Extreme Treatments for Extreme Obesity

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MN-AAP Obesity Webinar Series
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Disclosures

• I have no financial relationships to disclose
• I will discuss off-label use and/or investigational use of the following:
  – Metformin
  – Exenatide
  – Topiramate
  – Naltrexone
  – Bupropion
  – Gastric banding in adolescents
Objectives

• Identify **when** it is appropriate to consider special dietary, pharmacological or surgical therapy for pediatric obesity

• Identify the safety and efficacy of special **dietary interventions** used in the treatment of pediatric obesity

• Identify the safety and efficacy of **medications** used in the treatment of pediatric obesity

• Identify **surgical treatments** and outcomes of surgical interventions for pediatric obesity
Extreme Pediatric Obesity

• Definition:
  – Age and gender specific BMI ≥ 1.2 times 95\textsuperscript{th} percentile OR BMI ≥ 35

• Prevalence:
  – 3 to 7% of US children
Prevalence of BMI $\geq 99^{\text{th}}$ Percentile

NHANES Data

Health Consequences of Extreme Pediatric Obesity

- 84% have at least 1 cardiovascular risk factor
- 5% have impaired glucose tolerance
- Extreme obesity in childhood tracks very strongly to adulthood

When are “Extreme” Interventions Indicated for Pediatric Obesity?

- No clear guidelines
- Consider for children and adolescents with BMI ≥ 99th percentile who fail traditional dietary and physical activity interventions

Step-Wise Approach to “Extreme” Interventions

- Diet
- Pharmacology
- Surgery
Dietary Interventions

- Low Glycemic-Load Diet
- Protein-Sparing Modified Fast
- Meal Replacements
Glycemic Index and Glycemic Load

Glycemic Index = \frac{\text{blood glucose response after ingestion of 50 gm of test food}}{\text{blood glucose response after ingestion of 50 gm of reference food}}

Glycemic Load = \frac{\text{Glycemic Index} \times \text{CHO}}{100}
## Glycemic Index of Foods

<table>
<thead>
<tr>
<th>Low GI Foods (&lt;70)</th>
<th>High GI Foods (&gt;100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanuts</td>
<td>White rice</td>
</tr>
<tr>
<td>Lentils</td>
<td>Doughnuts</td>
</tr>
<tr>
<td>Soy milk</td>
<td>White bread</td>
</tr>
<tr>
<td>Apple</td>
<td>Cornflakes</td>
</tr>
<tr>
<td>Pizza</td>
<td>Watermelon</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Ebbeling et al 2003</td>
<td>16 teens</td>
</tr>
<tr>
<td></td>
<td>mean age 16</td>
</tr>
<tr>
<td></td>
<td>mean BMI 36</td>
</tr>
<tr>
<td>Spieth et al 2000</td>
<td>107 children</td>
</tr>
<tr>
<td></td>
<td>mean age 10</td>
</tr>
<tr>
<td></td>
<td>mean BMI 33</td>
</tr>
<tr>
<td>Fajcsak et al 2008</td>
<td>9 children</td>
</tr>
<tr>
<td></td>
<td>mean age 11</td>
</tr>
<tr>
<td></td>
<td>mean BMI 25</td>
</tr>
</tbody>
</table>

RCT of Low-Glycemic Load Diet In Young Adults

- N=73, ages 18-35, BMI > 30
- 6 months of intervention
  - Ad lib low glycemic load diet
  - Ad lib low fat diet
- 12 month of follow-up

Change in Body Weight on LGL or Low-Fat Diet by Patient Insulin Profile

Protein-Sparing Modified Fast

- Goal of obesity treatment is **selective** loss of body **fat** with preservation of lean tissue.

- Severe calorie deficit dieting in obese children may contribute to **negative nitrogen balance** and decreased growth rate.

- In adults, **PSMF preserves** normal rate of total body protein synthesis.
“Committed to Kids”

- Comprehensive program consisting of:
  - Weekly 2-hour visits for 1 year
  - Medical supervision
  - Nutrition instruction
  - Fitness counseling
  - Exercise
  - Behavior modification

“Committed to Kids”

- Dietary intervention for first 10 weeks
  - **High protein**: 2.0-2.5 gm/kg of IBW (avg 90-140 gm per day)
  - Reduced CHO: 50-75 gm/day
  - Reduced fat: 30-40 gm/day
  - Total energy: 1,000 kcal/day (depending on protein prescription)

“Committed to Kids”

- 93 adolescent enrolled
- 60% retention at 1-year

PSMF vs Hypocaloric Balanced Diet

• N=19, ages 7-16, mean BMI 33
• Weeks 1-10
  – PSMF (630 cal, 50% protein, 40% fat, 10% CHO)
  – Hypocaloric diet (840-1050 cal; 20% protein, 30% fat, 50% CHO)
• Week 10-14 months
  – Hypocaloric diet (1260 cal)

PSMF vs Hypocaloric Balanced Diet

PSMF vs Hypocaloric Balanced Diet

- Greater decrease in body fat in PSMF group
- No change in lean body mass in either group
- Growth velocity slowed from baseline to 6 months and approached normal as calories increased in both groups

Protein-Sparing Modified Fast

- Not clear if short-term PSMF causes temporary reduction in linear growth
- No data to support that transient slowing of growth velocity in obese children is associated with permanent stunting

Meal Replacements

- Obese adolescents underestimate their calorie intake by about 40-50%
- Meal replacements
  - Provide patients with a fixed amount of food with a known calorie content
  - Include liquid shakes, meal bars, and frozen food entrees
  - Designed to narrow stimuli and minimize ad lib food choices

RCT Meal Replacement vs Isocaloric Conventional Diet

• 12-month RCT
• 113 obese adolescents
  – Mean age 15.0
  – Mean BMI 37.1
• Randomized to lifestyle modification +
  – 1300-1500 kcal/day meal replacement diet (MR)
  – 1300-1500 kcal/day conventional diet (CD)

# RCT Meal Replacement vs Isocaloric Conventional Diet

<table>
<thead>
<tr>
<th>Phase 1 (months 1-4)</th>
<th>Phase 2 (months 5-12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR</td>
<td>MR or CD</td>
</tr>
<tr>
<td>CD</td>
<td>CD</td>
</tr>
</tbody>
</table>

RCT Meal Replacement vs Isocaloric Conventional Diet

Summary of Dietary Interventions

- All diets appear to be effective in the short term; little long-term data
- Data based on small sample sizes
- Severe calorie restriction (with or without protein sparing) may slow growth velocity
- Some diets may be better suited for specific obesity phenotypes
Step-Wise Approach to “Extreme” Interventions

- Diet
- Pharmacology
- Surgery
Indications for Pharmacotherapy for Childhood Obesity

• Significant weight related **health risks**

• **Failed structured** diet and lifestyle modifications

• **Understand the limitations** of available pharmacotherapy, including the need for concomitant lifestyle changes and short durability of medications

• Referred to a **tertiary care center** for evaluation and treatment

• Medication should be used **only as part of a multimodal weight loss therapy** that includes diet, physical activity, and behavior modification

Choice of Pharmacotherapy

• Made on an individual basis
• Take into account:
  – patient’s weight related health risks
  – mechanism of action
  – adverse side effects
  – patient/family preferences
  – cause of obesity, if known

FDA-Approved Pharmacologic Options

- Orlistat
- Phentermine
Orlistat

- Gastrointestinal lipase inhibitor
- Decreases intestinal fat absorption by 30%
- FDA-approved for children ≥ 12 yo
- No systemic action
- Results: 0.75 kg/m² reduction in BMI
- Side effects: defecation urgency, steatorrhea, abdominal discomfort
RCT Orlistat vs Placebo

Chanoine et al. JAMA. 2005;293:2873-2883
Phentermine

- Stimulates hypothalamus to release norepinephrine
- Promotes appetite suppression
- FDA approved adolescents >16 yo (1959)
- Schedule IV US DEA classification
- No studies in adolescents
- Average weight loss in adults = 3.6 kg over 2-24 weeks
- Side effects: abuse potential, increased BP, increased HR, GI symptoms

Non-FDA Approved Pharmacologic Options

- Metformin*
- Exenatide*
- Topiramate
- Naltrexone
- Bupropion
- Combinations
Metformin

- Used in the treatment of T2DM and lowers body weight in overweight and obese adults

- Weight reduction mechanism is not fully elucidated
RCT Metformin vs Placebo

- N=39 obese adolescents (age 13-18)
- Randomized to
  - Metformin XR 2000 mg qd
  - Placebo qd
- 52 weeks of intervention, then additional 48 weeks of follow-up

RCT Metformin vs Placebo

Exenatide

- Glucagon-like peptide-1 (GLP-1) receptor agonist
- Used in adults to treat T2DM
- Proposed mechanisms of weight loss
  - slows gut motility
  - heightens satiety via GLP-1 receptors in brain
Exenatide

- N=12 youth with extreme obesity, ages 9-16
- 6-month, randomized, open label clinical trial
  - Control phase: lifestyle
  - Drug phase: lifestyle + exenatide 10 mcg BID

Exenatide

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Summary of Pharmacological Interventions

• Very few medications have been studied in pediatric population
• FDA approved medications have a very modest effect
Step-Wise Approach to “Extreme” Interventions

- Diet
- Pharmacology
- Surgery
Rates of Bariatric Surgery

Data from US Academic Medical Centers
2002-2009

Who Should Get Bariatric Surgery?
2009 International Pediatric Endosurgery Group Guidelines

• BMI > 35 and **serious** comorbidity
  (T2DM, moderate OSA, pseudotumor cerebri, severe steatohepatitis)

• BMI > 40 and **mild** comorbidity
  (mild OSA, HTN, insulin resistance, dyslipidemia, severe psychological distress, significantly impaired QOL)
Attained or, depending on the severity of comorbidity, *nearly attained adult stature*

*Failed* at least 6 months of organized, *conventional* weight management treatment

*Shown commitment* to comprehensive psychological evaluation both before and after surgery, and agree to avoid pregnancy for at least 1-yr post-operatively

Evidence of *mature decision making*, social supports, ability to comply with recommendations
Bariatric Surgery

- Roux-en-Y gastric bypass
- Adjustable gastric banding
- Sleeve gastrectomy
Roux-en-Y Gastric Bypass

Illus: Nationwide Children’s Hospital
Roux-en-Y Gastric Bypass

- “Gold standard”
- Restrictive and malabsorptive
- Outcomes:
  - Decrease of 17.8 to 22.3 BMI units
  - Length of follow-up 1.0 - 6.3 years
- Complications:
  - PE, GI obstruction, shock, vitamin/mineral deficiency, protein-calorie malnutrition

Adjustable Gastric Banding

Illus: Nationwide Children’s Hospital
Adjustable Gastric Banding

- Not FDA approved for adolescents <18 yo
- Restrictive, “reversible”
- Outcomes:
  - Decrease of 10.6 to 13.7 BMI units
  - Length of follow-up: 1-3 years
  - 8% overall re-operation rate

Gastric Sleeve

Illus: Nationwide Children’s Hospital
## Strength of Evidence for Adolescent Bariatric Surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Outcome</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>RYGB (n=131)</td>
<td>Wt. loss at 1 yr</td>
<td>moderate</td>
</tr>
<tr>
<td></td>
<td>Wt. loss beyond 1 year</td>
<td>weak</td>
</tr>
<tr>
<td></td>
<td>Resolution of diabetes</td>
<td>insufficient</td>
</tr>
<tr>
<td></td>
<td>Resolution of hypertension</td>
<td>weak</td>
</tr>
<tr>
<td>LAGB (N=352)</td>
<td>Wt. loss at 1 year</td>
<td>moderate</td>
</tr>
<tr>
<td></td>
<td>Wt. loss beyond 1 year</td>
<td>weak</td>
</tr>
<tr>
<td></td>
<td>Resolution of diabetes</td>
<td>weak</td>
</tr>
<tr>
<td></td>
<td>Resolution of hypertension</td>
<td>weak</td>
</tr>
</tbody>
</table>

### Outcomes of Bariatric Surgery at academic centers (2002-06)

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers (N)</td>
<td>97</td>
<td>59</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>&gt;18</td>
<td>12-18</td>
</tr>
<tr>
<td>Females (%)</td>
<td>82</td>
<td>75*</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>74</td>
<td>70</td>
</tr>
<tr>
<td>Mean LOS (days)</td>
<td>3 ± 4</td>
<td>3 ± 4</td>
</tr>
<tr>
<td>30-day readmit (%)</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>ICU stay (%)</td>
<td>14</td>
<td>7*</td>
</tr>
</tbody>
</table>

*P < 0.05 vs. adults

Source: Areila et al. Surg Obes Relat Dis. 2007 3:537
<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure related (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Wound infection</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>- Reopening wound</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>- Perforation/laceration</td>
<td>1.7</td>
<td>0.3</td>
</tr>
<tr>
<td>- Bleeding/hematoma</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>- GI hemorrhage/ulcer</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Non-procedure related (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pneumonia</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>- DVT/PE</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>- Cardiac</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>- Pulmonary</td>
<td>1.1</td>
<td>0</td>
</tr>
</tbody>
</table>

Aurela et al. Surg Obes Relat Dis. 2007 3:537
Summary of “Extreme” Interventions

- Specialized dietary interventions produce only short term results.
- FDA-approved medications for extreme childhood obesity are scarce.
- Bariatric surgery is effective, but long-term outcomes are unknown.
Summary of “Extreme” Interventions

• Most studied strategies focus on weight loss and not weight maintenance.
• Many non-traditional treatments for childhood obesity are still investigational.
• It is appropriate to refer patients with extreme obesity to tertiary care centers.
Obesity is Complex!