Clinician's Guide for Pediatric Anti-obesity Medications

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KEYWORDS

• Pediatric obesity • Treatment • Pharmacotherapy • Anti-obesity medications

KEY POINTS

- Previous medication treatment gap between family based intensive health behavior and lifestyle treatment (IHBLT) and metabolic and bariatric surgery has now been filled with 4 Food and Drug Administration (FDA)-approved anti-obesity medications (AOM) commonly used in children: phentermine, phentermine/topiramate (Qsymia), liraglutide (Saxenda), and semaglutide (Wegovy).
- Orlistat and setmelanotide are also FDA-approved for pediatric use, but their application is limited. Metformin and topiramate are used off-label as well to facilitate weight loss.
- Pediatric clinicians should offer treatment for obesity that is individualized and available early in the treatment rather than offering a staged approach. Medications should be offered at 12 and older, and considered in younger children as more evidence emerges.
- AOM, in combination with IHLBT, ranges from 4% to 16% body mass index change when effective, depending on the specific treatment and response.
- Although structured weight loss in a medical setting is not associated with increased risk of eating disorders, assessment of eating disorder symptomatology or disordered eating prior to, and throughout treatment is important.

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BACKGROUND

Pediatric obesity is a complex and multifactorial disease. Knowledge of the underlying pathophysiology of obesity has evolved substantially over the last 10 years with promising options for anti-obesity medications (AOMs) in adults and now children as well. The weight set point, a defended level of body-fat mass, is regulated by the brain via complex, overlapping biologic and environmental mechanisms.[1] The neurologic control over this set point results in difficulty for some to lose weight, despite significant efforts to change lifestyle, as recommended by clinicians.[2] However, the recent advent of highly effective AOMs provide pediatric clinicians a powerful tool to treat obesity.

Pediatric obesity treatment guidelines have been released and updated over time in 1998,[3] 2007,[4,5] 2017,[6] and most recently in January of 2023,[7] respectively, all reflecting continued improvements in understanding of the pathophysiology and treatment of obesity. The most recent guidelines state "pediatricians and other pediatric health care providers should offer adolescents 12 years and older with obesity (body mass index [BMI] >95th percentile) weight loss pharmacotherapy, according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment".[7] The previous treatment gap between family-based intensive health behavior and lifestyle treatment (IHBLT) and metabolic and bariatric surgery has now been filled with 6 Food and Drug Administration (FDA)-approved medications for use in pediatrics, as well as an increasing literature base for other agents used in adults that can be used in the pediatric population.

The motivations, goals, and preferences of our patients, known as 'the patient voice', should be considered as clinicians communicate about obesity. Including the patient in the conversation is especially important to empower their role in shared-decision making and to increase treatment efficacy.

ASSESSMENT PRIOR TO STARTING ANTI-OBESITY MEDICATIONS

For many pediatric patients, especially those with severe obesity (Class 2 BMI 35 or BMI percentile 120% of the 95th percentile and Class 3 BMI 40 or BMI 140% of the 95th percentile), weight set point reduction is often necessary to allow successful sustained weight reduction and improvement in cardiometabolic risk.[8,9] Because IHBLT alone is unlikely to result in clinically meaningful weight reduction, frustration among patients, their family, and clinicians is a common experience in the clinical setting. AOMs can be especially effective in patients with obesity (BMI 30 or BMI percentile 95th percentile and above) for whom behavior modification has proven suboptimal for improving the control of obesity and targeting the treatment of obesity-associated comorbidities.[7,10] Reviewing expected weight loss outcomes from each AOM and other treatments can be helpful in shared-decision making with the patient and their family. Intensive lifestyle as monotherapy typically stabilizes weight or decreases by an average 1.8% BMI change from baseline with wide variability in response.[11] AOM in combination with IHLBT results in a variable BMI change when effective (ie, 4% for liraglutide – 16% for semaglutide with others agents between), depending on the specific treatment and response and surgery brings an average 33.8% percent BMI change. Layering multiple modalities may have additive effects. Each treatment also has a bell curve of response with some high responders, most moderate responders, and some non-responders.[11] Response to AOMs can usually be determined within the first 12 weeks, after titration to a clinically effective dose. A different medication or approach should be offered to non-responders.

Key historic components to review prior to selection of AOMs may include (1) assessment of phenotypic symptomatology, (2) current eating behaviors including screening for any disordered eating, and (3) assessment of any potential undertreated or undiagnosed comorbidities or endocrinopathies or medications that contribute to significant weight gain or are contraindications to starting AOM.

Phenotypic Symptomatology

Phenotypic symptomatology is a relatively new obesity medicine construct that includes patient experience of hunger, satiety, and satiation. Phenotype for AOM selection has the preliminary data in adult studies.[12] In pediatric practice, identified symptomatology may guide initial treatment selection.[13]

Eating Disorder Symptomatology

Eating disorder symptomatology is common in pediatric patients seeking weight management services. Although structured medical weight loss is not associated with an increased risk of eating disorders,[14] assessment of eating disorder symptomatology or disordered eating, prior to and throughout AOM therapy, is essential and can guide nutrition counseling and treatment. Appropriate treatment with AOMs can assist in normalizing hunger and fullness signaling, allowing remission or sometimes resolution of previous disordered eating symptoms.

Screening for Medical Conditions and Weight Gain Promoting Medications

It is important to screen for weight-related conditions (eg, hypertension [HTN], metabolic liver diseases, prediabetes/diabetes, hyperlipidemia [HLD], and obstructive sleep apnea) and endocrinopathies associated with obesity (eg, hypothyroidism and polycystic ovarian syndrome).[6,7] It is critical to check potential drug-drug interactions or for any concomitant weight-promoting medications. Often substitutions can be made that are weight neutral or facilitate weight loss.[15]

INITIATING PEDIATRIC ANTI-OBESITY MEDICATIONS

Initiating AOM with IHLBT is an iterative process with regular clinic visits for efficacy and safety. Current evidence supports treatment for obesity that is individualized and initiated early in the disease course versus a staged approach as previously recommended.[7] Close monitoring of BMI percentile and growth curves is important during initiation of AOMs. The goal should be gradual and sustained weight loss and adjustments of medication selection or dosage may be necessary if weight loss is too rapid or unhealthy eating patterns develop due to medication-induced anorexia. It is also beneficial to prepare families for the expected weight gain with the reduction or discontinuation of medications.

If patients ask if they will need to be on medications lifelong, discuss the chronic nature of obesity as a disease, similar to high blood pressure or diabetes. Likely the medications and dosages will change over time, but most patients, including adults and children, will need lifelong treatment for this chronic disease. All medications are intended to support improved healthy lifestyle implementation in addition to weight loss and will need adjustments based on treatment response.

AOM may not be appropriate if the clinician has identified significant body dysmorphia, poor self-esteem, or disordered eating that need treatment prior to initiation. Children with obesity have an increased prevalence and stable incidence of mental health needs, including pre- and post-surgery, supporting the need for assessment and treatment of mental health concerns throughout obesity care.[16]

ANTI-OBESITY MEDICATION SELECTION

Selection of AOM is based on medical history, clinical presentation, disease severity, insurance coverage, and availability of specific medications. An AOM algorithm can assist in selection (**Fig. 1**).

There are currently 4 FDA-approved AOM commonly used in children: phentermine, phentermine/topiramate (Qsymia), liraglutide (Saxenda), and semaglutide (Wegovy). Orlistat and setmelanotide are also FDA-approved for use in pediatrics, but their use is limited. Orlistat is not recommended per adult guidelines due to its side effect profile and poor efficacy.[17] Setmelanotide is currently indicated only for patients with specific genetic obesity syndromes.[7] Metformin and topiramate are used off-label as well to facilitate weight loss through different mechanisms (see **Table 1**).

Glucagon-like Peptide-1 receptor agonists reduce weight by delaying gastric emptying, resulting in increased satiety, and decreasing appetite and hunger. The most common side effects are nausea, vomiting, and diarrhea, and generally occur in the first few weeks and resolve over time.[17] For this reason, they are started at a low dose and titrated up to a therapeutic level over weeks to months. Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 is black box contraindications for this class due to thyroid C-cell tumors seen in rodents, but not yet seen in humans.[18]

Semaglutide (see **Table 1**) is a once weekly subcutaneous injection that has demonstrated the highest average weight loss response in pediatric obesity, and it is generally well-tolerated.[19,20] At a weekly dose of 2.4 mg with lifestyle intervention, semaglutide results in an average of 16.1% BMI reduction after 68 weeks[19] with a number needed to treat (NNT) of 2 to produce a BMI reduction of 5%.[19] Semaglutide is the first of the FDA-approved AOM for pediatrics to demonstrate improvement in weight-related quality of life.[19] Liraglutide is a once daily subcutaneous injection that is associated with a lower average response: 4.6% BMI reduction with an NNT of 4 to achieve a 5% BMI reduction.[21]

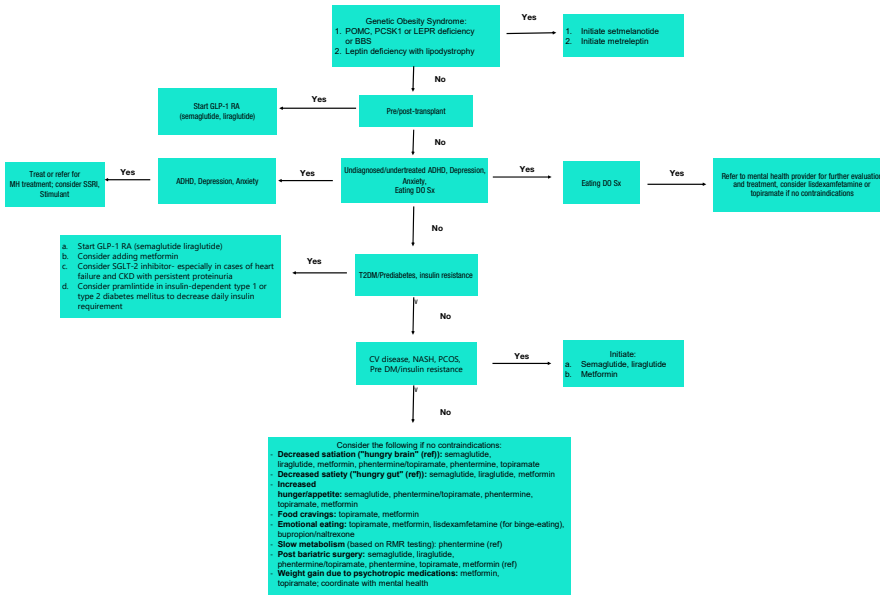

Fig. 1. AOM initial selection algorithm.

Table 1
Food and Drug Administration-approved anti-obesity medications in pediatrics

FDA-Approved AOMs in Pediatrics

Medication/FDA-Approval Age/ Mechanism of Action	Efficacy	Side Effects/Contraindications	Prescribing Information/ Management Tips	Ref
Semaglutide (Wegovy®) ≥ 12 year old GLP-1 receptor agonist	Mean change in BMI baseline to wk 68: *−16.1%* with semaglutide and 0.6% with placebo (95% CI, −20.3 to −13.2). Change in BMI ≥ 5% reduction: 76% ≥ 10% reduction: 63% ≥ 15% reduction: 57% ≥ 20% reduction: 40%	Primary side effects: Nausea, vomiting, diarrhea, constipation, gastroesophageal reflux, eructation, abdominal pain, dizziness, fatigue Additional side effects: • Thyroid C-cell tumor (Black Box Warning) • GLP-1 RA class effects: acute pancreatitis, gallbladder disease, hypoglycemia with concurrent glucose lowering medications, acute kidney injury, diabetic retinopathy complications, HR increase, suicidal behavior/ideation Contraindications: • Personal or family history of medullary thyroid cancer (MTC) or multiple endocrine neoplasia type 2 (MEN2)	Dosing: Wks. 1–4: 0.25 mg SQ weekly Wks. 5–8: 0.5 mg SQ weekly Wks. 9–12: 1.0 mg SQ weekly Wks. 13–16: 1.7 mg SQ weekly Wks. 17+: 2.4 mg SQ weekly Management Tips: • *Primary side effects peak at initiation and dose increases, often improve with continued use at stable dose.* • *Risk of side effects may decrease with a prolonged titration strategy (>4 w per dose level).* • *Titrate to the lowest effective dose to minimize side effects.* • *Regularly spaced small meals and adequate hydration can mitigate gastrointestinal side effects.* Patient selection to maximize benefits: • *History of prediabetes or diabetes, dyslipidemia, NAFLD, PCOS* • *History of pre-existing cardiovascular disease or heart failure with preserved ejection fraction* • *Abnormal satiety/"Hungry gut"*	19,43

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FDA-Approved AOMs in Pediatrics

Medication/FDA-Approval Age/ Mechanism of Action	Efficacy	Side Effects/Contraindications	Prescribing Information/ Management Tips	Ref
Liraglutide (Saxenda®) ≥ 12 y old GLP-1 Receptor Agonist	Mean change in BMI baseline to w 56: −*4.29%* with liraglutide and 0.35% with placebo (95% CI, −7.14 to −2.14). Change in BMI ≥ 5% reduction: 43.3% ≥ 10% reduction: 26.1%	As described earlier for semaglutide	Dosing: Wk. 1: 0.6 mg SQ daily Wk. 2: 1.2 mg SQ daily Wk. 3: 1.8 mg SQ daily Wk. 4: 2.4 mg SQ daily Wk. 5+: 3.0 mg SQ daily Management Tips: • *As described earlier for semaglutide* • *The variable dose pen design allows for a broader range of possible doses that may be considered for more gradual dose escalation to further limit GI side effects* Patient selection to maximize benefits: • *As described earlier for semaglutide*	21,44
Phentermine/topiramate-ER (Qsymia®) ≥ 12 year old Phentermine - sympathomimetic amine Topiramate – increases GABA activity, antagonizes glutamate receptors, inhibits carbonic anhydrase,	Mean change in BMI baseline to wk 56: −*7.11%* with top-dose PHEN/TPM (placebo subtracted −10.44%) (95% CI, −13.89 to −6.99) −*4.78%* with mid-dose PHEN/TPM (placebo subtracted	Primary side effects: Dizziness, pyrexia, paresthesia, dysgeusia, depression, anxiety, insomnia Additional side effects: Embryo-fetal toxicity, HR increase, mood disorders, sleep disorders, cognitive impairment (disturbances in	Dosing: Wks. 1–2: 3.75 mg/23 mg PO daily in AM Wks. 3–14: 7.5 mg/46 mg PO daily in AM • If <3% TBWL, then discontinue or increase Wks. 15–16: 11.25 mg/69 mg daily in AM	22,45

modulates neuronal voltage gated sodium channels	−8.11%) (95% CI, −11.92 to −4.31) Change in BMI with top-dose ≥ 5% reduction: 46.9% ≥ 10% reduction: 42.5% ≥ 15% reduction: 28.3% Change in BMI with mid-dose ≥ 5% reduction: 38.9% ≥ 10% reduction: 31.5% ≥ 15% reduction: 13.0%	attention, memory, or speech/ language), suicidal behavior/ ideation, risk of acute myopia and secondary angle closure glaucoma, slowing of linear growth, metabolic acidosis and decrease in renal function Contraindications: • History of glaucoma or hyperthyroidism • Monoamine oxidase inhibitor (MAOI) therapy within 14 d	Wks. 17–29: 15 mg/92 mg daily in the AM • If <5% TBWL, then discontinue Management Tips: • Pregnancy test prior to initiation and prn; recommend effective contraception • Consider dose reduction or discontinuation if abnormalities arise: BP, HR, neuropsychiatric conditions, electrolytes and creatinine • *Prescribing separately off-label may help reduce the cost compared to the combination capsule* Patient selection to maximize benefits: • *Abnormal satiety/"hungry gut"*
Phentermine ≥ 16 year old Sympathomimetic amine	Change in BMI baseline to 6 mo of phentermine 15 mg compared to standard of care was *−4.1%* (95% CI, −7.1 to −1.0). ≥ 5% reduction in BMI: 63.6%	Primary side effects: Dry mouth, palpitations, tachycardia, elevated BP, overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis, changes in libido Additional side effects: Primary pulmonary HTN (rare case reports), valvular heart disease (rare case reports), development of tolerance	Dosing: [23,46] • Capsules: 15 mg, 30 mg, and 37.5 mg (equivalent to 30 mg base) • Tablets: 8 mg, 37.5 mg (equivalent to 30 mg base) • *Typically start at 15 mg or 18.75 mg (1/2 tablet of 37.5 mg) PO daily for 1 mo. If no improvement in obesity or weight plateaued after 1 mo, then consider increasing to phentermine 30 mg or 37.5 mg daily*

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FDA-Approved AOMs in Pediatrics

Medication/FDA-Approval Age/ Mechanism of Action	Efficacy	Side Effects/Contraindications	Prescribing Information/ Management Tips	Ref
		Contraindications: • History of CV disease (eg, coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled HTN) • MAOI therapy within 14 d • Others: hyperthyroidism, glaucoma, agitated states, history of drug abuse	Management Tips: • Use lowest effective dose to limit side effects • Monitor BP, HR, and neuropsychiatric symptoms prior to initiation and periodically during use; consider dose reduction or discontinuation for clinically significant dysfunction • Development of tolerance to the anorexiant effect commonly develops; do not exceed recommended dose to overcome tolerance • *Long-term, off-label use of phentermine is common, but state law and state medical board guidance takes precedence* Patient selection to maximize benefits: • *Low predicted energy expenditure/"slow burn"*	

Orlistat ≥ 12 year old Inhibits gastrointestinal lipases	The change in BMI from baseline to trail completion ranged from −1.44 to −1.3 at 6 mo and *−0.55* at 12 mo. The between group differences ranged from −0.94 (95% CI, −1.58 to −3.0) to −0.50 (95% CI, −7.62–6.62) at 6 mo and −0.86 at 12 mo.	Primary side effects: Steatorrhea and oily discharge, soft stool, increased frequency/urgency of bowel movements, flatulence, fecal incontinence Additional side effects: Decreased absorption of fat-soluble vitamins, increased urinary oxalate (calcium oxalate nephrolithiasis), cholelithiasis, liver injury Drug interactions (cyclosporine, levothyroxine, amiodarone, warfarin, anticonvulsants, antiretrovirals, etc) Contrindications: • Chronic malabsorption • Cholestasis	Dosing: [24,47] • 120 mg TID with each meal containing fat (during meal or 1 h after meal) • *Orlistat 60 mg (Alli®) is available without prescription, but it is not approved for pediatrics* Management Tips: • Gastrointestinal symptoms are more common with a high fat diet • All patients should take a daily multivitamin that includes vitamin A, D, E, K and beta carotene • Monitor levels of other drug therapy more frequently. Patient selection to maximize benefits: • *Chronic constipation* • *Last resort*
Setmelanotide ≥ 6 year old with monogenic or syndromic obesity due to: POMC deficiency, PCSK1 deficiency, or LEPR deficiency confirmed on FDA-Approved genetic test resulting in biallelic variants interpreted as pathogenic, likely pathogenic, or undetermined significance; Bardet-Biedl Syndrome MCR-4 receptor agonist	POMC or PCSK1 • Mean % change in body weight baseline to wk 52 *−25.6%* (90% CI, −28.8 to −22.0) • ≥ 10% reduction in total body weight: 80% LEPR • Mean % change in body weight baseline to wk 52 *−12.5%* (90% CI, −16.1 to −8.8) • ≥ 10% reduction in total body weight: 45%	Primary side effects: Skin hyperpigmentation, headache, fatigue, dizziness, nausea, vomiting, diarrhea, abdominal pain, back pain, depression, and spontaneous penile erection Additional side effects: Disturbance in sexual arousal (males and females), depression and suicidal ideation, hypersensitivity reactions, skin hyperpigmentation and	Dosing: [25,48] • ≥12 year old start dose: 2 mg SQ daily • ≥6 to < 12 year old start dose: 1 mg SQ daily • Target dose: 3 mg SQ daily • Dose titration: If the starting dose is not tolerated, then reduce the dose by half. If the reduced dose is tolerated for at least 1 wk, then repeat a trail of the starting dose. If the starting dose is tolerated for 2 wk, then

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FDA-Approved AOMs in Pediatrics

Medication/FDA-Approval Age/ Mechanism of Action	Efficacy	Side Effects/Contraindications	Prescribing Information/ Management Tips	Ref
	BBS • Mean % change in body weight baseline to wk 52 *−5.2%* (SD 7.9) • ≥ 10% reduction in total body weight: 32.3%	darkening of pre-existing nevi, risk of benzyl alcohol reaction in neonates Contraindications: Hypersensitivity reaction to setmelanotide or its components	increase to 3.0 mg subcutaneously once daily Management Tips: • Perform a full body skin exam prior to initiation and periodically • Seek emergency care if erection longer than 4 h • Train patients on SQ injection, and how to withdraw from the vial • Assess efficacy for weight loss at 12–16 wk in patients with POMC, PCSK1, or LEPR deficiency or *1 y in patients with BBS*	

Non-FDA-Approved Mediations Commonly Used Off-Label for Obesity

Medication/FDA-Approved Indication/Mechanism of Action	Efficacy	Side Effects/Contraindications	Prescribing Information/ Management Tips	Ref
Tirzepatide (Zepbound®) GLP-1 receptor and GIP receptor co-agonist Overweight/obesity in adults with BMI ≥27 with obesity related comorbidity or a BMI ≥30; Type 2 diabetes in adults	There is no pediatric data available at this time but in clinical trials for adolescents. Double-blinded, randomized, controlled trial in adults (n = 2539) overweight/obesity (mean BMI 38) mean % change in total body weight baseline to 72 wk: −15.0%, −19.5%, and −20.9% with tirzepatide 5.0 mg,	Primary side effects: Nausea, vomiting, diarrhea, constipation, eructation, gastroesophageal reflux, abdominal pain, hair loss, fatigue Other side effects: • Thyroid C-cell Tumor (Black Box Warning) • Other GPL-1 RA class effects (see semaglutide)	Dosing: Wks. 1–4: 2.5 mg SQ weekly **Only do subsequent dose escalation if needed for further improvement in obesity is needed.* Wks. 5–8: 5 mg SQ weekly Wks. 9–12: 7.5 mg SQ weekly Wks. 13–16: 10 mg SQ weekly Wks. 17+: 15 mg SQ weekly	49,50

	10.0 mg, and 15.0 mg compared to −3.1% with placebo.	Contraindications: • Personal or family history of MTC or MEN2	Management Tips: • *As described above for semaglutide* • Recommend female patients switch to a non-oral contraceptive therapy or add a barrier method of contraception for 4 wk after initiation and subsequent dose escalations Patient selection to maximize benefits: • *As described above for semaglutide*	
Dulaglutide GLP-1 receptor agonist Type 2 diabetes mellitus in patients ≥10 year old; adverse cardiovascular disease reduction in adults with type 2 diabetes and established cardiovascular disease or multiple cardiovascular disease risk factors	In a double-blinded, placebo-controlled trial of dulaglutide 0.75 mg or 1.5 mg in pediatric (n = 154) who were 10–17 y (mean 14.5) with type 2 diabetes (mean HgbA1c 8.1%) there was no significant difference in body weight end-points from baseline to 52 wk. In a randomized control trial of adult patients with type 2 diabetes inadequately controlled with metformin, dulaglutide 4.5 mg was superior to 1.5 mg and there appeared to dose response relationship with body weight reduction. The mean weight loss from baseline to wk 52 was −3.5 kg, −4.3 kg, and −5.0 with dulaglutide 1.5 mg, 3.0 mg, and 4.5 mg respectively from a baseline weight of 95.5 kg, 96.3 kg, and 95.4 kg.	As described earlier for semaglutide	Dosing: [51,52,59] Wks. 1–4: 0.75 mg SQ weekly *Only do subsequent dose escalation if needed for further improvement in obesity. Wks. Wks. 5+: 1.5 mg SQ weekly • Only the 0.75 mg and 1.5 mg doses are approved for pediatric type 2 diabetes • 3.0 mg and 4.5 mg have not been studied in pediatrics Management Tips: As described earlier for semaglutide Patient selection to maximize benefits: • *As described above for semaglutide*	

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Non-FDA-Approved Mediations Commonly Used Off-Label for Obesity

Medication/FDA-Approved Indication/Mechanism of Action	Efficacy	Side Effects/Contraindications	Prescribing Information/ Management Tips	Ref
Metformin Biguanide – decreases hepatic gluconeogenesis, decreases intestinal glucose absorption, increases peripheral insulin sensitivity Type 2 diabetes mellitus in patients ≥10 year old	Systematic review and meta-analysis (8 studies, n = 616 patients 6–19 y with obesity (weighted mean BMI 36.0)) • Metformin (typical dose 1–2 g/day) with IHLBT • Change BMI z: – 0.10 (95% CI, −0.17 to −0.03) • Reduction in BMI was −0.86 (95% CI, −1.44 to −0.29).	Primary side effects: Diarrhea, flatulence, abdominal cramping, abdominal cramping, nausea/vomiting, headache Other side effects: Lactic acidosis (Black Box Warning), vitamin B12 deficiency, hypoglycemia with concurrent use of glucose lowering medications Contraindications: Acute or chronic metabolic acidosis	Dosing: *Typically start at 500 mg once daily with a meal. Gradually increase by 500 mg in 1–2 divided doses every 1–2 wk. Typical top dose for obesity management is 1000 mg to 2000 mg in 1–2 divided doses depending on formulation.* Management Tips: • Taking with a meal may reduce the risk of gastrointestinal side effects. • Slow dose escalation may improve tolerability Patient selection to maximize benefits: • *Patients with type 2 diabetes mellitus, prediabetes, or polycystic ovarian syndrome* • *Patients who have experienced weight gain due to psychotropic medications*	53,54

Topiramate Increases GABA activity, antagonizes glutamate receptors, inhibits carbonic anhydrase, modulates neuronal voltage gated sodium channels Epilepsy in patients ≥2 year old Migraine prophylaxis in patients ≥12 year old	Retrospective study 28 patients (mean 15.2 y, SD 2.5) with obesity (mean baseline BMI 46.2, SD 10.3) • Topiramate (most prescribed as 75 mg daily) with IHLBT • Mean % change in BMI at 6 mo: – 4.9 (95% CI, −7.1 to −2.8). ≥5% reduction in BMI: 50% ≥10% reduction in BMI: 13.6%	Primary side effects: Paresthesia, hypoesthesia, changes in taste, fatigue, somnolence, dizziness, changes in mood Additional side effects: Acute myopia and secondary angle closure glaucoma, oligohidrosis, and hyperthermia, metabolic acidosis, nephrolithiasis, teratogenic, may decrease efficacy of oral contraceptive therapy, suicidal behavior/ ideation, cognitive and psychiatric disturbances (psychomotor slowing, difficulty with memory, speech disorders, nervousness) Contraindications: Hypersensitivity reaction to topiramate or its components	Dosing: *Typically start at 25 mg PO daily in the evening for 2 wk then increase to 50 mg total daily dose in 1–2 divided doses.* *If not experiencing improvement in obesity or improvement has plateaued, then consider increasing by 25 mg (generally, 100 mg is the maximum daily dose for obesity in most patients).* Management Tips: • Check a basic metabolic panel at baseline and periodically to assess for metabolic acidosis • Assess for mood disorders and changes in mood at baseline and periodically during treatment • *Review potential to decrease efficacy of oral contraceptive therapy and recommend barrier contraception to prevent unintended pregnancy* • *Consider evening dosing if experiencing daytime fatigue/ somnolence* Patient selection to maximize benefits: • *Patients with migraines or idiopathic intracranial hypertension not on other carbonic anhydrase inhibiting therapy*	[55,56]

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Non-FDA-Approved Mediations Commonly Used Off-Label for Obesity

Medication/FDA-Approved Indication/Mechanism of Action	Efficacy	Side Effects/Contraindications	Prescribing Information/ Management Tips	Ref
			• *Used in combination with concurrent sympathomimetic therapy* • *Patients with impulsive eating, emotional/stress eating, binge type eating, or night eating syndrome*	
Naltrexone/bupropion ER tablets Naltrexone – opioid receptor antagonist Bupropion – inhibits reuptake of dopamine and norepinephrine Overweight/obesity in adults with BMI ≥27 with obesity related comorbidity or a BMI ≥30	There are no pediatric data available for naltrexone/ bupropion. There are no pediatric data available assessing the efficacy of naltrexone monotherapy or bupropion monotherapy on obesity. - BMI changes in adolescents (n = 296, mean age 16.3 year old) in a clinical trial evaluating bupropion for smoking cessation: decrease in BMI z-score (−0.16 (95% CI, −0.29 to −0.04)) from baseline to 6 wk in the 300 mg/day group, but this was not significant at 26 wk.	Primary Side effects: Headache, dizziness, fatigue, anxiety, irritability, insomnia, dry mouth, tremor, elevated blood pressure, palpitations, nausea, vomiting, diarrhea or constipation Other side effects: Suicidal Behavior and Ideation (Black Box Warning), neuropsychiatric symptoms have been reported in the setting of smoking cessation (Black Box Warning), increased blood pressure and heart rate, decreased seizure threshold, hepatotoxicity associated with naltrexone, angle closure glaucoma, hypoglycemia with concurrent glucose lowering medications	Dosing: • Tablet: 8 mg naltrexone/90 mg bupropion • Titration: 1 tablet once daily for 1 wk, then 1 tablet twice daily for 1 wk, next 2 tablets every morning and 1 tablet every evening for 1 wk, and lastly 2 tablets twice daily. Management Tips: • Assess for depression and suicidal ideation at baseline and periodically throughout treatment • Assess blood pressure (BP) and heart rate (HR) at baseline and periodically throughout treatment • *Prescribing separately off-label may help reduce the cost compared to the combination capsule*	[57,58]

		Contraindications: • Uncontrolled hypertension • Seizure disorders • Anorexia nervosa or bulimia • Abrupt discontinuation of alcohol, barbiturates, benzodiazepines, and anti-epileptic drugs • Concurrent opiate therapies • MAOI therapy within 14 d	• *If prescribing separately, then may start together or sequentially.* Patient selection to maximize benefits: • Abnormal hedonic eating/ "Emotional hunger"
Metreleptin Leptin analogue Leptin deficiency in patients with congenital or acquired generalized lipodystrophy	In a study of 3 pediatric patients with obesity and congenital leptin deficiency treated with recombinant human leptin, there were improvements in obesity as demonstrated by decreased BMI, decreased fat mass, and increased lean mass. There were also beneficial changes in feeding behaviors and endocrine function. The percentage BMI change from baseline to 6 mo was −13.9%, −18.1%, and −12.3% for patient A, B, and C respectively and −31.5% and −40.18% from baseline to 36 mo for patient A and B respectively.	*Metreleptin has a Risk Evaluation and Mitigation Strategy (REMS) program for prescribers and pharmacies.* Primary side effects: Headache, hypoglycemia with concurrent glucose lowering medications, decreased weight, abdominal pain, nausea, dizziness, fatigue, arthralgia Additional side effects: • Development of neutralizing antibodies (Black Box Warning) • Risk of T-cell lymphoma (Black Box Warning) • Progression of other autoimmune disorders • Benzyl alcohol toxicity	Dosing: [26,27] • ≤ 40 kg: starting dose is 0.6 mg/kg/day, increase or decrease by 0.02 mg/kg to a max daily dose of 0.13 mg/kg. • > 40 kg: ○ Males: starting dose is 2.5 mg/kg/day, increase or decrease by 1.25–2.5 mg/day to maximum dose of 10 mg/day ○ Females: starting dose is 5 mg/kg/day, increase or decrease by 1.25–2.5 mg/day to maximum dose of 10 mg/day Management tips: • Test for neutralizing antibodies in patients with severe infection or loss of efficacy to therapy • Consider benefits and risk of treatment in patients with hematologic abnormalities or acquired general lipodystrophy • Consider dose reduction of glucose lowering medications

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Non-FDA-Approved Mediations Commonly Used Off-Label for Obesity

Medication/FDA-Approved Indication/Mechanism of Action	Efficacy	Side Effects/Contraindications	Prescribing Information/ Management Tips	Ref
		Contrindications: • General obesity not associated with congenital leptin deficiency	• Use preservative-free sterile preparation in neonates and infants to avoid benzyl alcohol	

The combination oral medication phentermine/topiramate is FDA-approved for children 12 years and older with obesity. Phentermine is a monoamine sympathomimetic, which is believed to increase norepinephrine in the central nervous system (CNS) and decreased appetite. The weight loss mechanism of action of topiramate is thought to occur through modulation of gamma-aminobutyric acid receptors in the CNS.[17] Phentermine/topiramate extended release results in a 10.44% BMI reduction with an NNT of 3 to achieve a 5% BMI reduction.[22] Although uncontrolled HTN is a contraindication with phentermine, improved blood pressure was seen with phentermine/topiramate treatment. Topiramate is FDA-approved for seizures 2+ years old and migraine prophylaxis 12+ years old.[17] Female patients of child-bearing potential should be counseled of the teratogenic risks of topiramate and the importance of reliable contraception.[17] If insurance does not cover combination phentermine and topiramate, the provider can consider prescribing them separately, although results and side effects may vary with extended- versus immediate-release medications.

Tips for prescribing phentermine and topiramate separately:

- Start both together or start a single medication (phentermine or topiramate) and monitor for weight loss and tolerability for 1 month, then start the other medication if not meeting weight loss or lifestyle/comorbidity improvement goals.
- Phentermine
  - If not experiencing control of symptoms or lack of improvement in weight status after 1 month, consider increasing to phentermine 15 mg, 30 mg, or 37.5 mg daily in the morning.
- Topiramate
  - Typically start with 25 mg per os daily in the evening for 1 to 2 weeks then increase to 50 mg total daily dose in 1 or 2 daily doses.
  - If not experiencing improvement in symptoms, or weight status, consider increasing by 25 to 50 mg (generally 75–100 mg daily dose offers maximal effect for obesity; higher doses can be used if seeking migraine control).

In adolescents and children, monotherapy phentermine results in a 4.1% BMI reduction at 6 months with an NNT of 4 to achieve a 5% BMI reduction.[23] Durations of how long phentermine can be prescribed varies by state.

Orlistat is the least effective FDA-approved AOM and has the largest side effect burden. It works by inhibiting gastrointestinal tract lipase. It is generally taken 3 times a day with meals. In adolescents, orlistat has an NNT of 10 to achieve a 5% BMI reduction.[24]

Setmelanotide is a melanocortin-4-receptor agonist, which restores function in the melanocortin pathway for appetite regulation in patients with disruptions upstream of the MC4 receptor. Clinical studies are limited due to the rarity of the condition, but 80% of patients with POMC or PCSK1 deficiency and 45% of patients with LEPR deficiency achieved a 10% BMI reduction after 1 year.[25] Metreleptin is a leptin analogue used for leptin deficiency in patients with congenital or acquired generalized lipodystrophy.[26,27] In 3 pediatric patients with obesity and congenital leptin deficiency treated with recombinant human leptin, there were improvements in obesity as demonstrated by decreased percent BMI 12.3% to 18.1% at 6 months and 31.5% to 40.18% at 36 months.[26,27] Strongly consider screening children with hyperphagia and severe obesity for these genetic disorders.[7,25] Note that Bardet-Biedl Syndrome is considered a clinical diagnosis and does not require a confirmatory genetic test, as there are genes responsible that remain unknown (**Box 1**).[28]

As discussed in **Table 1**, some medications are often used off-label for weight management.[29] This means they are not FDA-approved for obesity, but show clear benefit

Box 1
Bardet Biedl syndrome

- Diagnosis *4 primary criteria* or *3 primary and 2+ secondary*
  - Primary
    - Visual impairment (retinal abnormalities)
    - Obesity (usually by age 1)
    - Hypogonadism
    - Renal anomalies (malformation or function)
    - Learning disabilities
  - Secondary
    - Developmental delays/neurologic problems
    - Olafactory dysfunction
    - Oral/dental abnormalities
    - Cardiovascular and other thoaco-abdominal abnormalities
    - GI abnormalities
    - Metabolic Abnoramlities:T2DM, metabolic syndrome, subclinical hypothyroid, PCOS
    - Strabismus, astigmatism, cataracts
    - Brachydactlyly/syndactyly

Clinical Diagnosis.[28]*Genetics not required, but may support diagnosis.

for weight loss. Off-label prescribing is a common and accepted practice in medicine, especially in pediatrics where pharmaceutic studies are conducted less often.[7,30] If prescribing medications off-label, be sure to discuss that the safety and side effect profiles of these medications, which are often are well-established even in pediatric patients for different indications (eg, topiramate) and document the discussion.[30]

MONITORING DURING MANAGEMENT WITH ANTI-OBESITY MEDICATIONS

hen determining effectiveness of AOM in pediatric patients, typical reference goal is 5% BMI reduction from baseline at 12 weeks.[17] In the pediatric population, weight stabilization and decreased rate of BMI% increase is also beneficial. Recommended follow-up visit after initiation of AOM is 2 to 4 weeks, depending on clinical availability. This can be facilitated by clinical nursing for "goal checks" as well. Remember to consider the "patient voice" and not use "weight check" as the reason for visit, as it can minimize the patient's efforts and overly focus on weight as a marker of improvement, rather than an improvement in quality of life, comorbidities, and lifestyle. At follow-up visits, continue to monitor any pubertal changes, anthropometrics including growth curves, side effects, and eating behaviors. Effective AOM typically leads to normalization of hunger and satiety, improved eating patterns, decreased snacking and portions, and improvement in weight.

AOMs can have central acting effects in the brain, which can disrupt the neuropsychiatric axis. Therefore, regular assessment of cognition, self-esteem, body image, and mood is essential. The clinician can consider using standardized tools such as Generalized Anxiety Disorder[31] or Beck Depression Inventory for adolescents and baseline and follow-up visits.[32,33]

Ongoing nutrition counseling after initiation of successful AOM to support healthy eating patterns, food choices, and water intake is important due to decrease in hunger and thirst cues. Some patients have AOM-induced anorexia with dramatic reduction in hunger drive with minimal consumption and/or rapid weight loss and will therefore need a reduction in dose or change to an alternate therapy to assure sufficient consumption of food throughout the day.

When initiating treatment with a GLP1 RA, the recommendation is to start with a low dose, monitoring closely for any side effects including nausea, vomiting, or other GI

side effects such as diarrhea, constipation, or bloating. Antiemetics, such as ondansetron, can be used in the short term to assist. However, ongoing nausea and vomiting is an indication for dose adjustment or discontinuation.

Monitoring body composition and physical activity is also essential throughout treatment.[34] Measurement of body composition using a bioelectrical impedance scale[35] or dual energy X-ray absorptiometry would be ideal but is not available in most settings. In the absence of direct measurement availability, screening for increased fatigue, feeling unwell, weakness, or decreased exercise performance can be signs of muscle loss. Ensuring adequate protein intake and physical activity can support preservation of muscle mass. Laboratory management is also important. Based on experience in post-bariatric patients, consider checking laboratories every 6 to 12 months during weight loss, including Vitamin D, iron, B1, and B12 levels. Also consider a daily multivitamin or bariatric vitamin and 1000 to 1200 mg of calcium daily, especially if there is a concern for poor nutritional intake.[36]

Finally, we recommend treating obesity like any other chronic disease and encourage the same prescribing practices. Due to weight bias, clinicians may try to dissuade families from using indicated AOMs and place requirements prior to treatment. These can include an increased frequency of pregnancy tests or specific lifestyle changes, requiring a family to "earn" AOMs. For other chronic diseases like diabetes, for example, the patient would not have to show they can adopt a healthy lifestyle prior to an anti-diabetic prescription.

The goal of treatment in obesity medicine is to help prevent and treat weight-related comorbidities, not simply achieve a "normal" BMI. Many conditions such as HTN, metabolic liver disease, type 2 diabetes mellitus, HLD, and sleep apnea can be significantly improved with weight loss of 10% to 20% from baseline weight.[37] Because this level of weight loss is now achievable with novel medications, such as GLP-1 RA medications and setmelanotide, which target underlying physiologic abnormalities, withholding these treatments is a disservice to our patients.

SPECIAL POPULATIONS AND ANTI-OBESITY MEDICATIONS

Pre- and Post- Bariatric Surgery

It is common to use AOM pre- and post-bariatric surgery as part of an intensive multidisciplinary program. In the immediate post-operative period, medications are generally held until 3 to 6 months post-surgery. Monitoring for weight regain or failure to achieve weight loss goals can be indications for AOM support, either starting or restarting AOM from prior to surgery.[36,38] Setting expectations before surgery that AOM may still be required can be helpful.

Patients with Special Needs/Genetic Disorders of Obesity

Children with secondary diagnoses and genetic disorders of obesity often have intellectual disability and behavioral dysregulation, requiring additional psychoactive medications. These medications are necessary, especially to control symptoms of aggression, irritability, impulsivity, depression, and anxiety. AOM may be needed to counteract weight gain associated with the child's diagnosis and other medications, commonly metformin, topiramate, and attention deficit hyperactivity disorder stimulants[39,40]

INPATIENT PEDIATRIC OBESITY MANAGEMENT

Inpatient treatment provides a controlled environment to practice lifestyle modifications, close monitoring of AOM response, and the opportunity to overcome barriers

to care, such as a lack of insurance coverage.[41] If obesity is considered a life-threatening risk factor, insurance coverage for potent AOMs (ie, semaglutide) can be secured through an appeal for medical-necessity prior to discharge. A timely outpatient follow-up visit should be scheduled to ensure continuity of care.

ROLE OF THE PRIMARY CARE CLINICIAN

Due to shortage of obesity specialists, the majority of obesity care will be offered by primary care providers (PCPs). However, many PCPs site significant barriers to using AOMs, including the lack of training, specialty support, time or availability, and obesity bias.[42] With additional training and support, there are advantages to PCPs managing treatment of obesity. PCPs have the benefit of managing chronic weight-related diseases in addition to obesity, which often improve with AOM therapy. The strong therapeutic relationship with the patient and their family and understanding of the patient's health goals can lead to increased efficacy of obesity treatment. Since PCPs have long-term relationships, they have many opportunities to counsel, encourage and congratulate patients on these changes.

ACCESS TO ANTI-OBESITY MEDICATIONS

Current access to AOM is, unfortunately, limited for many patients. Insurance coverage is improving but has also been limited and requires a time-consuming prior authorization process. When approved, current AOM shortages cause inconsistent treatment with patients having to stop and restart AOM. If there is a treatment gap for less than 6 weeks, it is recommended to restart at a lower dose, but not the starting dose if the patient had minimal side effects after initiation.

To facilitate starting AOM therapy, empower caregivers or patients to contact their insurance companies to inquire about coverage and, if covered, contact several pharmacies regarding supply. Consider waiting to start until they have 2 months of medication in hand. It can also be helpful to have a team to help complete prior authorizations and to follow-up with patients, as these are often required for AOM. If one AOM is denied by insurance or not available, consider using alternative oral medications, which are much less expensive (see **Table 1**). Limited insurance coverage and supply have commonly led to decreased access for those who are uninsured, underinsured, and economically disadvantaged.

SUMMARY

There is increasing evidence that obesity is a chronic disease with well-documented risks. The hesitancy of PCPs to use AOM is understandable, but also questioned, as the need for weight management is critical. PCPs are encouraged to embrace this evolving landscape, fortify their expertise, and actively engage in treating patients struggling with this chronic condition.

CLINICS CARE POINTS

- Assess patients for iatrogenic weight gain and other causes of obesity, eating disorder sympoms, and comorbidities; consider medication changes to prevent iatrogenic weight gain and treat comobidities when uncovered.
- Discuss advanced options for weight managment treatment and enter into shared decision making with the family.
- Select AOM based on patient needs, including starting BMI and symptamatology.

- Monitor for response and follow up frequently in the tritration phases of AOM. Once in remission and stable at new setpoint, continue to monitor at least every 6 months as you do for other stable chronic diseases.

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