Current options in obesity pharmacotherapy for children and adolescents
A narrative review

Hae Woon Jung
Department of Pediatrics, Kyung Hee University Hospital, College of Medicine, Kyung Hee University, Seoul, Korea

ABSTRACT
Obesity is pervasive from infancy to adulthood and presents a major challenge to healthcare systems worldwide. In children and adolescents, the prevalence of overweight and obesity continues to increase, especially in classes II and III, and in younger toddlers and preschool-aged children. Childhood obesity may be associated with comorbidities in all organ systems and increased cardiovascular risk, as it tracks into adolescent and adult obesity. Although intensive health and behavior lifestyle treatments form the foundation of obesity treatment, there are limitations in the extent and maintenance of weight loss with lifestyle modifications alone. The offering of obesity pharmacotherapy in adjunct to intensive lifestyle treatment in children aged > 12 years may improve outcomes in pediatric obesity. In this review, we discuss currently approved medications for childhood and adolescent obesity, focusing on orlistat, phentermine monotherapy, glucagon-like peptide-1 receptor agonists (liraglutide and semaglutide injections), and phentermine/topiramate combination.

Keywords: Anti-obesity medication; Drug therapy; Obesity, morbid; Pediatric obesity

INTRODUCTION
Obesity presents a major challenge to healthcare systems worldwide owing to its far-reaching prevalence and association with many comorbid diseases. Obesity is pervasive from infancy through adulthood and has worsened in prevalence [1] and severity [2] over the past five decades. In children, the global age-standardized prevalence of obesity increased from 0.9% (95% confidence interval [CI], 0.5% to 1.3%) to 7.8% (95% CI, 6.7% to 9.1%) in boys and 0.7% (95% CI, 0.4% to 1.2%) to 5.6% (95% CI, 4.8% to 6.5%) in girls between the years 1975–2016, with approximate increases in age-standardized mean body mass index (BMI) of 1.7 kg/m² in boys and 1.4 kg/m² in girls [3]. According to the World Health Organization, there were 37 million children under the age of 5 years, in addition to over 390 million children and adolescents aged 5 to 19 years who were overweight or obese in 2022 [4]. The worldwide prevalence of overweight and obesity in children and adolescents from 2000 to 2023 was 8.5% (95% CI, 8.2% to 8.8%) with the highest prevalence of childhood obesity reported in the Pacific Islands, followed by the United...
Studies on the prevalence of overweight and obesity over time in South Korea have generally reported ongoing increases in overweight and obesity from 1965 to 2021 [6-9], with a similar increasing trend observed in most countries [10]. Although some studies have speculated that the increase in obesity has slowed or plateaued, especially in high-income countries after 2000 to 2010 [3,10-12], there has been increased concern in recent years owing to the aggravation of obesity severity [2], obesity in younger children [13], and the upsurge in obesity during the coronavirus disease 2019 (COVID-19) pandemic lockdowns [14]. Obesity rates have increased by 1.0% in adolescents aged 13 to 17 years and by 2.6% in children aged 5 to 9 years [14], with an even greater increase of 2.8% to 3.9% reported in preschoolers aged 3 to 5 years [15]. The relatively greater effect of COVID-19 pandemic lockdowns on weight gain in younger (elementary school) children compared to older adolescents in middle school has also been reported in a study that examined school health examination data from 2018 to 2021 [16].

The consequences of obesity in children are multifold for both individual health and public healthcare systems. At the individual level, childhood obesity is associated with concurrent short-term comorbidities in all organ systems, including hypertension, dyslipidemia, fatty liver disease, gastroesophageal reflux, polycystic ovarian syndrome, pubertal disorders, intracranial hypertension, asthma, obstructive sleep apnea, skeletal and muscular acute injuries, and slipped capital femoral epiphysis [17]. Not all overweight or obese children or adolescents exhibit cardiometabolic abnormalities. While the prevalence of overweight/obesity increased from 18.8% in 2011 to 23.7% in 2019 in a study of adolescents from the Korea National Health and Nutrition Examination Survey, the prevalence of metabolically healthy obesity remained relatively stable between 34.8% and 35.7% [18]. However, cardiometabolic risk factors and the metabolic syndrome are clearly associated with the degree of obesity, with adjusted odds ratios for meeting the International Diabetes Federation criteria for the metabolic syndrome increasing sequentially from 54.2 to 283.3 to 950.3 for overweight, class I, and class II/III obesity respectively [19]. Severe obesity, an increasing problem in recent years, is associated with an increased number of comorbid cardiometabolic conditions [19-21]. A recent study suggested the need to add a line at 120% of the 95th percentile of the national BMI growth chart to distinguish children and adolescents with increased cardiometabolic risk [22]. Childhood obesity eventually tracks into obesity in 55% of adolescents, with 80% of obese adolescents remaining obese in adulthood [23]. In cases where childhood obesity continues into adult obesity, excess risk of morbidity and mortality from diabetes, certain types of cancers, and cardiovascular disease have been shown even in young adults under the age of 45 years [24].

The most recent clinical guidelines for the evaluation and treatment of overweight and obesity in children and adolescents were published by the American Academy of Pediatrics (AAP) in 2023 [25]. The detailed guidelines underscore obesity as a chronic disease that requires intensive and long-term treatment strategies, including continual monitoring and management of associated comorbidities. Intensive health behavior modification and lifestyle interventions are central to childhood obesity treatment, with a focus on healthy eating habits and increased physical activity. These interventions should be rigorous (measured in hours of direct face-to-face patient contact), family-based, comprehensive, and encompass behavioral adjustments. Intensive interventions totaling more than 26 hours over 3 to 12 months may lead to a reduction in BMI z-score between –0.1 and –0.5 [26-32], and improvements in blood pressure (BP), insulin, and glucose levels [33]. Although healthy eating and physical activity form the basis of successful obesity treatment, there are limitations in the extent and maintenance of weight loss with lifestyle modifications alone. In a real-world study of 129 outpatient pediatric obesity care centers in Europe that included 21,784 children and adolescents, only 7% achieved a reduction in BMI z-score of more than –0.25 after 2 years of lifestyle modification, with 92% of participants lost to follow-up [34]. The difficulty in attaining and maintaining weight loss with lifestyle modifications may be partly due to adaptive physiological changes in hormones, appetite, satiety, and adaptive thermogenesis, affecting the resting metabolic rate that favors regaining weight [35,36].

In the recent AAP guidelines, offering obesity pharmacotherapy in conjunction with intensive health behavior lifestyle treatment in children aged 12 years or older has been regarded as a paradigm shift that will hopefully improve outcomes in pediatric obesity [37]. This shift may reflect the recognition of obesity as a chronic, refractory, and relapsing disease with barriers to treatment that cannot be overcome with individual willpower and the recent introduction of newer and more effective pharmacotherapy options in children and adolescents. Furthermore, maintaining clinically significant weight loss of 10% or more over the long-term is difficult with lifestyle modifications alone but may be attainable with obesity pharmacotherapy [38]. The past few years have brought
about the approval of several medications for the adolescent population that could be effective adjuncts to lifestyle modifications for sustained weight loss.

We aimed to review the currently approved medications for childhood and adolescent obesity. The medications reviewed were orlistat, phentermine monotherapy, glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide and semaglutide), and phentermine/topiramate, with a focus on efficacy, adverse effects, and practical information regarding the usage of each of these medications in children and adolescents (Table 1).

**APPROVED PHARMACOTHERAPEUTIC OPTIONS FOR CHILDREN AND ADOLESCENTS**

**Phentermine**

*Mechanism of action*

Phentermine is a derivative of β-phenethylamine, which has a structural backbone similar to that of the neurotransmitters dopamine, norepinephrine (NE), and epinephrine. It is an indirect sympathomimetic that interacts with adrenergic receptors to stimulate and/or block the reuptake of NE, increasing the interactions of NE with post-synaptic receptors [39,40]. Its action in the hypothalamus leads to pro-opiomelanocortin/cocaine-and amphetamine-regulated transcript (POMC/CART) activation and, in turn, increased satiety [41]. It also acts on the prefrontal cortex to stimulate dopamine release, which results in improved inhibitory control and decreased food intake [41].

*Efficacy data*

Short-term use (within 12 weeks) of phentermine has been approved by the U.S. Food and Drug Administration (FDA) for weight loss since 1959 and is still available in several markets for use in adolescents over 16 years of age. No randomized controlled trials (RCTs) investigated the efficacy of phentermine monotherapy for weight loss in children and adolescents. Only two single-center retrospective chart reviews have assessed the effect of phentermine on weight loss in the pediatric population. Ryder et al. [42] compared the percentage change in BMI from baseline in adolescents with obesity who underwent lifestyle modifications alone or with phentermine administration. The addition of phentermine to lifestyle modification was associated with a mean percent change in BMI of –1.6%, –2.9%, and –4.1%, at 1, 3, and 6 months respectively [42]. Ali Ibrahim et al. [43] recently reported the results of a retrospective review of 30 adolescent patients (aged 10 to 18) who were prescribed phentermine monotherapy for 2 weeks to 2 years, at doses ranging from 8 to 37.5 mg per day. Twenty-three (77%) patients demonstrated a mean decrease in BMI percentage of 15% (range, 4% to 54%), while seven patients showed no difference or increase in BMI percentage [43].

**Safety data**

No serious adverse effects were noted in studies that included children and adolescents. The possible adverse effects of sympathomimetic amines include insomnia, dry mouth, constipation, restlessness, nervousness, tachycardia, increased BP, and addiction. Thus, phentermine is not indicated in patients with cardiovascular disease, hypertension, a history of drug abuse, or in those taking monoamine oxidase inhibitors [44]. However, observational studies on adults [45,46] and adolescents [42] have shown no adverse changes in either systolic or diastolic BP. The electronic health record data of 13,972 adults prescribed phentermine between 2010 and 2015 showed a slight temporary increase in the average heart rate among phentermine users, which normalized after discontinuation [47]. The same study reported no increase in the risk of cardiovascular disease or death related to the duration of phentermine use for up to 3 years after initiating medication.

**Orlistat**

*Mechanism of action*

Orlistat, derived from the endogenous lipostatin found in Streptomyces toxytricini, inhibits the action of gastric and pancreatic lipases within the gut. Orlistat covalently binds to and inactivates serine residues in the active sites of lipases. This prevents the hydrolysis of triglycerides into absorbable free fatty acids and monoglycerides, leading to a decreased absorption of free fatty acids from the gut. Orlistat acts locally within the gastrointestinal tract and has negligible systemic absorption [48]. At the recommended dose of 120 mg three times daily, orlistat has been reported to inhibit the absorption of approximately 30% of dietary fat in adults [49].

*Efficacy data*

Orlistat was approved by the FDA for use in adolescents (>12 years of age) in 2003 based on preliminary data from a multicenter, randomized, double-blind trial that tested the effect of orlistat in conjunction with a mildly hypocaloric diet on weight and body composition in 539 adolescents (357 treated with
<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval information</th>
<th>Indicated age</th>
<th>Recommended dosing</th>
<th>Adverse effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine monotherapy</td>
<td>FDA, MFDS</td>
<td>&gt;16 years</td>
<td>Capsules (15/30/37.5 mg)</td>
<td>Insomnia, dry mouth, constipation, restlessness, nervousness, tachycardia, increased blood pressure and addiction</td>
<td>Hypersensitivity to phentermine or other sympathomimetic amines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial dose: 15 mg once daily before breakfast (or 1–2 hours after breakfast)</td>
<td></td>
<td>History of cardiovascular disease (arrhythmias, heart failure, coronary artery disease, stroke, uncontrolled hypertension)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increase: to 30 or 37.5 mg once daily</td>
<td></td>
<td>Hyperthyroidism, glaucoma, history of drug abuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tablet (37.5mg)</td>
<td></td>
<td>Concurrent use of MAO inhibitor therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37.5 mg once daily before breakfast</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18.75 mg (1/2 tablet) once or twice daily may be appropriate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tablet (8 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 mg per dose, 3 times daily, 30 minutes before meals</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In some cases, 4 mg (1/2 tablet) may be appropriate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orlistat</td>
<td>FDA, EMA, MFDS</td>
<td>≥12 years</td>
<td>Capsules (60/120 mg)</td>
<td>Gastrointestinal: steatorrhea, fecal urgency, incontinence, oily spotting, flatulence</td>
<td>Hypersensitivity to orlistat or constituents, cholestasis, pregnancy, chronic malabsorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>120 mg per dose, 3 times daily with each meal</td>
<td>Decreased absorption of some fat-soluble vitamins and beta-carotene</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Solution pen-injector (18 mg/3 mL)</td>
<td>Gastrointestinal: nausea, vomiting, diarrhea</td>
<td>Serious hypersensitivity to liraglutide or any component formulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial dose: 0.6 mg once daily for 1 week</td>
<td>Dizziness</td>
<td>Personal or family history of medullary thyroid cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increase: as tolerated by 0.6 mg/day increments at weekly intervals</td>
<td>Headaches</td>
<td>Patients with MEN2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Target dose: 3 mg once daily or maximal tolerated dose by patient</td>
<td>Hypoglycemia</td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Solution auto-injector (0.25 mg/0.5 mL; 0.5 mg/0.5 mL; 1 mg/0.5 mL; 1.7 mg/0.75 mL; 2.4 mg/0.75 mL)</td>
<td>Fatigue, headache</td>
<td>Avoid in patients with history of suicidal attempt or ideation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weeks 1–4: 0.25 mg once weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weeks 5–8: 0.5 mg once weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weeks 9–12: 1 mg once weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weeks 13–16: 1.7 mg once weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥Week 17: 2.4 mg once weekly (if not tolerated, 1.7 mg once weekly or maximal tolerated dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semaglutide</td>
<td>FDA, EMA</td>
<td>≥12 years</td>
<td>Solution auto-injector (0.25 mg/0.5 mL; 0.5 mg/0.5 mL; 1 mg/0.5 mL; 1.7 mg/0.75 mL; 2.4 mg/0.75 mL)</td>
<td>Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain, increased transaminases, acute cholecystitis, gastritis, abnormal hepatic function, constipation, increased amylase and lipase</td>
<td>Hypersensitivity to semaglutide or any component of the formulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weeks 1–4: 0.25 mg once weekly</td>
<td>Fatigue, headache</td>
<td>Personal or family history of medullary thyroid cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weeks 5–8: 0.5 mg once weekly</td>
<td></td>
<td>Patients with MEN2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weeks 9–12: 1 mg once weekly</td>
<td></td>
<td>Avoid in patients with history of suicidal attempt or ideation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weeks 13–16: 1.7 mg once weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥Week 17: 2.4 mg once weekly (if not tolerated, 1.7 mg once weekly or maximal tolerated dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine/Topiramate</td>
<td>FDA</td>
<td>≥12 years</td>
<td>Capsules (immediate-release phentermine [mg]/extended-release topiramate [mg]: 3.75/23; 7.5/46; 11.25/69; 15/92)</td>
<td>Increased heart rate, decreased serum bicarbonate, constipation, dry mouth, headache, nausea, paresthesia, hypoesthesia, insomnia</td>
<td>Hypersensitivity to phentermine, topiramate, or any component of the formulation; hyperthyroidism; glaucoma; within 14 days of MAO inhibitor therapy; pregnancy</td>
</tr>
<tr>
<td>combination</td>
<td></td>
<td></td>
<td>Initial: 3.75/23 once daily for 14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increase to 7.5/46 once daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
orlistat vs. 182 placebo) aged 12 to 16 years with obesity [50]. The published results of the trial reported significant decreases in BMI from baseline in both groups, especially during the first 12 weeks after randomization. While the placebo group began to regain BMI after 12 weeks, the mean BMI of the orlistat group remained stable for 6 months, with a sustained significant between-group difference. Subsequently, the orlistat group also showed a regaining of weight however, the mean BMI of the orlistat group decreased from baseline by 0.55 kg/m², compared to an increase of 0.31 kg/m² in the placebo group at the end of the study. After 52 weeks of treatment, 26.5% of the treated adolescents achieved ≥ 5% reduction in BMI, compared to 15.7% of the placebo group. Dual-energy X-ray absorptiometry showed that the difference in BMI could be explained by changes in fat mass. A follow-up study showed that early weight loss ≥ 5% after 12 weeks of intervention predicted a favorable outcome in BMI at the end of the 52-week study and was two times more likely to occur in the orlistat group than in the placebo group [51]. Other smaller and shorter RCTs in adolescents with obesity have shown varying effects of orlistat on weight loss. A prospective, open-label, randomized, controlled pilot trial showed a decreased BMI of -4.09 ± 2.9 kg/m² in 15 adolescents of the orlistat group compared to an increase in BMI of 0.11 ± 2.49 kg/m² in the 15 adolescents of the control group after an average duration 11.7 ± 3.7 months (range, 5 to 15) of treatment [52]. Another double-blind, placebo-controlled RCT of 20 orlistat-treated and 20 placebo-treated adolescents showed significant decreases in BMI from baseline in both the treated and control groups at 3 months; however, the difference between the groups was not significant. Furthermore, the decrease in BMI from baseline within each group was not significant at 6 months. A recent meta-analysis of four RCTs and two semi-experimental studies on orlistat in children and adolescents reported significant effects of orlistat on waist circumference and serum insulin levels, without significant effects on body weight, BMI, lipid profile, or serum glucose levels [53].

**Safety data**

The main adverse events associated with orlistat are gastrointestinal effects that stem from its pharmacological effects on intestinal fat absorption. The frequently reported adverse effects include steatorrhea, fecal urgency, incontinence, oily spotting, and flatulence. While these gastrointestinal adverse effects were reportedly mild or moderate in severity, they were significantly more common in the orlistat groups [50,52,54] than the placebo groups with eventual discontinuation of use reported between 2% and 30%. A population-based study of prescription data between 1999 and 2006 in the United Kingdom showed that while orlistat accounted for 78.4% of all prescriptions in children and adolescents (0 to 18 years old), discontinuation of prescriptions occurred in 45% of patients within a month and in 90% within 6 months, suggesting poor tolerability or poor efficacy [55]. Although the results vary among studies, decreased absorption of some fat-soluble vitamins and beta-carotene has been reported following orlistat treatment [54,56]. Therefore, patients should be encouraged to take multivitamin-containing fat-soluble vitamins to ensure adequate nutrition [57].

**GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (LIRAGLUTIDE, SEMAGLU- TIDE)**

**Mechanisms of action**

GLP-1 receptor agonists are chemically modified mimetics of the incretin hormone GLP-1. Endogenous GLP-1 is naturally secreted by intestinal epithelial endocrine L-cells in response to food intake and exerts multifactorial direct and indirect effects on energy and glucose metabolism [58]. Chemically modified GLP-1 receptor agonists resist breakdown by dipeptidyl peptidase-4, resulting in a longer half-life than that of human GLP-1. GLP-1 promotes insulin secretion from pancreatic B-cells and reduces glucagon secretion from pancreatic α-cells, improving insulin sensitivity and repressing hepatic glucose production [59,60]. GLP-1 receptor agonists in the control of obesity are mostly central, through their actions on the GLP-1 receptors of hypothalamic feeding centers and the hindbrain matrix, to suppress appetite and promote satiety. GLP-1 also inhibits postprandial gastric emptying and duodenal peristalsis, thereby reducing appetite and food intake [60]. The long-acting GLP-1 receptor agonists, lirappeduglutide (once-daily injections) and semaglutide (once-weekly injections), have been approved by the FDA for the treatment of obesity in children and adolescents.

**Liraglutide**

**Efficacy data**

RCTs in adolescents (aged 12 to 17 years) [61] and children (aged 7 to 11 years) [62] were published in 2017 and 2018, respectively, while results from large-scale multicenter randomized double-blind trials consisting of a 56-week treatment period and an additional 26-week follow-up period in adolescents with obesity were published only recently in 2020 [63].
At the end of the 56-week treatment period, there was an estimated mean difference of –0.22 in the BMI-standard deviation score (SDS) of the treatment group compared to placebo. A 5% reduction in BMI was observed in 43.3% and 18.7% of the treated and placebo group respectively. Additionally, a 10% reduction was observed in 26.1% and 8.1% of the treated and placebo group, respectively. This study was instrumental in acquiring FDA approval for the use of liraglutide in adolescents (≥ 12 years of age) with obesity in December 2020. The drug was approved by the Ministry of Food and Drug Safety (MFDS) for use in Korean adolescents with obesity the following year. A post hoc analysis of this RCT [64] showed that liraglutide 3.0 mg (or the maximum tolerated dose) led to significant BMI reductions in adolescents with obesity, regardless of differences in baseline characteristics, including sex, race, ethnicity, age, pubertal stage, glycemic status, obesity category, severity of depression, and weight variability. Early response to liraglutide, defined as weight or BMI reduction ≥ 4% after 12 weeks at the maintenance dose, predicted greater mean weight loss at week 56 compared to early non-responders.

A recent meta-analysis that pooled efficacy data of liraglutide on weight loss in six studies of children and adolescents, including those with type 2 diabetes mellitus and Prader-Willi syndrome [65], showed a substantially lower BMI-SDS obtained in the population receiving liraglutide with a mean difference of –0.17 (95% CI, –0.26 to –0.08; I² = 19%). However, despite the significant efficacy of liraglutide shown in the pooled data of the meta-analysis, the efficacy of 52 weeks of treatment in children and adolescents with Prader-Willi syndrome was not significant with regard to changes in BMI-SDS [66]. Further limitations of liraglutide efficacy can be observed in the significant weight regain during the 26-week follow-up period after liraglutide discontinuation in the SCALE teens trial. Notably, weight regain was also observed in the placebo group, and the BMI-SDS score at the end of 86 weeks did not exceed the baseline in the liraglutide group, as it did in the placebo group.

Safety data

Earlier trials of liraglutide in pediatric obesity focused on assessing its safety and tolerability in adolescents [61], as well as in children aged 7 to 11 years [62]. In both studies, the most common adverse events were gastrointestinal events, which were significantly more frequently reported in the treatment groups. All adverse events in these two studies were mild or moderate in severity and none of the adverse events led to participant withdrawal. Hypoglycemia was reported in both studies, with a higher frequency in the liraglutide treatment groups than in the placebo group. Of the eight episodes of documented hypoglycemia in the trial that included adolescents, only half were symptomatic. Of the six hypoglycemic episodes in the trial including children, none were symptomatic; all occurred after an overnight fast, and the measured glucose ranged between 62 and 70 mg/dL. None of the hypoglycemic episodes were considered severe in either study. In the SCALE teens trial [63], the percentage of patients who reported adverse events during the treatment period did not differ between the treatment and placebo groups; however, gastrointestinal events were twice as frequent in the treatment group. Nausea, vomiting, gastroenteritis, and dizziness were adverse events that were significantly more reported in the treatment group. Most of these adverse events were reported within the first 4 to 8 weeks of treatment during dose escalation. Thirteen participants discontinued the trial due to adverse events, most of which were gastrointestinal.

There was one episode of moderately severe pancreatitis and 26 non-severe episodes of hypoglycemia in the liraglutide group. A potential association between acute pancreatitis and liraglutide use has been suggested through case reports in adults. However, a pooled analysis of phase 2 and 3 RCTs showed that while there was a trend toward an increase in the relative risk (2.1 [95% CI, 0.3 to 16.0] for liraglutide vs. 1.7 [95% CI, 0.2 to 13.2] for active comparators) of acute pancreatitis in the liraglutide group, the rarity of cases precluded firm conclusions [67]. Furthermore, no cases of pancreatitis were reported in trials involving adolescents treated with liraglutide. Studies on rodents have shown that GLP-1 receptor agonists, including liraglutide, cause thyroid parafollicular C-cell hyperplasia and tumors [68]. Although there have been no such reports in adolescents, real-world data from a population of approximately 48,000 adult patients with T2DM showed that exposure to a GLP-1 receptor agonist for 1 to 3 years was associated with a statistically significant increase in the risk of all thyroid carcinomas by 58% (hazard ratio, 1.58) and medullary thyroid cancer by 78% (hazard ratio, 1.78) [69]. Therefore, liraglutide is contraindicated in patients with a family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN2).

Semaglutide

Efficacy data

In 2022, results from a 68-week trial of once-weekly 2.4 mg injections of semaglutide in adolescents with obesity (STEP
Pediatric obesity pharmacotherapy

Teens) [70] reported significant weight loss, with a mean change in BMI from baseline of –16.1% with semaglutide, compared with 0.6% with placebo. By the end of the study, 73% (95 of 131 participants) had weight reductions of more than 5%, compared with only 18% (11 of 62 participants) in the placebo group. Over half (53%) of the semaglutide group showed a body weight loss of >15%, with 37% showing >20% weight loss. Semaglutide was shown to have favorable effects on cardiometabolic risk factors with significantly decreased percentage points in the liraglutide versus placebo groups reported for glycated hemoglobin (–0.4 vs. –0.1), total cholesterol (–8.3 vs. –1.3), low-density lipoprotein cholesterol (–10.2 vs. –3.4), triglycerides (–28.4 vs. 2.6), and alanine transaminase levels (–18.3 vs. –4.9). Based on the results of this study, the FDA approved the use of semaglutide injection (2.4 mg once weekly) for the treatment of obesity in children and adolescents aged 12 years and older in January 2023. A post hoc study [71] reported that semaglutide injections were highly effective in improving the BMI category by at least one in 73.7% of participants receiving semaglutide compared to 19.0% receiving placebo. The proportion of participants with the most severe degree of obesity (class III) decreased from 37.3% to 13.6% with treatment compared with the placebo. Furthermore, more than 40% of the treatment group reached a category below the obesity threshold.

Safety data
Participants taking semaglutide experienced gastrointestinal adverse events, with 62% reporting nausea, vomiting, and diarrhea compared to 42% in the placebo group [70]. Gastrointestinal symptoms were generally of mild or moderate severity for a short duration. Similar to liraglutide, these symptoms were most prevalent during or shortly after the initial 16-week dose escalation period. Serious adverse events occurred in 11% of participants in the treatment group, including three cases of cholelithiasis and two cases of appendicitis. Other reported serious adverse events include increased transaminase levels, abdominal pain, acute cholecystitis, depression, gastritis, abnormal hepatic function, constipation, sleep apnea, postoperative urinary retention, and vomiting. Although no cases of pancreatitis were reported, there were increases in both amylase and lipase from baseline to week 68 by ratios of 1.2 for amylase and 1.4 for lipase. The percentage of participants who discontinued the trial owing to adverse events did not differ between the treatment and placebo groups.

PHENTERMINE-TOPIRAMATE COMBINATION

Mechanisms of action
Phentermine is an indirect-acting sympathomimetic that increases the interactions of NE with post-synaptic receptors in the hypothalamus to suppress appetite and increase satiety [39,40]. It also stimulates the release of dopamine in the pre-frontal cortex to a lesser extent, resulting in improved inhibitory control of food intake. Topiramate, an anti-epileptic drug that is also prescribed for prophylaxis of chronic migraines, is effective in appetite suppression and weight loss. Although the mechanisms of action in obesity are not entirely clear, its actions as a gamma-aminobutyric acid agonist, glutamate antagonist, carbonic anhydrase inhibitor, and modulator of corticomesolimbic dopamine function [72] may be associated with appetite suppression and weight loss. Topiramate may also play a role in modulating neuropeptide Y gene expression and reducing leptin levels [73]. Limitations with regard to efficacy [74] and adverse events of phentermine and topiramate as monotherapies for obesity treatment have led to the development of low-dose phentermine and extended-release topiramate combination therapy to produce effective weight loss with minimal tolerability concerns [75]. Combination therapy was approved by the FDA for use in adult obesity in 2012 and recently for adolescent obesity in 2022.

Efficacy data
Thus far, two trials of phentermine-topiramate combination therapy have been conducted in children and adolescents with obesity. The first trial of an immediate-release phentermine and extended-release topiramate combination in adolescents included 42 obese participants aged 12 to 17 years who were randomized to receive a mid-dose (phentermine/topiramate 7.5 mg/46 mg), top-dose (phentermine/topiramate 15 mg/92 mg), or placebo [76]. After 8 weeks, the mean percent weight change from baseline at day 56 was –4.96% for the top-dose, –3.72% for the mid-dose, and 1.06% for placebo. The study showed that 13.3% of the adolescents assigned to the mid-dose and 50% assigned to the top-dose achieved ≥5% weight loss, compared to none in the placebo group. Moreover, treatment differences in the top-dose group were significant for waist circumference (–5.2 cm) and visual analog scale hunger scores (–1.83 cm) when compared with the placebo group. A trial of longer treatment duration that evaluated mid- and top-doses of phentermine/topiramate combination therapy in 227 adolescents 12 to 17 years of age
showed a difference in mean BMI at week 56 of –10.44 percentage points for the top-dose and –8.11 percentage points for the mid-dose, compared to placebo [77]. The treatment difference between the mid and top-doses were not significant (mean difference –2.33%). The percentages of participants who achieved ≥5% weight loss were 46.9%, 38.7%, and 5.4% for the top-, mid-, and placebo doses. Percentages of those who achieved ≥15% weight loss were 28.3% for the top-dose, 13% for the mid-dose, and none for the placebo. Cardiometabolic parameters, including triglycerides and high-density lipoprotein cholesterol, showed favorable changes with both doses of combination therapy compared to placebo, while fasting insulin, whole-body insulin sensitivity index, quality of life questionnaire scores, glycemic markers, and total or low-density lipoprotein cholesterol did not differ between the groups.

Safety data
Considering the possible adverse effects of sympathomimetics on BP and heart rate, the trials assessed possible changes in these parameters. The mean change in BP did not differ among the top, middle, and placebo groups in either study [76,77]. Heart rate was assessed in only one of the trials and showed the largest increases in heart rate from baseline (4.1 beats per minute) in the top-dose group, while those in the mid-dose showed a decrease in heart rate (–4.5 beats per minute). For other treatment-emergent adverse events (TEAEs), there were no differences in the prevalence of TEAEs among the top, mid, and placebo groups. Some adverse events that were reported at frequencies >3% to 4% included headache, nausea, paresthesia, hypoesthesia, dry mouth, nasal congestion, administration site conditions, pyrexia, decreased appetite and insomnia [76]. In a long-term trial by Kelly et al. [77], adverse events led to discontinuation of the trial in three participants (two in the placebo group and one in the top-dose group) and withdrawal in four patients (one in the placebo group, one in the mid-dose group, and two in the top-dose group). Two participants in the top-dose group reported three serious adverse events: bile duct stones, depression, and suicidal ideation. Events related to psychiatric disorders (including agitation, anxiety, depression, insomnia, mood alteration, and suicide ideation) were reported with more frequency in the top-dose group (n=10, 8.8%) and mid-dose group (n=4, 7.4%), compared to only one case in the placebo group.

CONCLUSION
Obesity in children is a chronic and complex disease associated with numerous comorbidities that persist into adulthood. While intensive health behaviors and lifestyle interventions are fundamental to weight loss, lifestyle modifications alone may be insufficient to effectively lose and maintain weight in children and adolescents. The addition of obesity pharmacotherapy may especially benefit children and adolescents who have proven unsuccessful in intensive behavioral and lifestyle interventions, remain above certain thresholds of BMI, with or without comorbid conditions. The recent approval of anti-obesity medications for children and adolescents and guidelines that stress the importance of offering pharmacotherapy adjunct to behavior and lifestyle treatment may improve weight loss outcomes and consequently decrease cardiovascular risk. The newly approved GLP-1 receptor agonists and phentermine/topiramate combinations are promising in terms of efficacy; however, there are still limitations with regard to long-term tolerability and safety, as well as unresolved issues with the duration of treatment and weight rebound with discontinuation. Further studies are warranted to establish evidence-based protocols and recommendations for the effective and safe use of these medications in pediatric obesity. Moreover, investigation of the efficacy and safety of newer anti-obesity drugs, including oral GLP-1 receptor agonists, GLP1-glucose-dependent insulinotropic polypeptide (GIP) co-agonists, and GLP1-GIP-glucagon tri-agonists, through active conduction and reporting of trials in the pediatric population holds great promise for more effective care of patients with pediatric obesity in the near future.

CONFLICTS OF INTEREST
No potential conflict of interest relevant to this article was reported.

ORCID
Hae Woon Jung https://orcid.org/0000-0003-0494-4626

AUTHOR CONTRIBUTIONS
Conception or design: HWJ.
Acquisition, analysis, or interpretation of data: HWJ.
Drafting the work or revising: HWJ.
Final approval of the manuscript: HWJ.
REFERENCES

11:222-3.
Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. JAMA 2005;293:2873-83.


