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Effective and appropriate use of weight loss medication in pediatric obesity: a narrative review

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Over the past few decades, there has been a notable increase in the incidence of pediatric obesity, which is a significant public health concern. Children who are obese have a greater risk of type 2 diabetes, hypertension, dyslipidemia, polycystic ovary syndrome, obstructive sleep apnea, and adult obesity. Lifestyle modification therapy is typically the initial approach to treat pediatric obesity. For patients who do not achieve success with lifestyle modification therapy alone, pharmacotherapy is the next logical treatment option. When selecting an anti-obesity medication (AOM), it is essential to first ascertain the medical background of the patient, including current medications and obesity-associated comorbidities. Evaluation of obesity phenotypes in patients may also be beneficial. AOMs for pediatric obesity include metformin, orlistat, glucagon-like peptide 1 agonists, phentermine, and the phentermine/topiramate combination. Sufficient lifestyle modification therapy should be administered before considering pharmacotherapy and continued after the initiation of AOM. To ensure healthy development, monitoring growth and puberty development during anti-obesity treatments is essential.

Keywords: Anti-obesity agents; Drug therapy; Pediatric obesity

Introduction

Pediatric obesity is not only a concern in our country but also a global trend [1-3]. This trend was exacerbated by lifestyle changes resulting from social isolation during the coronavirus disease 2019 pandemic [4,5]. Pediatric obesity can lead to adult obesity and trigger various complications such as pediatric type 2 diabetes, hypertension, hyperlipidemia, fatty liver disease, sleep apnea, and polycystic ovary syndrome (PCOS) [6-10]. Therefore, the prevention and treatment of pediatric obesity are essential.

In pediatric and adolescent age groups, obesity treatment has traditionally focused on lifestyle modifications, including dietary adjustments, exercise, and behavioral changes [11]. While some children and adolescents have successfully overcome obesity through these measures, many continue to struggle with obesity-related complications for various social, economic, and personal reasons. Consequently, ample research has been conducted on the use of anti-obesity medications (AOMs) in the pediatric population. Although AOM use has been somewhat cautious, the American Academy of Pediatrics guidelines released in 2023 recommend the active consideration of AOMs and surgical interventions as adjuncts to intensive health behavior and lifestyle treatment (IHBLT) for cases of severe obesity [12]. Even in South Korea, where severe childhood obesity was relatively uncommon a decade ago, there has been a noticeable increase in the number of children who are severely obese presenting with related complications [13]. Although dietary therapy, exercise, and behavioral interventions have been effective in many studies, it is essential to consider additional

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treatments for children who require further assistance. In this manuscript, we describe medications relevant to pediatric obesity, including metformin, orlistat, glucagon-like peptide 1 (GLP-1) agonists, phentermine, and phentermine/topiramate combination therapies.

Anti-obesity medication for pediatric and adolescent obesity: indications and decision to continue or discontinue

Pediatric and adolescent obesity is a significant public health concern that requires effective treatment strategies. The primary therapeutic approach involves lifestyle modifications that emphasize the correction of habits and behaviors. IHBLT is a foundational approach for reducing body mass or attenuating excess weight gain in children. This involves visits of sufficient frequency and intensity to facilitate sustained healthy eating and physical activity habits [14].

However, when lifestyle interventions alone do not yield successful outcomes, consideration of AOMs becomes relevant. Indications for AOM treatment in pediatric and adolescent obesity include individuals aged 10 years and above with a body mass index (BMI) at or above the 95th percentile, accompanied by weight-related comorbidities, or those with a BMI exceeding 120% of the 95th percentile without responding to lifestyle modifications [11,15]. Continuation of the medication is recommended if there is a ≥ 5% BMI reduction from baseline at 12 weeks on the optimal dose or if arrest or significant slowdown in weight gain is a reasonable clinical outcome, especially as linear growth occurs in adolescence [15]. Discontinuation of AOM is recommended if < 5% weight loss/BMI reduction from baseline is achieved within 12 weeks at the maximum appropriate dose [11,16,17]. The medication should also be discontinued if it is not tolerated by the patient or if dangerous side effects occur or persist despite dose titration.

Considerations before choosing anti-obesity medication for treatment of obesity in children

A comprehensive review of the patient's medical background, including prior and current medication use and obesity-associated comorbidities, is pivotal to ascertaining the optimal selection of AOMs. Medications can cause unintended weight gain, the extent of which may not be fully recognized by healthcare providers [18,19]. In such cases, providers should consider substituting weight-neutral medications or incorporating additional medications to offset the weight-promoting effects (Table 1 [20-22]) [19]. Specifically, factors related to satiety, satiation, emotional triggers of food intake, and reduced energy expenditure serve as essential guidelines for tailoring AOM selection to address the most prevalent symptomatology [23]. The questions used to assist in

Table 1. Medication classes and potential impact on weight [20-22]

Drug class	Drug	Impact on weight
Antipsychotics	Clozapine	↑ ↑ ↑
	Olanzapine	↑ ↑ ↑
	Chlorpromazine	↑ ↑ ↑
	Quetiapine	↑ ↑ ↑
	Risperidone	↑ ↑ ↑
	Aripiprazole	↔
	Haloperidol	↔
	Ziprasidone	↔
Antidepressants	Amitriptyline	↑ ↑ ↑
	Nortriptyline	↑ ↑
	Protriptyline	↓
	Duloxetine	↓
	Venlafaxine	↔
	Paroxetine	↑ ↑ ↑
	Lithium	↑ ↑ ↑
	Desipramine	↑ ↑ ↑
	Olanzapine	↑ ↑ ↑
	Imipramine	↑ ↑ ↑
	Citalopram	↑ ↑ ↑
	Escitalopram	↑ ↑ ↑
	Doxepin	↑ ↑ ↑
	Mirtazapine	↑ ↑ ↑
	Fluvoxamine	↔
	Sertraline	↔
	Trazodone	↔
	Fluoxetine	↔
	Bupropion	↓
Antiepileptic drugs	Divalproex sodium	↑ ↑ ↑
	Lamotrigine	↔
	Gabapentin	↑
	Topiramate	↓ ↓
Beta-blockers	Propranolol	↑
	Nadolol	↔
	Metoprolol	↑
Serotonin antagonists	Cyproheptadine	↑ ↑ ↑
Anxiolytics	Lorazepam	↔
	Diazepam	↔
	Oxazepam	↔
Calcium channel blockers	Verapamil	↔
	Flunarizine	↑ ↑

↑ ↑ ↑, significant impact on weight gain; ↑ ↑, considerable impact on weight gain; ↑, may increase body weight; ↔, neutral impact on body weight; ↓, may decrease body weight; ↓ ↓, considerable impact on weight loss.
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determining obesity phenotypes are listed in Table 2 [18]. In a recent study, four main obesity phenotype domains were identified based on dominant symptoms and screening tools: hungry brain (abnormal satiation), emotional hunger (hedonic eating), hungry gut (abnormal satiety), and slow burn (decreased metabolic rate) [23]. The recommended AOMs are phentermine/topiramate extended-release for hungry brain, oral naltrexone/bupropion sustained-release (not approved by the U.S. Food and Drug Administration [FDA] for use in pediatric cases) for emotional hunger, liraglutide for hungry gut, and phentermine plus increased resistance training for slow burn. After 12 months of treatment, the mean weight loss was –15.9% in the phenotype-guided group compared with –9.0% in the non-phenotype-guided group [23]. Screening tools should also be used before selecting AOM aids to identify personalized treatment approaches and achieve optimal outcomes.

Anti-obesity medications for pediatric and adolescent obesity

1. Metformin

Metformin, an insulin sensitizer, is primarily used as a therapeutic agent for type 2 diabetes in children and adolescents aged 10 years and above. Off-label indications for metformin include prediabetes, PCOS, and weight gain due to atypical antipsychotic medications [24]. In addition, metformin may be considered in cases of severe insulin resistance resulting from obesity. However, its use in obesity treatment is restricted because it falls outside the approval range set by regulatory authorities owing to ongoing debates and uncertainties surrounding its effectiveness.

Metformin is a biguanide that inhibits hepatic glucose production, reduces intestinal glucose absorption, and enhances insulin sensitivity to lower blood glucose levels. Although there have been reports suggesting that metformin reduces appetite, it has not been approved as an anti-obesity drug. A meta-analysis conducted in 2017 among pediatric and adolescent populations demonstrated a modest weight loss associated with metformin. Specifically, patients taking metformin showed lowered BMI z-scores (mean difference in change from baseline, –0.10; 95% confidence interval [CI], –0.17 to –0.03) and reduced overall BMI (mean difference in change from baseline, –0.86; 95% CI, –1.44 to –0.29) than controls [25]. In a randomized controlled trial involving children and adolescents who were severely obese (mean BMI, 34.6 kg/m^2) aged 6 to 12 years, metformin (1,000 mg twice daily) combined with lifestyle modification therapy resulted in an approximately 1 kg/m^2 reduction in BMI over 6 months [26]. Despite these findings, the effects of metformin on weight loss remain limited, and metformin is not classified as a primary anti-obesity treatment. Common side effects include abdominal bloating, nausea, vomiting, and diarrhea. Severe adverse effects such as lactic acidosis, which are common in the adult population, are rare in pediatric and adolescent populations [24].

Table 2. Questions for evaluating features of obesity phenotypes

Questions to assess phenotypic features
1. How many meals do you eat each day? How many snacks?
2. Do you eat more for hunger or for emotions (sadness, stress, anxiety)?
3. Do you eat to feel better when you are stressed, sad, anxious, etc.?
4. Do you feel hungry within 1/2 to 1 hour after eating a meal or snack?
5. Do you need to eat more or have larger portions to feel full at meals or snacks?
6. What do you eat for your meals? Snacks?
7. How often are you physically active?
8. In what kinds of activity do you engage throughout the day?

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2. Orlistat

Orlistat, a gastrointestinal lipase inhibitor, is approved for use as an AOM in individuals aged 12 years and older. By inhibiting pancreatic and gastric lipases, orlistat reduces fat absorption by approximately 30%. Studies have indicated that orlistat-treated groups experienced a decrease in BMI compared with that of placebo groups. Notably, a multicenter randomized controlled trial involving 539 adolescents aged 12 to 16 years with a BMI at or above the 95th percentile demonstrated a BMI reduction of 0.55 kg/m^2 in the orlistat group over 54 weeks, while the placebo group showed an increase of 0.31 kg/m^2 [27]. In a meta-analysis of 779 adolescents aged 12 to 17 years (baseline BMI, 37.4 kg/m^2) conducted in 2017, the change in BMI was –0.94 (95% CI, –1.58 to –0.30) for the orlistat group and –0.50 (95% CI, –7.62 to 6.62) for the placebo group. Absolute weight changes ranged from +1 lb to –12 lb [25].

The most common side effects of orlistat are gastrointestinal and include steatorrhea, fecal urgency, and flatulence [27]. Side effects may lead to early treatment discontinuation [27,28]. The recommended dose is 120 mg, up to three times daily. Since orlistat impairs the absorption of fat-soluble vitamins (A, D, and E), vitamin supplementation may be necessary.

3. Glucagon-like peptide 1 receptor agonists

GLP-1 receptor agonists (GLP-1 RAs) are a class of medications that mimic the effects of GLP-1, an incretin hormone involved in glucose regulation. These agents enhance glucose-dependent insulin secretion, slow gastric emptying, and reduce postprandial glucagon levels. GLP-1 RAs do not typically cause hypoglycemia un-

less combined with other therapies that do.

In pediatric and adolescent obesity, long-acting GLP-1 RAs, such as liraglutide, are approved for use in combination with lifestyle modification therapies. Eligible patients are aged 12 years or older, with an initial BMI exceeding 30 kg/m^2 (adult equivalent) or body weight exceeding 60 kg [29]. Regular assessments of treatment responses are necessary after initiating treatment. If a minimum of 4% reduction in BMI or BMI z-score is not achieved after 12 weeks of treatment, discontinuation and reevaluation are recommended.

Clinical trials involving exenatide, another GLP-1 RA, have demonstrated significant weight loss after 3 months of treatment in adolescents who were severely obese [30,31]. A 6-month randomized controlled trial using exenatide in youths who were severely obese showed improvements in BMI, blood glucose, and cholesterol levels [32]. A recent study confirmed the effectiveness of liraglutide in children and adolescents who were obese and not responsive to lifestyle therapy [33]. Over 54 weeks, patients treated with liraglutide exhibited a weight difference of approximately 4.5 kg compared to placebo, with a BMI reduction of approximately 5% and a standardized BMI reduction of approximately 0.22. The recommended starting dose of liraglutide is 0.6 mg subcutaneously once daily, which is gradually titrated up to a maximum of 3.0 mg daily. Common side effects include nausea and vomiting, and caution is advised in patients with a family history of multiple endocrine neoplasia as they may be at increased risk of medullary thyroid cancer [33].

Recently, once-weekly semaglutide has been approved by the FDA for the treatment of obesity in individuals over 12 years of age [34]. Semaglutide is a new GLP-1 RA that is structurally similar to liraglutide, with a longer half-life of 165 hours [35,36]. A 68-week randomized, placebo-controlled trial using a once-weekly, 2.4-mg dose of subcutaneous semaglutide in adolescents (12–17 years of age) who were obese or overweight and had at least one weight-related coexisting condition showed a mean BMI reduction from baseline of 16.1% (placebo, 0.6% BMI change; estimated difference, –16.7%; 95% CI, – 20.3 to –13.2; $p < 0.001$) [34]. The recommended starting dose of semaglutide for obesity is 0.25 mg once weekly for 4 weeks, followed by up-titration every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg once weekly. Adverse reactions among adolescents were consistent with those observed in adults and with those of the GLP-1 RA drug class in general [37]. Gastrointestinal events were the most common adverse events reported [34].

4. Phentermine

Phentermine, a central nervous system agent, inhibits the reuptake of norepinephrine, serotonin, and dopamine, thereby extending their durations of action and reducing appetite. Introduced as an anti-obesity drug in 1959, phentermine is approved by the FDA and Korean Ministry of Food and Drug Safety for short-term treatment (within 12 weeks) in conjunction with lifestyle modification therapy for individuals aged 16 years and older. A retrospective chart review of adolescents with obesity treated with phentermine plus lifestyle modification therapy indicated that phentermine use was associated with a greater percent change in BMI at 1 month (–1.6%; 95% CI, –2.6% to –0.6%; $p = 0.001$), 3 months (–2.9%; 95% CI, –4.5% to –1.4%; $p < 0.001$), and 6 months (–4.1%; 95% CI, –7.1% to –1.0%; $p = 0.009$) than lifestyle modification alone [38]. The recommended doses are 7.5, 15, 30, and 37.5 mg, which can be adjusted based on the treatment response. If satisfactory weight loss (a reduction of at least 1.8 kg or an amount agreed upon by both the doctor and patient) is achieved within 4 weeks, the treatment can be continued. Common side effects include increased blood pressure, dizziness, headache, trembling, dry mouth, and abdominal pain, which are dose-dependent but do not directly correlate with increased dosage [38].

5. Phentermine/topiramate combination

One combination drug therapy uses phentermine to suppress appetite and extended-release topiramate as an antiepileptic agent with appetite-modulating effects. Approved for weight control in adults, this combination medication was tested in a randomized controlled trial in adolescents aged 12 to 17 years who were obese and failed to achieve weight control through lifestyle modifications. After 56 weeks of treatment, the group taking 15-mg phentermine/92-mg topiramate exhibited a BMI reduction of approximately 7.1%, while the group taking 7.5-mg phentermine/46-mg topiramate showed a BMI reduction of approximately 4.8%. In contrast, the placebo group experienced a BMI increase of approximately 3.3%. Treatment also led to improvements in high-density lipoprotein cholesterol and triglyceride levels [39]. In a recent study, phentermine/topiramate was reported to be the most cost-effective AOM among the four currently approved for pediatric use [40]. Common adverse effects include depression, dizziness, and joint pain. Additionally, caution is advised because of the potential risks associated with an increased heart rate, suicidal impulses, suicide attempts, and growth impairment. In South Korea, this medication is only prescribed for individuals aged 18 years and older and necessitates careful consideration.

6. Others

Naltrexone/bupropion is a combination of the dopamine and norepinephrine reuptake antagonist bupropion and the opioid antagonist naltrexone. Naltrexone/bupropion achieved FDA approval

for the treatment of adults with a BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of at least one weight-related comorbidity. Nevertheless, the safety and efficacy of naltrexone/bupropion in individuals aged < 18 years have not been established; thus, the use of this medication is not recommended for pediatric patients [41]. Setmelanotide is a melanocortin-4 receptor agonist indicated for chronic weight management in adult and pediatric patients 6 years of age and older with proopiomelanocortin (POMC), leptin receptor (LEPR), or proprotein convertase subtilisin/kexin type 1 deficiency, as well as patients with Bardet-Biedl syndrome [42]. Setmelanotide suppresses appetite and increases resting energy expenditure in both obese animals and humans with obesity [43,44]. Single-arm, open-label, multicenter, phase 3 trials with participants aged 6 years or older with obesity due to POMC or LEPR deficiency received open-label setmelanotide for 12 weeks. Participants who had a weight loss of ≥ 5 kg then entered an 8-week placebo-controlled withdrawal sequence followed by 32 additional weeks of open-label treatment [45]. Eight participants (80%) in the POMC trial and five participants (45%) in the LEPR trial achieved at least 10% weight loss at approximately 1 year [45]. The most common adverse reactions to setmelanotide included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection [45]. The FDA recently approved tirzepatide for chronic weight management in adults with obesity. Tirzepatide activates the receptors of hormones secreted from the intestine (GLP-1) and glucose-dependent insulinotropic polypeptides to reduce appetite and food intake [46]. A clinical trial investigating the use of tirzepatide in pediatric participants with obesity is currently in progress (LY3298176).

Limitations of drug therapy for pediatric and adolescent obesity

Research has been conducted on the efficacy and side effects of anti-obesity drugs available to children and adolescents, but no study

Table 3. Anti-obesity medications (AOMs) utilized in pediatric obesity

Medication	Dose titration	Formulation	Age indication
Metformin[a]	500 mg with dinner, titrate to 500 mg BID if tolerated and needed, can titrate to 1,000 mg BID, if using ER, can take full dose once daily	500 mg 850 mg, 1,000 mg 500 mg ER, 750 mg ER	Not approved for AOM
Orlistat	120 mg TID [a]Skip dose for skipped meals	120 mg tablet	Aged 12 years and older
Liraglutide	Week 1: 0.6 mg SQ daily Week 2: 1.2 mg SQ daily Week 3: 1.8 mg SQ daily Week 4: 2.4 mg SQ daily Week 5: 3.0 mg SQ daily	Prefilled pen (6 mg/mL, 3 mL)	Aged 12 years and older
Phentermine	Dosage should be individualized to obtain an adequate response with the lowest effective dose [a]Starting dose (8 mg/15 mg daily) can be increased to BID if needed	8 mg, 15 mg, 30 mg, or 37.5 mg	Aged 16 years and older (within 12 weeks)
Phentermine/topiramate[a]	Starting dosage is 3.75 mg/23 mg phentermine/topiramate daily for 14 days; then increase to 7.5 mg/46 mg daily Increase dosage based on weight loss in adults or BMI reduction in pediatric patients After 12 weeks of treatment at 7.5 mg/46 mg, evaluate BMI reduction for pediatric patients aged 12 years and older If a pediatric patient has not experienced a reduction of at least 3% of baseline BMI percentile, increase the dosage to 11.25 mg/69 mg orally once daily for 14 days; increase the dosage to 15 mg/92 mg orally once daily as indicated After 12 weeks of treatment with 15 mg/92 mg, evaluate BMI percentile reduction for pediatric patients 12 years and older. If the reduction is less than 5% of baseline BMI percentile, discontinue medication; unlikely patient will achieve and sustain clinically meaningful weight loss with continued treatment	3.75 mg phentermine/23 mg topiramate 7.5 mg phentermine/46 mg topiramate 11.25 mg phentermine/69 mg topiramate 15 mg phentermine/92 mg topiramate	Only approved FDA for patients aged 12 years and older

BID, twice a day; TID, three times a day; ER, extended-release; SQ, subcutaneously; BMI, body mass index; FDA, U.S. Food and Drug Administration.
[a]Not approved by Korean Ministry of Food and Drug Safety as an AOM.
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has examined their long-term use. In addition, there is a dearth of research on the effects of these drugs on overall growth, including puberty and height. Because of the limited information and experience with AOMs, caution is necessary when using them. Furthermore, challenges include insurance coverage difficulties, potential side effects, unrealistic expectations regarding efficacy, and related financial burden [47]. Before initiating treatment, a thorough discussion with both the adolescent and his/her guardians regarding these aspects is crucial.

Conclusion

AOMs may be considered for the treatment of pediatric and adolescent patients who are obese and have not achieved successful outcomes with lifestyle modification therapy alone. Currently, the FDA-approved anti-obesity drugs for this population include orlistat, liraglutide, phentermine, and a combination of topiramate and phentermine. These medications are suitable for individuals aged ≥ 12 years who are obese. In South Korea, the domestically approved anti-obesity drugs for pediatric and adolescent use are orlistat and liraglutide (Table 3).

Prior to initiating pharmacological treatments for obesity, it is essential to prioritize comprehensive lifestyle modification therapies. If weight continues to increase or metabolic complications related to obesity persist despite lifestyle modifications, the concurrent use of AOMs can be considered. It is advisable to reserve medications for adolescents who are severely obese and have completed their growth and pubertal development. Additionally, a thorough assessment of pubertal development and growth should accompany AOM use.

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Conflicts of interest
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References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128•9 million children, adolescents, and adults. Lancet 2017;390:2627–42.
2. Kim JH, Moon JS. Secular trends in pediatric overweight and obesity in Korea. J Obes Metab Syndr 2020;29:12–7.
3. Yoo SE, Lee JH, Lee JW, Park HS, Lee HA, Kim HS. Increasing prevalence of fasting hyperglycemia in adolescents aged 10-18 years and its relationship with metabolic indicators: the Korea National Health and Nutrition Examination Study (KNHANES), 2007-2018. Ann Pediatr Endocrinol Metab 2022;27:60–8.
4. Park HK, Lim JS. Change of obesity prevalence and lifestyle patterns before and during COVID-19 among Korean adolescents. Ann Pediatr Endocrinol Metab 2022;27:183–91.
5. Kang S, Seo MY, Kim SH, Park MJ. Changes in lifestyle and obesity during the COVID-19 pandemic in Korean adolescents: based on the Korea Youth Risk Behavior Survey 2019 and 2020. Ann Pediatr Endocrinol Metab 2022;27:281–8.
6. Kim M, Kim J. Cardiometabolic risk factors and metabolic syndrome based on severity of obesity in Korean children and adolescents: data from the Korea National Health and Nutrition Examination Survey 2007-2018. Ann Pediatr Endocrinol Metab 2022;27:289–99.
7. Abbasi A, Juszczyk D, van Jaarsveld CH, Gulliford MC. Body mass index and incident type 1 and type 2 diabetes in children and young adults: a retrospective cohort study. J Endocr Soc 2017;1:524–37.
8. Turer CB, Brady TM, de Ferranti SD. Obesity, hypertension, and dyslipidemia in childhood are key modifiable antecedents of adult cardiovascular disease: a call to action. Circulation 2018;137:1256–9.
9. Wühl E. Hypertension in childhood obesity. Acta Paediatr 2019;108:37–43.
10. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr 2017;64:319–34.
11. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric obesity-assessment, treatment, and prevention: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2017;102:709–57.
12. Hampl SE, Hassink SG, Skinner AC, Armstrong SC, Barlow SE, Bolling CF, et al. Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. Pediat-

rics 2023;151:e2022060640.
13. Kim JH, Lim JS. Prevalence trends of metabolic syndrome among Korean children and adolescents from a population-based cross-sectional survey. Life (Basel) 2022;12:1404.
14. US Preventive Services Task Force; Grossman DC, Bibbins-Domingo K, Curry SJ, Barry MJ, Davidson KW, et al. Screening for obesity in children and adolescents: US Preventive Services Task Force recommendation statement. JAMA 2017;317:2417–26.
15. Srivastava G, Fox CK, Kelly AS, Jastreboff AM, Browne AF, Browne NT, et al. Clinical considerations regarding the use of obesity pharmacotherapy in adolescents with obesity. Obesity (Silver Spring) 2019;27:190–204.
16. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100:342–62.
17. Lenders CM. Paediatric obesity: can medications help. Curr Opin Endocrinol Diabetes Obes 2015;22:331–9.
18. O'Hara V, Cuda S, Kharofa R, Censani M, Conroy R, Browne NT. Clinical review: guide to pharmacological management in pediatric obesity medicine. Obes Pillars 2023;6:100066.
19. Cuda S, Censani M, Kharofa R, O'Hara V, Conroy R, Williams DR, et al. Medication-induced weight gain and advanced therapies for the child with overweight and obesity: an Obesity Medicine Association (OMA) Clinical Practice Statement 2022. Obes Pillars 2022;4:100048.
20. Tondt J, Bays HE. Concomitant medications, functional foods, and supplements: an Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022. Obes Pillars 2022;2:100017.
21. Hershey AD, Powers SW, Nelson TD, Kabbouche MA, Winner P, Yonker M, et al. Obesity in the pediatric headache population: a multicenter study. Headache 2009;49:170–7.
22. Oakley CB, Scher AI, Recober A, Peterlin BL. Headache and obesity in the pediatric population. Curr Pain Headache Rep 2014;18:416.
23. Acosta A, Camilleri M, Abu Dayyeh B, Calderon G, Gonzalez D, McRae A, et al. Selection of antiobesity medications based on phenotypes enhances weight loss: a pragmatic trial in an obesity clinic. Obesity (Silver Spring) 2021;29:662–71.
24. Corcoran C, Jacobs TF. Metformin [updated 2023 Aug 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Apr 4]. https://www.ncbi.nlm.nih.gov/books/NBK518983/.
25. O'Connor EA, Evans CV, Burda BU, Walsh ES, Eder M, Lozano P. Screening for obesity and intervention for weight management in children and adolescents: evidence report and systematic review for the US Preventive Services Task Force. JAMA 2017;317:2427–44.
26. Yanovski JA, Krakoff J, Salaita CG, McDuffie JR, Kozlosky M, Sebring NG, et al. Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. Diabetes 2011;60:477–85.
27. Chanoine JP, Hampl S, Jensen C, Boldrin M, Hauptman J. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. JAMA 2005;293:2873–83.
28. Ozkan B, Bereket A, Turan S, Keskin S. Addition of orlistat to conventional treatment in adolescents with severe obesity. Eur J Pediatr 2004;163:738–41.
29. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240–3.
30. Kelly AS, Metzig AM, Rudser KD, Fitch AK, Fox CK, Nathan BM, et al. Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. Obesity (Silver Spring) 2012;20:364–70.
31. Kelly AS, Rudser KD, Nathan BM, Fox CK, Metzig AM, Coombes BJ, et al. The effect of glucagon-like peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity: a randomized, placebo-controlled, clinical trial. JAMA Pediatr 2013;167:355–60.
32. Weghuber D, Forslund A, Ahlström H, Alderborn A, Bergström K, Brunner S, et al. A 6-month randomized, double-blind, placebo-controlled trial of weekly exenatide in adolescents with obesity. Pediatr Obes 2020;15:e12624.
33. Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, et al. A randomized, controlled trial of liraglutide for adolescents with obesity. N Engl J Med 2020;382:2117–28.
34. Weghuber D, Barrett T, Barrientos-Pérez M, Gies I, Hesse D, Jeppesen OK, et al. Once-weekly semaglutide in adolescents with obesity. N Engl J Med 2022;387:2245–57.
35. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. Front Endocrinol (Lausanne) 2019;10:155.
36. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. J Med Chem 2015;58:7370–80.
37. Lyseng-Williamson KA. Glucagon-like peptide-1 receptor analogues in type 2 diabetes: their use and differential features. Clin Drug Investig 2019;39:805–19.
38. Ryder JR, Kaizer A, Rudser KD, Gross A, Kelly AS, Fox CK. Effect of phentermine on weight reduction in a pediatric weight management clinic. Int J Obes (Lond) 2017;41:90–3.

39. Kelly AS, Bensignor MO, Hsia DS, Shoemaker AH, Shih W, Peterson C, et al. Phentermine/topiramate for the treatment of adolescent obesity. NEJM Evid 2022;1:10.1056/evidoa2200014.
40. Mital S, Nguyen HV. Cost-effectiveness of antiobesity drugs for adolescents with severe obesity. JAMA Netw Open 2023;6:e2336400.
41. CONTRAVE package insert revised 9/2014 (naltrexone HCl and bupropion HCl) extended-release tablets. La Jolla, CA: Orexigen Therapeutics, Inc; 2014.
42. Markham A. Setmelanotide: first approval. Drugs 2021;81:397–403.
43. Kievit P, Halem H, Marks DL, Dong JZ, Glavas MM, Sinnayah P, et al. Chronic treatment with a melanocortin-4 receptor agonist causes weight loss, reduces insulin resistance, and improves cardiovascular function in diet-induced obese rhesus macaques. Diabetes 2013;62:490–7.
44. Chen KY, Muniyappa R, Abel BS, Mullins KP, Staker P, Brychta RJ, et al. RM-493, a melanocortin-4 receptor (MC4R) agonist, increases resting energy expenditure in obese individuals. J Clin Endocrinol Metab 2015;100:1639–45.
45. Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. Lancet Diabetes Endocrinol 2020;8:960–70.
46. Garvey WT, Frias JP, Jastreboff AM, le Roux CW, Sattar N, Aizenberg D, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2023;402:613–26.
47. Gadde KM, Atkins KD. The limits and challenges of antiobesity pharmacotherapy. Expert Opin Pharmacother 2020;21:1319–28.