Obesity Management and Diabetes Prevention in General Pediatrics

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Disclosures

- Previous site investigator for studies sponsored by Rhythm Pharmaceuticals
  - No personal income from these studies
- Will discuss off-label use of medications
- Will use brand names in some cases

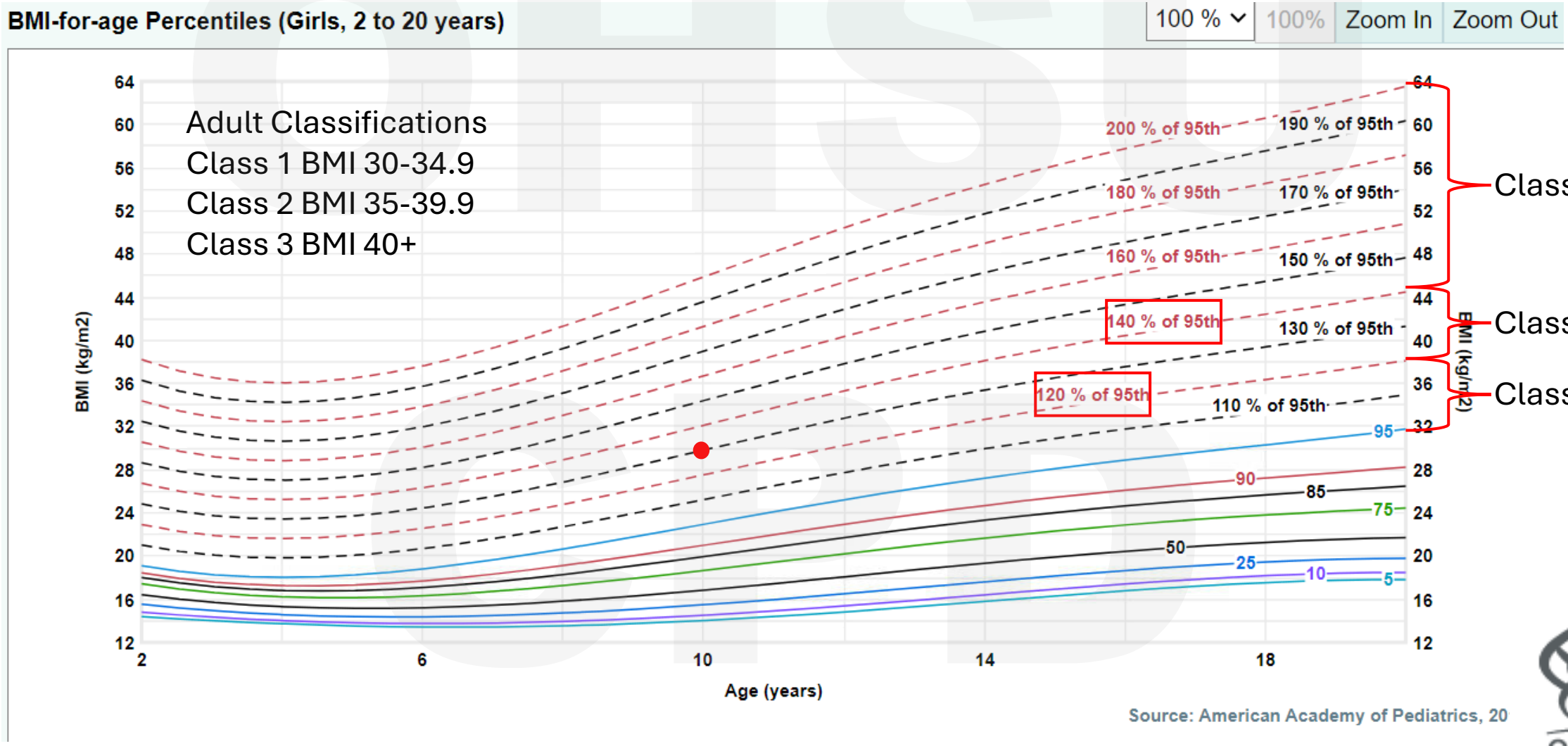
Objectives

- Review pediatric obesity classifications and categories of glucose dysregulation
- Review FDA approved anti-obesity medications for kids age 12 and over
- Discuss off label anti-obesity treatments
- Look at data for use of metformin in diabetes prevention
- Overview of who to refer, wait times and what to do while waiting for your patients to be seen

Underlying Tenets

- Obesity Medicine Association Definition - Obesity is a **chronic, relapsing, multi-factorial,** neurobehavioral **disease**, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences.
- Obesity is <u>not</u> due to lack of willpower, to ignorance or to inadequate parenting
- Weight loss is not simply a matter of eating fewer calories and exercising more
- Lifestyle intervention is necessary but usually not sufficient for the treatment of severe, longstanding obesity

Pediatric Obesity Classifications



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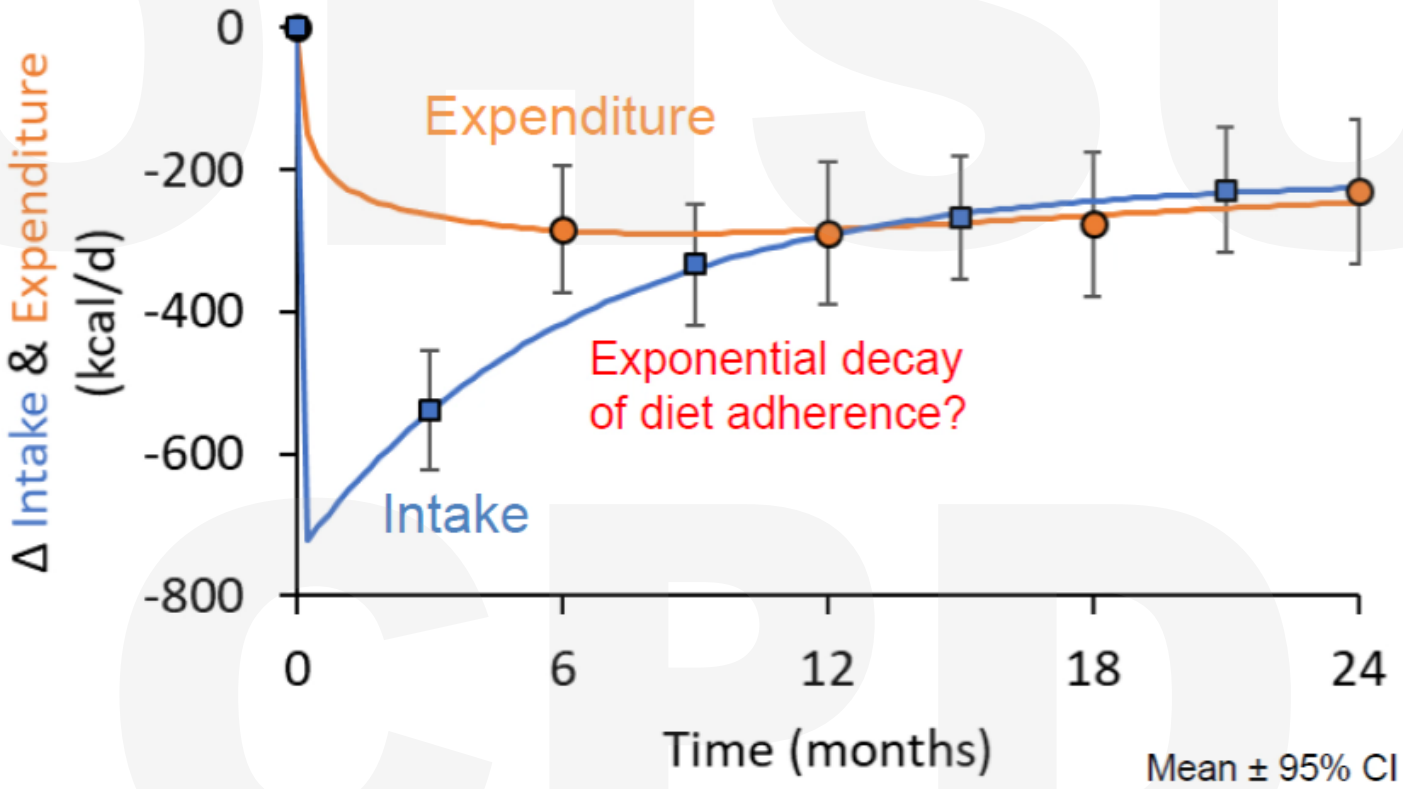
The Limits of Lifestyle Intervention

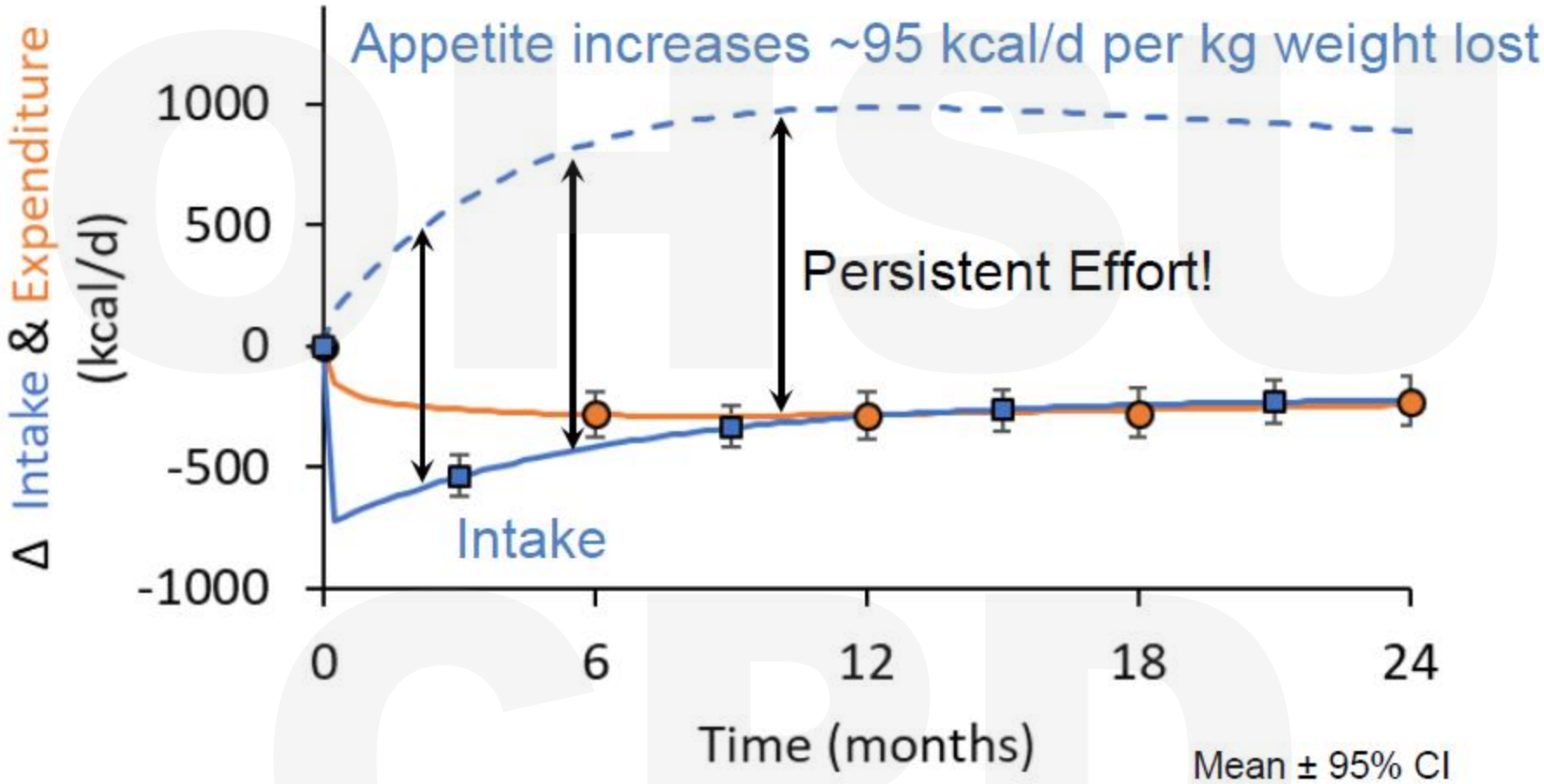
- 3,000 calorie “rule” vs myth
  - Reduction of intake by 3,000 calories = 1 pound of weight loss
  - Therefore reduction of intake by 100 calories per day will result in loss of 1 pound per month
  - If you trained at DCH, we probably taught you this!
- Why doesn’t this work?
  - If this was a continuous linear relationship, what would happen over time?

The person cutting calories would disappear!!

What Happens Instead?



J Guo et al. *Am J Clin Nutr* 107:558–65 (2018).



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What About Exercise?

- Studies show that exercise is more effective for weight maintenance or prevention of weight regain than for weight loss
- Adults need >300 minutes of moderate intensity physical activity per week to achieve >5% weight loss
- Children need 60 minutes or more per day of planned, supervised active play to achieve weight loss
- Important benefits of exercise beyond weight loss
  - Increased cardiovascular fitness
  - Improved insulin sensitivity
  - Maintenance/acquisition of lean body mass (muscle and peak bone mass)

Who Qualifies for Medical Weight Management?

- Any child with obesity can be considered for treatment – with or without complications
- Kids are resilient and may not show complications until they are older
- Although insurance companies frame treatment options as sequential – lifestyle, then medications in a certain order, then surgery – there is no reason this has to be the case
- Earlier onset of obesity, longer duration of obesity, strong appetite and family history increase likelihood of needing multimodal therapy

FDA-Approved Anti-Obesity Medications

- Age 2 and over
  - Setmelanotide – specific genetic forms of obesity
- Age 12 and over
  - Orlistat
  - Qsymia
  - GLP-1 receptor agonists
- Age 16 and over
  - Phentermine
- Age 18 and over
  - Vyvanse – binge eating disorder
  - Contrave – bupropion/naltrexone

Setmelanotide (Imcivree)

Drug description	Melanocortin-4 receptor agonist
Mechanism of action	Appetite suppression and increased resting energy expenditure
Indications	Obesity due to Bardet-Biedl syndrome, POMC, LEPR or PCSK-1 mutation (Free mutation analysis available through PreventionGenetics) Age 2 and over
Dosage	Start at 0.5 mg SQ daily (<6 years), 1 mg (6-12 years) or 2 mg (12 and over) Titrate up to 2 mg (<6 years) or 3 mg (6 years and over)
Anticipated weight loss	>/=10% - 45-80% achieved this degree of weight loss in early studies
Side effects	Injection site reactions Nausea, vomiting, abdominal pain, diarrhea, headache Diffuse hyperpigmentation and mole formation/progression Mood changes Priapism (Early/rapid pubertal progression)
Contraindications	Prior hypersensitivity reaction to setmelanotide or any ingredient in Imcivree

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Orlistat (Alli, Xenical)

Drug description	Pancreatic and gastric lipase inhibitor
Mechanism of action	Prevents absorption of ~30% of ingested fat
Indications	Obesity, age 12 and over
Dosage	60 mg (OTC) or 120 mg (Rx) orally TID with meals containing fat
Anticipated weight loss	2-4% overall >/=5% in 21% >/=10% in 12%
Side effects	Diarrhea, oily stools, fecal incontinence Malabsorption of fat soluble vitamins Increased urine oxalate Rare hepatotoxicity
Contraindications	Gallbladder disease Malabsorption syndrome History of kidney stones Pregnancy

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Qsymia

Drug description	Combined phentermine (sympathomimetic amine)/topiramate (carbonic anhydrase inhibitor) extended release
Mechanism of action	Appetite suppression and earlier satiety
Indications	Obesity, age 12 and over
Dosage	3.75 mg phentermine-23 mg topiramate PO daily x 14 days 7.5 mg phentermine-46 mg topiramate PO daily x 12 weeks If needed, 11.25/69 x 14 days then 15/92
Anticipated weight loss	>/=5% at 12 weeks
Side effects	Phentermine – increased HR/BP, jitteriness, anxiety, sleep disturbance, headache, dry mouth, constipation Topiramate – paresthesias, “brain fog,” kidney stones, glaucoma
Contraindications	Hypertension Hx arrhythmia/congenital heart disease Hx kidney stones Concomitant use of other stimulant medications Hyperthyroidism Glaucoma

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Liraglutide (Saxenda)

Drug description	GLP-1 receptor agonist
Mechanism of action	Delayed gastric emptying, reduced appetite, early satiety Increased insulin secretion and reduced glucagon secretion
Indications	Obesity, age 12 and over T2DM, age 10 and over (branded as Victoza)
Dosage	0.6 mg SQ daily starting dose Titrate by 0.6 mg every week to max dose 3 mg SQ daily
Anticipated weight loss	5-15%
Side effects	Abdominal pain, nausea, vomiting, constipation, diarrhea Headache Pancreatitis C-cell hyperplasia in rodents
Contraindications	History of pancreatitis Personal or family history of medullary thyroid cancer or MEN Use with caution in binge eating disorder

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Semaglutide (Wegovy)

Drug description	GLP-1 receptor agonist
Mechanism of action	Delayed gastric emptying, reduced appetite, early satiety Increased insulin secretion and reduced glucagon secretion
Indications	Obesity, age 12 and over T2DM in adults at lower dose (branded as Ozempic)
Dosage	0.25 mg SQ weekly starting dose Titrate monthly (0.5 mg, 1 mg, 1,7 mg, 2.4 mg) to max dose 2.4 mg SQ weekly
Anticipated weight loss	5-15%
Side effects	Abdominal pain, nausea, vomiting, constipation, diarrhea Headache Pancreatitis C-cell hyperplasia in rodents
Contraindications	History of pancreatitis Personal or family history of medullary thyroid cancer or MEN Use with caution in binge eating disorder

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Phentermine

Drug description	Sympathomimetic amine
Mechanism of action	Appetite suppression and earlier satiety
Indications	Obesity, age 16 and over, short term use (12 weeks)
Dosage	8 mg, 15 mg, 18.75 mg, 37.5 mg PO daily
Anticipated weight loss	~5%
Side effects	Increased HR/BP Jitteriness/anxiety Sleep disturbance Headache Dry mouth Constipation
Contraindications	HTN Hx arrhythmia/congenital heart disease Hyperthyroidism Use with caution if on SSRI/SNRI – can increase risk of serotonin syndrome

Off-Label Treatments for Obesity in Youth

- Topiramate as monotherapy – often covered by insurance

Topiramate

Drug description	Carbonic anhydrase inhibitor
Mechanism of action	Appetite suppression and earlier satiety for unclear reasons
Indications	Not approved as monotherapy but we understand safety in younger children from use for epilepsy
Dosage	25 mg PO daily starting dose Titrate up to 75-100 mg total daily dose
Anticipated weight loss	2-5% but with significant improvement in visceral fat and VLDL in at least one study
Side effects	Paresthesias “Brain fog” or worsening school performance Kidney stones Glaucoma Mood disturbance
Contraindications	Hx kidney stones Glaucoma

Off-Label Treatments for Obesity in Youth

- Topiramate as monotherapy – often covered by insurance
- ADHD stimulants – Adderall, Vyvanse – often covered by insurance
- Phentermine as monotherapy under age 16 and for longer than 12 weeks – often not covered by insurance, but very inexpensive
- Phentermine and topiramate prescribed individually when Qsymia is not covered
- Ozempic, Victoza or Trulicity (GLP-1 RAs branded for T2DM)
- Bupropion

What Does Success Look Like?

- Standard definition of response to treatment is loss of 5% or more of total body weight
- For younger children, weight stabilization while they continue to grow in height may be considered success
- Does 5% weight loss matter?

Modest Weight Loss- why bother?

5-10 % Weight Loss

- Improvement in lipids and other CVD risk factors
- Reduction in blood pressure
- Improved insulin sensitivity and glycemic control in T2DM
- Reduced likelihood of progression from pre-diabetes to T2DM

≥ 10 % weight loss

- Further improvement of above disorders
- NAFLD/NASH: beneficial in resolving steatosis and reversing fibrosis *Hyde et al*
- Significant improvement of OSA, joint pain and arthritic conditions
- Beneficial effect on PCOS and fertility

Pasanisi F et al, Jensen et al. see add references slide 77

Obesity Medicine Association

What Does Success Look Like?

- Even if a patient does not experience weight loss, if they have substantial relief of hyperphagia without significant side effects, this may be an indication to continue treatment
- If there is no response to a treatment, should discontinue
- Plateaus in weight loss should not be considered treatment failure
- Many patients will need to intensify therapy over time due to the body's compensatory mechanisms
- Need to taper topiramate due to risk of seizure with abrupt discontinuation
- Patients and families should expect that treatment will be chronic because obesity is a chronic disease

What Will Insurance Cover?!

- OHP covers obesity medications if:
  - Patient is 12 years of age or older
  - Patient has engaged in “intensive lifestyle intervention”
  - First line therapy is Qsymia for age 12 and over; possibly phentermine monotherapy for age 16 and older
  - If patient “fails” Qsymia (does not lose 5% body weight over 12 weeks) then will cover GLP-1 – Saxenda or Wegovy
  - For patients with a contraindication to Qsymia, you will almost always get a first-line denial of Wegovy and have to appeal
- Many private insurers have a blanket exclusion for weight loss medications – cannot appeal your way around this

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Categories of Glucose Dysregulation

- Based on A1C

- Based on glucose

	Fasting glucose	2-hour glucose (OGTT)
Normal	<100 mg/dL	<140 mg/dL
Impaired fasting glucose	100-125 mg/dL	<140 mg/dL
Impaired glucose tolerance	<126 mg/dL	140-199 mg/dL
Diabetes	>/=126 mg/dL	>/=200 mg/dL

Risk Factors for Pre-DM/T2DM

- Obesity
- Family history of T2DM/pre-DM/maternal gestational diabetes
- Decreased physical activity
- Physical evidence of insulin resistance – acanthosis nigricans
- MASLD
- Race/ethnicity – African American, Hispanic or Latinx, American Indian, Alaska Native
- Age of onset of T2DM is inversely correlated with morbidity and mortality; youth progress to beta cell failure faster than adults

Metformin for Diabetes Prevention

- Metformin = biguanide derivative – reduces hepatic glucose synthesis, improves insulin sensitivity, improves peripheral glucose uptake
- Approved for treatment of type 2 DM in children age 10 and over
- Dosing – 500 mg daily x1-2 weeks, increase in 500 mg increments; max daily dose 2,000 mg; when using ER can be given once daily
- Common side effects – abdominal pain, bloating, nausea, vomiting, diarrhea
- Can develop B12 deficiency with long term use
- Risk of lactic acidosis in setting of renal insufficiency
- Does not cause hypoglycemia

Metformin for Diabetes Prevention

- Diabetes Prevention Program study (age 18+) showed that lifestyle intervention achieved 58% reduction in progression to T2DM among those with prediabetes
- Adults: 2023 meta-analysis shows 42% reduction in progression from pre-DM to T2DM in those on metformin
- Children: 2023 Vanderbilt study showed time to progression from pre-DM to T2DM of 43 months in metformin group vs 28-29 months in non-metformin group
- Vanderbilt study did not report likelihood of progression on metformin vs not on metformin

Metformin Indications and Dosing

- Consider metformin initiation for:
  - Obesity plus A1C 5.7-6.4%
  - Obesity plus acanthosis nigricans plus ovarian hyperandrogenism
  - Obesity plus acanthosis plus other signs of metabolic syndrome
    - Elevated triglycerides and low HDL
    - Elevated ALT due to MASLD
- Dosing:
  - 500 mg ER with breakfast or dinner for 1-2 weeks, then…
  - Titrate by 500 mg every 1-2 weeks to total dose of 1,000-2,000 mg/day
- GI side effects are common, usually improve with time

Where to Refer

- Diabetes Prevention and Weight Management Clinic – MD, RD – wait list 18-24 months except for high-risk patients
  - Obesity plus prediabetes, <17 years old
  - Obesity plus short stature, dark striae, delayed puberty, hypothyroidism, irregular menses or other endo issues, <17 years old
  - Priority given to patients with higher A1C (6% or greater) and those with high likelihood of endocrinopathy

Where to Refer

- OHSU Healthy Lifestyles Clinic – MD, PT, RD, PhD Behavioral Health – wait list ~1 year
  - BMI >95th percentile
  - Complications of obesity but without prediabetes
  - Would benefit from PT and/or behavioral health services
- OHSU Adult Preventive Cardiology Clinic, Dr. Jon Purnell – wait list ~1 year
  - BMI >95th percentile, 17 years of age and older
  - With or without prediabetes

Where to Refer

- OHSU Harold Schnitzer Diabetes Center
  - A1C 6.5% or greater
  - Referrals are backed up centrally and are not being pushed out for medical review in as timely a fashion as we would like
  - If you have any concern that a patient may have type 1 DM, or for any A1C >8%, suggest calling to discuss with one of us
- OHSU Bariatric Surgery Program – MD, NP, RD, PT, Behavioral Health
  - Any patient 12 years or older interested in learning about surgery
  - Need not be considered a “last resort” treatment
  - Medical intake providers can start anti-obesity medications

What to do while your patient is on the waiting list…..

- Refer to RD
- If extreme picky eating or other behaviors are interfering with healthy lifestyle changes, refer to behavioral health
- If there are physical limitations preventing participation in exercise, refer to physical therapy
- Consider initiation of anti-obesity medication if you are comfortable doing so – I'm happy to help!

Future Vision

- Our goal is to establish a comprehensive pediatric obesity service line that will bring together the following services in a single multidisciplinary clinic
  - Obesity medicine specialists, both endocrine and general pediatrics
  - GI
  - Cardiology
  - RD
  - PT
  - Behavioral health
  - Possibly bariatric surgery

Questions?