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

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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

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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

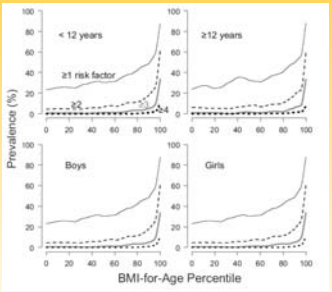
United States, ages 2-19 years old

- 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



Freedman, DS et al. J Pediatr 2007

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
Calcaterra, V et al. Clin Endocrinol 2008
Kelly, AS et al. Metab Syndr Relat Disord 2012

Inflammation and Oxidative Stress

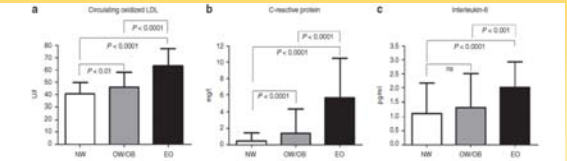


Figure 1 Oxidative stress and inflammation in three BMI groups. (a) Circulating oxidized low-density lipoprotein (LDL), (b) C-reactive protein, and (c) interleukin-6 in normal weight (NW), overweight/obese (OW/OB), and extremely obese (EO) children and adolescents. ns, not significant.

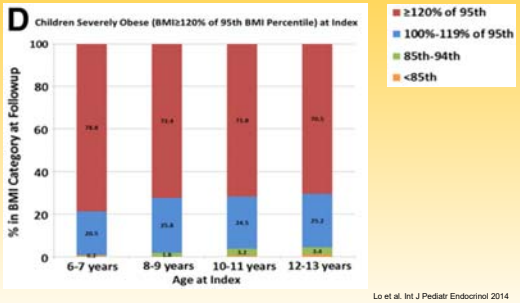
Norris et al. Obesity 2011

Other Co-Morbidities

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

Kalra, M et al. Paediatr Respir Rev 2006
Kohler, MJ et al. J Clin Sleep Med 2009
Xanthokos , S et al. Clin Gastroenterol Hepatol 2006
Montgomery, CC et al. J Pediatr Orthop 2010
Bhatia, NN et al. J Pediatr Orthop 2006
Zeller, MH et al. Pediatrics 2006
Schwimmer, JB et al. JAMA 2003
Reinehr, T et al. Pediatr Diabetes 2009

BMI Tracking in Childhood



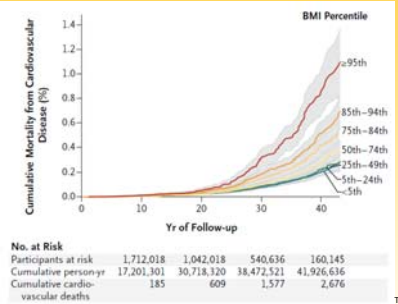
Lo et al. Int J Pediatr Endocrinol 2014

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/m^2
  - 88% developed adult BMI ≥35 kg/m^2
  - 65% developed adult BMI ≥40 kg/m^2

Freedman, DS et al. J Pediatr 2007

Adolescent BMI and Cardiovascular Death in Adulthood



Twig et al. NEJM 2016

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

Juonala, M et al. NEJM 2011

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

Hohenadel, MG et al. Int J Obes 2016

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

Barlow SE et al. Pediatrics 2007

Endocrine Society Guideline

Styne DM et al. JCEM 2017

Bariatric Surgery

Operation	Study	Sample Size	Mean Age	Baseline BMI	Follow-up	Postop BMI	BMI Change
RYGB	Inge 2010	61	17.2 years	60 kg/m^2	12-months	37.7 kg/m^2	-37%
RYGB	De la Cruz 2010	38	18.2 years	47.7 kg/m^2	12-months	32 kg/m^2	-33%
RYGB	De la Cruz 2010	7	Not specified	49 kg/m^2	12-months	32 kg/m^2	-35%
RYGB	Olbers 2012	81	16.5 years	45.5 kg/m^2	24-months	30.2 kg/m^2	-33.6%
AGB	O'Brien 2010	25	16.5 years	45 kg/m^2	24-months	32.6 kg/m^2	-28%
AGB	Nadler 2009	41	16.1 years	48 kg/m^2	24-months	35.8 kg/m^2	-25%
VSG	Al-Qahtani 2012	108	13.9 years	49.6 kg/m^2	12-months	32.4 kg/m^2	-35%
VSG	Boza 2012	40	18 years	38.5 kg/m^2	12-months	25.2 kg/m^2	-35%
VSG	Boza 2012	34	Not specified	38.5 kg/m^2	24-months	26.3 kg/m^2	-32%



Kelly AS et al. Circulation 2013

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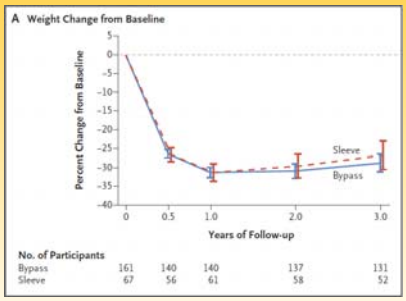
Teen LABS



Inge et al. NEJM 2015

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Lifestyle Modification Therapy

- Primary components:
  - Dietary counseling
  - Physical activity counseling
  - Behavioral modification counseling

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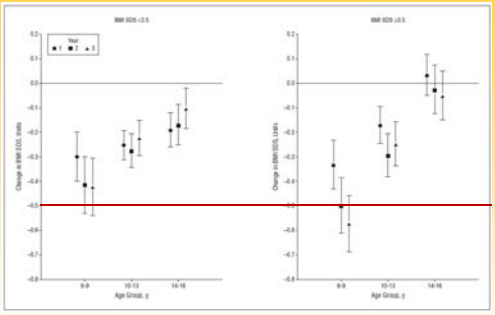
Lifestyle Modification Therapy



Danielsson, P et al. Arch Pediatr Adolesc Med. 2012

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Why is obesity so difficult to effectively treat?

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Appetite/Satiety Hormone Dysregulation
Reduced Metabolic Rate
Stigma/Body Image
Stress
Iatrogenesis
Binge Eating Disorder
Genetic Predisposition
Television
Moving Walkways
Pre-pregnancy BMI
Antibiotic Use
Developmental Programming
Microbiota
Anxiety
Large Portions
Gestational Weight Gain
Sedentary Lifestyle
Depression
Reduced Executive Functioning
Leptin Resistance
Less Gym Class
Race/Ethnicity
Poverty
Dysregulated Reward Pathways
Weight Cycling
Poor Sleep Hygiene
Devices
Escalators
Impulsivity
Less Recess
Adverse Life Experiences
Economics
Catch-up Growth
Elevators
Epigenetics
Calorie-Dense Foods
Video Games

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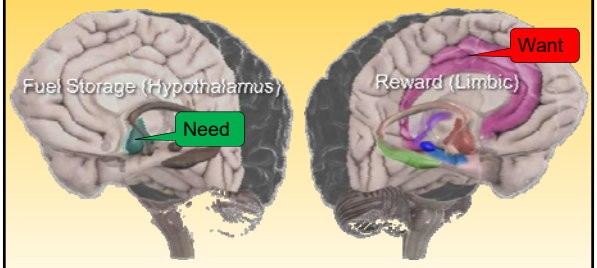
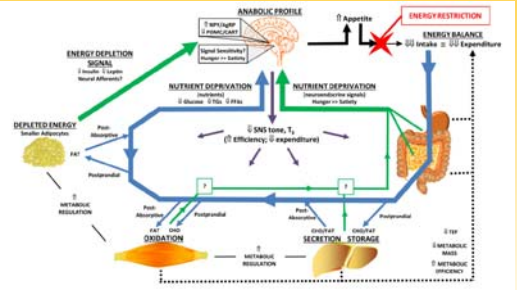
Fighting against Biology

- 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

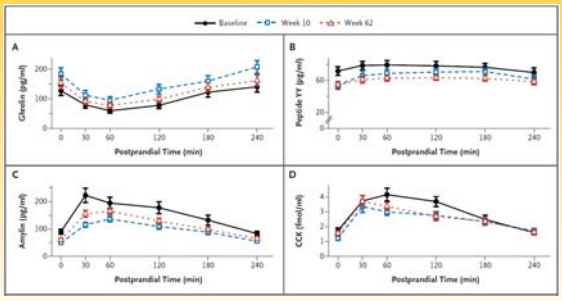


Regulation of Energy Balance



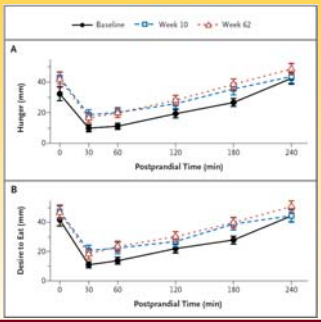
MacLean et al. Obes Rev 2015

Biology of Weight Loss-Regain



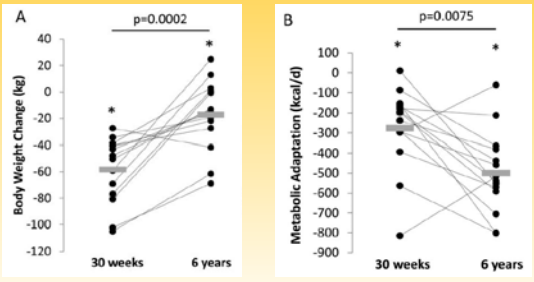
Sumithran et al. NEJM 2011

Biology of Weight Loss-Regain



Sumithran et al. NEJM 2011

Metabolic Adaptation



Fothergill et al. Obesity 2016

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Real Life Example

- 16 year old white female
- Reported gaining 35 pounds in the last year
- Current BMI = 38.8 kg/m^2 (severe obesity)
- Counseled to eliminate liquid calories and add fruits/vegetables to diet
- Later started on pharmacotherapy (buproprion + 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"

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Resting Metabolic Rate

- ~~1,888 kcals/day~~ = **1,089** kcals/day!

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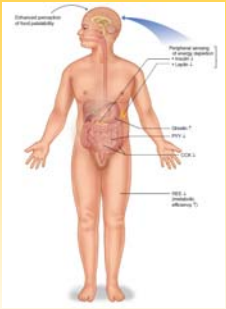
Biologically-Based Treatment

- 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

*For a comprehensive review of pediatric obesity pharmacotherapy see:
Sherafat-Kazemzadeh R, Yanovski SZ, Yanovski JA. Pharmacotherapy for childhood obesity: present and future prospects. Int J Obes (Lond) 2013 January;37(1):1-15.

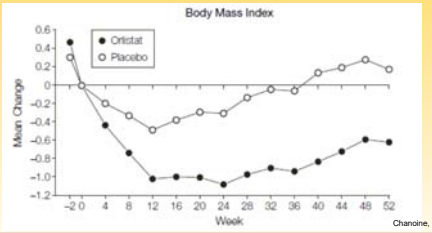
*For suggestions regarding best practices for the design and conduct of pediatric obesity pharmacotherapy clinical trials see:
Kelly AS, Fox CK, Rudser KD, Gross AC, Ryder JR. Pediatric obesity pharmacotherapy: current state of the field, review of the literature, and clinical trial considerations. Int J Obes (Lond). 2016 Jul;40(7):1043-50.

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

Orlistat

- Largest randomized, controlled trial (N = 539) reported BMI reduction of 2.4% at 1 year (mean baseline BMI = 36 kg/m^2)



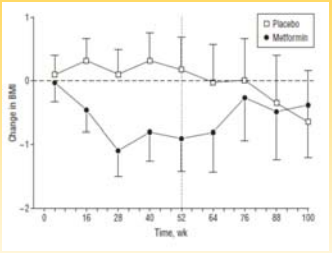
Chanoine, JP et al. JAMA 2005

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)



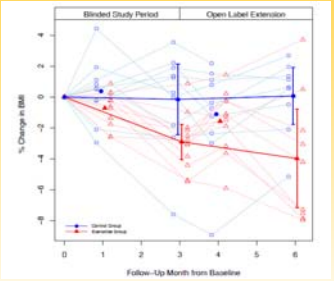
Wilson, DM et al. Arch Pediatr Adolesc Med 2010

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-HT_{2c} 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

Kelly et al. J Pediatr 2013
Daniels and Kelly Child Obes 2014
Kelly et al. Int J Obes 2016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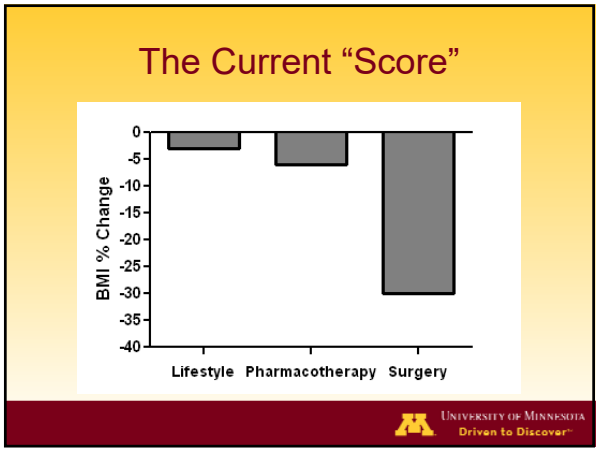
The Current "Score"
BMI % Change
0
-5
-10
-15
-20
-25
-30
-35
-40
Lifestyle
Pharmacotherapy
Surgery
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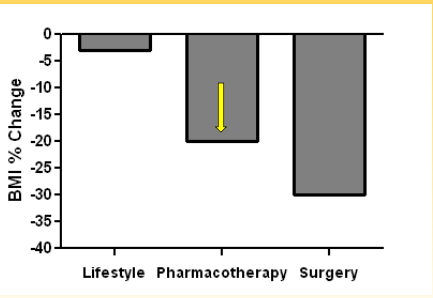
The Achievable Goal



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