

Advanced Obesity Treatment Options

Maine AAP Spring Conference 2017

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23 Million children in US with Overweight or Obesity

1 in 3 ME Kindergarteners have overweight or obesity

27.6% of ME high school students have overweight or obesity

4.5 million children in US with Severe Obesity

Need: Preventing and/or Reversing the many related co-morbid health diseases associated with BMI's >85th %

Prevalence

• **Overweight & obesity** affected 32% of the U. S. youth aged 2 to 19 years in 2012 (NHANES).³

• Preschool children (2-5 Years Old)

• 13.4% overweight

• 9.4% obese

• 6 to 11 year olds

• 16.8% overweight

• 17.4% obese

• adolescents 12 to 19 years of age

• 13.9% overweight

• 20.6% obese

• Prevalence by Obesity Class (2014 NHANES)²

• 17.4% of children met criteria for class I obesity (12.7 million children⁴)

• 6.3% for class II (Severe obesity)

• 2.4% for class III (Severe obesity)

• A clear, statistically significant increase in all classes of obesity continued from 1999 through 2014. ²

• Severe obesity (Class II & III) is the fastest-growing subcategory of obesity in youth³

Ogden, Carroll, Kit, et al. (2014)¹; Skinner, Perrin, Skelton (2016)²; Kelly et al. (2013)³; Ogden, Carroll, Fryar, et al. (2015)⁴

Current AAP & USPSTF Recommendations

AAP 2010 Guidelines

- Stages
 - Stage 1: PCP
 - Stage 2: PCP w/monthly f/u
 - Stage 3: Multidisciplinary
GAP
 - Stage 4: Multidisciplinary; consider adding surgical procedure
 - New flip charts 2015

USPSTF 2010 Recommendations

- Mod-High Intensity for BMI $\geq 85^{th}$ %
- Minimum of 25 hours in 6 months
- Must include behavioral component
- Grade B
 - Covered by ACA as Preventive Service
 - ? Grandfathered policy
 - No cost sharing

Endocrine Society Guidelines: April 2017

• Summary:



Multi-factorial Contributing Factors



Case Study

A parent of a 3 year old boy with a BMI >99th% shares that her son will *"have a tantrum if I say no to more crackers"* even if he just had large serving.

Obesity 1.0 Treatment Focus

- Express empathy
- Review positive parenting skills
- Redirection
- Tough love with limiting additional servings
- Behavior Modification in order to impact Physiology
- Likely to fail

Obesity 2.0

A calorie is not a calorie
Sugar is not sugar
Fat is not fat
Activity - not exercise
Energy management system
"Set point"
A gene is not a gene

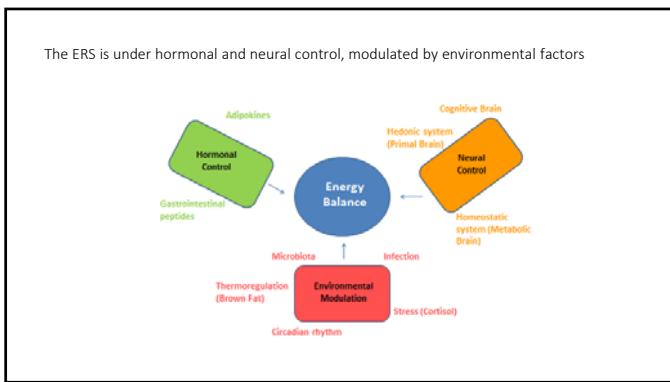
The ERS is an exquisitely complex, redundant, & essential foundation for human existence.

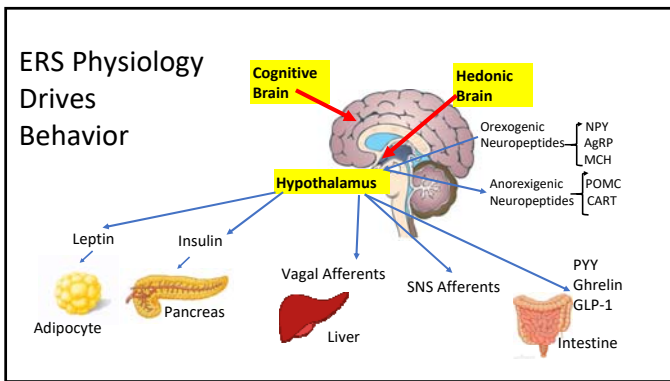
Human Metabolic Pathways

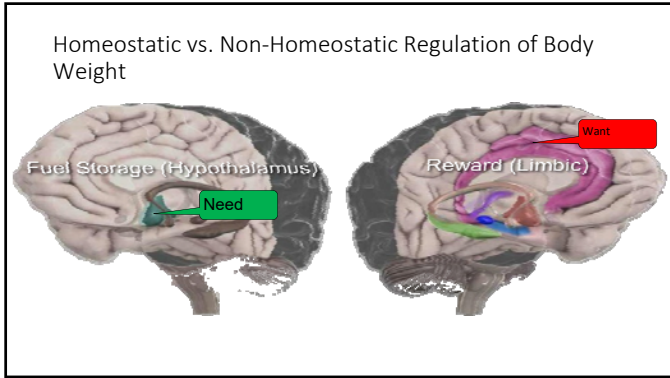
Washington, DC Metro Map

Which is more complicated?!!

Nelson, D. L. & Cox, M. M. (2017). Lehninger Principles of Biochemistry, 7th Ed. Freeman: New York, New York.







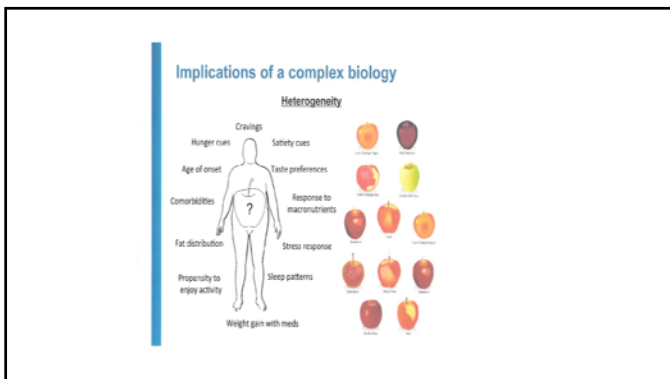
Phenotypes: exist with individual, unique responses
 Normal ERS physiology + phenotypic triggers= ERS pathophysiology

Modulate & Manage

- Diet
- Activity
- Responses to cues
- Stress
- Sleep
- Circadian rhythms
- Depression
- Anxiety
- Medications

Understand and accept

- Age
- Ethnicity
- Gender
- Genetics



" Gluttony and Sloth" or..

- Satiety center
- Hedonistic center
- Stress
- Epigenetics
- HFCS
- Obesogens
- Microbiome

**Obesity 2.0 Pathophysiology First:
Treatment Focus**

- Positive Parenting Skills
- Share the science and physiology that explains that physiology is driving the behavior.
- This reframes the discussion: replaces blame and "bad behavior" with a new starting place.

**So....
Obesity is a disease that:**

- Shortens ones lifespan
- Clinical comorbidities – which present during childhood
- Psycho-social comorbidities
- Economic consequences

Obesity 2.0 Treatment

Self-Directed Interventions

Primary Care Interventions

Diet and activity not enough for most people with obesity

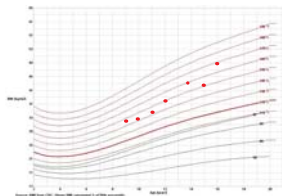
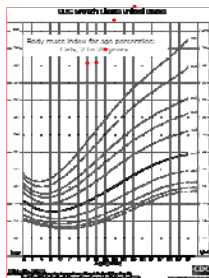
**Comprehensive Multi-disciplinary Treatment
by Obesity Specialists**

Surgery unacceptable for most people with obesity

Case #2: 17 yr old Female

PT initially referred to WOW age 9 yrs: BMI 32.5
PMHx: devel delay/?autism spectrum, hyperlipidemia, constipation
FHx: Obesity, Hyperlipidemia, CVD, T2DM, CA, OSA
SocHx: parents divorced, shared custody
Food Hx: food as replacement for finger sucking and for coping, +juice and soda
PA: involved in 4H, PE at school, had PT eval through school
Initial Labs: Tot Chol: 375 LDL 293 Trig 125 HDL 57
PE: at initial visit: Wt: 120lbs BMI 32.5 BP 110/50 P 84, exam wnl
Plan: Stage 3 Intensive Lifestyle Change in Comprehensive Team Model
Physician, RN, RD and PhD visits: Phase 1,2,3 over 12-15 months: also referred to lipid clinic.
Statin started. Sleep Study: Mild Apnea --no CPAP
Results: periods of BMI stability, however, by age 16: BMI=48.89
Phenotype: ? But needs MORE

Case: 17 yr old Female



Confronting Weight Bias

- Through positive Pt-Team relationship: Mother open to discussion
- Challenges:
 - Small volume of literature/trials on use of medications in children
 - Mother's personal medication experience and fears
 - Other providers involved in patients care unsure about medications
 - What to do? Mother not open to Bariatric surgical consideration now or in near future
 - Reviewed GAP – medications presently used in pediatrics for other diseases
 - Reviewed the safety issues with these medications
 - Shared the information and offered pt and mom time to reflect and follow up in 2-4 wks

Confronting Weight Bias - care givers

- Family members
- Teachers/PE Teachers /coaches
- Daycare providers

Confronting Weight Bias - health care team

- Providers – RNs – psychologists
- Waiting Rooms – seating that is appropriate for all patients
- Scales – where are they

Rudd Center Food Policy & Obesity
www.uconnruddcenter.org

Tools

- [Education](#)
- [Emotional and Physical Health](#)
- [Employment](#)
- [Health Care](#)
- [Media](#)
- [Theories of Weight Bias](#)
- [Weight Discrimination and the Law](#)
- [Weight Stigmatization in Youth](#)

Related Materials

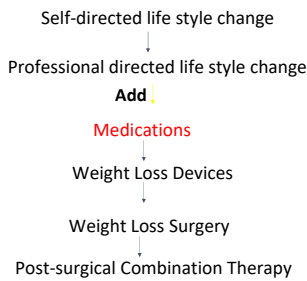
- [Tools for Researchers](#)
- [Web Links](#)

The Gap



• Sarah Armstrong - Duke University

Additive Treatment Strategies



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.

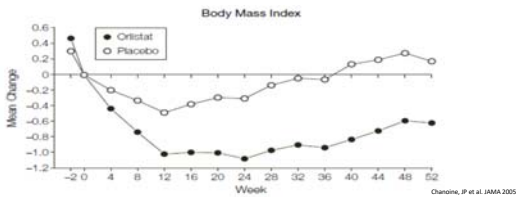
Orlistat

- 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/m²)



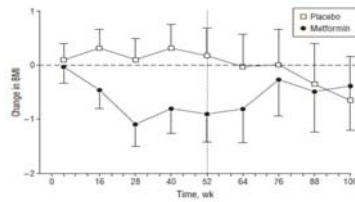
Metformin

- 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

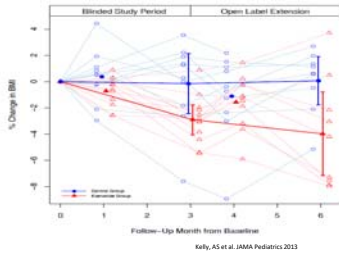
Exenatide

- 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



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
- Pregnancy Category X

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
- Pregnancy Category X (topiramate)

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

Vyvanse

- In February 2015, Vyvanse (lisdexamfetamine dimesylate) became the first and only medication approved to treat moderate to severe Binge Eating Disorder in adults. Vyvanse is not for weight loss. It is not known if Vyvanse is safe and effective for the treatment of obesity.
- Approved for ADHD for age 6 years old and up.
- Starting dose 30mg/day. Treatment range 50-75mg /day

Topiramate

- Anti-epileptic: enhances GABA receptor activity
 - inhibits carbonic anhydrase
- Dosage: 25 – 150 mg/day
- Interactions: AE: paresthesias, taste aversion, memory impairment
 - CI: Kidney Stones, glaucoma
 - Pregnancy Category X
 - Increased levels in combination with metformin
- Useful in antipsychotic-induced wt gain
- Useful in binge-eating
- Useful in PCOS

12 year old girl with BMI 40

- Lives 3 hours away
- HPI:
 - weight was normal until age 5-6 years old
 - met with "nutritionist" last year who recommended supplements
- Diet:
 - Breakfast – 2 cups cereal
 - Lunch – 3 hotdogs, no bun
 - Dinner – 2 grilled cheese sandwiches
 - Fast food 2-3 times/wk, frequent SSB
 - No food insecurity

12 year old girl with BMI 40

- Eating:
 - Hungry all the time
 - Feels out of control of eating daily
 - Eats until uncomfortable
 - Feels guilty after overeating
 - No food sneaking, stress eating, night eating
- Physical Activity:
 - Volleyball, gym 2x/week

12 year old girl with BMI 40

- Family History:
 - Dad – HTN, T2DM, obesity
 - Mom – obesity
 - Maternal aunt – bariatric surgery
- Social history:
 - Lives with both parents and sister
 - 6th grade, recently changed school due to bullying

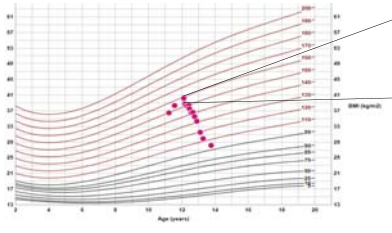
12 year old girl with BMI 40

- Physical exam
 - 185 lbs; 4"9"; BMI 40.2,
 - BP: 123/70; HR: 88
 - Normal; T2
- Labs
 - TC 148; HDL 38; LDL 64; TG 230
 - A1c 5.5, glucose 88
 - ALT/AST 29/23

12 year old girl with BMI 40

- Plan
 - 1400 kcal flex meal plan
 - Physical therapy

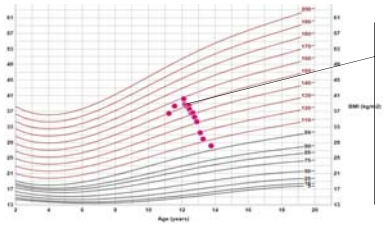
12 year old girl with BMI 40



Start 1400 kcal flex meal plan + food logging

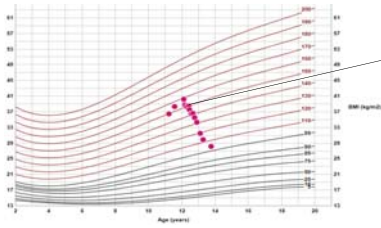
1 month: down 6 lbs

12 year old girl with BMI 40



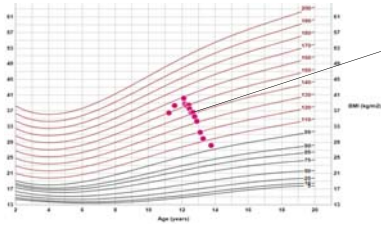
2 months: down 1 more lb
3.5 months: up 2 lbs;
frustrated; getting 2 lunches
from school so instructed to
remove \$ from school account

12 year old girl with BMI 40



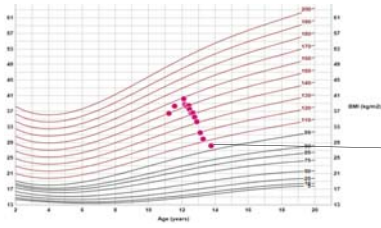
4.5 months: wt stable; patient is hungry
start phentermine 15 mg

12 year old girl with BMI 40



"She has been taking phentermine 15 mg daily for the past 2 months and lost only 5 pounds total. This weight loss occurred during her first month, with a slight increase during the second month. I expressed to mom my hesitancy to continue this medication if [patient] does not lose weight as the benefits will not outweigh the risks. Fortunately, [patient's] BP has been okay, though she is slightly tachycardic compared to before starting the phentermine. Mom and [patient] really wanted to continue the phentermine for another month. I told them that I will not refill it if she cannot lose about 1 lb per week."

12 year old girl with BMI 40

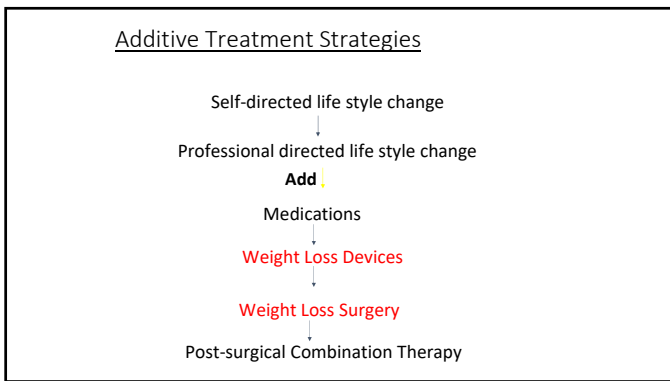


20 months:
Change in BMI - 29.6%
Change in weight - 40 lbs

Case: 17 yr old...
 Deeper History: ADD and BED Scored
 Plan: Add Vyvanse at 20mg daily, Close follow up: 2 weeks, then monthly

Back to 17 yr old case...
 2 month follow up: Vyvanse incr to 30mg

- Pt at 4 months after starting Vyvanse:
- Self-esteem
- School function
- BMI change from 48.89 to 45.09
- 6 months on Vyvanse: BMI 43.49
- 10 months on Vyvanse (30mg/day): BMI 41.6 (wt 240)
- Total change BMI: from 170th % to 140th %
- Total Weight Change: 275 lbs to 240 lbs (down 35 lbs)
- Repeat Sleep Study (after 30lbs wt loss): WNL
- Most recent labs: 4/2017:
 - Tot Chol: 208 Trig 73 HDL 72 Trig/HDL ratio: 1.01; LDL 122 (initial 293)
 - AST 13 ALT 10



Weight loss surgery

- Spectacularly successful
 - RYGB
 - Sleeve Gastrectomy
 - AGB
- Safe
- ? long term effects
- "unacceptable"

Endoscopic mimics

- AGB
- Sleeve

Weight Loss Devices

- most are temporary
- most are adjustable
- removable
- Less weight loss than with surgeries
- ? combinations with weight loss medications

Intragastric

- Balloons
 - single
 - double
 - multiple
 - saline filled
 - air filled
 - adjustable
 - swallowed
 - Pass spontaneously

Intragastric - II

- trans pyloric shuttle
- Gellelis capsules

Extra gastric

- gastric vest
- Extragastric balloon

Gastric drainage

- Aspire Device

Endosleeves

- Gastrojejunal
- Duodenal jejunal - Endo barrier

Duodenal

- satisphere
- duodenal resurfacing

Neuromodulation

- Vagal stimulator - Maestro
 - vagus at GEJ
- ? trans cutaneous vagal stimulation
- Gastric stimulator
- Transcranial stimulation

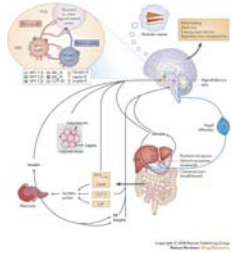
Kids and devices and meds

- Goals
 - ? weight loss
 - ? weight stabilization
 - ? care necessary after induction
 - ? clinical comorbidities
 - ? clinical risk factors
 - ? psycho-social comorbidities

Kids and devices and meds

- Plasticity
- Set Point flexibility
- Response to Healthy Living after healthy body composition attained

The Future is now: What is coming fast



- Defining of phenotypes
- Advanced treatments
- Focused treatments
- Combination treatments
- Intervention timelines

Advocacy and Policy Change

- Physiologically based prevention
- Physiologically based intervention
- Chronic disease model
- Multidisciplinary team
- Bundled payments

Advocacy and Policy Change - II

- Outcomes
 - weight based
 - BMI based
 - health based
 - clinical comorbidities
 - psychosocial comorbidities
 - Economically based
 - cost
 - productivity

Advanced Obesity Treatment

Based on Healthy Living as defined by **Physiology**

Utilize weight loss medications- in adults (FDA approved) and pediatrics(need for trials)

Utilize weight loss device therapies (multiple approved in adults- EMMC now offering wt. loss balloon) & need trials for pediatrics

Develop algorithms for combinations of weight loss medications and device therapies

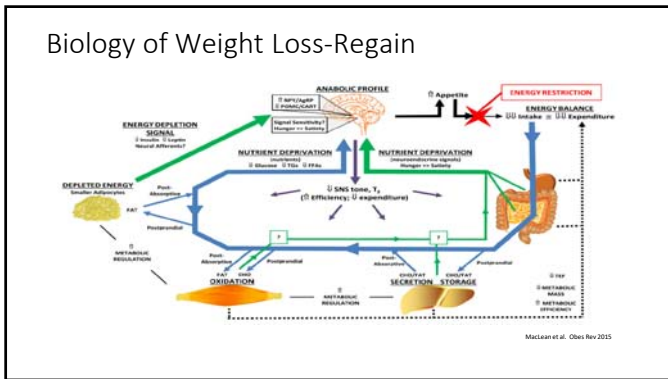
Understanding this is a **chronic disease**

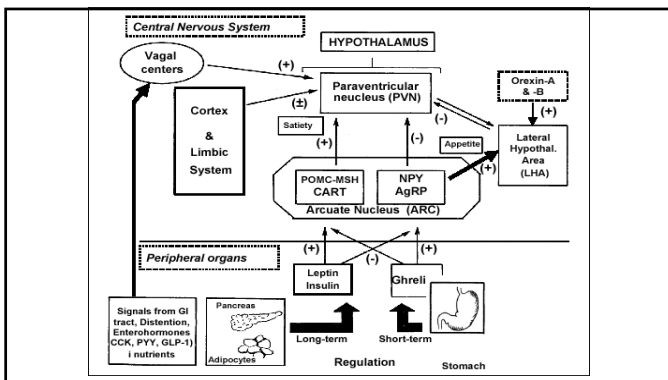
Staying with patients and families through successes and setbacks

Thank You

- Acknowledgements:
- Dee Kerry, Dr. Jan Pelletier, MAAP
- WOW Team

Additional Resources





ERS Hormones

Hormone	Source	Function
Leptin	Adipose tissue	Reduce hunger
Adiponectin	Adipose tissue	Stimulates catabolism
Insulin	Pancreas (beta cells)	Stimulates glucose uptake; synthesis glycogen & fat
Glucagon	Pancreas (alpha cells)	Stimulates gluconeogenesis & glucose release to body
Ghrelin	Stomach, intestine	Signals hunger
GLP-1, GIP	Intestine	Stimulate insulin release
PYYs	Intestine	Signals Satiety
Cortisol	Adrenals	Stimulates gluconeogenesis & glucose release to body

Nelson & Cox, 2017 p. 918

The Comorbidities of Obesity

Endocrine/Immune Response	Physical Response	Psychological Response
Adiposopathy <ul style="list-style-type: none"> Impaired fasting glucose Metabolic Syndrome Hypertension Menstrual Dysfunction (female) Delayed Puberty (Male) NAFLD Dyslipidemia Insulin Resistance Type 2 DM Increased uric acid, Microalbuminuria Gynecomastia Cholecystitis 	Fat Mass Disease <ul style="list-style-type: none"> Asthma Immobility Lipomastia Tissue Compression <ul style="list-style-type: none"> sleep apnea GERD HTN Tissue Friction (intertrigo) Stress on weight-bearing joints <ul style="list-style-type: none"> Slipped capital femoral epiphysis Blount disease scoliosis Osteoarthritis 	Quality of Life <ul style="list-style-type: none"> Isolation from peers Decrease in ability to participate in normal childhood activities Subject to bullying Lack of social/age appropriate relationships Anxiety/depression Binge eating disorder Night eating disorder Bulimia

Psychiatric Medications That Affect Weight

Category	Weight Gain	Small-Neutral Weight Gain	Weight Loss
Antipsychotics	Clozapine Olanzapine Chlorpromazine Quetiapine Risperidone	Aripiprazole Haloperidol Ziprasidone	
Anti-depressants	Paroxetine Amitriptyline Olanzapine Fluoxetine Citalopram Nortriptyline	Doxepin Desipramine Imipramine Duloxetine Escitalopram Lithium	Venlafaxine Fluvoxamine Sertraline Trazodone Fluoxetine
Mood stabilizers	Valproate Lithium Gabapentin		Topiramate
Anxiolytics		Lorazepam Diazepam Oxazepam	

Cuda et al. 2016. OMA Pediatric Obesity Algorithm

Additional Medications That Affect Weight

Category	Weight Gain	Small-Neutral Weight Gain	Weight Loss
ADHD		Guanfacine	Atomoxetine Lisdexamfetamine (Vyvanse) Amphetamine Methylphenidate
Anti-Seizure	Valproate Vigabatrin	Pregabalin Gabapentin	Carbamazepine Oxcarbazepine Levetoracetam
Migraine	Amitriptyline Divalproex Flunarizine	Propranolol Metoprolol Gabapentin	Timolol Levetoracetam
Diabetic medications	Insulin & analogs		GLP-1 Receptor agonists Metformin
Other medications	Glucocorticoids Gleevec Depo Provera	Benzodiazepines Statins Antihistamines (Cyproheptadine) Carvedilol Oral Contraceptive Pills	

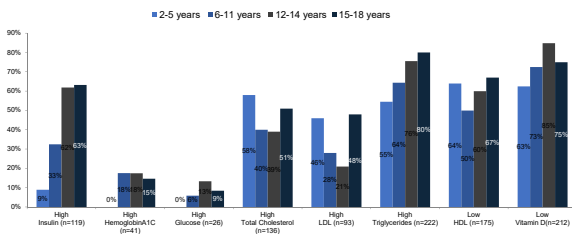
Cuda et al. 2016. OMA Pediatric Obesity Algorithm

Weight Gain Promoting Medications	Alternate Agents
Atypical antipsychotics: i.e.: clozapine, Zyprexa, Seroquel, risperidone, abilify	Ziprasidone (Geodon)
Anti-depressants: Tricyclics: trazadone, nortriptyline, amitriptyline SSRI: paroxetine, celexa, Lexapro Others: venlafaxine (Effexor), mirtazipine	Bupropion (Wellbutrin) Sertraline, fluoxetine
Anti-Epileptics: gabapentin, valproic acid, carbamazepine, oxycarbamezepine	Topiramate, zonisamide, lamotrigine
Miscellaneous: ie lithium	Topiramate, ziprasidone (Geodon)
Diabetes Medications: Insulin Sulfonylureas: glipizide Thiazolidinediones : pioglitazone	Pramlintide (symlin) GLP-1 agents: liraglutide (victoza), metformin, acarbose DPP4 Inhibitors: sitagliptin (Januvia)
Glucocorticoids: prednisone, methyl pred	Immunosuppressive agents
Hormonal contraceptives: Depo- medroxyl progesterone	Non hormonal contraception
Betablockers: propranolol, metoprolol, atenolol	Other anti-HTNs, carvedilol
Anti-histamines: Benadryl, hydroxyzine, cetirizine	Loratidine

Prevalence of obesity cardio-metabolic comorbidities in children (2-19 years old) enrolled in WOW from 2009 to 2016

- Insulin, Glucose, HbA1c, LDL, HDL, Cholesterol, Triglycerides, Vitamin D (all fasting)
- Obesity Class, Gender, Age groups
- Children with BMI > 95th percentile in each age category, gender, and weight class present with significant disease burden
 - particularly hyperinsulinemia, hypertriglyceridemia, and Vitamin D deficiency.
- Disease burden also present in the Overweight category
- 92% of children screened (337 of 382) had one or more abnormal cardio-metabolic risk factor (excluding Vitamin D)
- Data highlight the existing (not "at risk for") abnormal laboratory disease burden in pediatric patients (including 2-5 year olds) with obesity presenting to WOW.

Cardio-metabolic risk factors by age group



Cardio-metabolic risk factors by obesity class

