Approach to the Treatment of Children and Adolescents with Obesity

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KEYWORDS

• Pediatric obesity • Obesity pharmacotherapy • Metabolic and bariatric surgery
• Intensive health and behavior lifestyle modification

KEY POINTS

- Pediatric obesity remains a major public health concern that results in life-limiting complications if left untreated.
- The 2023 American Academy of Pediatric clinical practice guidelines emphasize that pediatric obesity is a complex, multifactorial, chronic disease and requires a comprehensive treatment approach.
- The treatment approach should incorporate intensive health and behavioral lifestyle modifications with concurrent use of obesity pharmacotherapy and bariatric surgery based on the severity of the disease at presentation.
- Life-limiting complications, such as type 2 diabetes and metabolism-associated steatotic liver disease, must be screened for routinely to ensure treatment is initiated early.
- The current evidence supports that obesity treatment is safe and effective. There is no evidence that the watchful waiting approach is appropriate.

INTRODUCTION

Pediatric obesity continues to be an omnipresent disease, 1 in 5 children and adolescents have obesity in the United States.[1,2] In pediatric cohorts, obesity is defined as a body mass index (BMI) greater than the 95th percentile for age and sex.[2,3] Increases in

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pediatric obesity have been accompanied with a rising incidence of youth-onset life-limiting comorbidities, such as type 2 diabetes, metabolism-associated steatotic liver disease (MASLD), and sleep apnea.[4] Pediatric obesity has a higher incidence in Latino and Black youth, as well as low-income and middle-income groups.[4,5] Acknowledging the increasing prevalence of pediatric obesity, the American Association of Pediatrics (AAP) produced new guidelines in January 2023 for the care of children and adolescents with obesity.[6]

The AAP recommends proactive and intentional screening of all pediatric patients, using BMI to screen and diagnose for overweight and obesity and systematic screening of risk factors such as family history, racial identity, adverse childhood experiences, and income status. This proactive screening is intended to provide early intervention and support for families. This recommendation is a deviation from the early "watch and wait" recommendations that arose out of the previous clinical practice guidelines published in 2007.[6–8] At yearly well-child examinations, pediatricians are encouraged to provide lifestyle modification recommendations such as screen time recommendations, nutrition, and physical activity advice.[6] At minimum, the AAP recommends screening for comorbidities associated with obesity and providing guidance on the risks associated with these comorbidities and living with elevated BMI throughout childhood with the goals of early diagnosis and intervention not being a certain number on the scale or size of one's body but reduction of life-limiting complications over time.[6,8]

There are multiple potential interventions for those patients identified with obesity.[6] The AAP recommends a comprehensive treatment approach in which intensive lifestyle modification, obesity pharmacotherapy, and bariatric surgery are offered concurrently as warranted by the severity of the presentation.[6,9,10] The current evidence suggests that the most effective intensive health behavior and lifestyle treatment (IHBLT) programs offer family-centered interventions with multidisciplinary counseling on nutrition and physical activity over a 3 to 12 month period.[11,12] There is growing evidence that virtual interventions are equally effective.[13–15] The impact of these interventions reflects a dose-dependent relationship between number of contact hours and treatment effectiveness.[6] Patients should be referred to IHBLT as soon as possible, once a patient has been diagnosed with obesity, as early intervention is essential to prevent youth-onset comorbidities. When referring patients to IHBLT, physicians should use motivational interviewing and a patient-centered, nonjudgmental approach.[16] The AAP emphasizes that while a comprehensive IHBLT approach is the gold standard, clinicians should be empowered to utilize whatever time and resources they have available, to deliver health education to their patients regardless of if they are able to meet the moderate-intensity to high-intensity contact hours recommended.[6] Studies have shown that repeat small doses of nutrition education, such as education on reduction of sugar-sweetened beverages, delivered at routine well-child visits, can lead to sustained behavior change and thus should be incorporated as well.[17–21]

The AAP consensus statement suggests that pediatricians and other pediatric health care providers should offer adolescents aged 12 years and older with obesity, weight loss pharmacotherapy, according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment.[6,22–27] In addition, the statement reports that pharmacotherapy may also be appropriate to children aged 8 to 11 years with more severe or life-threatening comorbidities. For youth aged 13 years and older with class II obesity, defined as a BMI 120% or greater of 95th percentile and an obesity-related comorbidity, or class III obesity, defined as a BMI 140% or greater of 95th percentile, without a comorbidity, bariatric surgery may be an appropriate recommendation.[6,28–30]

The comorbidities associated with youth-onset obesity tend to have a more severe disease progression in youth compared to their adult counterparts with the same obesity-related condition.[31–33] A comorbidity of focus in this study is MASLD, formerly called as nonalcoholic fatty liver disease. MASLD occurs in association with increased adiposity and insulin resistance and has rapidly evolved into the most common liver disease seen in the pediatric population.[34] MASLD has the highest prevalence in Hispanic children and a lower prevalence in black children. Growing evidence suggests that pediatric MASLD is a more severe disease than adult onset given the earlier age of disease of development and is believed to be the most common reason for liver transplant in the United States. Screening for MASLD should begin at the age of 10 years for patients with obesity by obtaining a lipid panel, fasting glucose, alanine aminotransferase, and aspartate aminotransferase every 2 years.[34] There is a direct association between the treatment of MASLD and the treatment of pediatric obesity. Best practices in the management of pediatric MASLD are not clearly defined, and thus, there is much to incorporate from the new AAP guidelines regarding how to best treat youth with obesity and MASLD. Currently, the first-line intervention for MASLD focuses on lifestyle modifications with a particular focus on the reduction of added sugars and increase in daily physical activity.[34] Children should avoid sugar-sweetened beverages, limit screen time to less than 2 hours per day, and exercise for 60 minutes per day. To date, there are no pharmacotherapies specifically Food and Drug Administration (FDA) approved for the treatment of MASLD in youth.

REVIEW OF DIETARY INTERVENTIONS FOR PEDIATRIC OBESITY MANAGEMENT

Behavioral interventions are the cornerstone for the management of obesity. The following section will summarize the major dietary interventions recommended for children with obesity. The overarching theme of these interventions is to reduce daily caloric intake, optimize healthful food consumption, and reduce BMI to, in turn, help decrease the risk of developing obesity-related comorbidities like MASLD. Increasing evidence suggests that the nutrition approach that results in the greatest reduction in BMI is that for which the family can adhere consistently. Sustained engagement with a nutrition approach is multifactorial; however, multiple studies have shown that families prefer nutrition approaches that allow for flexibility with daily schedules, availability of low-cost options, and are delivered in association with education to inform youth and families how these nutritional changes are resulting in improved health and wellness.[35–37]

Reduction in Added Sugar

The reduction of added sugar has been utilized as a dietary approach in the treatment of MASLD in youth.[38] Previous data have linked high intake of added sugars with severity of MASLD due to increased hepatic lipid accumulation. The AAP clinical practice guidelines highlighted education to reduce the intake of sugar-sweetened beverages as one of the best starting places for general pediatricians to target who have limited time and resources in patients with obesity.[6,34] Several clinical studies have investigated the association between reduction of dietary added sugar intake and alanine aminotransferase (ALT) levels in cohorts of youth with obesity compared to healthy control youth. Schwarz and colleagues[39] conducted a study in Latino and Black children aged 9 to 18 years with obesity with history of high added sugar intake (>50 g per day) and showed that by restricting their fructose intake to 4% of the participants daily energy intake for 10 days, there was an associated reduction in hepatic fat, de novo lipogenesis, and visceral fat. Schwimmer and colleagues[38] conducted a

randomized controlled trial investigating a low added sugar nutrition approach in youth with obesity and MASLD in 40 adolescent male individuals who were randomized to either control or a low-sugar approach with less than 3% of daily intake of sugar. At week 8, youth in the low-sugar group had a significant reduction in hepatic steatosis compared to control.

Carbohydrate Restrictions

A carbohydrate (CHO) restriction regimen restricts CHO consumption by limiting foods high in CHOs and replacing them with foods containing a higher percentage of fat and protein. Though there can be variability in specific dietary recommendations, the consensus is to limit CHOs from 20 to 50 g of total CHOs per day. CHO restriction interventions have been shown to decrease BMI compared to baseline and had a greater reduction in BMI compared to low-fat diets. Though the research is limited, some results have shown CHO restriction is associated with significant reduction in hepatic de novo lipogenesis, hepatic fat, and fasting insulin.[40–45] Goss and colleagues[46] investigated reducing daily CHO intake, by providing prepared meals to families of youth with obesity and MASLD for 8 weeks and reported at the end of the study that there was a significant reduction in hepatic lipid content in the CHO-restricted group compared to control.

Calorie Restriction

A calorie restriction nutrition intervention consists of daily caloric intake under the recommend intake for weight maintenance. To determine the weight maintenance recommendation, the resting energy expenditure (REE) and active energy expenditure (AEE) must be determined. There are many proposed predictive equations to determine the REE. Systematic reviews have found the Molnár formula to be most predictive for children with obesity.[47]

Molnar formula

Female individuals: $REE = 0.046 \times weight - 4.492 \times 1/height^2 - 0.151 \times race + 5.841$ ($R^2 = 0.824$)

Male individuals: $REE = 0.037 \times weight - 4.67 \times 1/height^2 - 0.159 \times race + 6.792$ ($R^2 = 0.884$)

To determine the AEE, the REE will be adjusted by a multiplier based off the patient's activity level. The multipliers based off the exercise levels as followed sedentary (little to no exercise) = 1.2, lightly active (light exercise/sports 1–3 d/wk) = 1.375, moderately active (moderate activity/sports 3–5 d/wk) = 1.555, very active (hard activity/sports 6–7 d/wk) = 1.725. Calorie restriction nutrition interventions have consistently shown reduction in weight or BMI in pediatric populations with obesity. When combined with an exercise regimen, weight reduction is even greater.

Dietary Approach to Stop Hypertension

The Dietary Approach to Stop Hypertension (DASH) recommends a higher intake of fruits, vegetables, and whole foods with a decreased intake of processed foods, salt, and refined sugar as a means to decrease the risk of developing hypertension.[48] The recommendations include 6 to 8 servings of whole grains, 6 or less servings of protein, 4 to 5 servings of fruit, 4 to 5 servings of vegetables, 2 to 3 servings of low-fat dairy products, and less than 2300 mg of sodium per day with an ideal goal of less than 1500 mg.[48–50] To quantify dietary adherence, the DASH score was created. A higher DASH score indicates greater adherence to the diet. There are conflicting results regarding the relationship between DASH score and change in BMI.[48,50]

Currently, there are no trials investigating the use of the DASH diet to treat MASLD in youth. However, several trials in adult cohorts have suggested that when compared to control, the DASH diet results in significant reductions in weight, waist circumference, serum ALT, triglycerides, and C-reactive protein levels.[51–53] These findings suggest that the DASH diet may provide metabolic improvement in the underlying etiology of MASLD in youth and may, therefore, be an appropriate approach.

Time-Restricted Eating

A time-restricted eating (TRE) diet confines all dietary and caloric beverage intake to a predefined window of time, typically to 8 hours per day.[54] There has been limited research evaluating the impact of TRE on BMI in pediatric cohorts. A case study of 4 pediatric patients with obesity showed a decrease in body mass index z-score (zBMI) after 4 months of TRE.[55] Vidmar and colleagues[56] demonstrated that 12 weeks of 8 hour TRE with a self-selected eating window resulted in a 3% reduction in weight in excess of the 95th percentile. In adult cohorts, TRE combined with an exercise program has been shown to decrease fat mass, reduce liver enzymes, and improve insulin sensitivity in adults with obesity, with and without diabetes.[57–59]

Mediterranean Diet

The Mediterranean (MED) diet is the traditional diet of those in MED countries and is characterized by a high consumption of vegetables and olive oil, a moderate consumption of lean protein and fish, and a minimal consumption of highly processed food. Adherence to the MED diet is associated with a decrease in BMI. In addition, higher adherence to the MED diet is inversely associated with the development of MASLD/metabolic associated steatohepatitis (MASH).[60–63] A meta-analysis assessing the MED diet as an intervention in adult patients with MASLD showed significant improvements in ALT and hepatic steatosis.[51,64] Akbulut and colleagues conducted a trial of MED diet versus low-fat diet in youth with obesity and non-alcoholic fatty liver disease (NAFLD) and found that 12 weeks of MED diet resulted in similar reduction in hepatic steatosis and liver stiffness as those in the low-fat diet group and both groups had a normalization of their ALT levels. However, children in the MED diet intervention group demonstrated more significant reductions in a total insulin levels, fasting blood glucose, and hemoglobin A1c.

How to Implement Dietary Interventions

When considering recommendation of a dietary intervention in youth, it is important to consider the financial and cultural background of the family. There are many possible dietary interventions, the intervention that is most feasible for the family should be recommended first as that is what is most likely to be effective and sustainable. Parents and caregivers play a crucial role in pediatric obesity interventions. Pediatric patients are more likely to achieve BMI reduction if the dietary changes are incorporated into the whole family. Additionally, it is important to promote intrinsic motivation and self-efficacy through motivational interviewing and patient/caregiver empowerment.

REVIEW OF NONDIETARY BEHAVIORAL INTERVENTIONS

Behavior modification is a foundational aspect of weight management in patients in conjunction with dietary and pharmacotherapy interventions.[65–67] The focus of behavioral intervention for weight management is to decrease sedentary behaviors and increase active time throughout the day.[68–70] Studies have shown that there is an inverse relationship between sedentary behavior and activity, such that an increase

in time spent doing physical activity is related to a decreased in sedentary time throughout the day.[70–74] Additionally, an increase in physical activity is associated with lower consumption of energy-dense food, higher consumption of fruits and vegetables and a lower BMI.[74]

Common approaches to behavior modification include stimulus control, self-monitoring, reinforcement, and modeling.[75–77] Family-based programs are recommended for children aged 5 to 12 years, with studies showing that parent adoption of healthy behaviors is associated with healthy behaviors in children.[78–82] Furthermore, parental weight loss is associated with weight loss in the child.[83–85] School-based programs have also been found to be an effective approach. A multifactorial approach with behavior modification combined with dietary intervention has been shown to be more effective in weight management when compared to diet or behavior modification alone.[6,7,11]

Cognitive behavioral therapy (CBT) is an additional approach to weight management that aims to identify triggers behind unhealthy eating habits. Patients who received CBT as part of a weight management regimen showed decreased rates of binge eating behaviors and sustained weight loss at 6 months follow-up.

Of note, the average total contact hours for behavioral modification programs in pediatric weight management is 27.7 hours over 6 months.[6] However, there is no statistical correlation between contact hours and treatment outcomes.[86] In a review of intervention efficacy, several intervention types were examined for their ability to achieve treatment goal. Interventions aimed at either increasing physical activity or decreasing sedentary time showed small, significant increase in activity and decreased sedentary behavior, respectively. The review also found that interventions aimed at increasing healthy eating behaviors showed statistical significance in trials that used reinforcement. Additionally, trials that aimed at reducing unhealthy eating behaviors were significantly more effective when treatment lasted longer than 6 months.[87]

REVIEW OF PHARMACOTHERAPY INTERVENTIONS

Pharmacotherapy may be a powerful tool to consider in patients who have not reached weight normality with dietary interventions alone.[22,24,88] The AAP consensus statement states that pediatricians and other pediatric health care providers should offer adolescents aged 12 years and older with obesity weight loss pharmacotherapy, according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment.[6,22–27] In addition, the statement reports that pharmacotherapy may also be appropriate for ages 8 to 11 years for patients with more severe or life-threatening comorbidities.[6] The overarching theme of these interventions is to reduce BMI to, in turn, help decrease the risk of developing or progression of obesity-related comorbidities like MASLD. **Tables 1** and **2** summarized the available pediatric obesity pharmacotherapies.

Glucagon-Like-Peptide-1 Receptor Agonist

Glucagon-like-peptide-1 (GLP-1) receptor agonists decrease hunger by slowing gastric emptying and acting on the central nervous system.[89–91] Depending on the medication, it is formulated as a daily oral medication or daily or weekly subcutaneous injection.[90] Exenatide is currently approved in children aged 10 to 17 years with type-2 diabetes.[92] Liraglutide is currently approved for long-term weight management in children aged 12 years or older.[93] Adverse effects include nausea, vomiting, diarrhea, and injection site reaction. Rare complications include pancreatitis, gallbladder disease,

Table 1
Summary of trials of obesity pharmacotherapy in pediatrics

Study	Design	Sample Size (n)	Age (y)	Main Inclusion Criteria	Dose	Duration	Efficacy	Safety	Quality of Evidence
Phentermine									
Lorber et al,[131] 1966	3 parallel-arm (phenmetrazine vs phentermine vs placebo) RCT Outcome measure: weight change (kg)	68	3–15	BMI >95th%	Phenmetrazine 12.5 mg daily Phentermine 15 mg daily	12 wk	Phentermine vs placebo: 0.1 kg	Phentermine arm: insomnia (n = 1)	Low
Rauh et al,[132] 1968	2 parallel-arm (chlorphentermine vs placebo) RCT Outcome measure: weight change (kg)	30	12–18	BMI >95th%	Chlorphentermine 65 mg daily	12 wk	Phentermine vs placebo: 6.7 kg	No SAEs	Low
Ryder et al,[97] 2017	Retrospective chart review Outcome measure: %BMI change	25	12–18	BMI >95th%	Phentermine 15 mg/d	24 wk	Phentermine vs placebo: 4.1% BMI	Phentermine arm: increased blood pressure, heart rate	Moderate
Ali Ibrahim et al,[133] 2022	Retrospective chart review Outcome measure: %BMIp95 change	30	12–18	BMI >95th%	Phentermine 8–37.5 mg/d	24 mo	Youth taking phentermine had mean reduction in %BMIp95 of −15%	AE (n = 6): agitation, sleep disturbances, increased blood pressure, anxiety, photophobia, and dehydration	Low
Topiramate									
Fox et al,[101] 2015	Retrospective chart review Outcome measure: %BMI change	28	14–18	BMI >95th%	Topiramate 25–125 mg/d	24 wk	Topiramate vs lifestyle modification: 4.9% BMI	No SAEs	Low
Fox et al,[134] 2016	2 parallel-arm (topiramate + meal replacement vs placebo) RCT Outcome measure: %BMI change	21	14–18	BMI >120% of the 95th%	Topiramate 75 mg/d	24 wk	Topiramate vs placebo: 1.9% BMI	No SAEs	Low
Consoli et al,[135] 2019	2 parallel-arm (topiramate vs placebo) RCT Outcome measure: %BMI change	62	15–45	Prader–Willi syndrome Youth: BMI >95th% Adult: BMI >30 kg/m^2	Topiramate 50–200 mg/d	8 wk	%BMI Change: Topiramate vs placebo: no difference Hyperphagia scores: Topiramate vs placebo: significant reduction in topiramate group	No SAEs	Low

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Table 1
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Study	Design	Sample Size (n)	Age (y)	Main Inclusion Criteria	Dose	Duration	Efficacy	Safety	Quality of Evidence
Berman et al,[102] 2023	Case series Outcome measure: %BMIp95 change	5	8–12	BMI >95th% Developmental delay	Topiramate 100 mg/d	16 wk	Topiramate group mean reduction in %BMIp95 −12%	4/5 No SAEs 1/5 drowsiness	Low
PHEN/TPM									
Kelly et al,[105] 2022	3 parallel-arm (PHEN/TPM 7.5 mg/46 mg, vs PHEN/TPM 15 mg/92 mg vs Placebo) RCT Outcome measure: %BMI change	223	14–18	BMI >95th%	PHEN/TPM 7.5 mg/46 mg PHEN/TPM 15 mg/92 mg	56 wk	High-dose PHEN/TPM: 10.44 % BMI vs Low dose PHEN/TPM: 8.11% vs +0.1% Placebo	3 SAEs: bile duct stone, depression, suicidal ideation	High
Liraglutide									
Kelly et al,[136] 2020	RCT	251	12–17	BMI ≥95th%, did not exclude if T2D	3.0 mg daily	56 wk + 26 wk follow-up	zBMI change (SD): ETD of −0.22, favoring intervention (P = .002) Reduction in BMI of ≥5%: 43.3% of intervention vs 18.7% of placebo Reduction in BMI of ≥10%: 26.1% of intervention vs 8.1% of placebo	GI AEs more frequent in intervention (64.8% vs 36.5%) AEs leading to discontinuation more frequently in intervention (10.4% vs 0%) Few SAEs (2.4% vs 4.0%)	High
Bensignor et al,[137] 2021	RCT	134	10–16	BMI ≥85th% and T2D	0.6 mg daily 1.2 mg daily 1.8 mg daily	52 wk	BMI change (kg/m^2): ETD of −0.89, favoring intervention (P=.036) % change in BMI (%): ETF of −2.73, favoring intervention (P=.028) %BMIp95 change (%): ETD of −4.42, favoring intervention (P=.038) Findings are significant at 52 wk, not at 26 wk	Not evaluated	High

Exenatide									
Kelly et al,[138] 2012	Randomized, open-label, crossover	12	9–16	BMI ≥1.2 times the 95th%, or BMI ≥35 kg/m^2	10 μg twice daily DE: 5 μg twice daily, 10 μg twice daily	6 mo	BMI change (kg/m^2): ETD of −1.71, favoring intervention (*P*=.01) % change in BMI (%): ETD of −4.92, favoring intervention (*P*=.009) Total body weight change (kg): ETD of −3.9, favoring intervention (*P*=.02) Insulin-related findings: Fasting insulin change (mU/L): ETD of −7.5, favoring intervention (*P*=.02) Insulin sensitivity: ETD of +6.1, favoring intervention (*P*=.02) β-cell function: ETD of +17.97, favoring intervention (*P*=.03)	Mild nausea in 36%, vomiting in 27%, headache in 27%, abdominal pain in 27%, injection site bruising in 9% (1 participant). No hypoglycemia or pancreatitis	High
Fox et al,[139] 2022	RCT	100	12–18	BMI ≥1.2 times the 95th%	2.0 mg extended release, weekly	52 wk	% change in BMI (%): ETD of −4.1, favoring intervention, did not reach significance (*P* = .078) Cardiometabolic findings: TG/HDL ratio: ETD of −0.61, favoring intervention (*P* = .05)	AE frequency similar between groups (96.9% of intervention vs 90.9% of placebo) GI AEs more common in intervention No serious adverse event directly related to the study drug	High
Semaglutide									
Weghuber et al,[94] 2022	RCT	201	12–17	BMI ≥95th% or BMI ≥85th% + weight-related coexisting condition	2.4 mg weekly	68 wk	BMI change from baseline ETD of −16.7, favoring intervention group (P ≤ .001) Weight loss of ≥5%: 73% of intervention vs 18% of placebo. Cardiometabolic findings: Improved waist circumference, HbA1c, lipids, AST were greater in intervention	GI AEs greater (62% of intervention vs 42% of placebo) 4% with cholestasis in intervention SAEs in 11% of intervention vs 9% of placebo	High

Abbreviations: %BMIp95, BMI in excess of the 95th percentile; AE, adverse event; BMI, body mass index; BMI >95th%, body mass index greater than the 95th percentile; ETD, endoscopic transluminaldrainage; GI, gastrointestinal; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; PHEN/TPM, phentermine/topiramate extended release product; RCT, randomized controlled trial; SAE, serious adverse event; TG, triglycerides.

Table 2
Overview of obesity pharmacotherapy in pediatrics

Agent	Phentermine	Topiramate	PHEN/TPM	Metformin	Liraglutide	Semaglutide	Orlistat	Setmenalotide	Naltrexone/ Bupropion
FDA Status	Yes ≥16yo for short-term use	No ≥ 2 year old for seizures ≥ 12 year old for migraine prophylaxis	Yes ≥ 12 year old	No	Yes ≥ 12 year old	Yes ≥ 12 year old	Yes ≥ 12 year old	Yes ≥ 6 year old with BBS, POMC, LEPR, PCSK1	No
Weight Loss Mechanism of Action	Norepinephrine (NE) reuptake inhibition Increases the release of NE in the central nervous system by releasing NE from presynaptic vesicles. Stimulates release of serotonin and dopamine, from nerve terminals Monoamine oxidase and serotonin reuptake inhibitor	Modulation of GABA Antagonizesalpha-amino-3-hydroxyl-4-isoxazole-propionic acid kainite receptors Carbonic-anhydrase inhibition	Phen + TPM	Decreases hepatic glucose production. Increases insulin sensitivity by increasing peripheral glucose uptake and utilization. Inhibits mitochondrial complex I activity	Glucagon-like peptide-1 receptor agonists (GLP1RA) augment glucose-dependent insulin release and reduce glucagon secretion and gastric emptying Decrease food intake through central modulation of appetite control		Inhibits gastric and pancreatic lipases	melanocortin-4 receptor agonist	Bupropion is a reuptake inhibitor and releasing agent of both norepinephrine and dopamine, and a nicotinic acetylcholine receptor antagonist, and it activates proopiomelanocortin (POMC) neurons. Naltrexone is a pure opioid antagonist
Mode of Administration and Dose	Oral 8 mg, 15 mg, 30 mg, 37.5 mg Daily in morning	Oral Up to 200 mg twice daily (obesity dosing varies widely); extended release formulation	Oral Mid-dose (phentermine7.5 mg/ topiramate extended release 46 mg) High-dose (phentermine15 mg/ topiramate extended release 92 mg) Once daily in the morning	Oral 1000 mg twice daily	3 mg daily	2.4 mg weekly	160 mg TID	3 mg SQ	extended-release tablet contains naltrexone 8 mg/bupropion 90 mg to max of naltrexone 32 mg/bupropion 360 mg
Controlled Substance	Yes Schedule IV	No	Yes Schedule IV	No	No	No	No	No	No

Side Effect Profile	Hypertensio Tachycardia Palpitations Pulmonary hypertensio Agitation Restlessnes Insomnia Anxiety Euphoria Tremor	Headache Paresthesia Dizziness Dysgeusia Cognitive Impairment potential Dry mouth Diarrhea ConstipationFetal toxicity Decreased visual acuity Worsening depression or suicidal thoughts Metabolic acidosis Elevation of creatinine,	SE for PHEN + TPM	Nausea Vomiting Diarrhea Lactic acidosis	Nausea, vomiting, diarrhea, fatigue, headache, hypoglycemia, mood changes	Rectal leakage Steatosis Diarrhea Nausea Bloating	Hyperpigmentation Injection site reaction Headache, Fatigue Nausea Vomiting Diarrhea Spontaneous penile erection	Xerostomia Constipation Dizziness Insomnia Nausea Vomiting Diarrhea Dream disorder Headache disorder Symptoms of anxiety Tinnitus Hypertension Pruritus of skin Urticaria Arthralgia Myalgia Hyperhidrosis Tremor Dysgeusia Skin rash
Contraindications	History of CVD or drug use; MAOI use; hyperthyroidism; glaucoma; agitated states; pregnancy	Pregnancy, glaucoma,	Same contraindications for phentermine and topiramate monotherapy	Renal failure; lactic acidosis	Family history of medullar thyroid carcinoma; pregnancy; breastfeeding	None	pregnancy; breastfeeding	pregnancy; breastfeeding
Use Cautions	High blood pressure, congenital heart disease, use of SSRIs, SNRIs, insulin, or valproic acid, renal disease, metabolic acidosis, history of kidney stones, depression, suicidal ideation, high risk for pregnancy	Kidney stones, glaucoma, high risk for pregnancy due to fetal toxicity, metabolic acidosis, active suicidal ideation, poor cognitive function, and academic struggles	Same use cautions recommended for phentermine and topiramate monotherapy	NA	Pancreatitis	Pancreatitis	None	High blood pressure Congestive heart failure/recent myocardial infarction Bipolar disorder/ thoughts of suicide Current or recent use morphine/ methadone/ buprenorphine Kidney disease Cirrhosis Glaucoma Use/abuse of drugs/alcohol Seizures

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Table 2
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Agent	Phentermine	Topiramate	PHEN/TPM	Metformin	Liraglutide	Semaglutide	Orlistat	Setmenalotide	Naltrexone/ Bupropion
Cost	Low	Low	Moderate	Low	High		Low	High	Moderate
Patient Selection	Strong hunger; low energy	Poor satiety, food cravings, symptoms of binge eating disorder, migraine, headaches, night eating, seizures	Dual therapy Insurance Coverage Desire for synergist effect with daily dosing	Insulin resistance; concomitant use of anti-psychotic medications	Insulin resistance, type 2 diabetes, polycystic ovarian syndrome; poor satiety; food cravings			Monogenic obesity	Concomitant mood disorder; poor satiety; binge eating disorder

Abbreviations: %BMIp95, BMI in excess of the 95th percentile; AE, adverse event; BMI, body mass index; BMI greater than 95th%, body mass index greater than the 95th percentile; CVD, cardiovascular disease; GI, gastrointestinal; GI, gastrointestinal; HbA1c, hemoglobin A1c; LDL, low density lipoprotein; MAOI, monoamine oxidase inhibitors; PHEN/TPM, Phentermine/topiramate extended release product; RCT, randomized controlled trial; SAE, serious adverse event; SNRIs, Serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TG, triglycerides.

and renal impairment. Liraglutide dosing at starts 0.6 mg up to 3 mg per day. Semaglutide 2.4 mg weekly was recently FDA approved for the treatment of pediatric obesity in youth aged 12 years and older. The seminal trialed showed a mean BMI reduction of 16% in more than 70% of participants.[94] Semaglutide dosing starts 0.25 mg up to 2.4 mg per week, dosed weekly.[93] These medications have been shown to be the most effective pharmacotherapy with the highest mean reduction in BMI and least amount of heterogeneity in response, unlike many of the other available pharmacotherapies that have significant heterogeneity in efficacy across individual response rates.[94] **Table 1** summarized pediatric efficacy data of GLP-1 agonists for obesity management.

Phentermine

Phentermine is an indirect sympathomimetic that increases the availability of norepinephrine, serotonin, and dopamine and reduces appetite.[95,96] Phentermine is FDA approved for weight loss as short course therapy (3 months or less) in adolescents aged 16 years or older.[97,98] Adverse effects include tachycardia, palpitations, hypertension, anxiety, dizziness, insomnia, headache, dry mouth, and gastrointestinal (GI) upset and are dose dependent. Dosing starts at 7.5 mg up to 37.5 mg per day. The weight loss benefit of phentermine is not always increased with increased dose.

Topiramate

Topiramate is an anticonvulsant and gamma-aminobutyric acid (GABA) receptor modifier, causing glutamate inhibition and increased dopamine release and is formulated as a daily oral medication.[98–101] Topiramate is not FDA approved for weight loss in adults or children and is used off-label. Adverse effects include paresthesia, sedation, mood disturbance, visual disturbance, GI upset, and migraine.[99,101,102] These adverse effects are typically dose dependent. Dosing starts at 25 mg to 100 mg daily in twice daily dosing. In youth with obesity, topiramate in combination with lifestyle modification is effective for decreasing BMI.[101,102]

Phentermine/Topiramate Combination

The phentermine/topiramate combination is a one capsule combination daily pill that is FDA approved for weight loss in youth aged 12 years and older with obesity.[103–105] The safety and efficacy of combining the 2 individual agents together has not yet been determined but is often done off-label to decrease patient financial burden. The phentermine/topiramate combination includes an immediate release of phentermine with an extended release of topiramate. This combination allows for a decrease in the individual dose of both drugs to decrease occurrence of adverse events. This combination is not recommended for anyone with cardiovascular disease due to rare but significant risk of cardiovascular ischemic events.[103,106] Adverse effects include dry mouth, constipation, paresthesia, sedation, mood disturbance, and visual disturbance.[107] These adverse effects are typically dose dependent. Dosing starts at 3.75 mg phentermine/23 mg topiramate up to 15 mg phentermine/92 mg topiramate daily. In adolescents with obesity, the combination therapy has been shown to provide significant reduction in BMI with the effects being dose dependent.[108–110]

Orlistat

Orlistat is a gastric lipase inhibitor, decreasing the gastric absorption of dietary fat and is formulated as a daily oral medication. Orlistat is currently FDA approved for long-term weight loss in adolescents and adults. Adverse effects include steatorrhea, fecal urgency, and flatulence, and fat-soluble vitamin deficiency and are not always dose

dependent. Dosing starts at is typically 120 mg, 3 times per day. The adverse effects limit the tolerability, and because of this, orlistat is rarely used in pediatric cohorts. Studies show orlistat produces a small decrease in liver enzymes in adolescents as well as a reduction in cholesterol, low-density lipoprotein, fasting glucose, insulin, and blood pressure.[111–115]

Bupropion/Naltrexone Combination

Bupropion is a dopamine-reuptake inhibitor. Naltrexone is an opioid receptor antagonist.[115] The combination is proposed to have a synergistic effect at reducing food intake and is formulated as a daily oral medication. Bupropion/naltrexone is FDA approved for weight loss in adults. There are currently no randomized controlled trials evaluating the impact on weight loss in pediatric cohorts. Adverse effects include nausea, headache, constipation, insomnia, dry mouth, and dizziness. Dosing starts at 8 mg naltrexone/90 mg bupropion up to 32 mg naltrexone/360 mg bupropion daily. Bupropion also has an FDA warning for increasing suicidal ideation in young adults.[110,113,114]

Metformin

Metformin is a biguanide drug that reduces glucose production in the liver, decreases intestinal absorption, and increases insulin sensitivity and is formulated as a daily oral medication.[116] Metformin is only FDA approved for the management of type 2 diabetes. Adverse effects are dose dependent and include bloating, nausea, flatulence, and diarrhea. Lactic acidosis is a rare but potentially fatal complication.[116] Metformin dosing is dependent on the indication and patient comorbidities. Metformin has been shown to result in modest reduction in BMI in pediatric cohorts; however, there is limited evidence to support its use as an obesity pharmacotherapy. Metformin has been shown to support weight reduction in youth taking weight gain promoting antipsychotic agents such as risperidone. In addition, for some adolescent female individuals with polycystic ovarian syndrome, metformin has been shown to be useful in combination with oral contraceptive agents to promote restoration of normal menstrual cycles and improve insulin sensitivity.

Setmelanotide

Setmelanotide is a melanocortin-4 receptor agonist developed for the treatment of obesity arising from proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency. The drug has received FDA approval for chronic weight management in youth aged 6 years and older with obesity caused by POMC, PCSK1, and LEPR deficiency and those with Bardet–Biedl syndrome. Setmelanotide is administered as a daily subcutaneous injection. The side effect profile includes hyperpigmentation, nausea, vomiting, headaches, spontaneous penile erection, and injection site reactions. The seminal trials have demonstrated significant reduction in BMI and improvement in hunger scores when compared to placebo.[117–119]

SURGICAL INTERVENTIONS

Several surgical procedures exist that are used to augment weight loss in patients with obesity. The AAP recommends bariatric surgery as a treatment option for those with either class 2 obesity with comorbidities or class 3 obesity with or without comorbidities. The AAP recommends bariatric surgery for youth aged 13 years and older who meet the above criteria. The American Society for Metabolic and Bariatric Surgery

agrees with the recommendations of the AAP regarding bariatric surgery for pediatric weight management.[1,29,120]

There are multiple bariatric procedures that can be performed; however, sleeve gastrectomy remains the most commonly completed surgery in youth with obesity. *Gastric bypass:* Gastric bypass surgery is characterized by the creation of a small pouch at the top of the stomach and bypassing a portion of the small intestine. This restricts the amount of food one can eat and decreased calorie absorption. *Sleeve gastrectomy*: A larger portion of the stomach is removed, leaving a small, sleeve-shaped pouch. Similar to gastric bypass, this limits the volume of food that can be consumed and also decreases the level of hunger-stimulating hormones that are released. This is the most common surgical procedure performed in pediatric weight management. *Vertical banded gastroplasty:* The stomach is stapled to create a small pouch, while a band is placed around the stomach to restrict the size of the gastric outlet.[28,121,122]

Several studies exist that examine the safety and efficacy of bariatric surgery in pediatric weight management. The Teen-LABS project is a prospective observational study of 242 adolescents as well as two 47 year outcome studies, which provide sufficient data to conclude that bariatric surgery in adolescents is as safe and effective as bariatric surgery in adults. Additionally, a review performed in 2021 supports the conclusions of the Teen-LABS project. Another review performed in 2021 found that early referral for bariatric surgery improves the quality of life in children with obesity.

ENDOSCOPIC THERAPIES

There is growing evidence exploring the use of endoscopic therapies for the treatment of pediatric obesity.[123–127] Several device-based endoscopic treatments have been utilized in adult cohorts with obesity including but not limited to the endoscopic sleeve gastroplasty, endoluminal procedure, and the transoral anterior-to-posterior greater curvature plication procedure.[128] There is a paucity of literature on these techniques in pediatrics cohorts despite the potential as an adjunct therapy to the comprehensive obesity care model.[126,127,129] Several studies have examined the use of the space-occupying intragastric balloon (IGB) in pediatric cohorts with severe obesity.[125–127,130] In pediatric patients, a retrospective study of 27 adolescents with a nonadjustable IGB showed a total body weight loss of 16.35% without any serious adverse events.[130] In addition, a recent study of a swallowable IGB showed an estimate weight loss of 20.1% in 16 children with obesity without any complications.[128] No pediatric studies have evaluated the IGB for MASLD. The most well-studied endobariatric treatment is the endoscopic sleeve gastroplasty (ESG). ESG is an endoscopic procedure that uses full-thickness sutures to plicate the greater curvature of the stomach, creating a tubular sleeve-like configuration. Alqahtani and colleagues[128] presented the first series of youth with obesity (n = 109) undergoing ESG and reported a mean total body weight loss of 16.2% at 12 months, 15.4% at 18 months, and 13.7% at 24 months. All obesity comorbidities were in complete remission from 3 months through the end of the study.[128]

DISCUSSION

Pediatric obesity remains a major public health concern that results in life-limiting complications if left untreated. The 2023 American Academy of Pediatric clinical practice guidelines emphasize that pediatric obesity is a complex, multifactorial, chronic disease and requires a comprehensive treatment approach.[6] The treatment approach should incorporate intensive health and behavioral lifestyles modifications with

concurrent use of obesity pharmacotherapy and bariatric surgery based on the severity of the disease at presentation.[6] The evaluation of pediatric obesity requires a thorough medical, medication and social history, screening for social determinants of health, assessment of mental health, detection of disordered eating concerns, and determination of readiness for change as well as physical examination. Life-limiting complications, such as type 2 diabetes and MASLD must be screened for routinely to ensure treatment is initiated early. The current evidence supports that obesity treatment is safe and effective. There is no evidence that the watchful waiting approach is appropriate. Pediatricians and other pediatric health care professionals should offer treatment options early and at the highest available intensity available. The clinical practice guidelines recommend using the framework of a medical home and the chronic care model with a motivational interviewing approach.[6] The goal of treatment is not the number on the scale but the prevention of life-limiting complications that can significantly impact the health of these youth over time.[131–139]

CLINICS CARE POINTS

- The evaluation of pediatric obesity requires a thorough medical, medication and social history, screening for social determinants of health, assessment of mental health, detection of disordered eating concerns and determination of readiness for change as well as physical examination.
- Pediatricians and other pediatric health care professionals should offer treatment options early and at the highest available intensity available.
- The clinical practice guidelines recommend using the framework of a medical home and the chronic care model with a motivational interviewing approach.
- The goal of treatment is not the number on the scale but the prevention of life-limiting complications that can significantly impact the health of these youth over time.

DISCLOSURE

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REFERENCES

1. Ogden CL, Martin CB, Freedman DS, et al. Trends in obesity disparities during childhood. Pediatrics 2022;150(2). https://doi.org/10.1542/PEDS.2022-056547.
2. Hales CM, Fryar CD, Carroll MD, et al. Trends in obesity and severe obesity prevalence in us youth and adults by sex and age, 2007-2008 to 2015-2016. JAMA 2018;319(16):1723–5.
3. DS F, NF B, EM T, et al. BMI z-Scores are a poor indicator of adiposity among 2- to 19-year-olds with very high BMIs, NHANES 1999-2000 to 2013-2014. Obesity 2017;25(4):739–46.
4. Ogden CL, Fryar CD, Martin CB, et al. Trends in obesity prevalence by race and hispanic origin - 1999-2000 to 2017-2018. JAMA, J Am Med Assoc 2020; 324(12):1208–10.
5. Ogden CL, Fryar CD, Hales CM, et al. Differences in obesity prevalence by demographics and urbanization in US Children and Adolescents, 2013-2016. JAMA 2018;319(23):2410–8.

6. Hampl SE, Hassink SG, Skinner AC, et al. Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. Pediatrics 2023; 151(2). https://doi.org/10.1542/PEDS.2022-060640.
7. SE B. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics 2007;120(Suppl 4).
8. Kelly AS, Barlow SE, Rao G, et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation 2013;128(15): 1689–712.
9. Salam RA, Padhani ZA, Das JK, et al. Effects of lifestyle modification interventions to prevent and manage child and adolescent obesity: a systematic review and meta-analysis. Nutrients 2020;12(8):1–23.
10. Cho K, Park S, Koyanagi A, et al. The effect of pharmacological treatment and lifestyle modification in patients with nonalcoholic fatty liver disease: An umbrella review of meta-analyses of randomized controlled trials. Obes Rev 2022;23(9). https://doi.org/10.1111/OBR.13464.
11. Styne DM, Arslanian SA, Connor EL, et al. Pediatric obesity-assessment, treatment, and prevention: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2017;102(3):709–57.
12. August GP, Caprio S, Fennoy I, et al. Prevention and treatment of pediatric obesity: An Endocrine Society clinical practice guideline based on expert opinion. J Clin Endocrinol Metab 2008;93(12). https://doi.org/10.1210/jc.2007-2458.
13. Cueto V, Sanders LM. Telehealth Opportunities and Challenges for Managing Pediatric Obesity. Pediatr Clin North Am 2020;67(4):647–54.
14. Calcaterra V, Verduci E, Vandoni M, et al. Telehealth: a useful tool for the management of nutrition and exercise programs in pediatric obesity in the COVID-19 Era. Nutrients 2021;13(11). https://doi.org/10.3390/NU13113689.
15. Shaikh U, Nettiksimmons J, Romano P. Pediatric obesity management in rural clinics in California and the role of telehealth in distance education. J Rural Health 2011;27(3):263–9.
16. Woolford SJ, Resnicow K, Davis MM, et al. Cost-effectiveness of a motivational interviewing obesity intervention versus usual care in pediatric primary care offices. Obesity 2022;30(11):2265–74.
17. Momin SR, Wood AC. Sugar-sweetened beverages and child health: implications for policy. Curr Nutr Rep 2018;7(4):286–93.
18. Nezami BT, Ward DS, Lytle LA, et al. A mHealth randomized controlled trial to reduce sugar-sweetened beverage intake in preschool-aged children. Pediatr Obes 2018;13(11):668–76.
19. Laverty AA, Magee L, Monteiro CA, et al. Sugar and artificially sweetened beverage consumption and adiposity changes: National longitudinal study. Int J Behav Nutr Phys Activ 2015;12(1). https://doi.org/10.1186/s12966-015-0297-y.
20. Copperstone C, Mcneill G, Aucott L, et al. A pilot study to improve sugar and water consumption in Maltese school children. Int J Adolesc Med Health 2019;33(2). https://doi.org/10.1515/IJAMH-2018-0134.
21. Seferidi P, Millett C, Laverty AA. Sweetened beverage intake in association to energy and sugar consumption and cardiometabolic markers in children. Pediatr Obes 2018;13(4):195–203.

22. Kelly AS, Fox CK, Rudser KD, et al. Pediatric obesity pharmacotherapy: current state of the field, review of the literature and clinical trial considerations. Int J Obes 2016;40(7):1043–50.
23. Ioannides-Demos LL, Proietto J, McNeil JJ. Pharmacotherapy for obesity. Drugs 2005;65(10):1391–418.
24. Kühnen P, Biedermann H, Wiegand S. Pharmacotherapy in childhood obesity. Horm Res Paediatr 2022;95(2). https://doi.org/10.1159/000518432.
25. Kelly AS, Fox CK. Pharmacotherapy in the management of pediatric obesity. Curr Diab Rep 2017;17(8). https://doi.org/10.1007/S11892-017-0886-Z.
26. Singhal V, Sella AC, Malhotra S. Pharmacotherapy in pediatric obesity: current evidence and landscape. Curr Opin Endocrinol Diabetes Obes 2021;28(1):55–63.
27. C B, E K, CK F, et al. Trends in prescribing anti-obesity pharmacotherapy for paediatric weight management: Data from the POWER Work Group. Pediatr Obes 2021;16(1). https://doi.org/10.1111/IJPO.12701.
28. Armstrong SC, Bolling CF, Michalsky MP, et al. Pediatric Metabolic and Bariatric Surgery: Evidence, Barriers, and Best Practices. Pediatrics 2019;144(6). https://doi.org/10.1542/PEDS.2019-3223.
29. JSA P, A B, NT B, et al. ASMBS pediatric metabolic and bariatric surgery guidelines, 2018. Surg Obes Relat Dis 2018;14(7):882–901.
30. Aikenhead A, Knai C, Lobstein T. Effectiveness and cost-effectiveness of paediatric bariatric surgery: a systematic review. Clin Obes 2011;1(1):12–25.
31. Tryggestad JB, Willi SM. Complications and comorbidities of T2DM in adolescents: Findings from the TODAY clinical trial. J Diabet Complicat 2015;29(2).
32. Kumar S, Kelly AS. Review of childhood obesity: from epidemiology, etiology, and comorbidities to clinical assessment and treatment. Mayo Clin Proc 2017;92(2):251–65.
33. F B, P C, RL G, et al. Racial and ethnic disparities in comorbidities in youth with type 2 diabetes in the pediatric diabetes consortium (PDC). Diabetes Care 2021;44(10):2245–51.
34. Vos MB, Abrams SH, Barlow SE, 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(2):319–34.
35. Johnston CA, Moreno JP, Hernandez DC, et al. Levels of adherence needed to achieve significant weight loss. Int J Obes 2019;43(1):125–31.
36. Jelalian E, Foster GD, Sato AF, et al. Treatment adherence and facilitator characteristics in a community based pediatric weight control intervention. Int J Behav Nutr Phys Activ 2014;11(1).
37. Berkowitz RI, Marcus MD, Anderson BJ, et al. Adherence to a lifestyle program for youth with type 2 diabetes and its association with treatment outcome in the TODAY clinical trial. Pediatr Diabetes 2018;19(2):191–8.
38. Schwimmer JB, Ugalde-Nicalo P, Welsh JA, et al. Effect of a low free sugar diet vs usual diet on nonalcoholic fatty liver disease in adolescent boys: a randomized clinical trial. JAMA 2019;321(3):256–65.
39. Schwarz JM, Noworolski SM, Wen MJ, et al. Effect of a high-fructose weight-maintaining diet on lipogenesis and liver fat. J Clin Endocrinol Metab 2015;100(6):2434–42.

40. Skytte MJ, Samkani A, Petersen AD, et al. A carbohydrate-reduced high-protein diet improves HbA1c and liver fat content in weight stable participants with type 2 diabetes: a randomised controlled trial. Diabetologia 2019;62(11):2066–78.
41. Tay J, Thompson CH, Luscombe-Marsh ND, et al. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. Diabetes Obes Metabol 2018;20(4):858–71.
42. Jenkins DJA, Wolever TMS, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34(3):362–6.
43. Jansen LT, Yang N, Wong JMW, et al. Prolonged glycemic adaptation following transition from a low- to high-carbohydrate diet: a randomized controlled feeding trial. Diabetes Care 2022. https://doi.org/10.2337/DC21-1970.
44. He M, Wang J, Liang Q, et al. Time-restricted eating with or without low-carbohydrate diet reduces visceral fat and improves metabolic syndrome: A randomized trial. Cell Rep Med 2022;3(10). https://doi.org/10.1016/J.XCRM.2022.100777.
45. Rasmussen L, Christensen ML, Poulsen CW, et al. Effect of high versus low carbohydrate intake in the morning on glycemic variability and glycemic control measured by continuous blood glucose monitoring in women with gestational diabetes mellitus-a randomized crossover study. Nutrients 2020;12(2).
46. Goss AM, Dowla S, Pendergrass M, et al. Effects of a carbohydrate-restricted diet on hepatic lipid content in adolescents with non-alcoholic fatty liver disease: A pilot, randomized trial. Pediatr Obes 2020;15(7).
47. Fuentes-Servín J, Avila-Nava A, González-Salazar LE, et al. Resting energy expenditure prediction equations in the pediatric population: a systematic review. Front Pediatr 2021;9:795364.
48. Bricarello LP, de Moura Souza A, de Almeida Alves M, et al. Association between DASH diet (Dietary Approaches to Stop Hypertension) and hypertension in adolescents: A cross-sectional school-based study. Clin Nutr ESPEN 2020;36:69–75.
49. Dashti HS, Gómez-Abellán P, Qian J, et al. Late eating is associated with cardiometabolic risk traits, obesogenic behaviors, and impaired weight loss. Am J Clin Nutr 2020;113(1):154–61.
50. Garaulet M, Lopez-Minguez J, Dashti HS, et al. Interplay of dinner timing and MTNR1B type 2 diabetes risk variant on glucose tolerance and insulin secretion: a randomized crossover trial. Diabetes Care 2022;45(3):512–9.
51. Paula Bricarello L, Poltronieri F, Fernandes R, et al. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on blood pressure, overweight and obesity in adolescents: A systematic review. Clin Nutr ESPEN 2018;28:1–11.
52. Costello E, Goodrich J, Patterson WB, et al. Diet quality is associated with glucose regulation in a cohort of young adults. Nutrients 2022;14(18).
53. Razavi Zade M, Telkabadi MH, Bahmani F, et al. The effects of DASH diet on weight loss and metabolic status in adults with non-alcoholic fatty liver disease: a randomized clinical trial. Liver Int 2016;36(4):563–71.
54. Fanti M, Mishra A, Longo VD, et al. Time-restricted eating, intermittent fasting, and fasting-mimicking diets in weight loss. Curr Obes Rep 2021;10(2):70–80.
55. AP V, MI G, JK R. Time-limited eating in pediatric patients with obesity-a case series. J Food Sci Nutr Res 2020;02(03).

56. Vidmar Alaina P. NMRJK, SSJHEWCPGMI. Time-limited eating and continuous glucose monitoring in adolescents with obesity: a pilot study. Nutrients 2021; 13(11):3697–712.
57. Manoogian ENC, Chow LS, Taub PR, et al. Time-restricted eating for the prevention and management of metabolic diseases. Endocr Rev 2022;43(2):405–36.
58. Gabel K, Cienfuegos S, Kalam F, et al. Time-restricted eating to improve cardiovascular health. Curr Atheroscler Rep 2021;23(5).
59. Crose A, Alvear A, Singroy S, et al. Time-restricted eating improves quality of life measures in overweight humans. Nutrients 2021;13(5).
60. Ben-Yacov O, Godneva A, Rein M, et al. Personalized postprandial glucose response-targeting diet versus mediterranean diet for glycemic control in prediabetes. Diabetes Care 2021;44(9):1980–91.
61. Carter P, Achana F, Troughton J, et al. A mediterranean diet improves HbA1c but not fasting blood glucose compared to alternative dietary strategies: A network meta-analysis. J Hum Nutr Diet 2014;27(3):280–97.
62. Al V, PV V, AA D. Fasting mimicking diets: A literature review of their impact on inflammatory arthritis. Mediterr J Rheumatol 2020;30(4):201.
63. Ismail S, Manaf R, Mahmud A. Comparison of time-restricted feeding and islamic fasting: A scoping review. East Mediterr Health J 2019;25(4).
64. Haigh L, Kirk C, El Gendy K, et al. The effectiveness and acceptability of Mediterranean diet and calorie restriction in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis. Clin Nutr 2022;41(9):1913–31.
65. Wheaton AG, Chapman DP, Croft JB. School start times, sleep, behavioral, health, and academic outcomes: a review of the literature. J Sch Health 2016; 86(5):363–81.
66. Tackett JL, McShane BB. Conceptualizing and evaluating replication across domains of behavioral research. Behav Brain Sci 2018;41:e152.
67. Frank HR, Ubel PA, Wong CA. Behavioral economic insights for pediatric obesity: suggestions for translating the guidelines for our patients. JAMA Pediatr 2020;174(4):319–20.
68. Tremblay MS, Carson V, Chaput JP, et al. Canadian 24-hour movement guidelines for children and youth: An integration of physical activity, sedentary behaviour, and sleep. Appl Physiol Nutr Metabol 2016;41(6):S311–27.
69. Füzéki E, Engeroff T, Banzer W. Health benefits of light-intensity physical activity: a systematic review of accelerometer data of the National Health and Nutrition Examination Survey (NHANES). Sports Med 2017;47(9):1769–93.
70. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-Country reliability and validity. Med Sci Sports Exerc 2003;35(8): 1381–95.
71. Hallal PC, Victora CG. Reliability and validity of the International Physical Activity Questionnaire (IPAQ) [2]. Med Sci Sports Exerc 2004;36(3):556.
72. Sriram K, Mulder HS, Frank HR, et al. The dose-response relationship between physical activity and cardiometabolic health in adolescents. Am J Prev Med 2021;60(1):95–103.
73. Kriska A, Delahanty L, Edelstein S, et al. Sedentary behavior and physical activity in youth with recent onset of type 2 diabetes. Pediatrics 2013;131(3).
74. Brazendale K, Beets MW, Armstrong B, et al. Children's moderate-to-vigorous physical activity on weekdays versus weekend days: a multi-country analysis. Int J Behav Nutr Phys Activ 2021;18(1).

75. Patel ML, Hopkins CM, Brooks TL, et al. Comparing self-monitoring strategies for weight loss in a smartphone app: randomized controlled trial. JMIR Mhealth Uhealth 2019;7(2).
76. Farage G, Simmons C, Kocak M, et al. Assessing the contribution of self-monitoring through a commercial weight loss app: mediation and predictive modeling study. JMIR Mhealth Uhealth 2021;9(7).
77. Darling KE, Sato AF. Systematic review and meta-analysis examining the effectiveness of mobile health technologies in using self-monitoring for pediatric weight management. Child Obes 2017;13(5):347–55.
78. Wright JA, Phillips BD, Watson BL, et al. Randomized trial of a family-based, automated, conversational obesity treatment program for underserved populations. Obesity 2013;21(9).
79. Quattrin T, Cao Y, Paluch RA, et al. Cost-effectiveness of family-based obesity treatment. Pediatrics 2017;140(3).
80. Goldfield GS, Epstein LH, Kilanowski CK, et al. Cost-effectiveness of group and mixed family-based treatment for childhood obesity. Int J Obes Relat Metab Disord 2001;25(12):1843–9.
81. Schmied EA, Madanat H, Chuang E, et al. Factors predicting parent engagement in a family-based childhood obesity prevention and control program. BMC Publ Health 2023;23(1):457.
82. Position of the American Dietetic Association: individual-, family-, school-, and community-based interventions for pediatric overweight. J Am Diet Assoc 2006;106(6):925–45.
83. Wilfley DE. Design of a family-based lifestyle intervention for youth with type 2 diabetes: The today study. Int J Obes 2010;34(2).
84. Janicke DM, Sallinen BJ, Perri MG, et al. Comparison of program costs for parent-only and family-based interventions for pediatric obesity in medically underserved rural settings. J Rural Health 2009;25(3):326–30.
85. Zanganeh M, Adab P, Li B, et al. Cost-effectiveness of a school-and family-based childhood obesity prevention programme in China: The "CHIRPY DRAGON" cluster-randomised controlled trial. Int J Publ Health 2021;66.
86. Heerman et al. 2017.
87. Kamath et al. 2008.
88. Fox CK, Kelly AS. Pharmacotherapy for severe obesity in children. Clin Pediatr (Phila) 2015;54(13):1302.
89. Zhao X, Wang M, Wen Z, et al. GLP-1 receptor agonists: beyond their pancreatic effects. Front Endocrinol 2021;12.
90. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metabol 2022;57.
91. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest 2014;124(10):4473–88.
92. Tamborlane WV, Bishai R, Geller D, et al. Once-weekly exenatide in youth with type 2 diabetes. Diabetes Care 2022;45(8):1833–40.
93. Tamborlane WV, Barrientos-Pérez M, Fainberg U, et al. Liraglutide in children and adolescents with type 2 diabetes. N Engl J Med 2019;381(7):637–46.
94. Weghuber D, Barrett T, Barrientos-Pérez M, et al. Once-weekly semaglutide in adolescents with obesity. N Engl J Med 2022;387(24).
95. Lewis KH, Fischer H, Ard J, et al. Safety and effectiveness of longer-term phentermine use: clinical outcomes from an electronic health record cohort. Obesity 2019;27(4):591–602.

96. Murali S. Knowledge gaps in long-term phentermine use: making the case for maintenance. Obesity 2019;27(8):1219.
97. Ryder JR, Kaizer A, Rudser KD, et al. Effect of phentermine on weight reduction in a pediatric weight management clinic. Int J Obes 2017;41(1):90–3.
98. Becker BA. Pharmacologic activity of phentermine (phenylt-butylamine). Toxicol Appl Pharmacol 1961;3(2):256–9.
99. Khalil NY, AlRabiah HK, AL Rashoud SS, et al. Topiramate: comprehensive profile. Profiles Drug Subst Excipients Relat Methodol 2019;44:333–78.
100. Glauser TA. Topiramate. Epilepsia 1999;40(Suppl 5):s71–80.
101. CK F, KL M, KD R, et al. Topiramate for weight reduction in adolescents with severe obesity. Clin Pediatr (Phila) 2015;54(1):19–24.
102. Berman C, Naguib M, Hegedus E, et al. Topiramate for weight management in children with severe obesity. Child Obes 2023;19(4).
103. Johnson DB, Quick J. Topiramate and phentermine. StatPearls 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK482165/. [Accessed 11 June 2023].
104. Dhillon S. Phentermine/Topiramate: Pediatric First Approval. Pediatr Drugs 2022;24(6):715–20.
105. Kelly AS, Bensignor MO, Hsia DS, et al. Phentermine/topiramate for the treatment of adolescent obesity. NEJM evidence 2022;1(6).
106. Smith SM, Meyer M, Trinkley KE. Phentermine/topiramate for the treatment of obesity. Ann Pharmacother 2013;47(3):340–9.
107. Kiortsis DN. A review of the metabolic effects of controlled-release Phentermine/Topiramate. Hormones (Basel) 2013;12(4):507–16.
108. Lei XG, Ruan JQ, Lai C, et al. Efficacy and safety of phentermine/topiramate in adults with overweight or obesity: a systematic review and meta-analysis. Obesity 2021;29(6):985–94.
109. Hsia DS, Gosselin NH, Williams J, et al. A randomized, double-blind, placebo-controlled, pharmacokinetic and pharmacodynamic study of a fixed-dose combination of phentermine/topiramate in adolescents with obesity. Diabetes Obes Metabol 2020;22(4):480–91.
110. Tek C. Naltrexone HCl/bupropion HCl for chronic weight management in obese adults: patient selection and perspectives. Patient Prefer Adherence 2016;10:751–9.
111. Ozkan B, Bereket A, Turan S, et al. Addition of orlistat to conventional treatment in adolescents with severe obesity. Eur J Pediatr 2004;163(12):738–41.
112. Chanoine JP, Hampl S, Jensen C, et al. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. JAMA 2005;293(23):2873–83.
113. Caklili OT, Cesur M, Mikhailidis DP, et al. Novel anti-obesity therapies and their different effects and safety profiles: a critical overview. Diabetes Metab Syndr Obes 2023;16:1767–74.
114. Chakhtoura M, Haber R, Ghezzawi M, et al. Pharmacotherapy of obesity: an update on the available medications and drugs under investigation. EClinicalMedicine 2023;58.
115. Naltrexone/bupropion for obesity. Drug Therapeut Bull 2017;55(11):126–9.
116. Masarwa R, Brunetti VC, Aloe S, et al. Efficacy and safety of metformin for obesity: a systematic review. Pediatrics 2021;147(3).
117. Clément K, van den Akker E, Argente J, 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(12):960–70.

118. Wabitsch M, Farooqi S, Flück CE, et al. Natural history of obesity due to POMC, PCSK1, and LEPR deficiency and the impact of setmelanotide. J Endocr Soc 2022;6(6):bvac057.
119. Ryan DH. Next generation antiobesity medications: setmelanotide, semaglutide, tirzepatide and bimagrumab: what do they mean for clinical practice? J Obes Metab Syndr 2021;30(3):196–208.
120. Bairdain S, Samnaliev PhD M. Cost-effectiveness of adolescent bariatric surgery. Cureus 2015;7(2).
121. Klebanoff MJ, Chhatwal J, Nudel JD, et al. Cost-effectiveness of bariatric surgery in adolescents with obesity. JAMA Surg 2017;152(2):136–41.
122. Xanthakos SA, Jenkins TM, Kleiner DE, et al. High prevalence of nonalcoholic fatty liver disease in adolescents undergoing bariatric surgery. Gastroenterology 2015;149(3). 623e8-634.e8.
123. Fittipaldi-Fernandez RJ, Guedes MR, Galvao Neto MP, et al. Efficacy of intragastric balloon treatment for adolescent obesity. Obes Surg 2017;27(10):2546–51.
124. Abu Dayyeh BK, Bazerbachi F, Vargas EJ, et al. Endoscopic sleeve gastroplasty for treatment of class 1 and 2 obesity (MERIT): a prospective, multicentre, randomised trial. Lancet 2022;400(10350):441–51.
125. Bazerbachi F, Vargas EJ, Rizk M, et al. Intragastric balloon placement induces significant metabolic and histologic improvement in patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2021;19(1):146–54.e4.
126. Chandan S, Mohan BP, Khan SR, et al. Efficacy and Safety of Intragastric Balloon (IGB) in Non-alcoholic Fatty Liver Disease (NAFLD): a Comprehensive Review and Meta-analysis. Obes Surg 2021;31(3):1271–9.
127. Abu Dayyeh BK, Kumar N, Edmundowicz SA, et al. ASGE Bariatric Endoscopy Task Force systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies Prepared. Gastrointest Endosc 2015;82(3):425–38.e5.
128. Alqahtani A, Elahmedi M, Alqahtani YA, et al. Endoscopic sleeve gastroplasty in 109 consecutive children and adolescents with obesity: Two-year outcomes of a new modality. Am J Gastroenterol 2019;114(12):1857–62.
129. Piester TL, Jagtap N, Kalapala R. Review of paediatric obesity and non-alcoholic fatty liver disease—A focus on emerging non-pharmacologic treatment strategies. Pediatr Obes 2023;18(10).
130. De Peppo F, Caccamo R, Adorisio O, et al. The Obalon swallowable intragastric balloon in pediatric and adolescent morbid obesity. Endosc Int Open 2017; 05(01):E59–63.
131. Lorber J. Obesity in childhood. A controlled trial of anorectic drugs. Arch Dis Child 1966;41(217):309–12.
132. Rauh JL, Lipp R. Chlorphentermine as an anorexigenic agent in adolescent obesity. Report of its efficacy in a double-blind study of 30 teen-agers. Clin Pediatr (Phila) 1968;7(3):138–40.
133. Ali Ibrahim AI, Mendoza B, Stanford FC, et al. Real-world experience of the efficacy and safety of phentermine use in adolescents: a case series. Child Obes 2022. https://doi.org/10.1089/CHI.2022.0147.
134. Fox CK, Kaizer AM, Rudser KD, et al. Meal replacements followed by topiramate for the treatment of adolescent severe obesity: A pilot randomized controlled trial. Obesity 2016;24(12):2553–61.
135. Consoli A, Çabal Berthoumieu S, Raffin M, et al. Effect of topiramate on eating behaviours in Prader-Willi syndrome: TOPRADER double-blind randomised placebo-controlled study. Transl Psychiatry 2019;9(1).

136. Kelly AS, Auerbach P, Barrientos-Perez M, et al. A randomized, controlled trial of liraglutide for adolescents with obesity. N Engl J Med 2020;382(22):2117–28.
137. Bensignor MO, Bomberg EM, Bramante CT, et al. Effect of liraglutide treatment on body mass index and weight parameters in children and adolescents with type 2 diabetes: Post hoc analysis of the ellipse trial. Pediatr Obes 2021;16(8).
138. Kelly AS, Metzig AM, Rudser KD, et al. Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. Obesity 2012; 20(2):364–70.
139. Fox CK, Clark JM, Rudser KD, et al. Exenatide for weight-loss maintenance in adolescents with severe obesity: A randomized, placebo-controlled trial. Obesity 2022;30(5):1105–15.