Treating Pediatric Obesity Seriously
The Role of Pharmacotherapy

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Disclosures

• I serve as a consultant for Novo Nordisk, Orexigen, and Vivus Pharmaceuticals but do not accept personal or professional income for any of these activities
• I receive research support in the form of drug and placebo from Astra Zeneca Pharmaceuticals
• I intend to discuss unapproved uses of commercial products in my presentation

Overview

• Pediatric (severe) obesity
  – Prevalence and trends
  – Cardiometabolic risk factors and co-morbidities
• Treatment approaches and biology of obesity
  – Bariatric surgery
  – Lifestyle/behavioral modification therapy
  – Pharmacotherapy
• Recently-approved medications, pediatric considerations, and future directions
Pediatric BMI Percentile Cutoffs

- BMI percentile based upon age- and sex-specific cutoffs:
  - <85th percentile = normal weight
  - ≥85th<95th percentile = overweight
  - ≥95th percentile = obesity (class 1)
  - ≥1.2 times the 95th percentile or 35 kg/m² = severe obesity (class 2)
  - ≥1.4 times the 95th percentile or 40 kg/m² = severe obesity (class 3)

Severe Obesity Examples

- 7 year old girl of median height
  - 23.4 kg/m²
  - 77 pounds
- 13 year old boy of median height
  - 30.1 kg/m²
  - 161 pounds

Pediatric Obesity Prevalence

- United States, ages 2-19 years old
- Class I: 17.4%
- Class II: 6.3%
- Class III: 2.4%
- Severe obesity (classes II and III):
  - 4-5 million youth in the U.S. alone
  - Fastest growing pediatric obesity category
  - Prevalence is increasing despite leveling-off of overweight/obesity rates in children and adolescents

Skinner et al. Obesity 2016
Cardiovascular Risk Factors

• Bogalusa Heart Study: 60% of the youth with severe obesity had ≥2 cardiovascular risk factors


Metabolic Risk Factors

• Insulin resistance
• Up to 25% seeking medical treatment have impaired glucose tolerance
• Youth with severe obesity 3 times more likely to have metabolic syndrome phenotype vs. peers with obesity
• Adipokines markedly abnormal

Weiss, R et al. Diabetes Care 2005
Kelly, A et al. J Pediatr Endocr Metab 2005

Inflammation and Oxidative Stress

Figure 1: Oxidative stress and inflammation in three BMI groups: a) Circulating oxidized low-density lipoprotein (LDL), b) C-reactive protein, and c) Interleukin 6. Associations were adjusted for age and sex and were significant only in overweight/obese children and adolescents. *p < 0.05, **p < 0.01, ***p < 0.001

Nemer et al. Obesity 2011
Other Co-Morbidities

- Obstructive sleep apnea
- Nonalcoholic fatty liver disease
- Musculoskeletal problems
- Psycho-social problems
  - Depression
  - Lower quality of life

Montgomery, CC et al. J Pediatr Orthop 2010
Montgomery, CC et al. J Pediatr Orthop 2010
Schwimmer, JB et al. JAMA 2003

BMI Tracking in Childhood


BMI Tracking to Adulthood

- Tracking of obesity is strong from childhood to adulthood among youth with severe obesity
- Bogalusa Heart Study:
  - 100% developed adult BMI ≥30 kg/m²
  - 88% developed adult BMI ≥35 kg/m²
  - 65% developed adult BMI ≥40 kg/m²

Adolescent BMI and Cardiovascular Death in Adulthood

Timing of Intervention
A Window of Opportunity

• Adults who had obesity in childhood, but not in adulthood, were equally as healthy as adult peers who never experienced obesity
• It is reasonable to conclude that long-term, cumulative exposure to obesity (and its co-morbidities) will lead to poor outcomes

Timing of Intervention
A Window of Opportunity

• The majority of genetic polymorphisms associated with lifetime BMI have their largest impact on BMI-change during childhood
• Obesity without the presence of co-morbidities is precisely the scenario in which to intervene
Treatment Approaches

Current Guidelines and Recommendations

- Expert committee on the assessment, prevention, and treatment of child and adolescent overweight and obesity recommended a staged approach:
  - Stage 1: prevention plus
  - Stage 2: structured weight management
  - Stage 3: comprehensive, multidisciplinary intervention
  - Stage 4: tertiary care intervention

Endocrine Society Guideline
### Bariatric Surgery

<table>
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<tr>
<th>Study</th>
<th>No.</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Follow-up Length</th>
<th>Baseline BMI (kg/m²)</th>
<th>Postop BMI (kg/m²)</th>
<th>BMI Change</th>
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<td>61</td>
<td>17.2</td>
<td>60</td>
<td>12-months</td>
<td>37.7</td>
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<td>RYGB De la Cruz 2010</td>
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<td>32.3</td>
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<td>RYGB De la Cruz 2010</td>
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<td>Not specified</td>
<td>40.6</td>
<td>24-months</td>
<td>32.2</td>
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<td>RYGB De la Cruz 2010</td>
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<td>16.5</td>
<td>45.5</td>
<td>24-months</td>
<td>30.2</td>
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<td>RYGB O'Brien 2010</td>
<td>25</td>
<td>18.5</td>
<td>37.5</td>
<td>24-months</td>
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<td>RYGB Nadler 2010</td>
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<td>16.1</td>
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<td>AGB Accottani 2012</td>
<td>92</td>
<td>13.9</td>
<td>46.6</td>
<td>12-months</td>
<td>32.4</td>
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<td>43</td>
<td>15</td>
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<td>38.6</td>
<td>24-months</td>
<td>26.3</td>
<td>-38%</td>
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</tbody>
</table>

### Teen LABS

#### A: Weight Change from Baseline

![Graph showing weight change from baseline over years of follow-up.](image)

### Lifestyle Modification Therapy

- **Primary components:**
  - Dietary counseling
  - Physical activity counseling
  - Behavioral modification counseling
Why is obesity so difficult to effectively treat?

Appetite/Satiety Hormone Dysregulation
Dysregulation Binge Eating Disorder
Iatrogenesis Moving Walkways
Television Large Portions
Antibiotic Use Depression
Anxiety Less Gym Class
Sedentary Lifestyle
Leptin Resistance
Poverty
Dysregulated Reward Pathways
Devices
Escalators
Adverse Life Experiences
Elevators
Epigenetics
Calorie-Dense Foods

Reduced Metabolic Rate
Genetic Predisposition
Pre-pregnancy BMI
Microbiota
Gestational Weight Gain
Reduced Executive Functioning
Race/Ethnicity
Poor Sleep Hygiene
Less Recession
Catch-up Growth
Video Games
Fighting against Biology

- History of biological adaptation favoring energy storage and metabolic efficiency
- Obesity has a strong genetic component
- Blaming obesity solely on a lack of willpower/motivation ignores the evidence supporting the biological complexity of the disease

Homeostatic vs. Non-Homeostatic Regulation of Body Weight

Need

Want

- Food Storage (Hypothalamus)
- Reward (Limbic)
Real Life Example

- 16 year old white female
- Reported gaining 35 pounds in the last year
- Current BMI = 38.8 kg/m² (severe obesity)
- Counseled to eliminate liquid calories and add fruits/vegetables to diet
- Later started on pharmacotherapy (bupropion + naltrexone) and 1,400 kcals/day meal replacement plan (calc. RMR = 1,888 kcals/day)
- Weight cycled and reported feeling frustrated: “did everything I was supposed to”

Resting Metabolic Rate

- 1,888 kcals/day = 1,089 kcals/day!
Biologically-Based Treatment

• Effective and durable treatment of obesity requires a multi-faceted, intensive, and chronic approach

Kelly and Fox, in press

Internal vs. External Environment

• Changing how an individual with obesity engages with the external environment in a sustainable fashion is extremely difficult without also changing the internal environment
• Targeting the central and peripheral mechanisms of obesity with pharmacotherapy is a physiologically-rational approach

Pediatric Obesity Pharmacotherapy

• Orlistat
• Metformin
• Exenatide


Orlistat

- Approved for obesity treatment ages 12+
- Administered orally three times daily with meals
- Mechanism of action = lipase inhibition
- 2.5% BMI reduction at one year
- No cardiometabolic risk factor improvements
- Oily spotting, flatus with discharge, fecal urgency, fatty/oily stool

Largest randomized, controlled trial (N = 539) reported BMI reduction of 2.4% at 1 year (mean baseline BMI = 36 kg/m²)

Metformin

- Used for glycemic control in type 2 diabetes
- Administered orally
- Weight-loss mechanism of action is largely unknown
- Not approved for weight loss by FDA
- 3% BMI reduction at one year
- Modest improvements in glucose, insulin, and HOMA-IR
- Nausea, vomiting, headache
Metformin

- Randomized, controlled trial in adolescents 13-18 years old reported 3% BMI reduction at 1 year with 2000 mg per day (XR)

Wilson, DM et al. Arch Pediatr Adolesc Med 2010

Exenatide

- Used for glycemic control in type 2 diabetes
- Administered by subcutaneous injection
- Probable weight-loss mechanisms
  - Central effect on hypothalamus (appetite)
  - Slowing of gastric motility and CNS effect (satiety)
- Not approved by FDA for weight loss
- 3-4% BMI reduction at six months
- Improvement in glucose tolerance
- Nausea, abdominal pain, diarrhea, headache, vomiting

Exenatide

- Randomized, controlled trial in adolescents 12-19 years old reported 3% BMI reduction at 3 months with 10 mcg dose twice per day

Kelly, AS et al. JAMA Pediatrics 2013
Pediatric Pipeline
Medications Recently Approved for Adults

Lorcaserin
- Administered orally twice daily
- Mechanism of action: selective serotonin 5-HT2c receptor agonist
- 1 year weight loss of 3-4% among adults
- Headache, dizziness, fatigue, nausea, dry mouth, constipation
- Juvenile animal toxicology and adolescent PK studies completed; timeline for initiation of adolescent safety/efficacy trial unknown

Phentermine + Topiramate
- Administered orally once daily
- Mechanisms of action: phentermine - norepinephrine release in hypothalamus; topiramate - unknown
- 1 year weight loss of 7-9% among adults
- Paraesthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth
- Juvenile animal toxicology and adolescent PK studies completed; timeline for initiation of adolescent safety/efficacy trial unknown
Naltrexone + Bupropion

- Administered orally twice daily
- Mechanisms of action: naltrexone – opioid antagonist; bupropion – dopamine and norepinephrine reuptake inhibitor
- 1 year weight loss of 3-4% among adults
- Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea
- Juvenile animal toxicology, adolescent PK, timeline for initiation of adolescent safety/efficacy trial unknown

Liraglutide

- Administered once daily by subcutaneous injection
- Mechanisms of action: central effect on hypothalamus (appetite); slowing of gastric motility and CNS effect (satiety)
- 1 year weight loss of 5-6% among adults
- Nausea, headache, diarrhea
- Juvenile animal toxicology and adolescent PK studies completed; initiation of adolescent safety/efficacy trial in 2016

Pediatric Obesity Medicine
Special Considerations/Future Directions

- Combination therapy
  - Lifestyle
  - Pharmacotherapy
  - Device therapy
  - Bariatric surgery
- Chronic treatment
- Potential risks of treatment should be weighed against known risks of persistent obesity (including early mortality!)
- Predictors of response/precision medicine
- Accelerated pediatric development
The Achievable Goal

![Graph showing BMI Change across different methods: Lifestyle, Pharmacotherapy, and Surgery.](image)