Clinical Considerations Regarding the Use of Obesity Pharmacotherapy in Adolescents with Obesity

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A growing number of youth suffer from obesity and in particular severe obesity for which intensive lifestyle intervention does not adequately reduce excess adiposity. A treatment gap exists wherein effective treatment options for an adolescent with severe obesity include intensive lifestyle modification or metabolic and bariatric surgery while the application of obesity pharmacotherapy remains largely underutilized. These youth often present with numerous obesity-related comorbid diseases, including hypertension, dyslipidemia, prediabetes/type 2 diabetes, obstructive sleep apnea, nonalcoholic fatty liver disease, musculoskeletal problems, and psychosocial issues such as depression, anxiety, and social stigmatization. Current pediatric obesity treatment algorithms for pediatric primary care providers focus primarily on intensive lifestyle intervention with escalation of treatment intensity through four stages of intervention. Although a recent surge in the number of Food and Drug Administration-approved medications for obesity treatment has emerged in adults, pharmacotherapy options for youth remain limited. Recognizing treatment and knowledge gaps related to pharmacological agents and the urgent need for more effective treatment strategies in this population, discussed here are the efficacy, safety, and clinical application of obesity pharmacotherapy in youth with obesity based on current literature. Legal ramifications, informed consent regulations, and appropriate off-label use of these medications in pediatrics are included, focusing on prescribing practices and prescriber limits.

Introduction

Purpose: rationale for formulation of opinion statement on use of medications to treat pediatric obesity

An independent panel of 12 pediatric obesity medicine and obesity surgery specialists identified an urgent and time-sensitive gap of evidence-based guidance on the clinical use of obesity pharmacotherapy in adolescents. Until such a time when additional scientific evidence is generated justifying the creation of clinical guidelines, this group of experts felt it necessary to develop an initial clinical road map for the practical application of obesity pharmacotherapy in pediatric tertiary care centers in the form of an opinion statement. The paper, in essence, reflects the views of the authors. The overall

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goals were to build a framework to (1) review published data about pediatric obesity pharmacotherapy (what is known and what is not known); (2) have an intelligent, well-informed discussion regarding the fact that, though these medications are approved in adults, there are limited safety, efficacy, and follow-up data in youth with obesity but that the consequences as well as risks of obesity may outweigh the potentially unknown risks of medications in these youth; (3) recommend that these obesity medications currently be used only by well-trained experts in a team interdisciplinary environment with conscientious monitoring; and (4) advocate for more research resources for pharmacological intervention trials in youth with obesity to provide data for the use of these medications.

State-specific rules and regulations beyond routine standard of care on weight-management practices in adults and children were determined by contacting individual State Medical Boards through either phone calls and/or email exchanges with the respective state's Department of Health prosecuting attorney or representative (online Supporting Information Table S1).

Currently, almost one out of five youth (18.5%) are afflicted with obesity (1), and 9.5% of adolescents have severe obesity (BMI ≥ 120% of the 95th percentile or ≥ 35 kg/m^2) (2). Treatment of childhood obesity is complicated by its intricate and multifactorial etiology with a myriad of contributing factors, including, but not limited to, genetics, developmental effects, fetal programming and epigenetics, environment, behavioral and psychosocial issues, physical activity, medications, eating patterns, illness, and cultural and family norms (3). Adolescent overweight and obesity have been associated with deteriorating cardiometabolic health, increased cardiovascular mortality, and future disease burden into adulthood (4-7) and strongly predict diabetes mortality up to the seventh decade (8). Furthermore, children and adolescents with obesity have lower health-related quality of life compared with children and adolescents with normal weight, a quality of life similar to those with cancer (9), and suffer from detrimental psychosocial stigmatization (10-12). Finally, obesity tracks strongly from childhood to adolescence and later adulthood, and reversion from having severe obesity to having moderate obesity or normal weight during childhood is rare (5,13,14).

Many studies have shown that only 2% to 15% of adolescents with severe obesity respond to lifestyle modification therapy and achieve clinically significant and durable weight or BMI reduction (15-19). Therefore, prompt recognition, evaluation, and treatment of obesity are warranted, including swift initiation of intensive lifestyle intervention with appropriate application of pharmacological and/or surgical modalities as needed. Pharmacotherapy and metabolic and bariatric surgery (MBS) for youth with obesity fall under the domain of Stage 3 and Stage 4 tertiary care intervention, respectively. In this staged approach, pharmacotherapy and/or MBS are further integrated with lifestyle modification in a stepwise progression.

Reflecting an increased understanding of the underpinnings of the complex energy regulatory pathways, there are now six Food and Drug Administration (FDA)-approved medications for the indication of obesity in adults (orlistat, phentermine, phentermine/topiramate extended release [ER], lorcaserin, bupropion sustained release [SR]/naltrexone SR, and liraglutide) (20). Obesity medications are FDA approved in adults 18 years and older (with the exception of orlistat [≥ 12 years] and phentermine [> 16 years]) for BMI ≥ 27 with the presence of at least one obesity-related comorbidity such as hyperlipidemia, sleep apnea, type 2 diabetes mellitus, or hypertension or BMI ≥ 30 irrespective of comorbidities. This major milestone in the development and recent approval of obesity pharmacotherapy paves a pathway for potential future pediatric obesity clinical trials and the burgeoning field of pediatric obesity medicine that is still in its infancy. Pharmacotherapy for obesity in conjunction with lifestyle therapy has the potential to target physiological hunger, cravings, appetite, and hedonic eating behaviors and elicit weight loss through the peripheral and central nervous systems, including reward–motivation pathways and executive decision-making function, that control food intake and satiety through efferent and afferent signaling cascades (20). However, long-term use, durability of effect, and safety profile might prompt concerns, especially when applied to the pediatric population, for whom treatment with pharmacotherapy is likely chronic. Therefore, determining overall risk:benefit ratios can be an arduous task for the clinician, particularly when no current consensus or structured guideline exists for pediatric obesity pharmacotherapy. The rapidly growing number of youth with this serious and intractable chronic disease hastens the need for more aggressive treatment, including pharmacotherapy. Moreover, the therapeutic application of obesity pharmacotherapy in pediatrics is not standardized across all practitioners, though there is consensus among pediatric obesity medicine specialists who routinely utilize available adult FDA-approved obesity medications and recognize the benefits of treatment in certain phenotypes of severe obesity, which has not yet been studied in clinical trials. *Consequently, we offer practical considerations regarding the responsible use of obesity medications by trained pediatric obesity medicine specialists in pediatric obesity care centers, taking into account existing evidence (unfortunately, currently limited), legal ramifications, and pertinent prescriber- and prescribing-related concerns. We also highlight a revised and updated clinical approach to the treatment of pediatric obesity (Figure 1). Though we outline the difficulty in the treatment of pediatric obesity once the diagnosis has been established, preventive measures to combat obesity cannot be understated.*

Definitions

The generally accepted measure for clinical screening of overweight or obesity in children and adolescents is age- and sex-adjusted BMI plotted on US Centers for Disease Control and Prevention growth charts (21-23). For the purposes of classification and terminology (Table 1), "obesity" in children and adolescents is defined as BMI-for-age/sex ≥ 95th percentile but < 120% of the 95th percentile (Class I obesity), and "severe obesity" is defined as BMI-for-age/sex ≥ 120% of the 95th percentile (Class II or higher; BMI > 35) (24). This terminology was derived as per Flegal et al., in 2009, when extreme percentiles extrapolated from the Centers for Disease Control and Prevention-supplied lambda-mu-sigma parameters did not match well to the empirical data for the 99th percentile (25). A better fit to the empirical data was obtained by using 120% of the smoothed 95th percentile. Furthermore, because we offer obesity pharmacotherapy clinical considerations in the context of adolescents, we define adolescence according to the World Health Organization definition (26) and the US Department of Health and Human Services definition (27), for which adolescence is the period of development corresponding to the onset of physiologically normal puberty and ending with adult identity and behavior, spanning ages 10 to 19. We also define intensive lifestyle modification therapy as per widely accepted guidelines (24,28-30), with the general aim of helping patients adopt healthier eating habits, increase physical activity, and decrease sedentary time while changes are made in stepwise progression and treatment (individual, group, and/or family based) is intensified if needed.
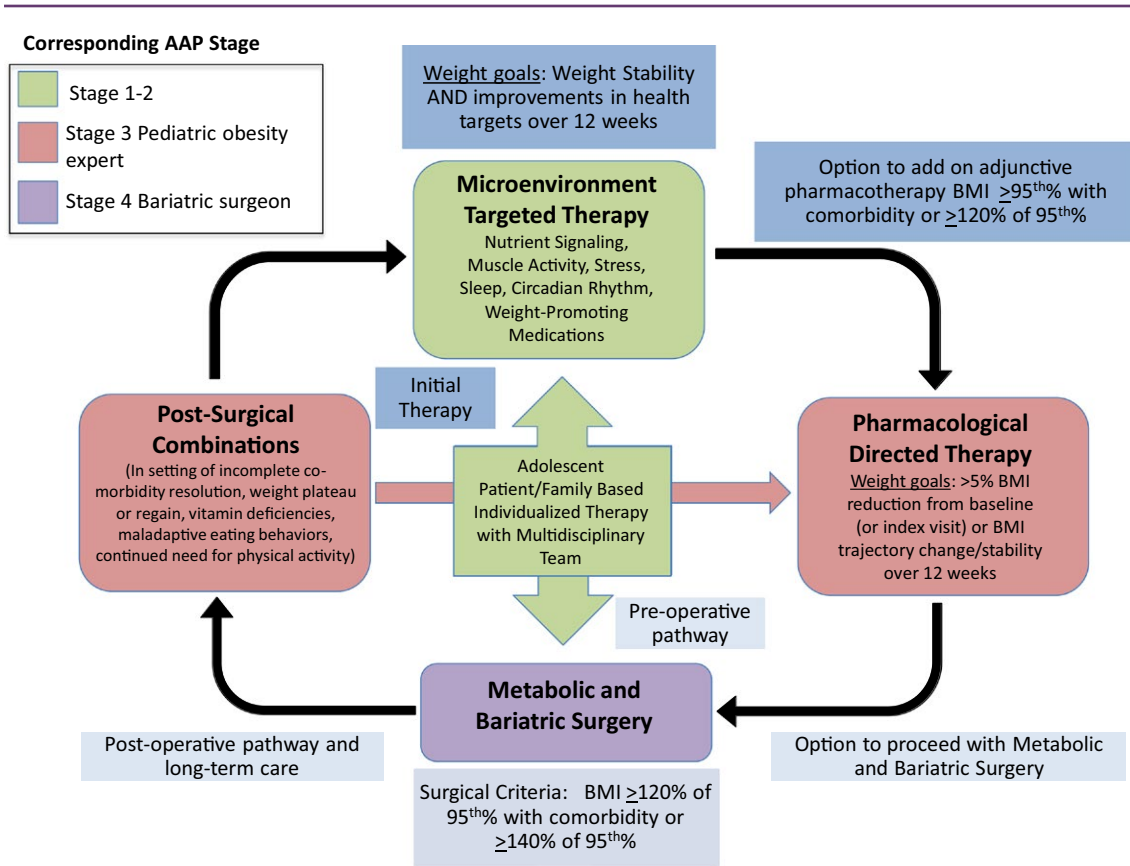
Figure 1 Proposed clinical approach to obesity treatment for adolescents with obesity. Progress through algorithm as clinically required for a patient with risk factors/ready to make change. Start with family-based therapy (can encompass basic education to more intensive therapy based on resources, time constraints, and psychosocial support) followed by microenvironment-targeted therapy with the help of ancillary services such as a dietitian, exercise specialist, nutritionist, and therapist if initial therapy is unsuccessful. Modifiable microenvironmental factors (20), such as nutrient signaling, muscle activity, sleep, stress, circadian rhythm, and iatrogenic causes (weight-promoting medications, which are frequently prescribed (60)), influence neurohormonal pathways affecting food intake and satiety. Prior to more aggressive intervention, these factors should be assessed and altered if perturbing the physiology leading to excess body fat accumulation. This may include physician and ancillary team evaluation providing more intense structure to weight management and medical evaluation with assessment of health targets and cardiovascular risk factors (usually prompting a corresponding AAP Stage 2-3 referral for intervention (24)). If microenvironment-targeted therapy fails, the option to add on adjunctive obesity pharmacotherapy falls under the domain of corresponding AAP Stage 3-4 intervention, either preceded or followed by metabolic and bariatric surgery (corresponding to AAP Stage 4 intervention). Because obesity is a lifelong disease, patients often experience weight regain post bariatric surgery and may continue to need aftercare more closely, especially in the adolescent population. As a result, they should continue to resume aftercare and may require lifestyle and/or combination pharmacological intervention later on in life. AAP, American Academy of Pediatrics.

Measuring clinical efficacy of obesity pharmacotherapy in pediatrics: percent BMI reduction

For children and adolescents, clinically meaningful weight loss based on observational and interventional studies has been defined by some as a BMI z score (or BMI SD) reduction between 0.20 and 0.25 SD over 6 to 12 months. This degree of BMI change has been associated with improvements in cardiovascular and metabolic risk factors (31-34). However, in children and adolescents with severe obesity, BMI z score correlates poorly to adiposity, with wide variation associated with differences in age, sex, and racial influences (5,35-37). Accordingly, alternative measures for monitoring weight outcomes have been recommended, including percent change in BMI and/or change in BMI

TABLE 1 BMI-for-age/sex percentile classification in pediatrics[a]

Underweight ($<$ 5th percentile)

Normal weight (5th to $<$ 85th percentile)

Overweight (85th to $<$ 95th percentile)

Obesity Class I (95th percentile to $<$ 120% of the 95th percentile)

Severe obesity Class II (120% to $<$ 140% of the 95th percentile or BMI 35.0 to $<$ 40.0 kg/m^2)

Severe obesity Class III ($\geq$ 140% of the 95th percentile or BMI $\geq$ 40.0 kg/m^2)

[a]Skinner AC, Perrin EM, Skelton JA. Prevalence of obesity and severe obesity in US children, 1999-2014. *Obesity (Silver Spring)* 2016;24:1116-1123.

TABLE 2 Criteria for obesity pharmacotherapy[a,b] initiation in adolescents[c]

(1) Multidisciplinary team recommended

(2) BMI ≥ 95th percentile (or BMI ≥ 30 kg/m^2, whichever is lower) plus the presence of at least one obesity-related comorbidity; or BMI ≥ 120% of 95th percentile (or BMI > 35 kg/m^2, whichever is lower) irrespective of comorbidity

(3) No upper BMI threshold for initiation of pharmacotherapy[d]

(4) Documentation of previous lifestyle therapies or attempts at initial medical encounter sufficient as proof of prior lifestyle intervention[c]

(5) Tanner stage[e,f]: no lower limit unless evidence suggests developmental risk of specific agent being prescribed

(6) Criteria for bariatric surgery are met, yet operation is not appropriate or possible at this time or medications are recommended as adjunct therapy

(7) Continuation of medication(s) if there is ≥ 5% BMI reduction from baseline at 12 weeks on the optimal dose or arrest or slowing of weight gain is considered a reasonable clinical outcome; medication(s) should be discontinued if not tolerated by the patient or if dangerous side effects occur or persist despite dose adjustment

[a]Exclusion criteria and contraindications may require astute clinical skills and complex decision-making prompting consultation of trained multidisciplinary team.
[b]Definition of adolescence age varies: World Health Organization, 10-19 years; US Department of Health and Human Services, 10-19 years; American Academy of Pediatrics, 11-21 years.
[c]Of note, exceptions may apply in select cases involving younger patients for whom clinical decision-making and consultation of multidisciplinary team on risk:benefit ratio is necessary.
[d]However, in cases of severe clinical severity, such as BMI > 120th of 95th percentile with at least one comorbidity or > 140th of 95th percentile in the absence of comorbidity, one should consider long-term goals and initial BMI in order to involve a bariatric surgeon early if surgery is likely also needed.
[e]In select cases, exceptions may apply such that clinical decision-making may be necessary in the case of serious health compromise (such as moderate to severe obstructive sleep apnea hypopnea index > 15 events/h, idiopathic intracranial hypertension poorly controlled type 2 diabetes mellitus) related to severe obesity that warrants more emergent intervention.
[f]Tanner stage 4-5 is advisable, though clinical judgment should be utilized on an individual patient basis if benefits outweigh risks of treatment. Clinical decision-making may be required when benefits far outweigh risks of obesity pharmacotherapy. Effects of obesity medications on puberty and Tanner staging are largely not known.

percent of the 95th percentile (35). A change in BMI z score of 0.2 is approximately equivalent to a 5% change in BMI. (Similarly, for adults, 3%-5% weight loss is considered clinically meaningful) (20).

Recommendations (Table 2)

Pediatric weight-management multidisciplinary team

We recommend that prescription of FDA-approved or off-label use of obesity medications be utilized with the support of a trained pediatric multidisciplinary team and monitoring of both treatment adherence and possible adverse events. The multidisciplinary team is also responsible for comprehensive obesity assessment and treatment recommendations for youth with obesity. Exclusions for obesity pharmacotherapy (e.g., pregnancy) and cautionary use (e.g., as in children with growth deficiency, other endocrinopathies, eating disorders, syndromes affecting bone health) may require astute clinical skills and complex decision-making prompting consultation of a multidisciplinary weight team and other specialists.

Team member qualifications

Team member qualifications for a pediatric weight-management center are similar to those required for adolescent MBS and are adapted from the American Society of Metabolic and Bariatric Surgery Pediatric Best Practice Guidelines (38).

Pediatric specialist. The trained or certified pediatric provider will hold an American Board of Pediatrics (or American Board of Surgery with pediatric surgery subspecialization) certification or appropriate family medicine or nurse practitioner or physician assistant certification eligible to practice under state-mandated rules and regulations. Currently, fellowship training and board certification in nutrition and in pediatric obesity are lacking. Training in pediatric cardiology, pediatric endocrinology, pediatric gastroenterology, adolescent medicine, pediatric surgery, general academic pediatrics, or general pediatrics with a focus study area such as in nutrition, lifestyles, motivational interviewing (39-41), and obesity represent the most common routes to expertise in the field of pediatric obesity. Frequent and continuing clinical care of patients with obesity, ongoing continuing medical education in pediatric obesity medicine, scholarly work in obesity research or education, and certification by entities such as the American Board of Obesity Medicine or the American Board of Nutrition can enhance advanced understanding of obesity. In general, these activities currently serve to designate experts in the field of pediatric obesity care. Primary care and subspecialty pediatricians without this expertise should refer to their colleagues with these skills and experience. Given the extensive prevalence of obesity, protocols and guidelines should be developed in the future wherein practitioners without expertise can be trained.

Registered dietitian. Experience in treating obesity and working with children and families as recommended by the Academy of Nutrition and Dietetics position statement on pediatric overweight and obesity (42); specialty certification in obesity care is available for registered dietitians (www.cdrnet.org). Experience with patients undergoing MBS may be preferable but not mandatory.

Mental health specialist. Psychiatrist, psychologist, or other qualified and independently licensed mental health specialist or social worker with specialty training in pediatric, adolescent, and family treatment and experience in treating eating disorders and obesity; certification examination such as through the International Association of Eating Disorders is suggested to enhance coverage for mental health services. Professionals trained in intensive cognitive behavioral therapy for obesity can effectively design and lead lifestyle modification programs.

Coordinator. Registered nurse, social worker, or other team member with the responsibility of coordinating the care for each child or adolescent and ensuring implementation of treatment plan and follow-up.

Exercise physiologist, physical therapist, or other individual specially trained to provide safe physical activity prescriptions to adolescents with severe obesity is recommended but not required.

Collaboration with the metabolic and bariatric surgeon. Pediatric surgeons who specialize in MBS, and/or adult bariatric surgeons who choose to include the treatment of adolescents

at their center by establishing a comprehensive adolescent obesity program in accordance with current accreditation guidelines put forth by the American College of Surgeons-Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program, are recommended if such expertise is accessible but not required for pharmaceutical obesity therapy.

Patient selection

BMI criteria. Pharmacotherapy is often considered to be a lower-risk and less invasive form of therapy than surgical intervention, in which a child may be exposed to risks of anesthesia (43) and potentially other complications (44,45). Established criteria for adult obesity pharmacotherapy utilize a lower BMI threshold (BMI > 27 with the presence of at least one obesity-related comorbidity [such as diabetes, sleep apnea, hypertension, or hyperlipidemia] or BMI > 30 with or without comorbidity) than MBS. For MBS, the adult criteria (BMI 35-39.9 in the presence of serious comorbidities or BMI ≥ 40 with or without comorbidity) are already recommended for adolescent indications (> 120% of the 95th percentile or BMI ≥ 35 with comorbidity, or > 140% of the 95th percentile or BMI ≥ 40 with or without comorbidity) (46).

We propose similarly that, for pharmacotherapy, the adult criteria should be modified for pediatric indications, i.e., when BMI is in the obese range (≥ 95th percentile for age and sex or BMI > 30 [whichever is lower]; Class I obesity) in the presence of at least one obesity-related comorbidity or when it is in the severe obesity range (≥ 120% of 95th percentile for age and sex or BMI > 35 [whichever is lower]; Class II and Class III obesity) irrespective of the presence of comorbidities. Of note, although adult clinical trials (20) studying obesity pharmacotherapy have recruited patients in the BMI range of 27 to 45, the efficacy of these drugs may decrease with the clinical severity of BMI given the complex progression of the disease state (47). Because no upper BMI threshold is mentioned for the practical application of obesity pharmacotherapy, one should consider the initial BMI and long-term goals to assess the need for early involvement of a bariatric surgeon if MBS is likely needed, especially in adolescents with BMI ≥ 120% of the 95th percentile with the presence of an obesity-related comorbidity or ≥ 140% of the 95th percentile with less severe comorbid conditions (45,48-50).

Age considerations. With regard to age, there are currently no data defining a lower limit for the application of pharmacotherapy or MBS in the pediatric population. The European Medicines Agency suggests that medication could be considered for children with severe obesity as young as 6 years of age (51), and the 2018 adolescent MBS guidelines adopted the lower limit of 10 years (46), consistent with the World Health Organization (26) and the US Department of Health and Human Services definition of adolescence (ages 10-19) (27). Furthermore, FDA-approved obesity pharmacotherapy is applicable to adults age 18 and older, which, interestingly, includes older "adolescents" as per the World Health Organization definition. Specifically, two obesity medications (orlistat and phentermine) are already FDA approved in younger adolescents. Notably, there are discrepancies in the definition of adolescence, and the American Academy of Pediatrics strongly discourages the establishment of arbitrary age limits in pediatric care by health care providers due to the multifaceted approach encompassing a child's overall physiological, physical, developmental, psychosocial,

and mental health (52). Care delivery must take into account the needs of the child and direct the provider to meet those needs. Of note, particularly in cases involving younger patients, clinical decision-making and consultation of a multidisciplinary team on risk:benefit ratio is paramount.

Intensive lifestyle therapy considerations. Intensive lifestyle therapy (without pharmacotherapy) can result in clinically meaningful weight loss in the short term in younger children (< 10-12 years), but older youth tend to respond less favorably to lifestyle intervention and have higher onset of disease progression with the development of comorbidities (15,16,19,53). Combining intensive lifestyle intervention with pharmacotherapy may have enhanced synergistic or additive weight-loss effects in patients with obesity as demonstrated in obesity pharmacotherapy trials (20,54,55). We recommend that documentation of previous (structured) attempts at lifestyle therapy upon initial encounter is sufficient as proof of nonresponse to lifestyle alone prior to consideration of obesity pharmacotherapy. It is understood that healthy behaviors and lifestyle modification be continued in conjunction with pharmacotherapy or MBS.

Growth and development considerations. Obesity affects adolescent growth and development (56,57). In girls, higher BMI is associated with earlier menarche age (58). If the medication being prescribed is known to interfere with normal pubertal progressions, Tanner stage (sexual maturity rating) is a particularly relevant factor to consider (59), although no lower limit of adolescent age is suggested unless evidence points to developmental risks of specific agents being prescribed. Certainly there is a paucity of data with regard to obesity medications on pubertal development as well as long-term effects on developing adolescent brain; further research and long-term studies are needed.

Clinical decision-making. Clinical decision-making is required when benefits far outweigh risks of obesity pharmacotherapy, such as in an adolescent with several obesity-related medical comorbidities and severe obesity. Clinical presentation of the patient is vital in pharmacotherapeutic selection, with dose titration for maximum benefit with minimal adverse effects. The patient is assessed for potential safety concerns and is followed closely during the medical management visits. Obesity pharmacotherapy should not be initiated in the setting of severe psychiatric disturbance, eating disorders such as bulimia, untreated endocrinopathies, or with concomitant use of medications that have adverse interactions. Furthermore, discontinuation or substitution of medications associated with weight gain with weight-neutral alternatives before initiation of obesity pharmacotherapy is a critical consideration. Because obesity is a chronic disease, long-term treatment and follow-up care will be necessary (potentially lifelong). One can expect a rebound in weight and disease pathology if treatment is discontinued. Patients and family members should be counseled on the long-term use of obesity pharmacotherapy and disease chronicity along with lifelong lifestyle modification.

Decision to continue or discontinue obesity pharmacotherapy. We also recommend that the medication be continued if there is ≥ 5% BMI reduction from baseline at 12 weeks on the optimal dose or if arrest or slowing of weight gain is considered to be a reasonable clinical outcome, especially as linear growth

occurs in adolescence. The medication should be discontinued if not tolerated by the patient or dangerous side effects occur or persist despite dose adjustment. This algorithm is consistent with adult and pediatric guidelines that recommend discontinuation of an obesity medication, at maximum appropriate dose, if less than 5% weight loss/ BMI reduction from baseline is achieved within 12 weeks (60-62). When a medication or a combination is started, it can be continued longer term based on therapeutic benefit, improvement of psychosocial comorbidities, tolerability, absence of or acceptable side effects, cardiovascular stability, and minimal effects on growth development and neurocognitive function with monitoring.

Assessment and safety. The initial medical encounter includes a thorough clinical history and physical examination with documentation of Tanner stage, hemodynamics, and anthropometric measurements. Eating behaviors and dietary intake, family patterns, cultural cues, sleep hygiene and disorders screening, school history, and psychological or neuropsychiatric metrics are assessed. In addition to usual laboratory evaluation recommended in the context of obesity (24), other laboratory assessments may be needed to monitor for side effects related to a given pharmacotherapy. Close follow-ups are recommended after the initial encounter. Pubertal stage, height, and weight should be serially measured at all follow-up visits to monitor for disruptions in pubertal development and linear growth. Because most obesity medications act through central nervous system pathways that may disrupt or affect neuropsychiatric axis, cognition and mood should be evaluated in the form of a clinical interview about school grades, concentration, memory, and worsening depression and/or anxiety at serial follow-up visits. Standardized clinical tools to track these potential side effects also need to be developed in the future. Given greater suicidality and depression risk among youth with obesity compared with youth of normal weight, specific medications that may precipitate suicide or depression occurrence (e.g., such as bupropion or topiramate) also warrant uniform screening for these conditions upon the initial assessment and during subsequent follow-up visits (63).

Understanding off-label drug use in pediatrics. Off-label drug use involves the prescription of medications for indications, or using a dosage or dosage form, that have not been approved by the FDA. Off-label drug use is especially common in pediatrics, a population for which conducting clinical trials might be challenging (64-69). More recently, in 2014, the American Academy of Pediatrics released a statement regarding off-label use of pharmaceuticals in children (64): "Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient." Because obesity medications are FDA approved for ages ≥ 18 (with the exception of orlistat [age ≥ 12] and phentermine [age > 16]), prescription of obesity medications in youth meeting patient selection criteria falls under the domain of off-label drug use. Because of limited efficacy and safety data in children coupled with potential unknown side effects, we caution off-label drug use in children. Though it is difficult to provide a generalized statement supporting or not supporting off-label drug use in pediatric obesity, we provide recommendations, based on our own combined clinical experience, regarding off-label use for specific medications as described in the pharmacotherapy section of this paper. Oftentimes, off-label drug use in pediatric obesity depends on the clinical presentation, age, medical comorbidities, family history, social history, etc., among other factors influencing benefit:risk ratio and clinical decision-making.

Medical malpractice: informed consent and negligence. Previous legal claims involving physicians due to adverse reactions related to off-label drug use have primarily involved the use of a research drug (not yet FDA approved), failure to provide informed consent for an off-label drug use, and medical negligence leading to direct harm to the individual patient. To date, court systems have not mandated a formal informed consent process for off-label drug use due to concerns about impingement of direct patient care and impediments to communications along with unnecessary concerns or alarms elicited to the individual patient and/or family members involved (65). We therefore recommend standard informed consent (and assent) documentation within the electronic medical record describing (1) that the conversation about off-label drug use occurred, (2) that the patient/family member(s) understand risks and benefits, (3) the potential major and minor drug side effects reviewed, (4) confirmation of the absence of contraindications to the drug, (5) that appropriate follow-up care was advised, 6) that the patient/family member(s) understand how to reach the medical provider should questions or concerns arise, and (7) that urgent medical attention was advised for emergencies including suicidal ideation and worsening depression. The clinical care team must also recognize the youth's cognitive, emotional, and social development and take this into consideration when obtaining assent in the shared decision-making process. Online Supporting Information Table S1 outlines the various medical-legal concerns with respect to individual State Medical Board rules and regulations surrounding weight management. Most states follow standard of care, with specific statutes and bylaws in some states. Obesity practitioners must understand and follow their respective state's rules and regulations.

Available Pharmacotherapy (FDA-Approved and Off-Label Drug Use for Obesity in Pediatrics)

Evidence for obesity medications in children is limited in scope due to the relatively small number of clinical trials conducted and small number of participants included in many of the trials; recent meta-analyses and systematic reviews have reported overall minimal or no benefit of obesity pharmacotherapy in children (62,70). However, an obesity specialist is well trained in the clinical application of obesity pharmacotherapy for successful therapeutic benefit (20). Furthermore, patient criteria, obesity phenotype, contraindications, and side effect profile must be considered when selecting specific agents for a pediatric patient. Table 3 provides a summary of the efficacy, safety, and clinical insights into the application of FDA-approved adult obesity medications and off-label drug use of specific, highly utilized medications in the pediatric obesity population.

FDA-Approved Obesity Medications in Pediatrics

Orlistat. This medication is FDA approved for treatment of obesity for ≥ 12 years of age. The mechanism of action is pancreatic and gastric lipase inhibitor.

- **Efficacy.** In a recent pediatric meta-analysis (31) involving 779 adolescents ages 12 to 18 with a baseline average BMI of 37.4 kg/m^2, there were small BMI differences between orlistat and placebo

TABLE 3 Summary of Food and Drug Administration-approved and commonly* prescribed medications for weight loss in pediatric population

Drug name	Mechanism of action	Original FDA indication	Off-label drug use	Side effects	Contraindications/warnings	Adolescent weight-loss outcomes data	Reference
FDA approved							
Orlistat	Pancreatic and gastric lipase inhibitor	Obesity ≥12 years of age	Not indicated	Flatulence, oily spotty stools, diarrhea, vitamin/mineral deficiency; Effects on Tanner stage: none reported (78)	Chronic malabsorption syndrome, cholestasis	Placebo-subtracted weight loss of 2.61 kg at 1 year	54, 71
Phentermine	Sympathomimetic amine	Obesity >16 years of age for "short term" based on 1959 labeling; combination phentermine/topiramate ER approved for long-term treatment of obesity in adults	<16 years of age or long term; beneficial in obesity with low-energy states, sleep apnea, hunger, decreased satiety	Increases in heart rate, blood pressure, dry mouth, insomnia, constipation, worsening anxiety, irritability; Effects on Tanner stage: not known	Cardiovascular disease hyperthyroidism, active drug use, glaucoma, agitated states	BMI reduction of 4.1% at 6 months	55
Not FDA indicated for obesity							
Metformin*	Activation of protein kinase pathway	≥10 years of age for type 2 diabetes mellitus	Polycystic ovarian syndrome, insulin resistance, prediabetes, metabolic syndrome, antipsychotic-medication-induced weight gain, stress eating/emotional eating	Bloating, diarrhea, flatulence; Effects on Tanner stage: not known	Hold 48 hours prior to contrast; lactic acidosis	BMI z score reduction of 0.10 and BMI 0.86	31
Topiramate*	Modulation of various neurotransmitters	Treatment of epilepsy >2 years of age and migraines >12 years of age; combination phentermine/topiramate ER approved for long-term treatment of obesity in adults	Weight loss in adult and pediatric patients; useful adjunct in binge eating disorders and weight regain post bariatric surgery	Cognitive dysfunction, kidney stones, metabolic acidosis; teratogenic; adolescents must be counseled against pregnancy because of decrease in efficacy of oral contraceptives; Effects on Tanner stage: unclear	Inborn errors of metabolism with hyperammonia and encephalopathy, acute myopia and secondary angle-closure glaucoma; rapid withdrawal can precipitate seizures; neuropsychiatric dysfunction, metabolic acidosis	BMI reduction of 4.9% on topiramate 75 mg daily for at least 3 months	86
Exenatide*	GLP-1 agonist	Type 2 diabetes mellitus in adults	<18 years of age for obesity (polygenic with presence of diabetes, hypothalamic, syndromic)	Bloating, nausea/vomiting, abdominal pain, elevation of pancreatic amylase and lipase; Effects on Tanner stage: not known	Postmarketing reports: pancreatitis, renal impairment, severe GI disease	BMI reduction of 3.42% at 3 months	93-95

TABLE 3 (continued).

Drug name	Mechanism of action	Original FDA indication	Off-label drug use	Side effects	Contraindications/ warnings	Adolescent weight-loss outcomes data	Reference
Liraglutide*	GLP-1 agonist	Liraglutide 3.0 mg (Saxenda) dosing approved for obesity in adults; liraglutide (Victoza) approved for type 2 diabetes in adults	<18 years of age	GI: abdominal pain, nausea, vomiting, diarrhea, potential hypoglycemia Effects on Tanner stage: not known	Postmarketing reports: pancreatitis, renal impairment, severe GI disease	Trials ongoing	101
Lisdexamfetamine§	Central nervous system stimulant	Age ≥6 years of age for ADHD; short-term use of binge eating disorder in adults	Beneficial for younger children with ADHD and obesity or binge eating disorder	Anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting Effects on Tanner stage: animal studies have shown neuroplasticity effect on peripubertal period which may negatively impact maturation of brain structures (106, 107)	Serious cardiovascular reactions such as sudden death; blood pressure and heart rate increases; psychiatric adverse reactions; suppression of growth; peripheral vasculopathy such as Raynaud's; serotonin syndrome with use of serotonergic agents	In 6- to 12-year-old age group, mean weight loss was 2.5 lb with 70-mg dose over 4 weeks; in 13- to 17-year-old age group, mean weight loss from baseline was 4.8 lb with 70-mg dose over 4 weeks	105
No pediatric data							
Lorcaserin	5-hydroxytriptamine receptor 2C agonist	Long-term treatment of obesity in adults	<18 years of age with obesity	Headache, dizziness, fatigue, dry mouth, constipation; headache, back pain, cough in patients with diabetes Effects on Tanner stage: not known	Serotonin syndrome or neuroleptic malignant-like syndrome when coadministered with other serotonergic or antidopaminergic agents; discontinue with signs of valvular heart disease	Safety and outcomes data not available for <18 years	20
Naltrexone/bupropion SR	Blockage of opioid-receptor-mediated POMC autoinhibition (naltrexone) and selective inhibition of reuptake of dopamine and noradrenaline (bupropion)	Long-term treatment of obesity in adults	Children and adolescents: WARNING for increased suicidal ideation	Nausea, constipation, headache, dizziness, insomnia, dry mouth, diarrhea Effects on Tanner stage: not known	Uncontrolled hypertension, seizures, anorexia nervosa, or bulimia, active alcohol or chronic opioid use, angle-closure glaucoma, increase in suicidal thought and ideation	Safety and outcomes data not available for <18 years	20

TABLE 3 (continued).

Pending new FDA approval

Drug name	Mechanism of action	Original FDA indication	Off-label drug use	Side effects	Contraindications/ warnings	Adolescent weight-loss outcomes data	Reference
Setmelanotide	Melanocortin-4 receptor agonist	Phase 3 trials for monogenic obesity; FDA approval pending for monogenic obesity in adults and children	None; drug will be approved for pediatric patients as well	Dry mouth, mild induration at injection site, darkening of skin nevi Effects on Tanner stage: not known	Caution use in structural heart disease and arrhythmias because of potential to increase heart rate and blood pressure	Sustainable reduction in hunger and substantial weight loss of 20.5 kg after 12 weeks in one patient and 51.0 kg in another after 42 weeks	118

GLP, glucagon-like 1 receptor; POMC, proopiomelanocortin; GI, gastrointestinal.
†Not FDA indicated for treatment of obesity but commonly prescribed by trained providers for adolescents with obesity.
§Not FDA indicated for treatment of obesity but prescribed for eating disorder.

groups: −0.94 (95% CI: −1.58 to −0.30) to −0.50 (95% CI: −7.62 to 6.62), with absolute weight changes ranging from +1 to −12 lb with orlistat. The largest randomized-controlled trial evaluating orlistat combined with a hypocaloric (30% fat calories) diet, exercise, and behavioral therapy in adolescents ($N = 352$; also included in the above meta-analyses) showed a −2.61-kg placebo-subtracted weight loss at 1 year after treatment ($P < 0.001$) (54).

- **Safety.** Gastrointestinal adverse effects were quite common with orlistat use: abdominal pain or cramps (16%-65% of participants vs. 11%-26% placebo), flatus with discharge (20%-43% vs. 3%-11% placebo), and fecal incontinence (9% vs. 0%-1% placebo); changes in glucose, insulin, and lipid profile were not statistically significant in adolescents with obesity (54,71). Rare but serious associations of hepatic and renal illness with orlistat use have been described in the product brochure (72).
- **Additional insight.** Orlistat is also available over-the-counter in a lower-dosage formulation. A multivitamin is recommended with orlistat use due to increased risks of fat-soluble vitamin and mineral deficiencies. Due to little cardiometabolic benefit, expense, and adverse tolerability in adolescents attending school where bathroom privileges may be limited, orlistat is not considered a first-line drug for the treatment of pediatric obesity as monotherapy.
- **Effects on pubertal development or puberty.** Based on data from several human studies, treatment with orlistat for 1 year does not appear to affect pubertal development or the expected increase in lean body mass during puberty (73). Longer-term studies are needed to understand the effects of orlistat on pubertal development.

Phentermine. This medication is FDA approved for age > 16 years for short-term treatment (often interpreted as 12 weeks but unspecified on the label) based on 1959 labeling, which has not been updated. Off-label drug use is recommended for obesity when used in age < 16 years or long term as monotherapy.

Combination therapy with phentermine/topiramate ER is FDA approved for chronic weight management in adults. The mechanism of action is that of a sympathomimetic amine, release of catecholamines from the hypothalamus, including insignificant dopamine release.

- **Efficacy.** A small retrospective chart review compared adolescents (mean age 16.1 ± 1.3 years) treated with phentermine 15 mg once daily plus lifestyle modification therapy ($n = 25$) to lifestyle modification therapy alone ($n = 274$) (55). The study found a −4.1% BMI reduction at 6 months (95% CI: −7.1 to −1.0%; $P = 0.009$) with phentermine plus lifestyle modification therapy compared with lifestyle therapy alone, which resulted in no changes in baseline systolic or diastolic blood pressure readings (55). This is comparable to an adult study that found −5.1% weight loss at 28 weeks with phentermine 15 mg once-daily monotherapy (74).
- **Safety.** In the same retrospective study, though no changes were elicited in baseline blood pressure measurements in the treatment arm, heart rate was higher at all time points in the phentermine group compared with lifestyle modification therapy alone for adolescents (55). Phentermine is a sympathomimetic which can cause increases in heart rate, blood pressure, nervousness, and/or insomnia. Adverse effects can also include dizziness, dry mouth, difficulty sleeping, irritability, nausea/vomiting, diarrhea, and constipation. Phentermine is contraindicated in patients with cardiovascular disease, hyperthyroidism, glaucoma, or history of drug abuse or women who are

pregnant. Phentermine should not be used while taking, and for 14 days after stopping, a monoamine oxidase inhibitor because of the risk of hypertensive crisis (20).

- **Additional insight.** Phentermine is a Class IV controlled substance, and state bylaws and statues should be followed. Baseline electrolytes, kidney function, blood pressure measurements, and heart rate need to be assessed in adolescents along with screening for congenital heart disease or other cardiac pathology, such as family history of sudden death, Wolff-Parkinson-White syndrome, and newly auscultated murmurs; obtain cardiology clearance if concerns arise prior to phentermine prescribing because there have been case reports of myocardial infarction when taking phentermine (75,76).
- **Off-label drug use.** Off-label drug-use documentation, along with consent for treatment from the patient's parent or guardian, is recommended.
- **Effects on pubertal development or puberty.** The effects of phentermine on pubertal development in humans are not known.

Non-FDA-Approved Medications for Obesity but With Pediatric Evidence

Metformin. This medication is FDA approved for ≥10 years of age for type 2 diabetes, with off-label drug use for other indications. The mechanism of action is mainly activation of activated protein kinase.

- **Efficacy.** In a meta-analysis ($N=616$) comparing the use of metformin versus placebo for weight loss as part of pediatric obesity or endocrine clinics (baseline BMI of 36.0, with metformin dose ranging from 1-2 g per day), metformin treatment reduced BMI z score (−0.10 [95% CI: −0.17 to −0.03]) and BMI (−0.86 [95% CI: −1.44 to −0.29]) (31).
- **Safety.** The medication in the same meta-analysis was well tolerated with minimal discontinuation rates (<5%), with no reported cases of lactic acidosis and hypoglycemia in children (31). Commonly reported side effects are usually gastrointestinal, including bloating, diarrhea, and flatus. Metformin-associated lactic acidosis is quite rare, with incidence estimated to be 3-10 per 100,000 person-years (77), and although quite rare, there are a few cases reports of rhabdomyolysis in the literature (78).
- **Additional insight.** Metformin is usually a first-line medication in a patient with insulin resistance, prediabetes, or metabolic syndrome given the minimal safety concerns and tolerability. Though the meta-analyses showed only a small reduction in excess weight in youth, metformin has been effective for weight regain related to antipsychotic medications (79) in nondiabetic children (−4.1% weight reduction [95% CI: 2.2-6.0]) (80) and in adults, for weight gain related to mood disorders, steroid exposure, stress eating, and emotional eating related to cognitive dysfunction, possibly related to aberrant insulin signaling, inflammation, and glucocorticoid activity, which may be emanated by iatrogenic causes (81). Metformin is extensively utilized for polycystic ovarian syndrome treatment with or without obesity diagnosis in children and adolescents, with improvement seen on lipid profile, hirsutism, and weight loss (82-84).
- **Off-label drug use.** Off-label drug-use documentation, along with consent for treatment from the patient's parent or guardian, is recommended.
- **Effects on pubertal development or puberty.** Effect of metformin on pubertal development is unknown.

Topiramate. This medication is FDA approved for the treatment of epilepsy in ≥2 years of age and migraine prophylaxis in ≥12 years old and causes weight loss in adult obesity trials. The combination obesity medication phentermine/topiramate ER is FDA approved for chronic weight management in adults. The mechanism of action is possibly through modulation of various neurotransmitters, including the inhibition of voltage-dependent sodium channels, glutamate receptors, and carbonic anhydrase and the potentiation of γ-aminobutyrate activity. Off-label drug use is recommended for obesity treatment and also binge eating disorder in adults.

- **Efficacy.** A small randomized, placebo-controlled pilot clinical trial evaluating topiramate in 30 adolescents ages 12 to 17 with severe obesity (BMI≥120% of the 95th percentile or BMI≥35) showed a 2% BMI reduction on 75 mg topiramate at 6 months, which did not reach statistical significance compared with placebo following a short-term (1-month) meal-replacement phase (−1.9%; 95% CI: −5.2% to +1.5%; $P=0.291$). Significant improvements in visceral fat and very-low-density lipoprotein cholesterol were observed in the topiramate compared with the placebo group (85). Another study, a retrospective chart review examining the effect of topiramate 75-mg once-daily dosing for at least 3 months plus lifestyle intervention on BMI reduction in adolescents with severe obesity ($N=28$; mean age 15.2 ± 2.5 years; mean baseline BMI 46.2 ± 10.3 kg/m^2), found a clinically meaningful −4.9% BMI reduction (95% CI: −7.1 to −2.8; $P<0.001$) with no significant adverse effects (86).
- **Safety.** In both trials, there were no concerning changes in neurocognitive function with low-dose topiramate in adolescents (85,86). Of the 28 patients in one of the trials, only two experienced paresthesia (86). Adult clinical trials using combination therapy with phentermine/topiramate ER reported paresthesia, depression, and anxiety as common side effects, most likely related to the topiramate component of the combination (20). The drug is a teratogen with potential to cause cleft palate and/or lip during the first trimester of pregnancy. It might also decrease the efficacy of oral contraceptives, though this is less likely at dosages <200 mg/day (20). Adolescents must be strongly counseled against pregnancy, with effective contraception in place; a monthly urine pregnancy test in all adolescents is recommended.
- **Additional insight.** Topiramate has documented efficacy in eating disorders, including binge eating (87-90), and weight regain post bariatric surgery (91). Topiramate can cause reversible cognitive and psychiatric dysfunction as well as metabolic acidosis. Adolescents with fatigue, sleep disturbances, and worsening school performance need to be evaluated for possible cognitive side effects related to topiramate. Quick withdrawal may prompt seizures in children, and therefore gradual titration downwards for discontinuation is recommended.
- **Off-label drug use.** Off-label drug-use documentation, along with consent for treatment from the patient's parent or guardian, is recommended.
- **Effects on pubertal development or puberty.** Topiramate affects BMI, weight, insulin, leptin, and adipocytokine levels in prepubertal children (92). The effect on puberty is unknown.

Glucagon-like 1 receptor agonists: exenatide and liraglutide. Exenatide is FDA approved for type 2 diabetes mellitus in adults; off-label drug use is recommended in <18 years of age. The mechanism of action is glucagon-like 1 receptor (GLP-1) agonist.

Liraglutide 3.0 mg dosing is FDA approved for obesity in adults; off-label drug use is recommended <18 years of age for patients. The mechanism of action is GLP-1 agonist.

- **Efficacy (exenatide).** In a small randomized, controlled, crossover trial of 12 adolescents and children (9-16 years of age) with severe obesity, 3 months of treatment with exenatide plus lifestyle modification therapy significantly reduced BMI (−1.7 kg/m^2 [95% CI: −3.0 to −0.4; P=0.01]), body weight (−3.9 kg [95% CI: −7.11 to −0.69; P=0.02]), and fasting insulin (−7.5 mU/L [95% CI: −13.71 to −1.37; P=0.02]) (93). In another randomized, placebo-controlled clinical trial of 26 adolescents (ages 12-19 years) with severe obesity followed by a 3-month open-label extension, treatment with exenatide elicited a greater reduction in percent change in BMI compared with placebo (−2.70% [95% CI: −5.02% to −0.37%; P=0.03]) and in body weight compared with placebo (−3.26 kg [95% CI: −5.87 to −0.66 kg; P=0.02]); during the open-label extension, BMI was further reduced in those initially randomized to exenatide (cumulative BMI reduction of 4%) (94). Pooled data (n=32; mean age 14.3±2.2 years; 69% female; mean BMI 39.8±5.8 kg/m^2) from these near identical trials showed an absolute BMI reduction of −3.42% (95% CI: −5.41 to −1.42) compared with placebo at 3 months (95).

  GLP-1 agonists may have some role in syndromic obesity such as Prader-Willi syndrome (PWS) though more robust studies are needed. A 6-month, open-label, nonrandomized longitudinal study recruited 10 patients (13-25 years) with PWS and placed them on diabetes dosing exenatide without dietary modification. Though appetite scores and hemoglobin A1c decreased significantly after treatment, weight and adiposity were unaffected, with no significant changes in ghrelin (96).

- **Safety (exenatide, liraglutide).** GLP-1 agonists such as exenatide and liraglutide have been associated with pancreatitis on postmarketing surveillance reports though this association has not been statistically significant or clearly evident (20). GLP-1 agonists have also been associated with acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis, and therefore are not recommended in severe renal impairment or end-stage renal disease and should be used with caution in renal transplant patients (97,98). Newer ER formulations such as dulaglutide have a better safety profile in renal impairment (99). GLP-1 agonists are not recommended in patients with severe gastrointestinal disease such as gastroparesis (97-100). GLP-1 agonists are contraindicated in patients with a family or personal history of medullary thyroid carcinoma or patients with multiple endocrine neoplasia type 2 (20) syndrome (100). In adolescent trials, compliance with the injection regimen was excellent (≥94%), and exenatide was generally well tolerated (the most common adverse event was mild nausea in 36%, followed by vomiting, headache, abdominal pain, and diarrhea) (93-95). Though the safety and tolerability of newer GLP-1 agonists such as dulaglutide and semaglutide have not been assessed in adolescents, these preliminary adolescent studies provide support for safety, tolerability, and feasibility of GLP-1 agonists in this patient population.

- **Safety and tolerability (liraglutide).** A randomized, placebo-controlled, double-blind study to assess safety, tolerability, and pharmacokinetics of liraglutide 3.0 mg in adolescents (12-17 years of age; Tanner staging 2-5; n=21; BMI ≥95th percentile for age and sex [30≤BMI≤45]) was recently completed (101). Adolescents were randomized (2:1) to receive 5 weeks of treatment with liraglutide (0.6 mg with weekly dose increase to a maximum of 3.0 mg for the last week; n=14) or placebo (n=7). The most common adverse events associated with liraglutide 3.0 mg dose were gastrointestinal (abdominal pain, nausea, vomiting, and diarrhea). Twelve hypoglycemic episodes occurred in eight patients, while two similar events occurred in a patient in the placebo group. Participants did not have symptoms or need assistance from another person; the hypoglycemia was found only during routine glucose monitoring (102,103). Liraglutide had a similar safety and tolerability profile compared with adults when administered to adolescents with obesity, with no unexpected safety or tolerability issues. Results suggest that the dosing regimen approved for weight management in adults may be appropriate for use in adolescents (101). Further studies evaluating the efficacy of liraglutide in the adolescent population are currently ongoing.

- **Additional insight.** GLP-1 agonist therapy has potential for weight loss and weight stabilization in patients with syndromic and hypothalamic obesity with hyperphagia. In patients with hypothalamic obesity as a result of tumor or trauma injury, exenatide therapy may help stabilize weight and increase satiety (104). GLP-1 agonist therapy is frequently considered next in line for patients with poorly controlled type 2 diabetes mellitus and obesity in conjunction with metformin and intensive lifestyle modification (60). Because insurance coverage for GLP-1 agonists may be limited in adolescents, especially for newer GLP-1 agonists, older generic analogs such as exenatide are more likely to be covered in some states for adolescents with type 2 diabetes mellitus.

- **Off-label drug use.** Off-label drug-use documentation, along with consent for treatment from the patient's parent or guardian, is recommended.

- **Effects on pubertal development or puberty.** The effects of GLP-1 agonists on puberty are unknown.

FDA-Approved Medication for Eating Disorder (Non-FDA-Approved for Obesity) but With Pediatric Evidence

Lisdexamfetamine. Lisdexamfetamine is FDA approved for attention deficit hyperactivity disorder (ADHD) in children ≥6 years and adults, and binge eating disorder in adults. It is not FDA indicated for weight-loss treatment in either children or adults. The mechanism of action is dopamine agonist.

- **Efficacy (children, likely with normal weight, with ADHD in the study).** In a controlled trial of children ages 6 to 12 years being prescribed lisdexamfetamine for ADHD, mean weight loss from baseline after 4 weeks of therapy was −0.9, −1.9, and −2.5 pounds, respectively, for patients receiving 30 mg, 50 mg, and 70 mg (vs. +1 lb weight gain, placebo) (105). In adolescents ages 13 to 17 years, mean weight loss from baseline to endpoint was −2.7, −4.3, and −4.8 lb, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of lisdexamfetamine over 4 weeks (vs. +2.0 lb weight gain, placebo) (105).

- **Safety.** Careful follow-up of children who received lisdexamfetamine for over 12 months showed that they had a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development (105). Sudden death has been reported in children and adolescents with

structural cardiac abnormalities and other serious heart problems taking amphetamines at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Central nervous system stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Central nervous system stimulants can also provoke preexisting psychiatric disorders and psychosis, delusions, or hallucinations in children and adolescents with no prior mental illness. Postmarketing reports have also associated lisdexamfetamine with Raynaud's phenomenon in adults (105).

- **Additional insight.** Because lisdexamfetamine is FDA approved younger than age 10 years, it may be a beneficial option in younger children ≥6 years of age with ADHD and binge eating disorder. Though it is approved for binge eating disorder in adults, it is not approved for the same indication in children in the absence of an ADHD diagnosis. Long-term safety of amphetamines has been studied in the pediatric population, with concerns for developmental growth retardation and careful monitoring for cardiac arrhythmias. Treatment of children and adolescents who have impulsive behaviors, such as impulsive excessive food intake as a manifestation of their ADHD, may find benefit from lisdexamfetamine or other ADHD medications in achieving healthier eating behaviors. Given the history of abuse potential of amphetamines in the past coupled with potential adverse psychiatric side effects, caution is advised if used for the long-term treatment of obesity. In youth with obesity or binge eating disorder, regardless of an ADHD diagnosis, there are limited data, if at all, reporting potential benefits with lisdexamfetamine use.
- **Off-label drug use.** Off-label drug use is not recommended at this time.
- **Effects on pubertal development or puberty.** Animal studies have demonstrated that amphetamine drug exposure during different development stages such as peripubertal versus prepubertal result in distinct neurobehavioral abnormalities (106,107).

FDA-Approved Obesity Medications With No Pediatric Evidence

Lorcaserin. This medication is a 5-hydroxytryptamine receptor 2C agonist that acts on anorexigenic proopiomelanocortin (POMC) neurons in the hypothalamus.

- **Efficacy.** Lorcaserin is FDA approved for the chronic treatment of obesity in adults (20). However, there are no pediatric outcome data available with regards to lorcaserin. Adult clinical trials have demonstrated 3% placebo-subtracted weight loss from baseline (20).
- **Safety.** No adverse cardiovascular safety signals have thus far emerged with lorcaserin from the large cardiovascular safety trial (108). Common adverse effects of lorcaserin reported in clinical trials are headache, dizziness, fatigue, nausea, dry mouth, and constipation. Lorcaserin should not be prescribed concurrently with a serotonergic medication due to the risk of serotonin syndrome (20).
- **Off-label drug use.** Off-label drug-use documentation, along with consent for treatment from the patient's parent or guardian, is recommended.
- **Effects on pubertal development or puberty**. The effects of lorcaserin on pubertal development in humans are not known.

Naltrexone SR/bupropion SR (NB). This medication blocks opioid receptor-mediated POMC autoinhibition (naltrexone) and selectively inhibits reuptake of dopamine and noradrenaline (bupropion, an antidepressant), and it is FDA approved for the chronic treatment of obesity in adults (20). NB has shown benefit in patients with obesity with addiction behaviors, reward pathways, and hedonic drive. Though there are no pediatric outcomes data available regarding obesity for NB, naltrexone and bupropion monotherapy have been used for other indications in children. Adult clinical trials have demonstrated 4.8% placebo-subtracted weight loss from baseline for NB on the highest optimal dose (20).

- **Safety.** Common adverse effects of NB reported in clinical trials are transient nausea during the dose-escalation period, constipation, headaches, vomiting, dizziness, and dry mouth (20). NB did not increase rates of depression and suicidal ideation more than placebo in the clinical trials (20). Though monotherapy with bupropion has been utilized in adolescents (ages 12-17) for depression, with weight loss noted as a side effect in a majority of patients (109), caution is needed because bupropion, as with other antidepressants, may increase risk of suicidal ideation in children, adolescents, and young adults (110). Therefore, NB carries a black-box warning regarding increased suicidal risk and ideation in young adults and is not approved for pediatric patients (110). Of note, bupropion monotherapy has not been FDA approved for the treatment of depression or other conditions in youth.
- **Additional insight.** Limited pediatric data are available for naltrexone monotherapy. Naltrexone monotherapy has been studied for opioid drug use in adolescents (age 13 and older) (111) and PWS for appetite reduction (112) since the 1980s, although long-term safety has not been established in the pediatric population. There is one case report in the literature of using NB combination therapy for PWS in a 13-year-old girl, with a small reduction in BMI and improvements in hyperphagia (113).
- **Off-label drug use.** Off-label drug-use documentation, along with consent for treatment from the patient's parent or guardian, is recommended.
- **Effects on pubertal development or puberty.** The effects of naltrexone and bupropion on pubertal development in humans are not known. In an animal study, bupropion did appear to alter pubertal onset (114). On the other hand, naltrexone effects on puberty have been studied. In female rat models, naltrexone has been shown to advance first ovulation through changes in pituitary responsiveness to luteinizing-releasing hormone (115). One human study demonstrated a more sensitive luteinizing hormone surge in pubertal boys than prepubertal, sexually immature boys after chronic 1-month exposure of naltrexone (116). Another study found no effect on puberty in boys with confirmed bone age 10 to 15 years when given naltrexone for 1 month (117).

New FDA Approval Pending for Pediatric Obesity: Setmelanotide

FDA approval of setmelanotide is pending for monogenic obesity. The mechanism of action is melanocortin-4 receptor agonist.

- **Efficacy.** Setmelanotide is currently being evaluated for the treatment of the following genetic disorders of obesity: POMC deficiency obesity, leptin receptor deficiency obesity, PWS, Bardet-Biedl

syndrome, Alström syndrome, POMC heterozygous deficiency obesity, and POMC epigenetic disorders. In an investigator-initiated, open-label study, two patients with POMC deficiency were treated with setmelanotide, with a sustainable reduction in hunger and substantial weight loss (51.0 kg after 42 weeks in patient 1 and 20.5 kg after 12 weeks in patient 2) (118).

- **Safety.** Dry mouth, mild induration at injection site, and darkening of skin nevi were notable adverse effects. There were no increases in blood pressure, with improvements in both heart rate and blood pressure in one of the patients (118).
- **Additional insight.** Setmelanotide provides promise for rare genetic obesity disorders, which should be considered in children with hyperphagia, early adiposity rebound, and severe obesity at a young age.
- **Effects on pubertal development or puberty.** The effects of setmelanotide on pubertal development in humans are not known.
- **Off-label drug use.** Off-label drug use is not recommended at this time.

Conclusion

Childhood and adolescent obesity is already a global epidemic and poses significant health risks. As adolescent obesity often leads to obesity in adulthood and is already accompanied by a multitude of weight-related comorbidities, including an increased risk for cardiovascular disease and certain types of cancers, treating obesity in children/adolescents should not be delayed. As an adjunct to intensive lifestyle therapy and MBS, the potential role of pharmacotherapy in the treatment of pediatric obesity should not be ignored and may represent a useful additional option for some patients who suffer from obesity. Additionally, in clinically severe obesity, pharmacotherapy may play a larger role as adjunct to MBS (91). This therapeutic need highlights the value of experienced pediatric obesity medicine specialists at tertiary care centers and yet presents challenges as clinical trials evaluating long-term safety and efficacy of obesity medications remain scant in the pediatric population. Emphasis needs to be placed on the concurrent development of appropriate, high-quality, well-designed pediatric obesity clinical trials to validate the use of medications for obesity in adolescents. Moreover, there exists a great need to develop specialized pediatric obesity medicine training programs, applicable protocols, screening tools, and guidelines to further advance the burgeoning field of pediatric obesity medicine.**O**

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