The Treatment of Pediatric Obesity: Beyond Lifestyle Modifications

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Conflict of Interest Disclosure

I have no conflicts of interest to disclose

I will be discussing off-label use of medications

Objectives

1. Review the prevalence and trends in pediatric obesity and severe obesity
2. Discuss how to personalize treatment depending upon the cause
3. Review treatments for obesity including lifestyle modifications, anti-obesity pharmacotherapy and metabolic/bariatric surgery
Definitions: Pediatric Obesity

- **Overweight**: BMI ≥ 85th but < 95th for age and sex
- **Obese**: BMI ≥ 95th
- **Severe Obesity**: BMI ≥ 120% of the 95th percentile or BMI ≥ 35 mg/m²

Alarming Trend in Pediatric Obesity

- 18.5% of all children and adolescents in US have obesity
- **Severe Pediatric Obesity**:
  - Fasting growing obesity category
  - 3.8 - 5.4 million children/adolescents in US
  - Greatest risk for developing obesity-related health consequences: T2D/CVD
  - Lifestyle modifications generally ineffective in this population

Alarming Trend in Obesity

- **Projected obesity trends**
  - By 2030, additional 65 million adults with obesity in US
  - 6-8 million additional cases of DM
  - 5-7 million additional cases of heart disease/stroke
  - 500,000 additional cases of cancer
  - Associated additional cost: $48-66B a year

- **The economic burden of obesity worldwide**
  - Global Costs:
    - 0.7-2.8% of total health care expenditures for obesity
    - 0.1% of total health care expenditures for overweight and obesity

1 Freedman et al, J Peds, 2007
2 Yang et al, Lancet, 2011
3 Withrow and Alter, Obes Rev, 2011
Relation of Childhood BMI to Adult BMI

Sinaiko et al, Circulation, 1999

BMI AT MEAN AGE 7

BMI AT MEAN AGE 24

$r = 0.638$

$p = 0.0001$

Atherosclerosis begins in Childhood

Berenson et al, NEJM, 1998

Screening for Obesity

USPSTF Recommendation Statement

Clinical screening for obesity in children 6 years and older

Offer/refer to comprehensive, intensive behavioral interventions to promote improvements in weight status

Category B Recommendation
Causes of Obesity in Youth

Appetite/Segmentation
Sedentary Lifestyle
Anxiety

Dysregulation
Depression
Large Portions

Intergenesis
Leptin Resistance
Socioeconomic status

Television
Less Gym Class
Reward Pathways

Antibiotic Use
Dysregulated
Escalators

Risk Regulators
Dysfunctional
Epigenetics

Cultural norms
Food quantities
Impulsivity

Parental
Body-image norms

Built environments & Area Deprivation
Walkability

Deprivation
Local food environment

Runaway

Commercial messaging
Less Recess

Health
Calorie-Dense Foods

behaviors

Feeding behaviors
Physical activity

Internal Factors

Huang et al, Prev Chronic Dis, 2009

Increasing body weight over time
Interactions among hormonal and neural pathways that regulate food intake and body-fat mass

Organs: large intestine, small intestine, stomach, adipose tissue, brain

Hypothalamic Involvement: PVN, LH, NST, Arcuate nucleus of the accumbens

Hormones: leptin, ghrelin, PYY, NPY, MSH, AgRP, GLP

Energy Balance and Steady State

Energy Balance and Steady State: Weight Regain
**Weight Management in Youth:**

*General Principles*

- Intensive, age-appropriate, culturally sensitive, family-centered lifestyle modification therapy
- Healthy eating habits
- Physical activity: min 20 minutes daily; goal 60 minutes
- Evaluate and treat psychosocial co-morbidities
- Consider pharmacotherapy
- Consider bariatric surgery

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**Pediatric Obesity Treatment: General Principles**

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*Styne et al, JCEM, 2017*

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**Weight Management Visit**

- Annual and symptom-based screening for conditions associated with obesity in all patients with BMI ≥ 30 kg/m²
  - T2DM, HTN, HL, OSA, NAFLD, Depression
- Identify contributing factors:
  - Sleep disorders, disordered eating, socioeconomic issues
- Screening for secondary causes of obesity (as indicated)
- Identify medications that may be contributors
- Develop treatment plan

*Adult Practice Guidelines, JCEM, 2015*
Lifestyle Modifications:

The Background for All Treatments

Evidenced-Based Dietary Principles

- Decrease fast foods, added table sugar, high-fructose corn syrup
- Decrease high-fat, high-sodium, or processed foods
- Reduce saturated dietary fat intake (>2 years)
- Consume whole fruit rather than fruit juices
- Eliminate sugar-sweetened beverages
- Educate on Portion control
- Follow USDA intake of dietary fiber, fruits, and vegetables
- Timely, regular meals; avoid constant “grazing”
- Recognize eating cues (boredom, stress, loneliness, or screen time)
- Encourage single portion packaging and improved food labeling for easier use by consumers
  - Ungraded good practice statement

Skene et al., JCEM, 2017

Benefits of Juice

A Glass Full of Nutrition

- A 1/2 cup sits in a cup glass of juice is the equivalent to 4 other servings of fruits
- 1/2 cup sits in a cup glass of water is the equivalent to 4 other servings of fruits
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Evidence-Based Exercise Principles

• 60 min/day moderate to vigorous physical activity
  • “Talk Test”
    • Moderate activity: can talk but not sing
    • Vigorous activity: cannot talk without pausing to catch breath
  • Provide written prescription to engage in physical activity, including a “dose” describing duration, intensity, and frequency
    • May improve compliance
  • 60 minutes do not have to be accomplished in 1 session

DM Clinical Practice Guidelines, Pediatrics, 2013

Evidence-Based Exercise Principles

• Facilitate
  • Ability to safely walk to/from school
  • Increased use of stairs (improved signage to indicate their location)
  • Increased breaks for movement in classroom
  • Increased movement during recess/gym
  • Limit non-academic screen time: < 2 hours per day
    • US Department of Health (< 2 hours)
    • American Academy of Pediatrics (< 2 hours)
    • Endocrine Society (1-2 hours per day)

DM Clinical Practice Guidelines, Pediatrics, 2013
Anti-Obesity Pharmacotherapy in Youth

FDA-approved anti-obesity medications in children

- Orlistat: for adolescents 12-16
- Just orlistat
FDA-approved anti-obesity medications in children

- Orlistat: for adolescents 12-16
- Just orlistat
- Really, just orlistat

In adolescents ≥ 16 years old with BMI ≥ 30 kg/m² or ≥ 27 kg/m² with 1+ obesity co-morbidities: can consider adults medications

Endocrine Society Clinical Practice Guideline – Pharmacotherapy Use

"Physicians should be discouraged from prescribing weight loss medications off-label to those <16 years old because of: 1) the lack of FDA approval for use; 2) the limited number of well-controlled safety and efficacy studies in obese children and adolescents, 3) the limited efficacy demonstrated in adults for most agents, and 4) the need to weigh the relative risk of drug-induced adverse events in children and adolescents against a medication’s long-term theoretical potential for reducing obesity-related morbidity and mortality."

If you are obese as a 4 year old, 75% chance you will be obese as an adolescent

Geserick et al, NEJM 2018

Need for Earlier Interventions

In adolescents with obesity, most rapid weight gain occurred between ages 2 and 6

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**Anti-Obesity Pharmacotherapy Options**

- Orlistat
- Phentermine
- Topiramate
- Phenterine + Topiramate XR
- Exenatide
- Liraglutide
- Metformin
- Naltrexone
- Naltrexone + Bupropion
- Lorcaserin
- Zonisamide
- Lisdexamfetamine

**Medication Selection: Factors to Consider**

1. Mechanism of action
2. Side effect profile and contraindications
3. Patient eating phenotype
4. Patient co-morbidities
5. Cost/access
6. Patient/family preference
Medication Selection: Factors to Consider

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Mechanisms of Action

Orlistat: Gastrointestinal lipase inhibitor
Lorcaserin: Serotonin 2C receptor agonist
Phentermine/Topiramate: Sympathomimetic amine with anorectic effect/mecanism unknown
Naltrexone/Bupropion: Opioid receptor antagonist and aminoketone antidepressant
Liraglutide: GLP-1 receptor agonist
Mechanisms of Action

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**Side Effect Profiles and Contraindications**

- **Orlistat:**
  - *Side Effects:* GI distress; decreased fat-soluble vitamin absorption
  - *Contraindications:* chronic malabsorption; gallbladder disease

- **Phentermine:**
  - *Side Effects:* cardiac; restlessness; insomnia; potential abuse/dependence
  - *Contraindications:* history of CVD; hyperthyroidism; uncontrolled hypertension; glaucoma; agitated states; seizures; MAOI use; history of drug abuse

- **Topiramate:**
  - *Side Effects:* paresthesia; concentration and memory impairment; TERATODEN
  - *Contraindications:* secondary angle closure glaucoma; Ca oxalate renal stones

*Not exhaustive*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>• GI distress; decreased fat-soluble vitamin absorption</td>
<td>• chronic malabsorption; gallbladder disease</td>
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<tr>
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<td>Topiramate</td>
<td>• paresthesia; concentration and memory impairment; TERATOGEN</td>
<td>• secondary angle closure glaucoma; Ca oxalate renal stones</td>
</tr>
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<td>Lorcaserin</td>
<td>• headache, dizziness, fatigue, nausea, dry mouth, constipation</td>
<td>• MAOI use, caution in patients on SSRIs (serotonin syndrome)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>• elevated liver enzymes, GI distress</td>
<td>• opioid dependence, current use of opiates, liver failure</td>
</tr>
<tr>
<td>Bupropion</td>
<td>• increased HR, agitation, dry mouth, insomnia, headache, tremor, GI distress</td>
<td>• seizure disorder, eating disorder, MAOI use</td>
</tr>
</tbody>
</table>

*Not exhaustive
Side Effect Profiles and Contraindications*

- Lorcaserin:
  - **Side Effects:** headache, dizziness, fatigue, nausea, dry mouth, constipation
  - **Contraindications:** MAOI use, caution in patients on SSRIs (serotonin syndrome)

- Naltrexone:
  - **Side Effects:** elevated liver enzymes, GI distress
  - **Contraindications:** opioid dependence, current use of opiates, liver failure

- Bupropion:
  - **Side Effects:** increased HR, agitation, dry mouth, insomnia, headache, tremor, GI distress
  - **Contraindications:** seizure disorder, eating disorder, MAOI use

*Not exhaustive

Side Effect Profiles and Contraindications*

- GLP-1 Agonists (e.g. liraglutide, exenatide):
  - **Side Effects:** GI distress, increased HR, headache, hypoglycemia, pancreatitis, cholecystitis
  - **Contraindications:** history of pancreatitis, personal/family history of MTC or MEN 2

- Metformin:
  - **Side Effects:** GI distress, reduced vitamin B12
  - **Contraindications:** history of lactic acidosis (none reported in pediatric trials); renal failure

*Not exhaustive

Side Effect Profiles and Contraindications*

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Proposed Eating Phenotypes

Treat the Cause!
Treat the Cause!

- Poor Satiety
- Strong Hunger
- Emotional Eating
- Binge Eating

Volumetrics-Based Eating Appetite Suppression

Impulsive Eating
Hedonic Eating

OBESITY

Treat the Cause!

- Poor Satiety
- Strong Hunger
- Emotional Eating

Treat Depression and/or Anxiety

Impulsive Eating
Hedonic Eating

OBESITY

Treat the Cause!

- Poor Satiety
- Strong Hunger
- Emotional Eating
- Binge Eating

Focus on Sleep

Impulsive Eating
Hedonic Eating

OBESITY

Treat the Cause!

- Poor Satiety
- Strong Hunger
- Emotional Eating

Impulsive Eating
Hedonic Eating

OBESITY
Treat the Cause!

Poor Satiety  Strong Hunger  Emotional Eating
Night Eating  Binge Eating

OBESITY

Impulsive Eating  Hedonic Eating

Medications Approved for Binge Eating

Treat the Cause!

Poor Satiety  Strong Hunger  Emotional Eating
Night Eating  Binge Eating

Treat Impulsivity

Impulsive Eating  Hedonic Eating

Treat the Cause!

Poor Satiety  Strong Hunger  Emotional Eating
Night Eating  Binge Eating

Determine Alternative Rewards

Impulsive Eating  Hedonic Eating

Treat the Cause!

Poor Satiety  Strong Hunger  Emotional Eating
Night Eating  Binge Eating

Treat Impulsivity

Impulsive Eating  Hedonic Eating

Determine Alternative Rewards

Impulsive Eating  Hedonic Eating
Medication Selection: Factors to Consider

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Consider Patient Co-Morbidities

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Option(s) to Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 DM</td>
<td>GLP-1 agonist; SGLT-2; basal insulin before adding combination or pre-mixed insulin</td>
</tr>
<tr>
<td>DM + HTN</td>
<td>ACEI/ARB or CCBs before β-blockers</td>
</tr>
<tr>
<td>Depression/Psychiatric</td>
<td>Shared decision making; naltrexone/bupropion</td>
</tr>
<tr>
<td>Smoking or Alcohol Cessation</td>
<td>Naltrexone/bupropion</td>
</tr>
<tr>
<td>Desiring Contraception</td>
<td>OCPS over injectable contraceptives</td>
</tr>
<tr>
<td>Atypical Antipsychotics</td>
<td>Metformin, topiramate, GLP-1 agonists</td>
</tr>
<tr>
<td>Hypercholesterolemia + Constipation</td>
<td>Orlistat</td>
</tr>
</tbody>
</table>

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4. **Patient co-morbidities**
5. **Cost/access**
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Cost/Access

• Many insurances require prior authorization for anti-obesity pharmacotherapies and will not approve off-label use (in patients < 18 years)
• Coverage under Medicaid and State Health Insurance Programs

<table>
<thead>
<tr>
<th>State Employee Health Programs</th>
<th>Medicaid</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>2017</td>
</tr>
<tr>
<td>Nutritional Counseling</td>
<td>24</td>
</tr>
<tr>
<td>Medications</td>
<td>14</td>
</tr>
<tr>
<td>Bariatric Surgery</td>
<td>35</td>
</tr>
</tbody>
</table>

• Occasionally need letter of appeal to even be seen in weight management clinic

To Defray Costs

• Consider alternative diagnoses
  • Hypertriglyceridemia, diabetes, hypertension, etc.
• Check manufacturer website for coupons and discounts
• Shop Pharmacies
  - 15, 30 mg Phentermine Capsules
    - Walgreens $23
    - CVS $20
    - Costco $14
  - Request or activate a Savings Card

To Defray Costs

• Prescribe phentermine 37.5 mg tab and split pill
• Prescribe components separately
Medication Selection: Factors to Consider

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Patient/Family Preference

• Importance of discussing benefits and risks
• Status as not FDA-approved as appropriate
• Shared decision making
Metabolic and Bariatric Surgery in Youth

Bariatric Surgery Recommendations: ASMBS

**Indications**

- BMI ≥ 40 kg/m² or 140% of 95th percentile\(^*\)
- BMI ≥ 35 kg/m² or 120% of 95th percentile with clinically significant co-morbidities\(^*\)

**Multidisciplinary team:**

- must consider whether patient/family have ability and motivation to adhere to recommended treatments pre- and postoperatively

**Contraindications**

- Medically correctable cause of obesity
- Ongoing substance abuse problem (within the preceding year)
- Medical, psychiatric, psychosocial, or cognitive condition preventing adherence to post-operative dietary and medication regimens
- Current or planned pregnancy within 12 to 18 months of procedure

\(^*\) Whichever is lower

Pratt et al., Surg Obes Rel Dis, 2018

Bariatric Surgery Recommendations: Endo Society

**Indications**

- BMI ≥ 40 kg/m² with mild comorbidities or BMI ≥ 35 kg/m² with significant extreme comorbidities
- Tanner 4-5 and final or near-final adult height
- Extreme obesity and comorbidities persist despite compliance with formal LMT program (+/- pharmacotherapy)
- Psychological evaluation confirms stability and competence of family unit (may have psychological distress or impaired QOL from obesity, but no other untreated psych conditions)
- Demonstrates ability to adhere to principles of healthy dietary and activity habit
- Experienced surgeon and plan for long-term patient care afterwards

**Contraindications**

- Pre-adolescent children
- Pregnant or breast-feeding (or planning to become pregnant within 2 years of surgery)
- Has not mastered principles of healthy dietary and activity habits
- Unresolved substance abuse, eating disorder, or untreated psychiatric disorder

Styne et al, JCEM, 2017
Definitions of Comorbidities: ASMBS vs Endocrine Society

<table>
<thead>
<tr>
<th></th>
<th>ASMBS(^1)</th>
<th>Endocrine Society(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(BMI ≥35 kg/m(^2))</td>
<td>Major (BMI ≥35 kg/m(^2))</td>
<td>Mild (BMI ≥40 kg/m(^2))</td>
</tr>
<tr>
<td>T2DM</td>
<td>T2DM</td>
<td></td>
</tr>
<tr>
<td>OSA (AHI &gt; 5)</td>
<td>OSA (&quot;Moderate to Extreme&quot;)</td>
<td>OSA (&quot;Mild&quot;)</td>
</tr>
<tr>
<td>NASH</td>
<td>NASH with Advanced Fibrosis</td>
<td>NASH</td>
</tr>
<tr>
<td>Orthopedic (SCFE or Blount’s)</td>
<td>Debilitating Orthopedic Problems</td>
<td>Moderate Orthopedic Problems</td>
</tr>
<tr>
<td>Pseudotumor Cerebri</td>
<td>Pseudotumor Cerebri</td>
<td>Hypertension</td>
</tr>
<tr>
<td>GERD</td>
<td></td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extreme Psych Distress from Obesity</td>
</tr>
</tbody>
</table>

\(^1\) Pratt et al., Surg Obes Rel Dis, 2018
\(^2\) Styne et al., JCEM, 2017

Summary

- Pediatric severe obesity: fastest growing category
- Causes are multi-factorial and must be considered in treatment plan
- Lifestyle modification: background for all treatments
- When considering medications, should account for:
  - Mechanism of Action
  - Side Effect Profile and Contraindications
  - Eating Phenotypes
  - Co-Morbidities
  - Cost/Access
  - Patient/Family Preference
- Metabolic/bariatric surgery should be considered in select cases depending upon degree of obesity, co-morbidities, and other factors