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A New Era in Pediatric Weight Management: Anti-Obesity Medications for Adolescents

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Speaker Disclosure

- We have no financial disclosures.

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Off-Label Use

- We will discuss off-label use.

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Learning Objectives

- Acknowledge selected key action statements of the 2023 AAP Clinical Practice Guideline for children and adolescents with obesity.
- Describe anti-obesity medications available to treat pediatric obesity.
- Identify important considerations when choosing an anti-obesity medication for an individual patient.
- Recognize how to monitor patients prescribed anti-obesity medications.

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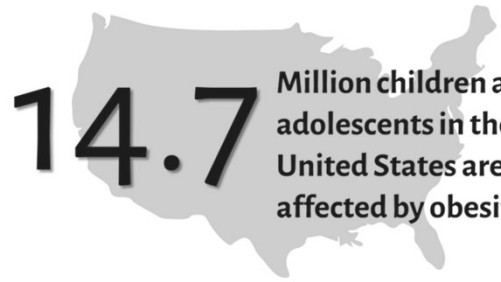

Center for Disease Control and Prevention, 2022

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Obesity affects the immediate and long-term health of children

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2023 AAP Clinical Practice Guideline (CPG)

- First ever CPG for pediatric obesity
- Recognizes obesity as a chronic disease with multiple etiologies
- Expands role of the primary care provider
- Removes the staged approach for treatment
- Recommends early evaluation and treatment at the highest intensity level
  - There is no place for "watchful waiting"
- Treat comorbidities concurrently
- Earlier consideration of anti-obesity medications (12yo+) & bariatric surgery (13yo+)

Executive Summary: Hampl SE et al. *Pediatrics* 2023, PMID 36622135
Clinical Practice Guideline: Hampl SE et al. *Pediatrics* 2023, PMID 36622115
Technical Report Part 1 (Interventions): Skinner AC et al. *Pediatrics* 2023, PMID 36622110
Technical Report Part 2 (Comorbidities): Skinner AC et al. *Pediatrics* 2023, PMID 36622098

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Comprehensive Obesity Treatment

KAS 9. Pediatricians and other PHCPs should treat overweight and obesity in children and adolescents, following the principles of the medical home and the chronic care model, using a family-centered and non-stigmatizing approach that acknowledges obesity's biologic, social, and structural drivers.

Clinical Practice Guideline: Hampl SE et al. *Pediatrics* 2023, PMID 36622115

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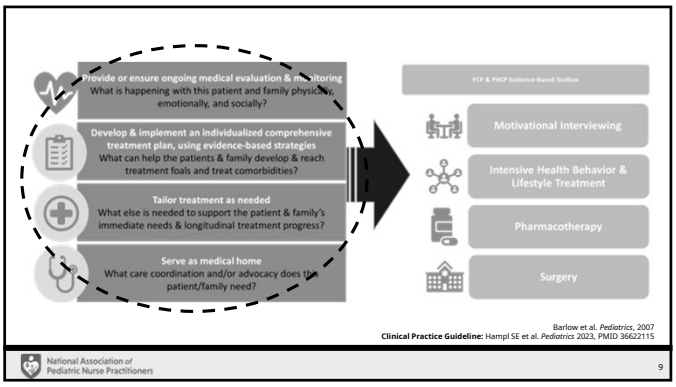

Barlow et al. *Pediatrics*, 2007
Clinical Practice Guideline: Hampl SE et al. *Pediatrics* 2023, PMID 36622115

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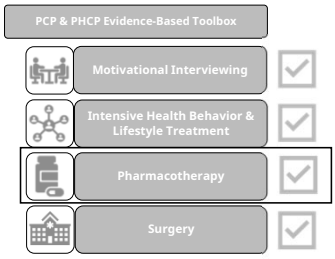
Provide the most intensive longitudinal treatment in the medical home….
Treatment Take-Aways: "As soon as possible, as intensive as available"



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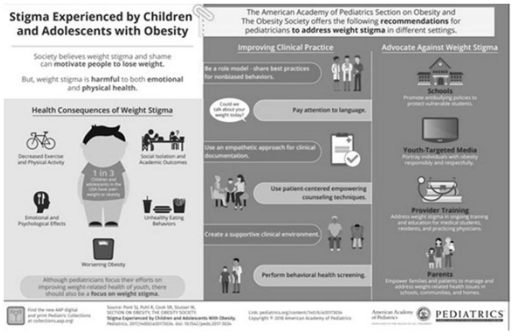
MJ0



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Use of Pharmacotherapy

KAS 12. Pediatricians and other PHCPs should offer adolescents 12 y and older with obesity weight loss pharmacotherapy, according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment.

Consensus Recommendation: Pediatric health care providers may offer children 8 through 11 years of age with obesity weight loss pharmacotherapy, according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment.

Clinical Practice Guideline: Hampl SE et al. *Pediatrics* 2023, PMID 36622115

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FDA Approved Anti-Obesity Medications (AOMs) for Pediatrics

To discuss in detail today:
- Orlistat
- Liraglutide
- Phentermine/Topiramate ER
- Semaglutide

Additionally:
- Phentermine monotherapy (age >16)
- Setmelanotide (for selected monogenetic obesity syndromes only)

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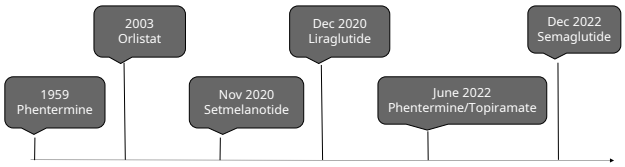
Timeline of FDA Approval for Pediatrics



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Patient Selection For Anti-Obesity Medication*

- FDA Indication: Adjunct to a reduced calorie diet and increased physical activity for chronic weight management in:
  - Pediatric patients aged 12 years and older with an initial BMI at the 95th percentile or greater for age and sex (obesity).
- Additional considerations:
  - Level of engagement in lifestyle modification
  - Ability to adhere to safety monitoring
  - No contraindication to selected medication

*For orlistat, liraglutide, phentermine/topiramate, semaglutide

Wegovy (semaglutide). Novo Nordisk, 2017

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Patient Education: What Do Patients Need To Know About Anti-Obesity Medication?

- **Adjunct** to lifestyle modification.
- **Expect long term use.**
  - Risk of weight re-gain
- If medication is having no effect at 3 months, stop use.
  - How do we measure effect?
- Variable insurance coverage.
  - Some insurances have processes to obtain exceptions.
- Supply shortages are real!

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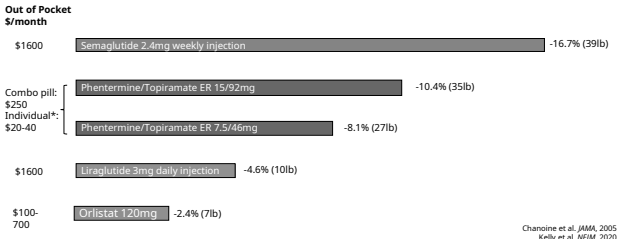
Overview of Cost and Efficacy for Medications Approved for Long-Term Treatment of Primary Obesity in Adolescents



Chanoine et al. *JAMA*, 2005
Kelly et al. *NEJM*, 2020
Kelly et al., *NEJM Evidence*, 2022
Weghuber et al. *NEJM*. 2022

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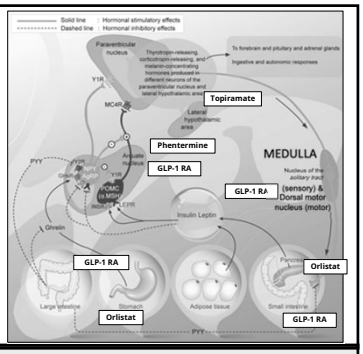
Mechanisms of Action



Apovian et al. *JCEM*, 2015, PMID 25590212
Drucker et al. *Cell Metab*, 2018, PMID 29617641

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Orlistat

Mechanism of Action	Gastric/pancreatic lipase inhibition. Inhibits fat absorption by 30%
Dosing	RX: 120mg TID with meals OTC: 60mg TID with meals Add in MVI with fat-soluble vitamins (taken 2+ hours before/after orlistat)
Side Effects	fatty/oily stool; oily spotting; abdominal pain; nausea; flatulence; fecal urgency; fecal incontinence; flatus with discharge; decreased absorption of fat-soluble vitamins
Pre-Medication Work Up and Monitoring	-LFTs if concerned about hepatic impairment -Renal function if at risk for renal impairment or there is a history of calcium oxalate nephrolithiasis or hyperoxalyuria
Patient Education	Take with meals. Combine with balanced reduced calorie diet with approximately 30% of calories from fat. Distribute daily fat, carbohydrate, and protein intake evenly over 3 meals.
Contraindications	Chronic malabsorption or cholestasis Caution with levothyroxine, antiepileptics, liver disease, renal impairment
Discontinuation Criteria	No effect at 3 months or intolerable side effects

Chanoine et al. *JAMA*, 2005
Xenical (orlistat). Vivus, 1999

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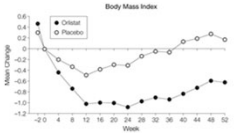
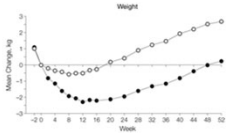
Orlistat (120mg TID vs placebo)

RCT Overview:
- 54 wk treatment | n = 539
- Age: 12-16 years
- Lifestyle + orlistat (120mg TID) vs. placebo
- Mean initial BMI: 35.6 kg/m2

Primary Outcome:
- -2.4% placebo-subtracted BMI reduction

Secondary End Points:
- Treatment group had significantly reduced waist circumference vs placebo
- No significant improvements: glycemia, lipids, BP





Chanoine et al. *JAMA*, 2005

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Liraglutide

Mechanism of Action	-Glucagon-like peptide 1 receptor agonist: increases post-prandial insulin, reduces glucagon secretion -Delays gastric emptying; reduces appetite and energy intake
Dosing	Daily SC into abdomen, thigh, or upper arm Dose escalation: 0.6mg x 1 week --> 1.2mg x 1 week --> 1.8mg x 1 week --> 2.4mg x 1 week --> 3.0mg thereafter Pre-filled multi-dose pens Any time of day regardless of meal timing Consider antiemetics during dose escalation prn
Side Effects	Nausea, vomiting, diarrhea (68%) – typically during dose escalation, mild-moderate Other: abd pain, GERD, distention, flatulence, belching, dry mouth, HA, dizzy, fatigue, injection site reaction, modest increase in HR
Pre-Medication Work Up and Monitoring	Thyroid exam (pre/post initiation) CMP at initiation and during dose escalation if severe GI SE Consider hepatic panel and lipase if severe GI SE and/or significant rapid weight loss (gallstones)
Patient Education	Injection teaching Rare risks: pancreatitis, cholecystitis. Warnings: Suicidal behavior and ideation - One suicide occurred in RCT, but unlikely related to treatment. No clinically relevant differences on MH questionnaires in the RCT
Contraindications	Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2) Hypersensitivity to liraglutide or any product components
Discontinuation Criteria	No effect after 3 months of treatment dose, or intolerable side effects

Kelly et al. *NEJM*, 2020
Saxenda (liraglutide). Novo Nordisk, 2014

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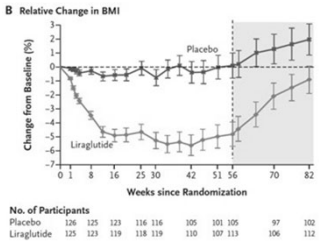
Liraglutide (3mg vs placebo)



RCT Overview:
- 56 wk treatment + 26 wk follow-up | n = 256
- Age: 12-17 years
- Lifestyle + liraglutide (3mg daily injection) vs. placebo
- Mean initial BMI: 35.5 kg/m2

Primary Outcome:
- -4.6% placebo-subtracted BMI reduction (10lb)

Secondary End Points:
- No significant improvements: glycemia, lipids, BP, or weight related quality of life.

Kelly et al. *NEJM*, 2020

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Phentermine/Topiramate ER

Mechanism of Action	Phentermine: Exact MOA is unknown. Stimulates norepinephrine release in the lateral hypothalamus to decrease hunger and increase fullness. Topiramate: Exact MOA is unknown. Thought to act on GABA to decrease hunger and increase fullness.
Dosing	Daily tablets Mid dose: 7.5mg/46mg High dose: 15mg/92mg Separate dose escalation (off-label): - Phentermine 8mg. Increase to 15mg if needing additional appetite suppression. - Topiramate 25mg: 25mg daily x 1 week --> 50mg daily x 1 week --> 75mg daily x 1 week --> 100mg daily thereafter
Side Effects	Phentermine: increased HR and BP, anxiety, insomnia, restlessness, dry mouth, n/v/d/c. Rare, but serious: chest pain, SOB, exercise intolerance, edema. Topiramate: paresthesia, fatigue, cognitive impairment, mild metabolic acidosis. Rare, but serious: mood changes/SI/depression, kidney stones, oligohidrosis, acute myopia/secondary angle closure glaucoma.
Pre-Medication Work Up and Monitoring	Prior to starting and routinely: -BMP to establish normal creatinine and bicarbonate -Pregnancy test (unless LARC) -Consider EKG if there are concerns on cardiovascular-focused patient/family history or exam.
Patient Education	-T + OCPs: reduced OCP concentration --> possible spotting -Avoid pregnancy -Do not stop abruptly (increased seizure risk)
Contraindications	Pregnancy; glaucoma; hyperthyroidism; MAOI use; CVD (arrythmias, CAD, uncontrolled HTN); pulmonary HTN; alcohol use/abuse. Note: SSRI + phentermine is generally ok. Be mindful if there are multiple serotonergic meds on board
Discontinuation Criteria	No effect at 3 months or intolerable side effects

Qsymia (phentermine and topiramate extended release). *Vivus*, 2012
Kelly et al. *NEJM Evidence*, 2022

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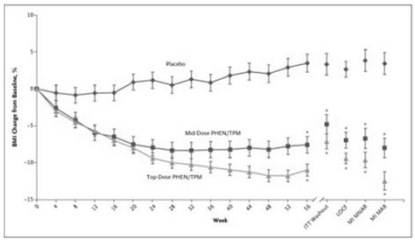
Phentermine/Topiramate ER
(7.5/46mg vs 15/92mg vs placebo)



RCT Overview:
- 56 wk treatment | n = 223
- Age: 12-16 years
- Lifestyle + placebo, mid dose, or top dose phen/tpm
- Mean initial BMI: 37.8kg/m2

Primary Outcome:
- -8.1% and -10.4% BMI placebo-subtracted difference at mid and top doses

Secondary End Points:
- Improved HDL and TGs
- No significant improvements: insulin sensitivity or weight-related QOL.
- No sig difference in BP or HR

Kelly et al. *NEjM Evidence*, 2022

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Semaglutide

Mechanism of Action	-Glucagon-like peptide 1 receptor agonist: increases post-prandial insulin, reduces glucagon secretion -Delays gastric emptying; reduces appetite and energy intake
Dosing	Weekly SC into abdomen, thigh, or upper arm Dose escalation: 0.25mg x 4 weeks --> 0.5mg x 4 weeks --> 1mg x 4 weeks --> 1.7mg x 4 weeks --> 2.4mg onward. If can't tolerate 2.4mg, can use 1.7mg for maintenance Single-dose pen Consider antiemetics during dose escalation prn
Side Effects	Nausea, vomiting, diarrhea (62%) – typically during dose escalation, mild-moderate Other: constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distention, belching, flatulence, gastroenteritis, GERD, nasopharyngitis, injection site reactions, modest increase in HR
Pre-Medication Work Up and Monitoring	Thyroid exam (pre/post initiation) CMP at initiation and during dose escalation if severe GI SE Hepatic function panel and lipase if severe GI SE or significant rapid weight loss (gallstones)
Patient Education	Injection teaching Rare risks: pancreatitis, cholelithiasis AKI risk: post-marketing, most had severe GI SE and volume depletion Missed dose and 48hr+ from next, give it. Otherwise hold for next dose Warnings: Suicidal behavior and ideation (as seen with other GLP1s; not seen in semaglutide trial)
Contraindications	Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2) Hypersensitivity to semaglutide or any product components
Discontinuation Criteria	No effect after 3 months of treatment dose, or intolerable side effects

Weghuber et al. *NEjM*. 2022
Wegovy (semaglutide). Novo Nordisk, 2017

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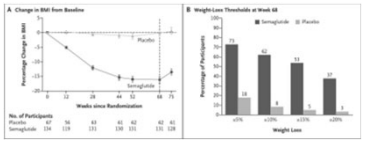
Semaglutide (weekly 2.4mg injection vs. placebo)



RCT Overview:
- 68 wk treatment | n = 201
- Age: 12- <18 years
- Lifestyle + semaglutide (2.4mg) vs. placebo
- Mean initial BMI: 37.0kg/m2

Primary Outcome:
- -16.7% placebo-subtracted BMI reduction

Secondary End Points:
- Improvements in waist circumference, A1c, TC, LDL, TGs, ALT, weight-related QOL.
- No significant improvement: HDL or BP.
- No differences in mental health questionnaires.
- No effect on growth or puberty.

Weghuber et al. *NEjM*. 2022

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How Do I Choose?

- Degree of BMI reduction desired
- Individual risk factors: Comorbidity? Family history?
- Absolute or relative contraindications:
  - Severe untreated anxiety – caution with phentermine
  - Severe untreated depression or sexually active without reliable birth control – caution with topiramate
- Patient preference: oral vs injection
- Step-wise and layering approaches: Phen/top --> GLP1
- Don't forget – **intensive behavioral interventions**

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Practical Considerations

- Insurance coverage. Is a coverage exception possible?
- Cost: e.g. Semaglutide vs Phentermine/Topiramate
- Access/Supply shortages
- Maximize other tools in the "toolbox"

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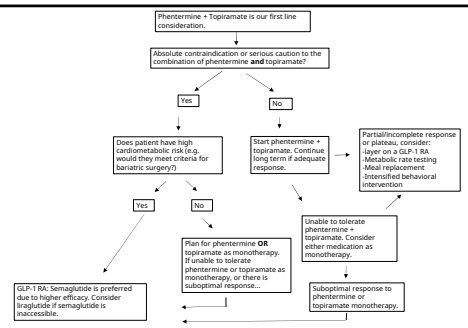

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	Phentermine	Topiramate	Phentermine + Topiramate	GLP1-RA
	Medication interaction check at baseline & with any change to med list Baseline and follow up mood assessment per clinical standard			
Baseline	HR, BP, BMI BMP, hCG, ALT +/- cardiac testing	HR, BP, BMI BMP, hCG, ALT	HR, BP, BMI BMP, hCG, ALT +/- cardiac testing	HR, BMI A1c, CMP, hCG
3mo f/u	HR, BP, BMI BMP, hCG	BMI BMP, hCG, ALT	HR, BP BMP, hCG, ALT	HR, BMI A1c (if baseline is ≥ 6% or concerning symptoms)
12mo f/u and annually	HR, BMI	BMI hCG	HR, BMI hCG	HR, BMI Consider screening CMP annually and as needed if abdominal symptoms,
"Sick Day" Plan	Hold if po intake is poor to prevent further blunting of appetite. Re-start when well and adequate po intake resumes. May interact with pseudoephedrine and other combo cold/flu products	May continue topiramate (no dose change required)	Hold phentermine if po intake is poor to prevent further blunting of appetite. Re-start when well and adequate po intake resumes. Phentermine may interact with pseudoephedrine and other combo cold/flu products Ok to continue topiramate	Ok to continue GLP-1 RA (no dose change typically required)
Surgical Plan†	Stop 1 week prior to elective surgery and resume after the immediate postop course and when po intake has normalized.	May continue topiramate (no dose change required)	Stop phentermine 1 week prior to elective surgery and resume after the immediate postop course and when po intake has normalized. Ok to continue topiramate	Evaluate on individual basis (consider risk of hypoglycemia and delayed gastric emptying/risk of aspiration)

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Case Study #1

Scenario	**18-year-old female with obesity, hypometabolism, premature ovarian insufficiency, anxiety, and mild depression currently engaged in mental health counseling.**
Questions	You are considering weight loss medications. Are anxiety and depression contraindications to phentermine and topiramate?

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Case Study #2

Scenario	**13-year-old male with severe obesity, OSA, elevated clinic BPs, and pulmonary hypertension. Cardiology referred him to Lifestyle Medicine for help with weight loss.**
Questions	1. You are considering weight loss medication. Which agents could you use?

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Case Study #3

Scenario	**18-year-old male with severe obesity, autism, ADHD, hidradenitis suppurativa, depression and anxiety. Current medications include: fluoxetine, topiramate and phentermine**
Questions	1. Patient had an initial decrease in weight on phentermine/topiramate, and then plateaued. What do you consider doing next?

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Clinical Pearls

- Ongoing lifestyle counseling and goal setting are critical.
- Expect medication to be used long-term.
- Follow up frequently: At least every 3 months.
- Prepare for a plateau.
- Weight re-gain?
- Clinical support tools: EHR smartphrases, smartsets, staff training on exceptions/appeals workflow, medication websites
- We are just scratching the surface…

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What's Next in the Pipeline?

- Tirzepatide: Received adult approval Nov 2023 (20% weight loss)
  - Pediatric trials are underway Age 6-18
- Semaglutide: trials underway for age 6-11
- Setmelanotide: Current approval for BBS; POMC, PCSK1, or LEPR deficiencies age 6+. Trials underway for age 2-6; heterozygous genetic mutations (age 6+); and hypothalamic obesity

clinicaltrials.gov

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Acknowledgments

- Jaime Moore, MD MPH
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- Jennifer Disabato, DNP, PNP
- Children's Hospital Colorado Lifestyle Medicine program faculty, staff, patients, and families

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Resources

- AAP Clinical Practice Guidelines: https://www.aap.org/obesitycpg
- AAP Institute for childhood healthy weight: https://www.aap.org/en/patient-care/institute-for-healthy-childhood-weight/
- University of Connecticut Rudd Center (Weight bias and Stigma): https://uconnruddcenter.org/research/weight-bias-stigma/healthcare-providers
- Advanced Therapies for Pediatric Obesity (ATPO) Conference: University of Minnesota Center for Pediatric Obesity Medicine: https://med.umn.edu/pediatrics/events/advanced-therapies-pediatric-obesity-atpo-conference

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References

(fda.gov)

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Questions?

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