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Clinical review: Guide to pharmacological management in pediatric obesity medicine

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1. Introduction

Obesity is a chronic, relapsing, progressive disease that occurs throughout the lifespan, including infancy, when genetic and epigenetic risks interface with complex obesogenic environmental factors resulting in excess adiposity through dysregulation of the energy regulatory system. Current understanding acknowledges maintaining energy balance is more complex than voluntary behavioral decisions to eat less and move more. Physiologic controls driving intake or increasing expenditure function at the subconscious level [1–3].

Unfortunately, outdated models of energy regulation and obesity treatment persist. There is little evidence that watchful waiting of the child with obesity is associated with improvements in outcomes [4,5]. Delaying obesity treatment is associated with disease progression and obesity-driven complications while early initiation of advanced obesity treatments supported by intensive lifestyle therapy (ILT) stabilizes and mitigates obesity and related disease [6].

Treatment with anti-obesity medications (AOM) is rapidly changing previous treatment paradigms. For over 2 decades, the focus of obesity treatment for children has been ILT necessitating multiple contact hours with interdisciplinary providers, large programs, and extensive commitment of time by patient and family [7]. The addition of AOMs to obesity medicine management achieves results that exceed the use of ILT alone.

AOMs offer a new bedrock of obesity treatment for children and adolescents. Current AOMs offer diversity in the mechanism of action (MOA) required to treat the heterogenous causes of obesity. Like other chronic diseases, multiple medications will be essential to treat obesity effectively [8]. As individualized therapeutic options are offered to pediatric patients and families, the shared decision-making process is utilized to share accurate outcome data for each intervention, heterogeneity of individual patient responses, and the expectation for life long chronic management.

This review, a companion to the Obesity Medicine Association's Clinical Practice Statement on advanced therapies for pediatric obesity [4], offers in depth guidance of obesity pharmacotherapy that includes emerging knowledge of obesity phenotypes, AOM mechanisms of action and pairing of obesity therapy to best meet the patient's specific needs.

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2. Where to begin

Communication of efficacy of therapeutic options provides the basis of shared decision making in choosing treatment plans. Therapeutic outcomes are influenced by phenotypes, co-occurring obesity-driven diagnoses, and patient preferences [9]. Treatment success is measured in multiple ways, including physiologic, psychologic, and metabolic parameters. Cessation of any obesity treatment modality carries the high risk of return to unhealthy adiposity storage and adiposopathy [10,11]. If a treatment is ineffective, the MOA of the therapeutic agent did not match the energy regulation injury; the patient did not fail, the treatment did.

2.1. Assessment of the child diagnosed with the disease of obesity

Comprehensive patient assessment guides treatment decisions. The clinician considers the duration of disease, medical and psychological complications, disease progression and trajectory, age, and predicted outcomes with or without intervention [12]. Weight promoting effects of current medications are considered. The complete assessment of obesity in children is detailed in the first four Obesity Medicine Association's (OMA) Clinical Practice Statements and the OMA Pediatric Obesity Algorithm 2023–2024 [4, 13–17; Table 1].

Recent data show that patients with obesity are inadequately screened for obesity-driven complications [18]. When a child is diagnosed with obesity, baseline laboratory evaluations include lipid panel, glucose regulation, and liver function tests. Other commonly ordered tests include 25 OH vitamin D, CBC, and renal function evaluation. Assessment also includes mental health screening along with assessment for bullying, eating disorders, social determinants of health, sleeping disturbances, menstrual irregularities, and other obesity driven conditions [4,15,17]. Managing obesity-driven diseases is an integral component in the overall treatment protocol.

2.2. The role of intensive lifestyle therapy (ILT)

ILT is not a specific treatment for the disease of obesity. All children, regardless of body mass index (BMI) percentile status, are counseled to consume a healthy diet and pursue activities that increase cardiorespiratory fitness. Few children with obesity will achieve clinically significant improvements in obesity status with ILT alone [9,17,19]. This data is discussed openly with the patient and caretakers to make informed decisions. ILT is used with all obesity-specific interventions and tailored to address the severity of the disease status for each individual patient. Through shared decision making, evidence informed treatment plans are developed that improve patient outcomes, quality of life, and obesity driven-complications. This holistic approach serves to replace obesity bias and stigma (particularly internalized bias) with knowledge, hope, and empowerment (Fig. 1).

Table 1
Assessment of the child with obesity [4]
Adapted from: Table 1. Intensive Lifestyle Therapy Components: Patient Evaluation & Management. Copyright © 2022 Cuda et al. [4]. This is an open access article distributed under the terms of the Creative Commons Attribution License.

Components	
Education	Obesity is a chronic disease
Clinical Assessment	Weight-promoting medications
	Obesity-related complications
	Diet
	Activity
	Genetic causes of obesity, early onset of obesity, family history of obesity
	Co-occurring conditions with obesity
	Attention-deficit Hyperactivity Disorder, Behavioral Health disorders
	Mental health conditions
	Loss of Control Eating Disorder/Binge Eating Disorder
	Sleep quality &/or disorders
Psycho-social	Weight-based victimization
	Microaggressions
	Teasing
Environmental	Social Determinants of Health (Adverse Childhood Events, Trauma)
	Chronic stress & sequelae

2.3. Impact of weight promoting medications (WPM)

The comprehensive evaluation of the child with obesity includes history of past and present medications to determine if weight trajectory has been negatively impacted by a WPM [4]. Medications can cause unintended weight gain, the degree to which may not be appreciated by the prescribing provider. An understanding of the underlying MOA of commonly used medications associated with significant weight gain assists in creating treatment plans in pediatric obesity management. Providers should consider alternate weight neutral medications or addition of secondary medications to counteract the WPM effects.

2.3.1. Frequently prescribed WPM in children

Table 2 lists medication classes and potential impact of specific medications on weight while Table 3 describes their proposed mechanisms of action of weight gain.

2.3.1.1. Antipsychotics. Data support that most antipsychotics cause weight gain, with olanzapine and clozapine being the most weight promoting [34]. Weight promoting properties are highest in youth (vs. adults), with 80% of children experiencing significant weight gain after antipsychotic initiation [35]. Initial weight gain is generally the most rapid and can extend several years after the medication is initiated [36]. When prescribing an antipsychotic, consider weight neutral or minimal weight promoting medications. Monitor hunger, appetite, and weight after initiation and adjust medication or dosing as needed.

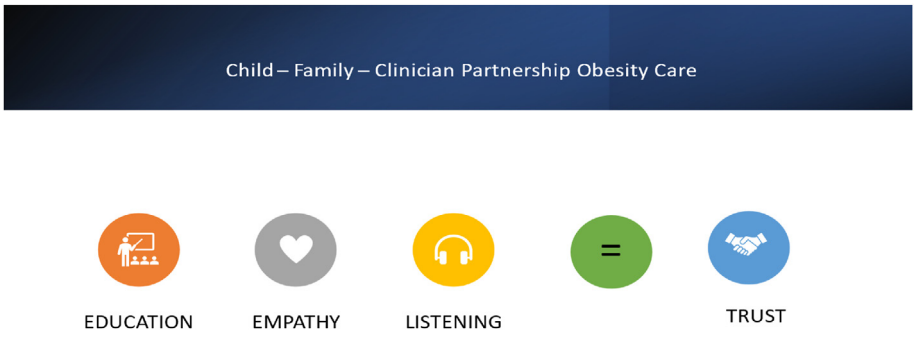

Fig. 1. Child-family-clinician partnership obesity care.

Table 2
Medication classes and potential impact on weight [20–22]. Adapted from Table 3. Risk Factors for Weight Gain. Copyright © 2022 Cuda et al. [4]. This is an open access article distributed under the terms of the Creative Commons Attribution License.

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

Medications that mitigate hyperphagia associated with antipsychotics include metformin and topiramate. Metformin's mitigating MOA includes decreasing hepatic gluconeogenesis and improving insulin and leptin sensitivity, resulting in reduced appetite [37,38]. Topiramate's MOA for weight mitigation is associated with increasing both energy metabolism and adiponectin, while reducing the leptin to adiponectin ratio [39]. A recent study demonstrated that topiramate significantly reduces body weight, BMI, and waist-hip ratio in patients with antipsychotic-induced obesity [40].

When considering the use of metformin or topiramate as a mitigating medication, review of other co-occurring diagnoses guides selection, utilizing a medication's MOA to treat more than one condition. Metformin is preferable in the presence of type 2 diabetes mellitus (T2DM), prediabetes, insulin resistance, or polycystic ovary syndrome (PCOS), while topiramate is recommended in the presence of migraines, seizure disorder, or binge eating patterns or cravings.

2.3.1.2. Anti-depressants. Selective serotonin reuptake inhibitors (SSRI) are the first-line pharmacotherapy treatment for depression in children and adolescents. Studies of SSRI's effect on weight gain provide mixed results, with weight loss observed in some patients after initiation of SSRIs, while subsequent studies of long-term SSRI use resulted in small amounts of weight gain [28, 41; Table 2]. SSRI and serotonin-norepinephrine reuptake inhibitors (SNRI) are both pharmacotherapy options for anxiety [42,43]. The MOA of SNRI weight gain is similar to SSRI. Benzodiazepines have a more limited role in pediatric anxiety, with studies supporting weight neutrality for this drug class [44].

Table 3
Proposed mechanisms of action of weight gain for specific medications.

Classes of Weight-Promoting Medications	Potential MOA of Weight Gain
Antipsychotic	• Related to the modification of neuropeptides associated with hunger control. • Leptin metanalysis: patients on antipsychotics had higher leptin levels. • Leptin excess leads to leptin resistance leading to a loss of inhibitory function and a rise in overeating, as a result [23]. • Ghrelin: After initiation of antipsychotic, triphasic increase in ghrelin. ghrelin decreases due to the negative feedback-loop from the medication-induced weight gain witheventual return to a new baseline [24–27].
Anti-Depressants: Selective serotonin reuptake inhibitor (SSRI) Serotonin–norepinephrine reuptake inhibitor (SNRI)	• Acute effects of SSRIs secondary to the initial activation of 5-HT2C receptors in the hypothalamus. • Weight gain later in treatment may be explained by decreases in responsiveness of these receptors [28]. • SSRIs also decrease dopamine turnover, which provides another possible MOA for weight gain with SSRIs. • Dopamine agonists reduce body fat stores & improve carbohydrate and lipid metabolism; SSRIs may interfere with these processes.
AED: 1. Valproic Acid (VPA) 2. Gabapentin, Vigabatrin, Carbamazepine	• The exact MOA for weight gain associated with VPA unknown. Possible MOA include: increased insulin and proinsulin secretion, decreased leptin levels & reduced energy expenditure [29]. • Pathways for weight gain for each of these medications unknown. • Vigabatrin increases the level of gamma-aminobutyric acid (GABA) in the brain (gabapentin is structurally related to GABA). • GABA increases carbohydrate consumption & decreases energy expenditure, possibly explaining the weight-promoting effects [29].
Migraine: 1. Amitriptyline 2. Propranolol	• Possible MOA for weight gain include noradrenergic or antihistaminergic inhibition of satiety and decreased metabolic rate [30]. • The MOA possibly related to decrease in energy metabolism [31].
Diabetes 1. Insulin 2. Sulfonylureas	• Anabolic effects of insulin leading to stimulation of lipogenesis in muscle and adipose tissue, correction of glucosuria with reduced energy loss leading to improved utilization of calories, and control of uncontrolled diabetes induced weight loss [32]. • Sulfonylureas can cause weight gain but are not commonly prescribed in adolescent patients [33]

2.3.1.3. Anti-epileptic drugs (AED). Multiple AEDs are associated with significant weight gain. Studies of valproic acid (VPA) show a weight gain in 40% of children using VPA, with 33% of children gaining >10% of body weight after VPA initiation [45]. Weight gain is seen with gabapentin, vigabatrin, and to a lesser extent carbamazepine [29]. AEDs with a weight loss side effect include topiramate (section 2.3.1.1), zonisamide, and felbamate; these medications are used preferentially unless contraindicated [45,46].

2.3.1.4. Migraine. An association exists between migraines and obesity [47], with the risk for migraines 60% higher in children with overweight or obesity compared to children with normal BMI [48]. Neurotransmitters and peptides (orexins, serotonin, and adiponectin) involved in the development of migraine headaches are involved in hypothalamic regulation of appetite [49].

Treatment of migraines involves medications to prevent or treat headache symptoms. The primary medications utilized to treat migraines include amitriptyline, propranolol, and topiramate. Amitriptyline (tricyclic antidepressant) and propranolol (beta blocker) are associated with appetite stimulation and weight gain [41]. Topiramate (section 2.3.1.1) is associated with weight loss and is the preferable choice in patients with co-occurring obesity and migraines. Limited studies exist that assess the impact of ILT and weight loss on migraine frequency [47].

2.4. Obesity-driven/related diseases

Children frequently present with multiple obesity-related diseases that can be treated utilizing medications with the dual benefit of treating obesity and specific co-occurring diagnoses. In this section, screening tools for common obesity-related diseases are presented [Table 4] followed by guidance for medications with dual benefit to the treatment of obesity and specific obesity-related conditions [Fig. 2] [4].

2.4.1. Prediabetes/T2DM

The prevalence of youth onset T2DM has increased dramatically over the past 20 years (tripling in adolescents) [50,51], a result of the significant increase in pediatric obesity and severe obesity [51]. Diagnostic criteria for T2DM include: 1.) HbA1c $\geq$ 6.5%, 2.) fasting blood glucose >126 mg/dl, 3.) blood glucose >200 mg/dl utilizing 2-hour oral glucose tolerance test (OGTT), or 4.) classic symptoms of hyperglycemia, such as polyuria and polydipsia and a random glucose measurement of >200 mg/dL [15,52,53]. Non-modifiable T2DM risk factors include strong family history (first- or second-degree relatives), race/ethnicity, or maternal gestational diabetes mellitus in pregnancy. T2DM in youth initially is marked by insulin resistance and nonautoimmune beta cell failure and can progress rapidly to pancreatic beta cell decline and accelerated development of diabetes complications [51,54,55]. In adolescents with T2DM, insulin sensitivity has been shown to be 50% lower than adults with a 50% chance of disease progression despite intervention and treatment [56,57].

Insulin and insulin analogs such as insulin glargine can cause excessive weight gain in adolescents [58]. The goal for pediatric patients with T2DM and obesity is a 7%–10% BMI percentile reduction (children who have completed linear growth) or a BMI <85th percentile for age and sex (children still undergoing growth) [54,59].

Use of AOMs in patients with T2DM can reduce obesity and resolve many obesity-related conditions including hypertension, obstructive sleep apnea, and dyslipidemia, in addition to playing an integral role in addressing T2DM itself. Metformin has been shown to be effective in the management of T2DM in adolescents in addition to ILT, with a decrease in hepatic glucose output and enhancement of hepatic and muscle insulin sensitivity, without a direct effect on beta cell function or risk of hypoglycemia [4,60]. In pediatric patients who are incidentally diagnosed with T2DM or metabolically stable with HbA1c <8.5% and asymptomatic, the American Diabetes Association currently recommends metformin as the initial medication treatment of choice with normal renal function [61]. If glycemic targets are not met with metformin with or without incorporation of insulin management, glucagon-like peptide 1 (GLP-1) agonist liraglutide, approved in 2019 for children $\geq$10 years of age with T2DM, is considered [15,61,62]. Both metformin and liraglutide are Food and Drug Administration (FDA) approved in children 10 years and older for the indication of T2DM with the once weekly GLP-1 receptor agonist exenatide being approved for children aged 10–17 years with T2DM in 2021. Clinical trials are currently ongoing for the evaluation of tirzepatide, a novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, in pediatric and adolescent participants with T2DM [63].

2.4.2. Polycystic ovary syndrome (PCOS)

Using the Rotterdam Criteria [64], the diagnosis of PCOS is made if two of the following criteria are present: oligo or anovulation; biochemical or physical evidence of hyperandrogenism; and polycystic ovaries on ultrasound. The pathophysiology of PCOS is strongly tied to insulin resistance. Higher insulin levels are associated with post receptor defects that lead to increased ovarian steroidogenesis, thereby producing excess androgens and impairing ovarian follicle development [65]. Obesity is a common finding in patients with PCOS (>50% have obesity), as excess adipose tissue can promote insulin resistance and hyperandrogenism. Treating the diseases of obesity and insulin resistance can have a positive impact on PCOS management.

Treatment of patients with PCOS and obesity is twofold. ILT provides baseline therapy and assists with insulin resistance management. A 5–10% loss of total body weight is beneficial in improving ovarian function and insulin sensitivity [65]. AOMs approved by the FDA to treat the indication of obesity are used as an adjunct to ILT when ILT alone is insufficient. Few studies are available assessing newer AOMs on PCOS [66]. Metformin is used in patients with PCOS of any weight to improve ovarian insulin sensitivity and restore menstrual function. Hormonal contraceptives are also used to manage menstrual regularity but are weight promoting. Combination estrogen-progesterone forms are associated with less weight gain than progesterone-only forms [67]. Frequently, a decrease in insulin resistance is associated with an improvement in menstrual regularity.

2.4.3. NAFLD

Nonalcoholic fatty liver disease (NAFLD; defined as fat accumulation in >5% of hepatocytes) encompasses a spectrum of liver disease which includes nonalcoholic hepatic steatosis, nonalcoholic steatohepatitis, cirrhosis, and liver failure [68]. Insulin resistance is exacerbated by hepatic fat accumulation and can promote free fatty acid accumulation in the liver [69]. While not all children with obesity have NAFLD, a strong association exists between the two conditions. Improvement in liver function and insulin resistance is seen with improvements in obesity disease.

Table 4
Specific screening tools for most common obesity driven diseases [4,15–17]. Abbreviations: HgbA1c = Glycated hemoglobin; OGTT = oral glucose tolerance test; DHEA = Dehydroepiandrosterone; FSH = Follicle-stimulating hormone; LH = Luteinizing hormone; ADHD = Attention-deficit/hyperactivity disorder; ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents; STOP-BANG = Questionnaire for obstructive sleep apnea; ADO-BED = adolescent binge eating disorder questionnaire; CBBEQ = Children's Brief Binge-Eating Questionnaire; ChEDE = Children's Eating Disorder Examination; PHQ-9 = patient health questionnaire measuring depression; PHQ-A = patient health questionnaire measuring depression in adolescents; GAD = generalized anxiety disorder; SCARED = Screen for Child Anxiety Related Disorders; HIT-6 = headache impact test.

Condition	Screening Tool/Test
Prediabetes/T2DM	Fasting blood sugar, HgbA1c, OGTT
PCOS	DHEA sulfate, free testosterone, thyroid function tests, 17 OH progesterone, FSH, LH, beta HCG, prolactin.
NAFLD	liver biopsy, liver function tests, liver ultrasound
Sleep Dysregulation	sleep study, ESS-CHAD, STOP-Bang modified for pediatrics
Binge Eating Disorder (BED)/Loss of Control Eating Disorder	BED: ADO-BED, BED-7, CBBEQ, Dyken Hyperphagia Questionnaire, ChEDE
Depression	PHQ-9, PHQ-A
Anxiety	GAD-7, SCARED, Social Phobia Inventory
ADHD	Vanderbilt, Pediatric Symptom Checklist
Migraine	HIT-6

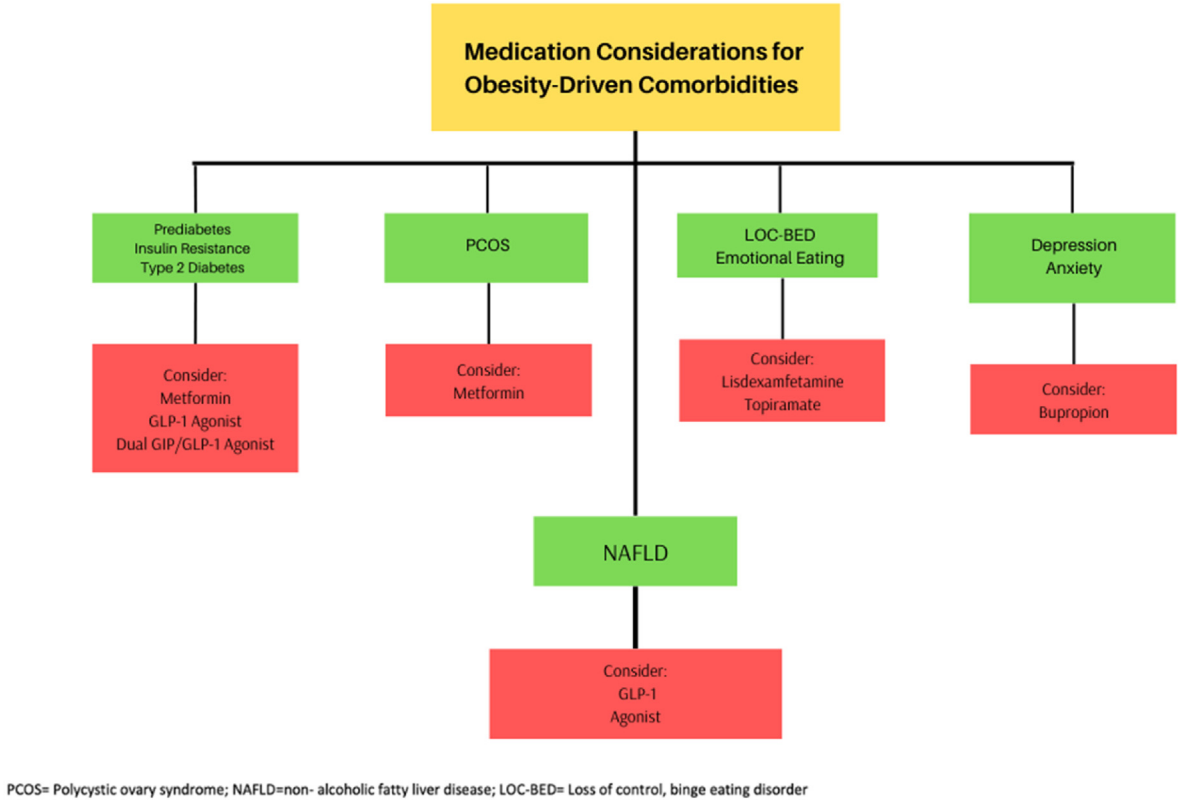

Fig. 2. Decision Tree: Medication considerations for obesity-driven comorbidities [4]; Figure 14. Decision Tree: Medication considerations for obesity-driven comorbidities Copyright © 2022 Cuda et al. [4]. This is an open access article distributed under the terms of the Creative Commons Attribution License.

Treatment of NAFLD in children with obesity centers around lifestyle modification and weight loss. There is no specific dietary intervention that is superior in obesity treatment in NAFLD and little consensus on amount of weight loss that is needed. Medical management with metformin, vitamin E and antioxidant therapy have not been found to offer benefits over placebo in the treatment of NAFLD, thus the focus remains on ILT. Some adult studies show potential benefits with glucagon-like peptide-1 receptor agonists (GLP-1RA), but more research is needed [70–72].

2.4.4. Binge eating disorder (BED)

BED is the most common eating disorder in the United States affecting 1.3–3% of children and adolescents [73]. The prevalence is significantly higher (20–35%) for children with overweight/obesity [74,75]. Validated BED-screening questionnaires in adolescents with overweight or obesity exist [Table 4] but are limited [76].

BED impacts the nutrition plan, mental health specialist involvement, and medication choice (if applicable) for obesity management. Insulin resistance is associated with increased hunger and can drive binge eating behavior. BED treatment is optimized when both BED and obesity are treated simultaneously. First-line treatment for BED is psychotherapy. Studies consistently support that psychotherapy alone is more beneficial than medication alone in treatment of BED [77]. Psychotherapy, however, has not been shown to lead to weight loss. Medication is considered a second-line treatment for BED, but its importance increases when co-managing BED in the setting of obesity. Patients with BED and obesity may benefit more from dual diagnosis medications such as lisdexamfetamine and topiramate.

Lisdexamfetamine and topiramate are both medications used to treat BED. Lisdexamfetamine is FDA approved for the indication of BED for adults. Weight loss and decreased appetite are known side effects [78]. Lisdexamfetamine is not FDA approved for the indication of obesity. Topiramate has been used to independently treat BED as well as obesity but is off-label for both indications. When used for both conditions simultaneously, topiramate has been associated with reduction in BED symptoms and improvement in BMI [78].

2.4.5. Loss of control eating disorder (LOC-ED)

The diagnosis of LOC-ED is used for children 6–12 years of age with binge-type behaviors who do not meet full criteria for BED. Data supports that LOC-ED is associated with overweight and obesity. No medications have been approved or studied for the indication of LOC-ED. Theoretically, the same medications that are effective in BED can be used to treat LOC-ED off-label for indication. When assessing for response to BED or LOC-ED, the decision to continue therapy is based on whether symptoms have improved, independent of BMI changes.

2.4.6. Depression/anxiety

According to data from the National Survey of Children's Health (NSCH), 1 in 11 U S. children are diagnosed with anxiety and 1 in 22 children are diagnosed with depression [79]. The disease burden of anxiety and depression for children with obesity is greater, with multiple studies supporting an association between excess adiposity and increased mental health diagnoses [80]. Some research suggests a bidirectional relationship between depression and obesity [80].

In a met-analysis examining the association of structured, professionally run pediatric obesity treatment and its effect on youth anxiety and depression, the researchers concluded that obesity treatment is not associated with an increased risk of depression or anxiety [81. Authors suggest that for youth with depression and obesity, obesity treatment may offer the opportunity to reduce a worsening progression of depression during this crucial developmental stage [81]. A greater decrease in

symptoms was seen in programs offering increased structure and longer duration with ongoing support of the obesity management team [81]. If pharmacological treatment for anxiety and depression is utilized, weight sparing medications are preferred. Table 2 shows commonly used mental health medications and their effect on weight.

2.4.7. Attention-deficit hyperactivity disorder (ADHD)

One in ten children (ages 3–17 years) is diagnosed with ADHD [79]. Mounting evidence supports a significant association between ADHD and obesity. In a systemic review by Cortese et al., pooled prevalence of obesity was 40% higher in children with ADHD (10.3%, 95% CI = 7.9–13.3) compared to those without (7.4%, 95% CI = 5.4–10.1), based on 46,115 children with ADHD and 616,228 comparison subjects [82]. While this association may initially seem counterintuitive (hyperactivity central to ADHD with an expectation of increased energy expenditure), obesity and ADHD actually share multiple common neuroendocrine pathways [83], where neuroendocrine injury can contribute to both disease processes. If impulsivity is present with ADHD, BED may develop or be exacerbated while inattentiveness associated with ADHD may lead to difficulty focusing on ILT goals. Sleep disturbances associated with ADHD can lead to altered sleep schedules and/or insufficient sleep duration [84], which in turn lead to delayed onset of melatonin, high levels of ghrelin, and leptin resistance.

When the ADHD diagnosis is made, treatment with appropriate pharmacotherapy is recommended for children ≥6 years [85]. Given their efficacy, stimulants (e.g., methylphenidate, amphetamine, lisdexamfetamine) are considered first line therapy for children and adolescents (6–18 years) and associated with moderate decreases in BMI Z-scores [86]. Guanfacine has low efficacy in treating ADHD, is associated with weight gain, and is not recommended for treating co-occurring ADHD and obesity.

When initiating a stimulant, family education is provided regarding potential for meal skipping, particularly lunch, due to decreased hunger, which can lead to rebound hunger when the medication wears off. To prevent rebound, lunch should include a healthy source of protein. Additionally, some children may require a second dose of a short-acting stimulant after school to help with homework, rebound hunger and prevent impulsivity with food choices later in the day. When ADHD presents along with a positive screen for BED or LOC-ED, utilizing lisdexamfetamine offers dual therapy as it is FDA approved for indication of BED ≥18 years and the indication of ADHD for ≥6 years.

2.4.8. Migraine

Migraine prevalence and etiology are discussed in section 2.3.1.4. Topiramate can provide dual management in migraine relief for patients who also suffer from obesity and BED. Topiramate, as a part of the combination medication phentermine/topiramate, is FDA approved for the indication of obesity in adults and children 12 years and older [4].

3. Genetic (monogenic and polygenic) and syndromic causes of obesity

The heritability of obesity was first established in the 1980s by studying identical twins reared together and apart, identifying a 70% heritability factor. Individuals with healthy thinness (BMI ≤18 kg/m^2) show genetic heritability like those with obesity. Over the past 10 years, free genetic testing has become widely available for rare causes of genetic obesity. Genetic testing yields positive findings in many patients, including multiple affected genes in some individuals. Many genetic variants exist, and phenotypic expression can differ even with similar variants. Knowledge of a genetic cause for obesity can be reassuring and the family is counseled that the disease is treatable.

Future research into the extremes of adiposity levels (severe obesity and healthy thinness) will examine shared loci between these two groups to increase knowledge of regulation of gene control [87]. Free genetic testing has led to a rapidly expanding database of genetic findings. Family members of probands with identified known pathological or likely pathological genetic variants are offered free testing, yielding more information on heritability. Heterozygotic variants make up most of the genetic variants discovered with genetic testing. Heterozygotic variants, especially compound heterozygotic variants, can qualify for treatment with setmelanotide. Genetic mutations that have specific indications for setmelanotide include Bardet-Biedl syndrome (BBS), leptin receptor deficiency (LEPR), proopiomelanocortin deficiency (POMC), and proprotein convertase subtilisin/kexin type 1 (PCSK1). Free genetic counseling is available for families and providers. Although only a handful of genetic causes of obesity meet criteria for treatment with setmelanotide, children with genetic causes of obesity can be treated with the same AOMs that are used in children with polygenic obesity.

Table 5
FDA medication approval process includes off-label for indication and population [88].

History of FDA	• Established: 1906 Pure Food and Drugs Act • Responsible for Medication Safety (1938) • Responsible for Medication Efficacy & Indication for use (1962)
Definition of Approval ("on label")	• Medication approved for safety & efficacy for a specific indication & population. • 2 independent clinical trials human subjects • Expensive: $19 million for approval of one indication • Lengthy: 10–15 years
What is Off-Label usage	• Definition: Medication currently FDA approved for safety and efficacy for a *specific indication & population* • Insufficient (or no) evidence from FDA trials for efficacy for a *different indication or population* • Does not imply improper, illegal, contraindicated, or investigational use • Medication therapies for pediatric conditions are guided by clinical practice statements and guidelines along with clinical best practice • Practitioners [should] document the decision-making process to use a drug off label in the patient's medical record
Populations affected by lack of FDA indication	• Many populations excluded from FDA drug trials ○Pediatrics, mental illness, pregnant women, elderly ○Result: not included in FDA indications • New indication approval costly, time-consuming, not mandated, & rarely undertaken
Incidence of off-label for indication use in pediatric population	• 51.6% probability children <1 year old • 29.3% probability for 20-year-old

4. Initiation of anti-obesity medications on and off-label

AOMs are initiated after a discussion with the patient and family involving shared decision-making, including FDA approved medications used off-label for an obesity indication (Table 5).

As mentioned previously, delaying treatment with AOMs pending improvement in diet, activity, psychological health, or any obesity-driven comorbidities will not improve outcomes. While the family's wishes are always respected, the family must also be made aware of the evidence that only a 1–3% improvement in obesity status is expected with ILT alone [5]. Discussion with the family includes treatment options, potential adverse effects, expected duration of therapy, and anticipated improvement. In the following sections, medications available in pediatric obesity management practice are reviewed; a case study provides practice guidance.

Table 6
A summary of medications utilized in obesity care.
Abbreviations: BID = twice a day; ml = milliliter; mg = milligram; ER = extended release; OTC = over the counter; SQ = subcutaneously.

Medication	Dose Titration	Formulations	Mean % weight loss/% decrease BMI
Phentermine	Dosage should be individualized to obtain an adequate response with the lowest effective dose. *starting dose (8mg/15 mg daily) with increase to bid if needed.	8 mg, 15 mg, 30 mg, or 37.5 mg	5–7.8% weight loss
Phentermine/ Topiramate	• starting dosage is 3.75 mg/23 mg daily for 14 days; then increase to 7.5 mg/46 mg daily • Escalate dosage based on weight loss in adults or BMI reduction in pediatric patients. • After 12 weeks of treatment at 7.5 mg/46 mg, evaluate BMI reduction for pediatric patients aged 12 years and older. • If a pediatric patient has not experienced a reduction of at least 3% of baseline BMI percentile, increase the dosage to 11.25 mg/69 mg orally once daily for 14 days; increase the dosage to 15 mg/92 mg orally once daily as indicated. • After 12 weeks of treatment with 15 mg/92 mg, evaluate BMI percentile reduction for pediatric patients 12 years and older. If no reduction of at least 5% of baseline BMI percentile, discontinue medication; unlikely patient will achieve and sustain clinically meaningful weight loss with continued treatment.	3.75 mg Phentermine/23 mg Topiramate 7.5 mg Phentermine/46 mg Topiramate 11.25 mg Phentermine/69 mg Topiramate 15 mg phentermine/92 mg topiramate	Moderate dose: -8.11% BMI Top dose: -10.44% BMI
Orlistat	OTC: 60 mg TID Prescription: 120 mg TID *skip dose for skipped meals	OTC: 60 mg tab Prescription: 120 mg tab	2.9–3.4% weight loss
Liraglutide	Week 1: 0.6 mg SQ daily Week 2: 1.2 mg SQ daily Week 3: 1.8 mg SQ daily Week 4: 2.4 mg SQ daily Week 5: 3.0 mg SQ daily	Prefilled pen: (6 mg/ml.3 ml); each pen contains 3 ml	7% weight loss over placebo
Semaglutide	Week 1–4: 0.25 mg SQ weekly Week 5–8: 0.5 mg SQ weekly Week 9–12: 1 mg SQ weekly Week 13–16: 1.7 mg SQ weekly Week 17-on: 2.4 mg SQ weekly	Prefilled single dose pens (0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg)	16.1% BMI reduction 10% weight loss in 62% participants in trial 20% weight loss in 37% of trial participants
Setmelanotide	**Patients 6 to less than 12 years**: *starting dose is 1 mg (0.1 mL) injected SQ once daily for 2 weeks. Monitor patients for GI adverse reactions. * If the starting dose is not tolerated, reduce to 0.5 mg (0.05 mL) once daily dose. If the 0.5 mg once daily dose is tolerated and additional weight loss is desired, titrate to 1 mg (0.1 mL) once daily. • If the 1 mg dose is tolerated, increase to 2 mg (0.2 mL) once daily. • If the 2 mg once daily dose is not tolerated, reduce to 1 mg (0.1 mL) once daily. * If the 2 mg once daily dose is tolerated and additional weight loss is desired, the dose may be increased to 3 mg (0.3 mL) once daily. **Patients 12 years and older:** *starting dose is 2 mg (0.2 mL) injected SQ once daily for 2 weeks. Monitor patients for gastrointestinal (GI) adverse reactions. • If the starting dose is not tolerated, reduce to 1 mg (0.1 mL) once daily. *If the 1 mg once daily dose is tolerated and additional weight loss is desired, titrate to 2 mg (0.2 mL) once daily. • If the 2 mg daily dose is tolerated, increase to 3 mg (0.3 mL) once daily. *If the 3 mg once daily dose is not tolerated, maintain 2 mg (0.2 mL) once daily.	10mg/1 ml multiple-dose vial	9.7% weight loss (LEPR) 23.1% weight loss (POMC/PCSK1) −7.9% BMI reduction from baseline (BBS), *(61.3% of BBS patients achieved a ≥5% BMI decrease from baseline, 38.7% had ≥10% decrease in BMI)
Naltrexone/ Bupropion	Week1:1 tablet in am, week2:1 tablet bid, week 3:2 tablets in am, 1 tablet in pm, Week 4 onward: 2 tablets bid	Extended-Release tablets: 8 mg naltrexone, 90 mg Bupropion	4.8–6.0% weight loss over placebo
Metformin	500 mg withdinner, titrate to 500 mg bid, if tolerated & needed, can titrate to 1000 mg bid, if using ER, can take full dose once daily	500 mg, 850 mg,1000 mg 500 mg ER, 750mgER	2.5% weight loss over placebo
Topiramate	25 mg daily x 1week Titrate to 50 mg daily ×1 week Titrate to 75–100 mg if needed *evening dosing may help with fatigue	25 mg, 50mg100mg,200 mg tablets Sprinkles: 15 mg, 25 mg ER: 25 mg,50 mg, 100 mg, 150 mg, 200 mg	2–4% BMI reduction

4.1. A summary of medications utilized in obesity care is outlined in Table 6

4.2. Choosing AOM for treatment of obesity in children

4.2.1. Phenotypes

As outlined in Fig. 3 [4], the patient's history, particularly as it pertains to satiety, satiation, emotional triggers for food intake, and sense of reduced energy expenditure, guides the selection of AOMs to match the most prevalent symptomatology [89]. Acosta et al. identify 4 main phenotype domains based on dominant symptoms and screening tools [89]. When multiple obesity phenotypes occur, treatment focus is the dominant category. Many patients have overlapping symptoms, highlighting the heterogeneity and complexity of obesity pathophysiology. The complexity of obesity is evidenced by potentially multiple metabolic injuries leading to increased adipose storage (obesity). Medications with multiple MOA may be needed for effective treatment [90]. Targeting nutrition interventions, activity, and pharmacotherapy based on obesity phenotype has been effective in studies, however, it is not currently standard of care or formally assessed in pediatric patients [89]. Studies in pediatric patients are needed to determine the effectiveness of phenotypic-targeted therapy. Table 7 lists questions used to assist in

determining phenotype.

4.2.1.1. Hungry Brain: assess satiation. When assessing Hungry Brain dominant subtype, eliciting history regarding large portions, difficulty with satiation, quantity of food per meal where patient feels full (if ever) guides treatment selection. Exploring how the child experiences fullness (stomach stops growling, or "delight" in taste of food) provides insight into the child's eating behaviors, such as thoughts of food, physical hunger, or the sight of highly palatable foods. Food diaries or snapshots of meal size are helpful in assessing this component. Screening tools for BED and hyperphagia questionnaires assist in determining symptom severity. Foods that are nutrient dense and higher in protein and fiber can promote satiation. Cognitive behavioral therapy (CBT) utilizing stimulus control and stimulus narrowing is beneficial. Phentermine or combination phentermine/topiramate can be effective medication options to address these symptoms and support obesity management goals [91].

4.2.1.2. Hungry Gut: assess satiety. The Hungry Gut subtype involves diminished satiety. In this phenotype, hunger returns shortly after food is consumed, leading to frequent meals and snacks throughout the day. When assessing this subtype, patients and families describe frequent between-meal hunger and a short time of feeling full after a meal. Parents may report the child asking when the next meal will occur, even while eating the current meal. Some children present with a history of sneaking or hiding food between meals, often with related shame. Outlining this subtype's pathophysiology replaces shame with knowledge by explaining the dysregulation at the level of the hypothalamus occurring at the subconscious level. A food diary that records meal timing, patterns, and when the child feels most hungry guides treatment options. Hungry Gut phenotype is associated with increased gastric emptying [89,92]. In addition to dietary goals of high fiber foods with strong protein sources, consider a GLP-1 RA to improve satiety and complement obesity management strategies.

4.2.1.3. Emotional/reward center drive eating. Emotional/Reward Center Drive phenotype presents as eating to help cope with various emotional states such as stress, sadness, anxiety, or a combination of these emotions. In this phenotype, food is used as a soothing mechanism and is not consumed out of energy needs. Often, these symptoms present when underlying anxiety or depression are present, therefore utilizing screening tools (Table 4) can help with assessment and treatment focus. Encouraging nonfood coping strategies, in addition to reducing highly palatable foods can decrease emotional/reward center drive eating. When considering AOMs, medications such as combination naltrexone/bupropion, can provide effective therapy. In cases of co-occurring BED, topiramate is considered.

4.2.1.4. Slow burn: energy expenditure/resting energy expenditure (REE). The Slow Burn phenotype describes patients who have slow basal metabolic rates and/or experience lower amounts of energy expenditure through physical activity. This phenotype is suggested with a history of eating less calories with added physical activity yet without improvement in obesity. Review of food diaries as well as consideration of indirect calorimetry can inform therapy options. Tailoring ILT to structure daily physical activity (both aerobic and anaerobic) can help increase metabolic rate. The addition of an AOM is indicated; phentermine has shown positive results in small increases in resting metabolic rate.

4.3. Anti-obesity medications and phenotype considerations

At present, the most common AOMs used to treat children and adolescents with obesity are phentermine and topiramate. Liraglutide was approved for obesity management in 2020 [93] and semaglutide was approved in 2022 [94], resulting in increased use of GLP1-RAs. Poor insurance coverage and high out-of-pocket costs have limited widespread use of these medications. Orlistat, although FDA-approved for indication of obesity, is rarely used due to gastrointestinal adverse effects. Table 8 lists mechanisms of action, side effects, and contraindications of AOMs used in pediatric obesity therapy. Table 9 lists AOM considerations related to phenotype, co-occurring diagnoses, and monitoring advice.

When phenotypic presentations of children with obesity prompt consideration of multiple AOMs to address distinct MOAs, all phenotypic expressions benefit from a trial of AOM concurrently. Because of the robust outcomes associated with the use of GLP-1RA, this class provides a first line option to obesity management. If coverage with a GLP1-RA is not possible, the clinician considers using both phentermine and topiramate. Even when GLP-1RAs are utilized, multiple AOMs may be required due to the heterogeneity and variability of response.

4.3.1. Phentermine

Phentermine, first approved for obesity management in 1959, is a sympathomimetic amine (Drug Enforcement Agency [DEA] Schedule IV) stimulant agent approved for short-term use (12 weeks; state law specific). Phentermine is well tolerated in children and adolescents and acts to decrease hunger. Energy regulatory system dysregulation may result in poor satiety feedback at the unconscious level, making conscious choices of overcoming poor satiety cues difficult. Phentermine is infrequently covered by insurance but the out-of-pocket cost for most families is reasonable. The FDA has approved the use of phentermine in adolescents (>16 years) as well as phentermine combined with topiramate for children ≥12 years, both for the indication of obesity. While few studies have examined phentermine use in children, it is frequently prescribed due to efficacy, minimal side effect profile, and low cost. Use of phentermine in the morning can decrease potential for insomnia.

4.3.2. Topiramate

Topiramate is a long-acting neuro-stabilizer approved as monotherapy for seizure disorders, migraine headache prevention, and for the indication of obesity management in combination with phentermine for adolescents ≥12 years. Because of poor insurance coverage of phentermine/topiramate combination formulation, single agent use of phentermine and topiramate is an available treatment option. When prescribed separately, the obesity medicine specialist can titrate doses of both phentermine and topiramate. Lower topiramate dosages are associated with fewer side effects (paresthesia, cognitive fogging), which may interfere with functioning at school. When used for obesity management, topiramate augments treatment for children with food cravings and between meal food seeking, and is a mitigating treatment in WPM usage. Simultaneous use of topiramate and phentermine has a synergic effect [93]. Topiramate usually has little effect on renal function in children, even when used concurrently with metformin. Combined use of metformin and topiramate can produce metabolic acidosis on a laboratory panel, often not associated with clinical symptoms. Due to potential teratogenicity during pregnancy, appropriate counseling is recommended.

4.3.3. Glucagon like peptide receptor agonists (GLP-1 RA)

4.3.3.1. Semaglutide. Semaglutide was approved December 2022 for use in pediatric patients ≥12 years with BMI ≥ the 95th percentile. Dosing is similar to that in adults: begin at the lowest formulation and increase monthly until desired obesity status, comorbidity resolution, or peak dose is achieved. With the recommended dose escalation, the patient reaches a maximum dose in 5 months. Dose escalation may be slower if adverse effects occur.

4.3.3.2. Liraglutide. Liraglutide was approved in 2020 for use in pediatric patients ≥12 years with a BMI ≥ the 95th percentile [93]. The indication for use is similar to semaglutide. Patients with co-occurring prediabetes or T2DM will benefit from first-line trial of these

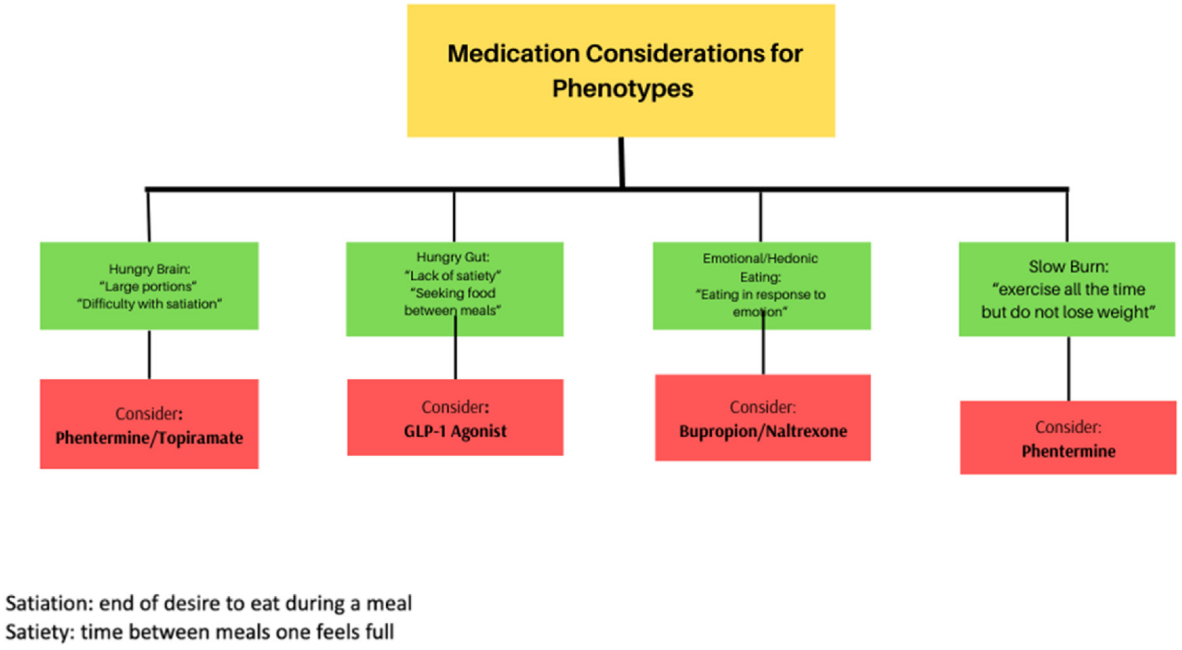

Fig. 3. Decision Tree: Medication Considerations for Phenotypes
[89] From: Figure 15. Decision Tree: Medication Considerations for Phenotypes

Table 7
Questions to clinically assess obesity phenotypic features.

	Questions to Assess Phenotypic Features
1	How many meals do you eat each day? How many snacks?
2	Do you eat more for hunger or for emotions (sadness, stress, anxiety)?
3	Do you eat to feel better when you are stressed or sad, anxious etc.?
4	Do you feel hungry within ½ - 1 h after eating a meal or snack?
5	Do you need to eat more or have larger portions to feel full at meals or snacks?
6	What do you eat for your meals? Snacks?
7	How often are you physically active?
8	In what kinds of activity do you engage throughout the day?

medications given the dual indications. Patients with positive screens in the "Hungry Brain" phenotype with lack of satiety also benefit from GLP-1 RA usage.

Use of either semaglutide or liraglutide is limited due to poor insurance coverage. Many state Medicaid programs do not offer coverage for these medications in children which leaves the most vulnerable patients without access to these therapeutic options. Many private insurance companies have either plan exclusions or requirements of "step therapy" that may require treatment with diet and exercise for 6 months prior to authorization of medication. Treatment delays are not associated with improved outcomes [4,5]. Little scientific evidence supports these outdated policies and restricts access to care for children. If these medications receive insurance approval, prior authorization practices further delay treatment.

Table 10 summarizes pharmacotherapy options and FDA indications for use in the pediatric population.

4.4. Monitoring AOM treatment effectiveness

4.4.1. AOM follow up: initial

After beginning an AOM, initial follow up at 2–4 weeks is an important milestone. Access to the obesity medicine specialist and team within 1–2 weeks of AOM initiation can help with medication concerns. Close follow up and clear discussion of adverse effects prior to AOM prescribing alleviates potential issues, however many patients will not be cognizant of issues until experiencing them firsthand. Timely, ongoing communication between the family and the obesity medicine specialist facilitates a smoother experience.

4.4.1.1. AOM adverse effects. A discussion of adverse effects with the patient and parent includes the positive effects of the medication (improvement in weight status, increase in self-confidence, improved glycemic control) along with the reassurance that many adverse effects are alleviated with time. Adverse effects can usually be addressed with adjustment of doses, timing of medication, and slowing the advancement of dosing. Once adjustments are made to alleviate any side effects, consider re-titration to full dose as side effects may be eased with slower titration. This process requires frequent and chronic follow-up appointments or points of contact with the families in a supportive environment.

4.4.1.2. Assess for medication response. Response to AOM is very individual. A reduction in an obesity-related behavior or improvement in the co-occurring condition, even in the absence of obesity status improvement, is a positive response. If using lisdexamphetamine to treat obesity and ADHD for example, monitor for improvement in impulsivity, attention, focus on ILT goals, and binge eating patterns as indicators of positive effectiveness. These improvements may occur with or without changes in BMI percentile; lack of BMI percentile improvement would not be an indication to discontinue the medication. The appropriate management of these diagnoses frequently improves success of other aspects of the environmental and behavioral goals integrated into the overall obesity treatment plan.

In younger children, a slowing of weight gain is a positive response. Failure to respond to AOM in children and adolescents is rare. The obesity medicine specialist should address adherance and potential mitigating factors if obesity status is not improving. If emotional eating is occurring, counseling is pursued. Other co-existing behavioral problems deserve and require concurrent treatment. Attention should be directed to adjusting behavioral health WPM in conjunction with mental health colleagues.

Table 8
Mechanisms of action, side effects, and contraindications of AOMs used in pediatric obesity therapy.Abbreviations: LFT = liver function tests; GI = gastrointestinal; IR = insulin resistance; CMP = comprehensive metabolic panel; MAOI = Monoamine oxidase inhibitors; T1DM = Type 1 diabetes mellitus, LEPR = leptin receptor deficiency; POMC = proopiomelanocortin deficiency; BBS= Bardet-Biedl syndrome; PCSK1 = proprotein convertase subtilisin/kexin type; SI = suicidal ideation.

Medication	MOA	SEs	Contraindications
Phentermine	Appetite suppression via stimulation of hypothalamus to release norepinephrine	Increase in BP, heart rate, anxiety	Pregnancy Use caution in congenital heart disease, hypertension, renal impairment
Phentermine/ Topiramate	Appetite suppression via release of norepinephrine, enhances GABA release while inhibiting AMPA and NMDA	Increase in BP, heart rate, anxiety, paresthesia, cognitive dulling, fatigue, dizziness, dysgeusia, insomnia, dry mouth, constipation, SI, possible seizures if stopped abruptly	Pregnancy, use of MAOIs, glaucoma, black-box warning for worsening depression in 18–24 year olds
Orlistat	Reversible inhibitor of gastric and pancreatic lipases, thus inhibiting absorption of dietary fats by 30%	Oily rectal leakage, abdominal pain, flatulence with discharge, bowel urgency, steatorrhea	Pregnancy, breastfeeding, chronic malabsorption syndrome or cholestasis
Liraglutide	Mimics GLP-1 incretin, stimulates post-prandial insulin secretion, reduces glucagon, delays gastric emptying, reduces hunger and food intake	GI symptoms: abdominal pain, nausea, vomiting, diarrhea, and hypoglycemia	Personal or family history of medullary thyroid carcinoma, MEN2
Semaglutide	Mimics GLP-1 incretin, stimulates post-prandial insulin secretion, reduces glucagon, delays gastric emptying, reduces hunger and food intake	GI symptoms: abdominal pain, nausea, vomiting, diarrhea, and hypoglycemia	Personal or family history of medullary thyroid carcinoma, MEN2
Setmelanotide	MC4R agonist	Hyperpigmentation, GI symptoms, depression, dizziness, fatigue, headache, insomnia, prolonged penile erections	Pregnancy
Naltrexone/ Bupropion	Reuptake inhibitor of norepinephrine and dopamine, and opioid antagonist	Nausea, vomiting, headache, dizziness	Black-box warning worsening depression or SI in youth, uncontrolled hypertension, seizure disorder, anorexia, bulimia, drug or alcohol withdrawal, MAOI use
Metformin	Increases insulin and leptin sensitivity, which decreases hunger, may also increase secretion of GLP-1	GI upset, vitamin B12 deficiency, lactic acidosis	Severe renal dysfunction and acute/chronic metabolic acidosis
Topiramate	Appetite suppression via enhanced GABA release while inhibiting AMPA and NMDA	Paresthesia, cognitive dulling, fatigue, worsening depression	Pregnancy

4.4.1.3. Medication adjustment review. Every clinical encounter is an opportunity to review the need for medication dose adjustment (lowering or titration, titration rate). An AOM is titrated down for intolerable adverse effects and titrated up to achieve maximal effect. Frequently after a period of adjustment, the AOM dose can be increased again to achieve the desired therapeutic benefit.

Dosing of AOM in children is not adjusted based on age or size, rather on response to treatment. Children often tolerate doses as high or higher than adults with minimal adverse effects, may metabolize AOM at a faster rate, and may require more frequent dosing than adults. Factors such as school attendance and eating multiple meals in the school setting are factors that affect timing of medication and dietary compliance.

AOMs can be prescribed concurrently with other frequently prescribed medications used in the pediatric population, specifically with other stimulant medications. The obesity medicine specialist may consider giving the stimulant at one time of day and if using phentermine, prescribe for a different time (e.g. prescribe stimulant in the morning before school and phentermine at lunch). This schedule is useful for the patient with co-occurring obesity and ADHD who experiences rebound symptoms when long-acting stimulant levels are declining.

If intolerable side effects occur or there is no therapeutic response, the AOM should be discontinued, and additional options reviewed with the family. When a specific AOM is not effective, the medication fails to target the area(s) of energy dysregulation specific to the patient. Heterogeneity of response across all obesity therapies (including ILT, AOMs, and metabolic & bariatric surgery [MBS]) is expected, highlighting the need for ongoing, close monitoring by the obesity medicine team [89, 90]. As previously discussed, the patient did not fail to achieve a response, the medication did.

4.4.2. Long term follow-up appointments

Periodic follow-up is a critical part of chronic care in obesity management. No end date is placed on treatment; rather patient and family are counseled to expect frequent communication touch points during the initiation and progression of treatment. Patients and families are welcomed back for care at any point regardless of adherence with prior medical care or current obesity disease status. Encouraging patients to reconnect with the obesity interdisciplinary team especially when experiencing challenges is vital, as obesity is a chronic disease with expected relapses and treatment adjustments.

The duration of treatment should be discussed with the patient. Obesity is a chronic disease, and the management is lifelong. Management may not always involve pharmacotherapy. Similar to other chronic diseases, there will be periods of time when management will have to intensify and others when less management is necessary. The patient should be counseled on the nature of the disease and encouraged to seek treatment throughout the lifespan when necessary.

Children with obesity are often confronted with multiple, complicated chronic disorders requiring ongoing medical care. If the obesity medicine specialist makes the clinical assessment that the co-occurring disease is likely to improve or resolve with improvement in obesity status, then the obesity medicine specialist may wait to pursue complex and costly additional testing. Examples of co-occurring diseases that are likely to improve or resolve with improvement of obesity status are: the dyslipidemia of obesity, glycemic dysregulation (including T2DM), menstrual irregularities, PCOS, minor joint or back pain, NAFLD, and mild obstructive sleep apnea (OSA). In addition, many behavioral health disorders improve along with improvement in weight status.

If the co-occurring disease is significant and the obesity medicine specialist assesses that management will require more than obesity status improvement, then appropriate referrals are made. Examples of co-occurring diseases that should be addressed concurrently with treatment of obesity include but are not limited to: T2DM, dyslipidemia not likely to improve with nutritional modifications, debilitating joint or

Table 9
AOM considerations related to phenotype, co-occurring diagnoses, and monitoring advice in pediatric population
Abbreviations: AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA= N-methyl-D-aspartate; CI = contraindicated; SI = suicidal ideation, LFT = liver function tests.

Medication	Phenotype	Co-Occurring Dx	Monitoring Considerations
Phentermine	Difficulty feeling full		Monitor BP, particularly when titrating dose, monitor for side effects every 6–8weeks (more frequently during titration may be needed)
Phentermine/ Topiramate	Hungry brain, Food cravings	Migraine, BED, LOC-ED, to mitigate weight-promoting medications	Monitor the rate of weight loss in pediatric patients. If weight loss exceeds 2 pounds (0.9 kg)/week, consider dosage reduction.
Orlistat	Patient who wants to try over the counter med		Check baseline LFT, creatinine CI: Chronic malabsorption, cholestasis Counsel regarding: gastrointestinal side effects, use caution with levothyroxine, cyclosporine, AEDs, liver disease, renal impairment. Recommend multivitamin with fat-soluble vitamins hours before or after dosing.
Liraglutide	Hungry Gut	Prediabetes, insulin resistance, T2DM	Check baseline comprehensive metabolic panel, HgbA1c
Semaglutide	Hungry Gut	Prediabetes, insulin resistance, T2DM	Check baseline comprehensive metabolic panel, HgbA1c
Setmelanotide	LEPR, POMC, PCSK1 deficiency, BBS	Ongoing trials for other indications	Monitor for depression and SI, not recommended when breastfeeding
Naltrexone/ Bupropion	Hedonic/ emotional eating	Depression	Uncontrolled hypertension, seizures, taking MAOIs, pregnancy
Metformin		Prediabetes/T2DM, PCOS, insulin resistance to mitigate weight-promoting medications	Check BMP/CMP, HgbA1c if concerns for T1DM, creatine kinase autoantibodies, endocrinology consult Monitor Vitamin B12 in prolonged use, risk of metabolic acidosis
Topiramate	Food cravings, BED, compulsive eating pattern	Seizure, to mitigate weight-promoting medications	Check comprehensive metabolic panel, Urine pregnancy. To stop: wean slowly as abrupt cessation can precipitate seizure.

back pain, nonalcoholic steatohepatitis, severe behavioral health conditions, and severe OSA.

As part of ongoing chronic management, obesity medicine specialists consider combination therapies based on the patient's response to monotherapy as well as co-management of related diagnoses. Our understanding of the complexity of obesity pathophysiology, like many other complex, chronic diseases, illustrates that more than one medication, particularly one that offers a different MOA, will likely be required. Given that many children will overlap between phenotypes, utilizing combination therapy will provide more effective management. For example, a patient may achieve 8–11% BMI percentile reduction treated with phentermine/topiramate [95], yet continues to have glycemic dysregulation, whereby adding a GLP-1RA can provide further improvements in glucose metrics as well as provide an additional 7–16% BMI percentile reduction [94]. Ongoing research on triple-agonist medications may provide BMI percentile improvements approaching those observed via MBS, providing more tools to improving health outcomes for children.

Table 10
Adapted from: Table 10. Summary of pharmacotherapies including indications and minimum patient age. Copyright © 2022 Cuda et al. [4]. This is an open access article distributed under the terms of the Creative Commons Attribution License.

Pharmacotherapy Summary	Medication	Minimum Age (years)
FDA Approved for Indication of Pediatric & Adult Obesity	Orlistat	12
	Liraglutide (3.0 mg daily dose) * *Also has separate formulation that is FDA approved for indication of T2DM for ages 10 and older	12
	Phentermine/Topiramate	12
	Phentermine	>16
	Setmelanotide	6
	Semaglutide (2.4 mg weekly dose) * *Also has separate formulation that is FDA approved for indication of T2DM for 18 and older	12
FDA Approved for Indication of Adult (> 18 years) Obesity	Naltrexone/Bupropion	18
FDA Approved for Indication of T2DM	Metformin	10
	Exenatide	10
	Dulaglutide	18
	Tirzepatide	18
	Liraglutide (0.6, 1.2 or 1.8 mg daily dose) * *Also has a separate formulation that is FDA approved for indication of pediatric and adult obesity for ages 12 years and older	10
	Semaglutide (0.5, 1, or 2 mg weekly dose) * *Also has separate formulation that is FDA approved for indication of adult obesity for 18 years and older	18
FDA Approved for Alternate Indication(s)	Topiramate (Indication: Seizures) *Also indicated for migraine for 12 and older	2
	Lisdexamfetamine (Indication: ADHD) * *Also, FDA approved for indication of binge-eating disorder for 18 and older	6
	Bupropion (Indication: Depression/ Smoking Cessation)	18

4.5. Case (fictional) study: [Fig. 4]

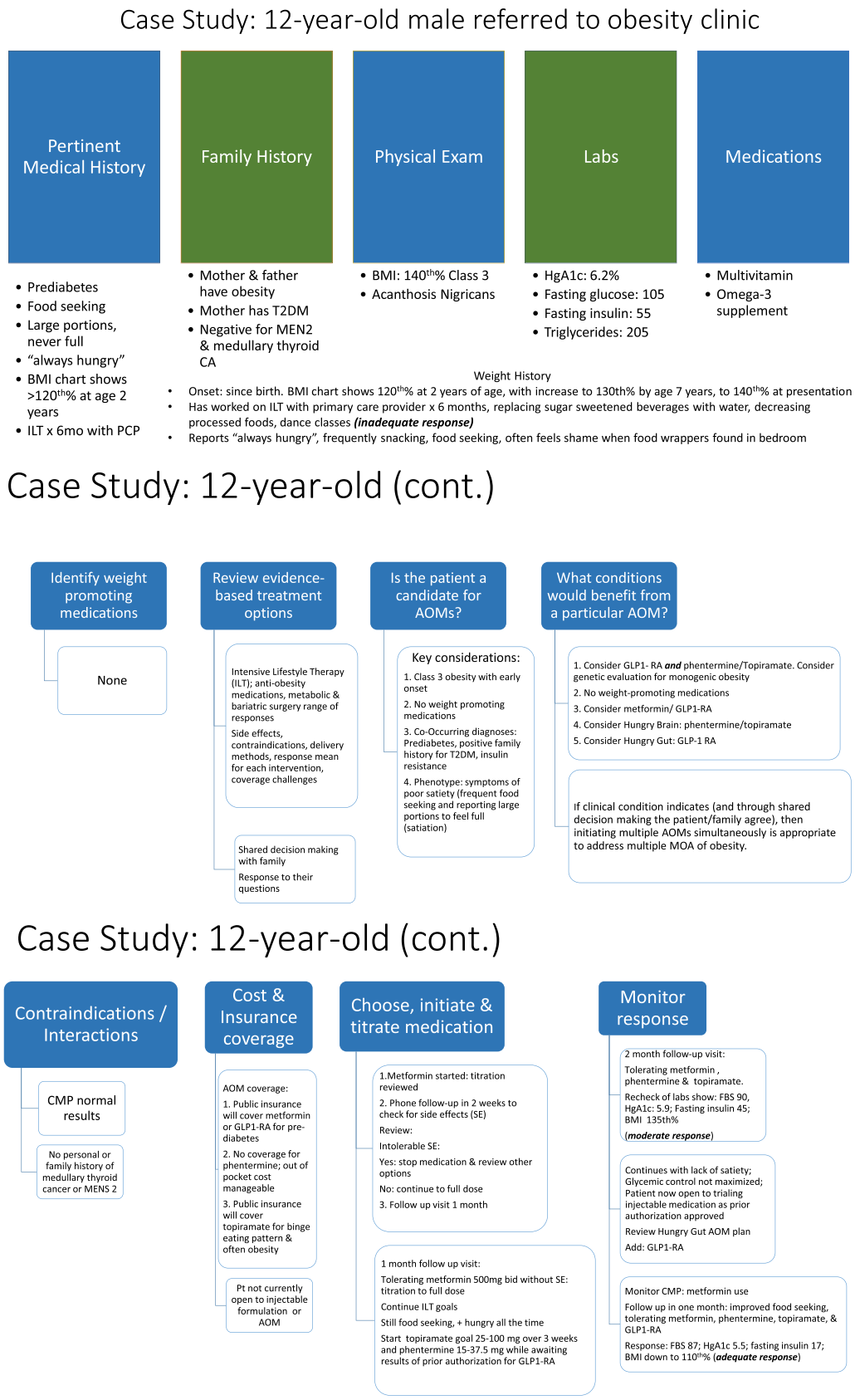

Fig. 4. Case study.

5. Conclusion

Pediatric patients living with the disease of obesity require the best evidence-based care available. The present cultural belief that children will "grow out of their obesity" is not supported by the last 20 years of data. As outlined in the OMA Pediatric Clinical Practice Statements [4, 13–16] as well as the American Academy of Pediatrics' 2023 Clinical Practice Guideline for treatment of childhood obesity [17], watchful waiting is no longer acceptable for a progressive chronic disease with far-reaching, profound, and negative outcomes. Significant data outlines that early and aggressive intervention for children and adolescents is required, particularly for those presenting with early severe onset of obesity with rapid upward trajectories, and class 2 and 3 obesity. Assessing each patient for weight-promoting medications, co-occurring obesity-related diseases, as well as considering key symptoms related to satiation, satiety, and energy regulation can all assist the obesity medicine specialist in guiding the development of a shared decision treatment plan. This plan builds on the foundation of healthy living goals. In many circumstances, addressing areas of dysregulation can allow for improved attainment of ILT goals, as their physiology is working with and not against their efforts.

The availability of AOMs, with varying MOA, has significantly increased, allowing for precision medicine treatment plans that address the complex pathophysiology of each individual patient. Ongoing research for additional dual and triple receptor pharmacotherapies hold additional treatment options. Communicating AOM outcome data, benefits, side effects and contraindications with patients and families is essential for shared-decision making. Current data indicate that obesity, as a chronic and relapsing disease, will require lifelong management similar to other chronic diseases. A new era has emerged with expanding therapeutic options that treat obesity as a chronic disease, not a behavioral lack of willpower. Meaningful obesity treatment improves physical and psychological health leading to removal of weight stigma and increased quality of life for children.

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Valerie O'Hara: Novo Nordisk Invited speaker.

Suzanne Cuda: Rhythm Gold Panel Speaker Bureau, Rhythm Advisory Board, and Novo Nordisk Adolescent Advisory Board.

Roohi Kharofa: Rhythm Pharmaceuticals: EMANATE trial; Rhythm Gold Panel Speaker Bureau.

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Nancy Browne: None.

Author contribution (CRediT authorship contribution statement)

All authors were involved in the conception of the article, contribution to the literature searches, and identification of pertinent articles. All authors critically reviewed the manuscript, and had final approval of the submitted version.

Ethical review

This submission represents the original work of the authors, supported by appropriately cited professional literature. This work did not involve human subjects. This case study represents an illustrative aggregate of clinical experiences encountered by the authors but does not represent the case history or presentation of any individual patient.

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Declaration of competing interest

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