptying, which prolongs the satiety after meals and reduces overall caloric intake, crucial for weight loss [26, 27]. Notably, natural GLP-1 has a very short half-life in circulation due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) [28]. To circumvent this, DPP-4 inhibitors were initially used to prolong the action of endogenous GLP-1 [29]. However, synthetic GLP-1 agonists like Liraglutide and Semaglutide have been modified to be less susceptible to DPP-4 degradation, thereby extending their action and enhancing their duration of action [30]. This advancement has significantly improved the therapeutic utility of GLP-1 receptor agonists in treating obesity, particularly by impacting the central nervous system and promoting a sustained feeling of fullness.

Melanocortin 4 Receptor Agonists (MC4R)

MC4R agonists target receptors involved in the melanocortin pathway, a critical regulator of appetite and energy homeostasis in the hypothalamus [31]. The MC4R is activated by alpha-melanocyte-stimulating hormone (α-MSH) and inhibited by agouti-related peptide (AgRP) [32]. Setmelanotide, a potent MC4R agonist, mimics the action of α-MSH, reducing food intake and increasing energy expenditure [33].

MC4R agonists are particularly effective in conditions characterized by leptin signaling disruptions, such as proopiomelanocortin (POMC) and leptin receptor (LEPR) deficiencies [34]. By activating MC4R, these agents compensate for the defective leptin signaling, leading to decreased appetite and significant weight loss. Besides reducing appetite, some evidence suggests that MC4R agonists may also enhance basal metabolic rate and energy expenditure, contributing further to weight loss [35]. This dual action makes them highly effective in treating obesity, especially in genetically predisposed individuals.

Sympathomimetic/γ-aminobutyric Acid (GABA) Inhibition

Phentermine/topiramate (immediate-release/extended-release), marketed as Qsymia, effectively treats obesity by reducing appetite and enhancing satiety [36]. Phentermine is a sympathomimetic amine that primarily functions as an appetite suppressant, elevating neurotransmitters like dopamine, norepinephrine, and serotonin, primarily acting in brain regions such as the nucleus accumbens, prefrontal cortex, and hypothalamus which are integral to controlling hunger and fullness [37]. Thus, helping to regulate eating behaviors and support weight management efforts. Conversely, topiramate, an antiepileptic drug, aids in weight control potentially by making foods taste less appealing, increasing basal metabolic rate, and amplifying satiety through its effects on GABA receptors and other central nervous system pathways [38]. Together, these medications offer a two-pronged approach by decreasing caloric intake and modifying metabolic and appetite signals, proving effective for weight management in patients with obesity [39, 40].

Tirzepatide

Tirzepatide is a novel therapeutic that targets both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, enhancing its effectiveness in treating type 2 diabetes and obesity [41]. By activating GLP-1 receptors, tirzepatide stimulates glucose-dependent insulin secretion, reduces glucagon production, and slows gastric emptying, which collectively contribute to lower blood glucose levels and increased satiety [42]. Concurrently, its stimulation of GIP receptors enhances insulin release and improves lipid metabolism, supporting further reductions in blood glucose and body weight [43]. This dual mechanism offers a novel approach for managing obesity by targeting two critical incretin pathways.

Clinical Efficacy

Liraglutide

Liraglutide's efficacy in pediatric obesity was primarily assessed in a randomized, double-blind, placebo-controlled trial [20]. The trial involved 251 adolescents aged 12 to 18, who had previously shown a poor response to lifestyle interventions. Participants were randomly assigned to either receive Liraglutide or a placebo, alongside a standardized lifestyle intervention program. The treatment phase lasted

56 weeks, followed by a 26-week observation period without the medication to assess long-term effects and potential weight regain. The primary endpoint was the relative change in BMI from baseline after 56 weeks. The results indicated a significant relative change in BMI of 4.29% in the Liraglutide group, compared to 0.35% in the placebo group. BMI loss was followed by a period of weight gain once medication was discontinued [20].

Semaglutide

Similar in design to the Liraglutide trial, the Semaglutide study was also a randomized, double-blind, placebo-controlled trial that involved a weekly injection of Semaglutide – escalating up to a dose of 2.4 mg [22]. The trial included an extended treatment period of 68 weeks, followed by a 7-week follow-up phase off the medication, to study the sustainability of weight loss. Participants included adolescents aged 12 to 18 years. Semaglutide showed a % BMI reduction of 16.1% compared to 0.6% for placebo [22]. After cessation of medication, the group treated with semaglutide experienced a more noticeable increase in weight despite ongoing lifestyle interventions.

Setmelanotide

In a study involving patients with POMC deficiency, Setmelanotide significantly reduced hunger and body weight, with an average weight loss of 51 kg over 42 weeks and sustained weight reduction over several years while taking the medication [21]. Similarly, for patients with LEPR deficiency, the drug led to meaningful reductions in appetite and absolute body weight across various time frames, showing a decrease of 21.6% over 26 weeks among others [44]. In a single-arm, open-label, multicenter study, 10 individuals aged 6 and older with POMC deficiency and 11 with LEPR deficiency were enrolled. Participants received setmelanotide treatment for 12 weeks, followed by a medication-free 8-week phase for those achieving at least 5% weight loss, and then continued treatment for another 32 weeks. By the end of the year, 80% of the POMC group and 45% of the LEPR group had lost a minimum of 10% of their body weight and experienced reduced hunger [21]. Furthermore, Setmelanotide has also been effective in treating obesity associated with Bardet-Biedl syndrome, with a trial showing relative reduction in BMI of 4.8% compared 2.3% in the placebo group after 14 weeks of treatment [45]. These findings emphasize Setmelanotide's potential as a targeted therapeutic option for managing pediatric obesity in genetically predisposed populations.

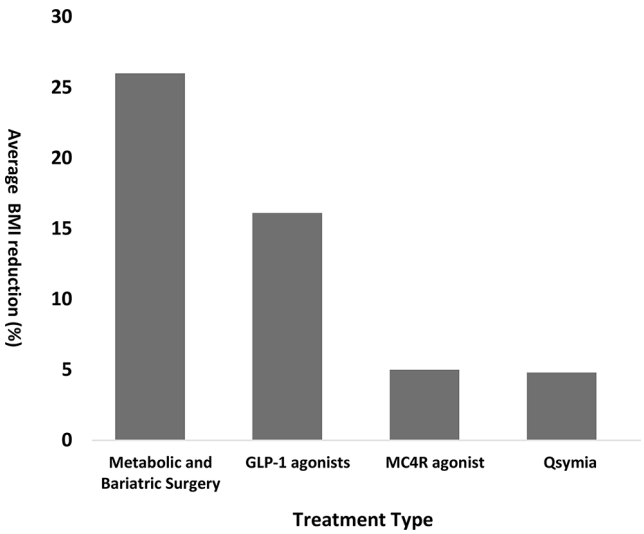

Fig. 1 Comparative efficacy of pharmacologic and surgical treatments of obesity in adolescents

Qsymia

Recent clinical trials have demonstrated the efficacy of Qsymia (phentermine/topiramate) in managing pediatric obesity among adolescents [40, 46]. These studies involved adolescents with obesity aged 12 to less than 18 years and those with significant cardiovascular, metabolic, or psychiatric conditions were excluded. Initial findings from a randomized, double-blind trial, which utilized adult doses over 56 days, showed that Qsymia was well-tolerated, with only minimal increases in blood pressure and heart rate [40]. In another trial, Qsymia was compared against a placebo with all participants receiving lifestyle modification advice over 56 weeks [46]. The results were significant, with the mid (7.5 mg/46 mg) and high-dose (15 mg/92 mg) groups achieving BMI reductions of 4.78% and 7.11%, respectively—far surpassing the 3.34% reduction seen in the placebo group. Moreover, a substantial portion of the treatment groups achieved at least a 5% reduction in BMI, significantly outperforming the placebo group. These findings reinforce Qsymia as a promising therapeutic option for adolescent obesity (Fig. 1).

Tirzepatide

The clinical efficacy of Tirzepatide when compared to semaglutide was assessed in adults with type 2 diabetes [47]. It demonstrated superior weight loss outcomes, with participants at the highest 15 mg dose experiencing an average weight loss of 20.9%, surpassing the 15% reduction seen with semaglutide at 1 mg per week dose [47]. This efficacy was consistent across all dosages and varied patient demographics, establishing Tirzepatide not only as effective but also as a potentially superior option for managing obesity in patients with diabetes.

Metabolic and Other Effects

Second-generation anti-obesity medications not only facilitate weight loss but also exhibit a broad spectrum of metabolic effects that contribute to overall health improvement.

GLP-1 receptor agonists have emerged as a promising avenue for addressing metabolic health, demonstrating a multifaceted positive impact [23, 48]. Specifically, these medications have shown a remarkable ability to improve cardiovascular health by reducing blood pressure, improving lipid profiles, and mitigating inflammation [49].This cardiovascular benefit translates to a potential reduction in the risk of adverse events such as heart attack and secondary prevention of major cardiovascular events is now a FDA approved indication for use of these agents in adults. GLP-1 receptor agonists have also demonstrated improvement in metabolic dysfunction-associated steatotic liver disease (MASLD) likely by improving insulin sensitivity and facilitating weight loss, and thus reducing liver fat accumulation and hepatic inflammation [50]. Additionally, these medications may offer a protective effect on kidney function, particularly for individuals with diabetes potentially by reducing the progression of albuminuria and stabilizing kidney function [51]. Furthermore, they have also shown a promise in treating binge eating disorder and alcohol addiction [52, 53]. By modulating appetite and satiety signals in the brain, these drugs can reduce binge eating episodes and potentially curb alcohol cravings by affecting brain reward pathways [52, 53]. More research is needed to further clarify the effect of GLP-1 analogs in addiction behaviors.

Qsymia offers not just weight loss but also modest improvements in blood pressure in adults [39]. Specifically, it has demonstrated reductions in both systolic and diastolic blood pressure after long term use, contributing to overall heart health in adults [39]. Additionally, this study also reported significant enhancements in lipid profiles, including a reduction in total cholesterol and triglycerides, along with an increase in HDL (high-density lipoprotein) cholesterol levels [39].

Tirzepatide reduces HbA1c and is an effective treatment for adults with type 2 diabetes [47]. In addition to its glycemic benefits, Tirzepatide has demonstrated potential cardiovascular advantages in adults [54].This includes improvements in systolic and diastolic blood pressure and favorable alterations in lipid profiles, such as reductions in LDL cholesterol and increases in HDL cholesterol [54]. Furthermore, treatment with Tirzepatide for 52 weeks has been recently shown to be more effective than placebo with respect to resolution of metabolic dysfunction–associated steatohepatitis (MASH) without worsening of fibrosis [55]. The mechanism likely involves improvements in insulin sensitivity and reductions in liver fat content, driven by weight loss and metabolic improvements.

Safety Profile

While generally considered safe, each class of weight-loss medications carries its own potential side effects. GLP-1 receptor agonists are most commonly associated with gastrointestinal issues like nausea, vomiting, and diarrhea, which are typically mild to moderate and often subside with continued use [56]. Less common but potentially serious adverse effects include pancreatitis and gallbladder disease, necessitating careful monitoring, especially when initiating treatment [57]. There is also a concern with medullary thyroid carcinoma, particularly highlighted in animal studies, which necessitates vigilance in long-term human studies [58]. MC4R agonists may cause increased blood pressure, heart rate, skin pigmentation changes, nausea, penile erections, mood alterations, and are under review for their effects on pediatric growth and development [33]. Data on the long-term safety profile of MC4R agonists in pediatric populations, particularly regarding potential risks for depression and suicidal ideation, remains limited and requires further investigation [21]. Qsymia, while effective, can lead to increased heart rate and blood pressure in the short term, requiring careful consideration and monitoring [59]. Tirzepatide, being a relatively new medication, necessitates ongoing surveillance to fully ascertain its long-term safety profile [47].

Patient Selection and Treatment Guidelines

AAP obesity guideline suggests initiating anti-obesity medications in children and adolescents who have BMI at or above the 95th percentile, prior unsuccessful weight management efforts, and potential comorbid conditions like type 2 diabetes or hypertension [13]. The choice of medication depends on individual's health profile; for instance, Liraglutide and Semaglutide are preferred for their effects on weight and glucose control, whereas Setmelanotide targets monogenic obesity like POMC deficiency [20, 22, 33]. Treatment efficacy and safety should be monitored through regular follow-ups to adjust dosages and assess health indicators, alongside screening for comorbidities and psychological support to manage the potential emotional impacts of obesity treatment [60]. Management and discontinuation of these medications prior to any surgical process is vital as these medications can affect glucose metabolism and gastrointestinal function, which could complicate surgical and anesthetic outcomes and recovery [61]. The need for long term consumption of these medications should be discussed with families prior to initiation in the context of

obesity being a chronic, relapsing disease and the current data suggesting weight regain once the medication is discontinued. It is vital that these treatments are considered part of a comprehensive approach to obesity that includes continued lifestyle support, nutrition and exercise counseling, and, where appropriate, other therapeutic interventions [13]. By adhering to these, healthcare providers can ensure that anti-obesity medications are used appropriately, maximizing benefits and minimizing risks for pediatric patients.

Emerging Therapies

Numerous clinical trials are currently being conducted to evaluate innovative therapeutic options for pediatric obesity (Table 2). These therapies are exploring diverse mechanisms to effectively target and manage obesity.

Table 2 Newer trials for pediatric anti-obesity medications

Treatment name	Description	Target mechanism	Notable outcomes
Bimagrumab [62]	Anti-myostatin monoclonal antibody	Reduces fat mass and increases muscle mass	Only treatment to increase muscle mass during weight loss
Retatrutide [63] (LY3437943)	Potent triple agonist of GIP, GLP-1, and glucagon	Modulates insulin, glucagon, and appetite suppression	Showed 24.2% weight reduction over 48 weeks in adults
Orforglipron [64]	Oral nonpeptide GLP-1 receptor agonist	Regulates appetite and metabolism centrally	Under investigation, specifically in adolescents
Livoletide (AZP-531) [65]	Unacylated ghrelin analog	Regulates appetite and metabolism centrally	Showing promising preliminary results especially in Prader-Willi syndrome
Cagrilintide [66]	Amylin analogue (currently being evaluated as a dual analog with Semaglutide)	Not specified	Demonstrated significant weight loss in adults
Oxytocin [67]	Intranasal Hypothalamic Oxytocin	Decreased food intake (via modulation of homeostatic, reward-related, and impulse control neural circuitry) and increased energy expenditure	Showed weight change of -0.6 kg compared to a control group receiving a placebo

Challenges

In pediatric obesity treatment, several challenges and considerations must be addressed to ensure effective management. Barriers such as high costs and limited insurance coverage can prevent optimal use of necessary medications and create disparity in obesity treatment [14]. The psychosocial impacts of obesity and its treatment, including potential stigma and mental health issues, underscore the need for holistic care approaches [68]. A multidisciplinary strategy that integrates medication with dietary, behavioral, and physical activity interventions is essential. Some medications such as the GLP-1 agonists may adversely impact bone density and muscle composition, which are critical during the growth phases of adolescents [69]. Additionally, long-term compliance with these treatments poses a challenge, as adherence can wane, especially during major life transitions such as emerging adulthood or pregnancy [70]. These transitions require careful management to ensure the safety and efficacy of obesity treatments continue into adulthood. The use of these agents during adolescence could also have next-generation effects, potentially impacting the metabolic health of offspring mediated by changes in developing gametes and parental metabolism [71]. Hence further research is needed to explore emerging therapies and personalized treatments based on genetic, metabolic, and environmental factors [72]. Moreover, there is a crucial need for long-term studies to evaluate the sustained effectiveness of treatments and their impact on obesity-related health complications [73]. Further, training and resources must be expanded to ensure that providers are equipped to handle the complex needs of patients with pediatric obesity, enabling them to deliver care that not only addresses the condition but also supports the overall well-being of affected children and their families [74].

Conclusion

In conclusion, the management of pediatric obesity presents a complex and multifaceted challenge that demands a comprehensive and integrated approach. As we recognize the availability of many effective and safe pharmacological treatments for obesity, with more promising drugs on the way, it is imperative that generalists and pediatricians become well-versed in these therapies. This is essential for ensuring broad access and proper implementation of these treatments. Embracing a multidisciplinary strategy that combines pharmacological interventions with dietary, behavioral, and physical activity modifications is critical for achieving sustainable health outcomes.

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Declarations

Competing Interests The authors declare no competing interests.

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