ANTI-OBESITY MEDICATIONS FOR PEDS

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Disclosures

- Currax Pharmaceuticals- Speaker
- Nestle Nutrition- Co-Medical Director
- Pri-Med CME- Speaker
- Gelesis – Advisory Board Member

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THE COMPREHENSIVE APPROACH

WHAT MAKES WEIGHT MANAGEMENT SO DIFFICULT?

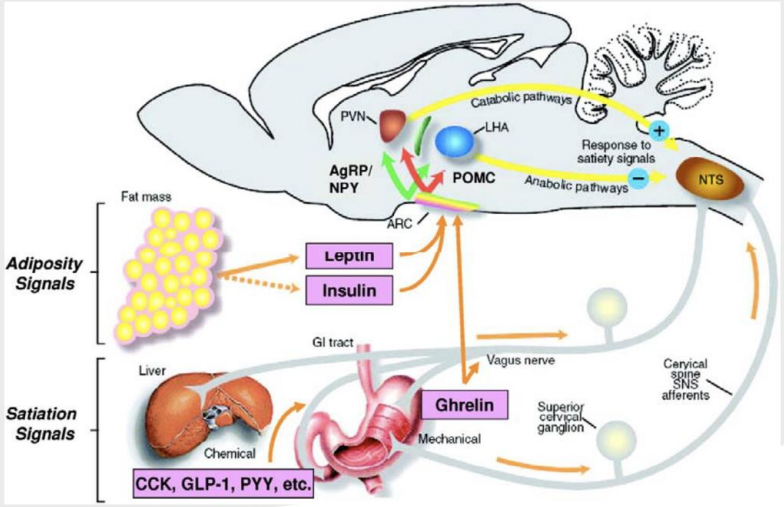
Behavioral Triggers

Hedonic Response

Emotional Triggers

Social Triggers

Habits



Biologic Regulators

Leptin

Adiponectin

Ghrelin

Orexin

GLP-1

PYY

CCK

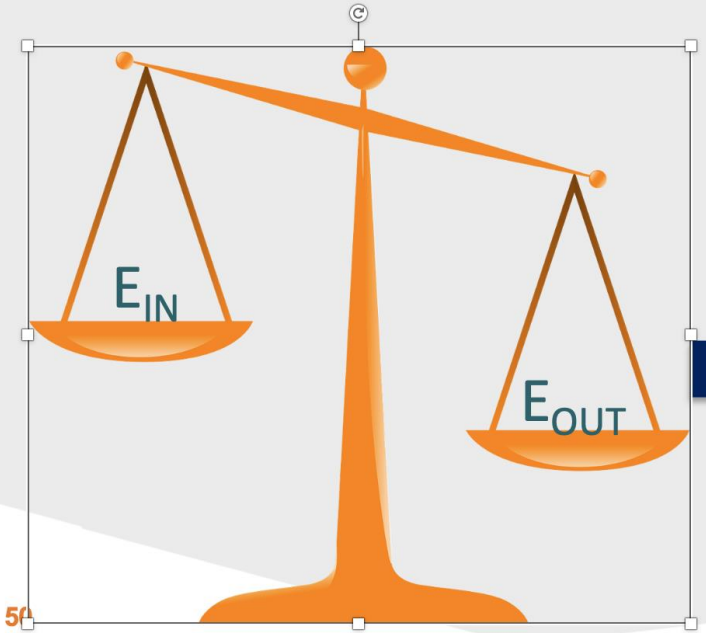
2011 STUDY-– NEJM SUMITHRAN

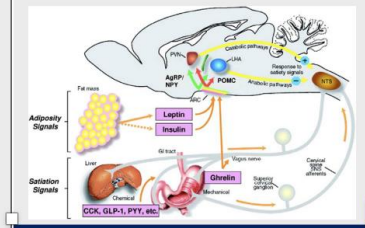
CHANGED OUR UNDERSTANDING OF

LEPTIN AND GHRELIN

PHYSIOLOGIC RESPONSE TO A CALORIC DEFICIT

- Negative energy balance triggers a physiologic increase in hunger and decrease in satiety





↑ Hunger
↓ Satiety

WHY USE MEDICATIONS (AOMS)

Medication | Anti-obesity Medications

Adjunct to nutritional, physical activity, and behavioral therapies.

Objectives:

- Treat disease
  - Adiposopathy or sick fat disease (SFD)
  - Fat mass disease (FMD)
- Facilitate management of eating behavior
- Slow progression of weight gain/regain
- Improve the health, quality of life, and body weight of the patient with overweight or obesity
- May be an effective adjunct to bariatric surgery in enhancing weight loss or preventing weight regain

5-10% weight loss may improve both metabolic and fat mass disease.

OBESITY IS A SERIOUS, CHRONIC AND TREATABLE DISEASE

- Medications should be prescribed chronically or not at all
- Treatment is effective only as long as it is continued
  - Discontinuation of treatment generally results in regain of the weight that was lost

PHARMACOTHERAPY!

1 FDA Approved for Indication of Obesity: Pediatric and Adult

- Phentermine/Topiramate
- Phentermine
- Liraglutide**
- Semaglutide
- Orlistat
- Setmelanotide

2 FDA Approved for Indication of Obesity: Patients > 18 years of Age

- Naltrexone/Bupropion

3 FDA Approved for Indication of Type 2 Diabetes Mellitus: Used off-label for indication of obesity

- Tirzepatide
- Metformin*
- Exenatide
- Dulaglutide
- Liraglutide*
- Semaglutide

4 FDA Approved for Other Indications: Used off-label for indication of obesity

- Topiramate
- Lisdexamfetamine
- Bupropion

PHENTERMINE

- **Mechanism of Action:**
  - Sympathomimetic; works on hypothalamus
- **Considerations:**
  - **Approved >16 years !/?**
  - Dose: 37.5mg tablets (1/2 to 1)
  - also as: 8mg tablets (1/2-1 qd-tid; 15mg, 30mg, & 37.5mg capsules
  - SE: stimulant; caution with active CAD
  - DEA: Schedule 4 Controlled
  - Approved 1959! with continuous use in the US
  - Label: 12-week approval; longer term use is NECESSARY! (off-label recommendation)

Thomas et al. Obesity (online) 2015

Apovian, J Clin Endo Metab 2015

PHENTERMINE

- My First Choice for Most Patients
  - Inexpensive
  - Stood the test of time (1959)
  - Predictable results and SE
- Start a 37.5mg tablet but only half first thing in the am
- SE: For 2-3 nights, may lose sleep, may have dry mouth ("but helps you drink the water I want you to drink")
- If not lasting long enough, move start to between 9am -12pm and if late enough in day that hungry in the am, then add 2nd half to dosing regimen

PHENTERMINE/TOPIRAMATE ER

- **Mechanism of action**: Sympathomimetic (Mild Stimulant) effect on hypothalamus (Phentermine) + Topiramate (GABA system)
- **Benefits**:
  - more weight loss than phentermine alone (studies not performed head-to-head)
    - BMI change= -10.44% top dose; -8.11% points mid dose
  - Great option for patient desiring one pill per day
  - Generally well-tolerated
  - Dose is 3.75/23, **7.5/46**, 11.25/69,**15/92**
- **Considerations:**
  - Requirement for women of child-bearing potential to use adequate contraception and perform monthly pregnancy testing. REMS: increase in cleft lip and palate (6/1000)
  - Moderately Expensive
  - Approved 2012
  - DEA: Schedule 4 Controlled

PHENTERMINE/TOPIRAMATE ER

- Topiramate is a great add on to Phentermine
- With 4 doses- can titrate medication for effect
- Currently the most potent combo drug!
- Side Effects
  - Cleft Lip/Palate - estimated at 6/1000
  - Paresthesias- nuisance
  - Word Recall- goes away in 48 hours if med stopped
  - Dysgeusia- Carbonated drinks taste ”flat” or ”metallic”
  - REMS: monthly pregnancy tests (does not have to be in office) and 2 forms of contraception recommended

LIRAGLUTIDE 3.0MG

- **Mechanism:**
  - GLP-1 Agonist (half life 13 hours)
- **Benefits:**
  - Long-acting appetite control vs stimulant class
  - Extra benefit in those with pre-diabetes/diabetes (class available since 2010)
  - Weight Loss over placebo: 7%
- **Considerations:**
  - **Approved >12Y and T2DM >10Y (different max dose)**
  - Dose: start 0.6, 1.2, 1.8, 2.4 and 3 mg daily with weekly increase
  - SE: GI related (nausea), delayed gastric emptying
  - Warnings/REMS: Avoid if history of thyroid cancer (MTC), multiple endocrine neoplasia (MEN-2); Precaution/Warning if history of pancreatitis
  - Limited use if patient does not have coverage for AOMs
  - SC injection
  - Approved 2015

LIRAGLUTIDE 3.0MG

- Have not used more than a few times since semaglutide has come out
- Consider combination with phentermine (off-label recommendation)
- Titration can be done slowly by using clicks – each dosing interval is 10 clicks
- Use of antacids and H2 blockers may reduce associated nausea symptoms from gastroparesis

ORLISTAT

- **Mechanism of Action:**
  - Lipase inhibitor
- **Considerations:**
  - 120 mg tid, now OTC @60mg TID
  - Side Effects
  - Steatorrhea
  - Flatulence
- Interesting that in early 2000s this was $140/month

ORLISTAT

- I do not use this drug
- Now OTC
- Steatorrhea and other embarrassing SE

SEMAGLUTIDE 2.4MG

- Titrate dose 0.25 SC weekly, 0.5, 1mg, 1.7mg then 2.4mg
- MOA: GLP-1 agonist
  - Central satiety, Decreases gastric emptying
- Contraindications: Pregnancy, Personal or FH of Medullary Thyroid Cancer/MEN2
- Precautions: acute pancreatitis, serious hypoglycemia with secretagogues, HR increase, Renal Impairment
- Common Adverse Reactions:
  - N/V, dyspepsia, constipation and diarrhea
  - Headache, dizziness, fatigue
  - Hypoglycemia, abd pain, increased lipase

SEMAGLUTIDE

- Very, Very popular right now Everywhere (social media)
- Can be quite expensive and very poor coverage (unless DM2)

SETMELANOTIDE

- FDA approved >6Y
- For Rare Genetic Causes of Obesity
  - Proopiomelanocortin (POMC) Deficiency
  - Proprotein Convertase 1 (PCSK1) deficiency
  - Leptin Receptor (LEPR) Deficiency
  - Bardet-Beidl Syndrome (BBS)
  - Other variants in POMC, PCSK1, LEPR or BBS

SETMELANOTIDE

- Mechanism: Melanocortin 4 (MC4R) receptor agonist
- Weight loss
  - LEPR -9.7%
  - POMC or PCSK1 -23.1% at one year
- SE: hyperpigmentation, GI, depression, dizziness, fatigue, HA, insomnia, vertigo and prolonged penile erections
- Once daily injection

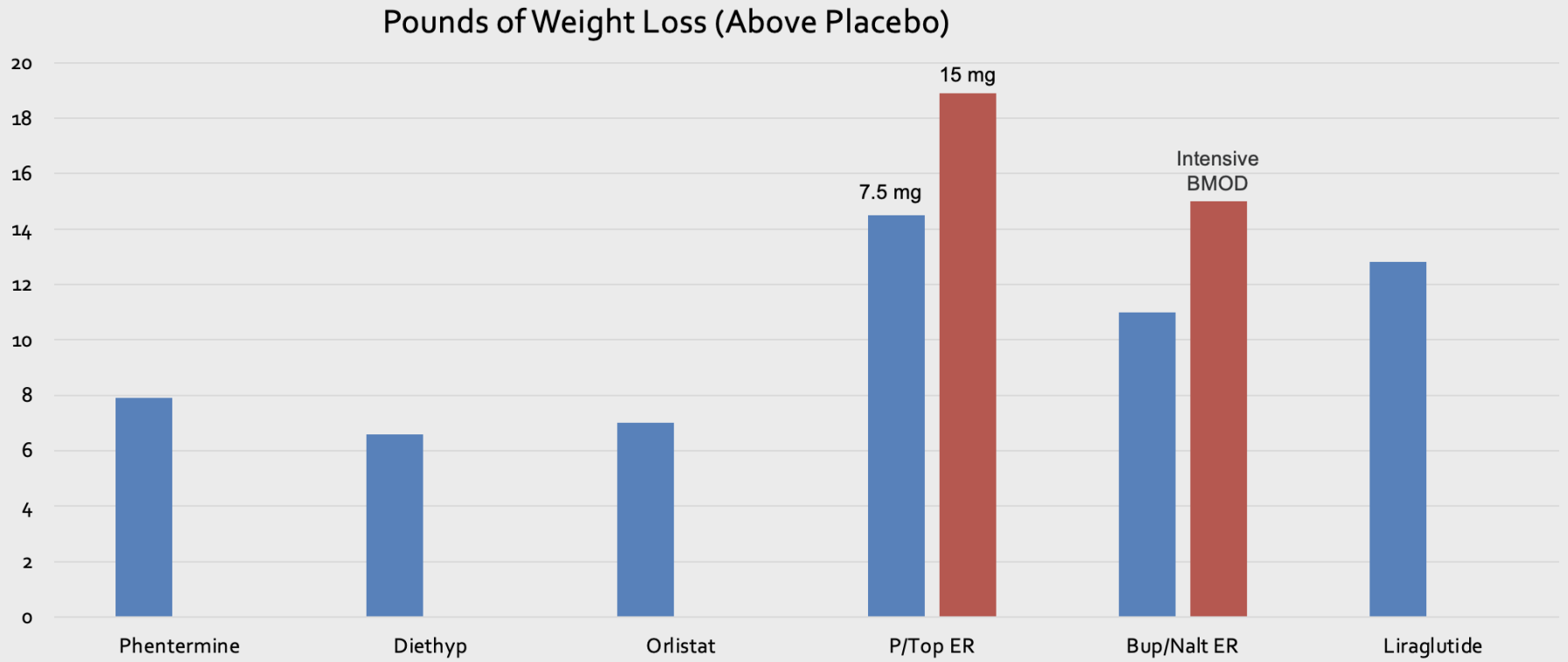
➢ www.UncoveringRareObesity.com

  - Early onset, severe obesity--indication is <18 w/BMI >= 97th % and
  - Hyperphagia

CONTRAVE

- Indicated >18 years…
- Bupropion and Naltrexone ER
- Works on appetite center and cravings center
- Cost about ~$105 without coverage

Percent Weight Loss



Information from package inserts, Apovian 2015, Greenway 2004, Wadden 2013, Astrup 2012.

Obesity Medicine Association

OFF LABEL MEDICATIONS

FOR WEIGHT LOSS

METFORMIN

- May help improve adiposopathic disorders:
  - Insulin resistance
  - Polycystic ovarian syndrome
  - Fatty liver
  - Cardiovascular disease (especially when compared to sulfonylurea)
- May help treat complications of other concurrent drug treatments:
  - Antipsychotic-related weight gain
  - Human immunodeficiency virus (HIV) protease inhibitor-associated abnormalities (i.e., HIV lipodystrophy)
- May help reduce the overall cancer rate and help improve the treatment of multiple cancers:
  - Colon
  - Ovary
  - Lung
  - Breast
  - Prostate
- May reduce appetite with via multifactorial effects, such as enhancing the effects of gastrointestinal hormones applicable to weight loss (e.g., glucagon-like peptide-1, Peptide YY)
- May help facilitate long-term weight loss
- In addition to improving insulin sensitivity, metformin may also improve leptin sensitivity, reduce neuropeptide Y levels, and increase glucagon like peptide-1 (GLP-1) activity (i.e., increased GLP-1 levels and receptors).

TOPIRAMATE

- Can be used Solo (Studies were performed with phentermine/topiramate ER approval studies)
  - 25 or 50mg tabs
    - Week 1- 25mg at night
    - Week 2 - 25mg am and night
    - If working, continue this dose
    - If needed,
    - Week 3 - 25 am and 50pm
    - Week 4 - 50mg bid (continuing dose)
  - Also, in some binge disorder patients
  - inexpensive

DISCLAIMER FOR INDIVIDUAL PATIENTS

- Everyone is different
- For every person that gains, another may lose
- None of these studies are done head-to-head

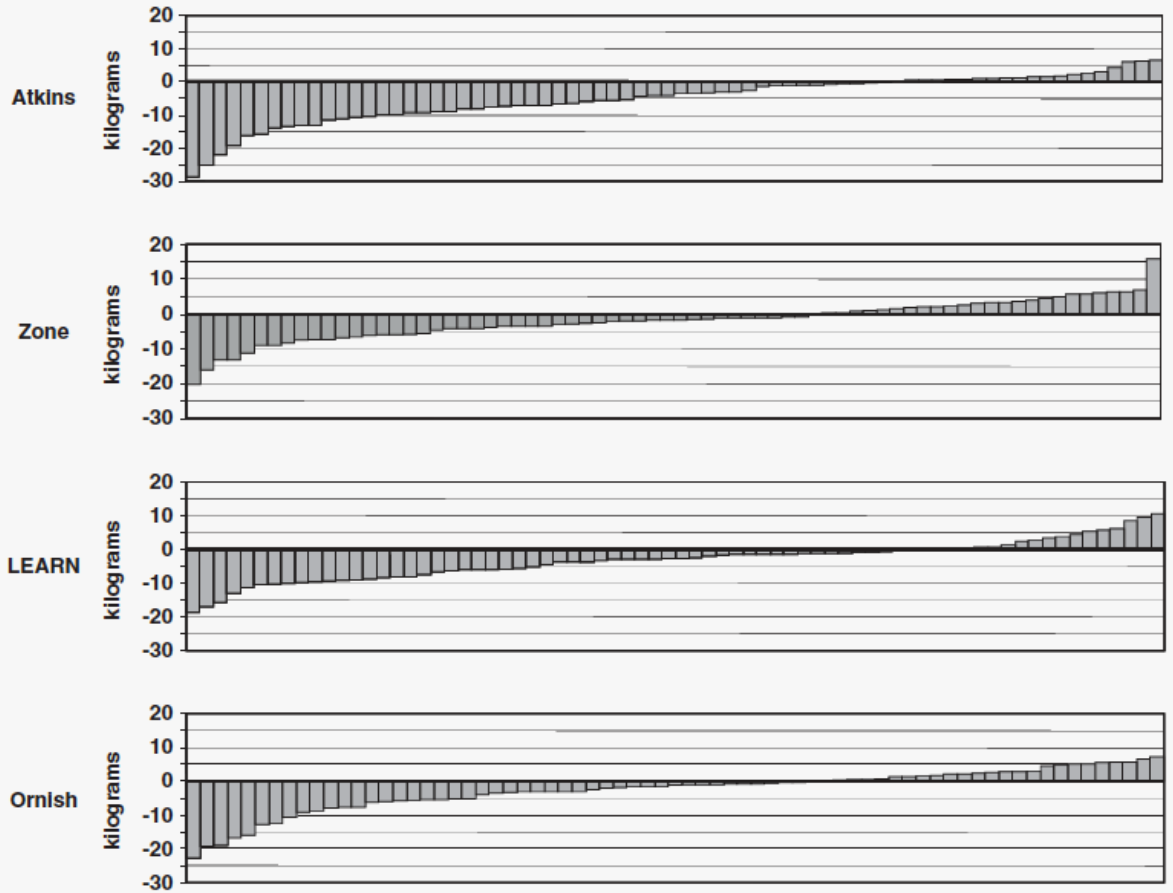


Figure 1. The 12-month weight change of individual study participants who completed the full study protocol of the A TO Z Study, by diet group, ordered from greatest loss to greatest gain. Each bar represents an individual study participant. Missing data for 12, 23, 24 and 22% for the Atkins, Zone, LEARN and Ornish groups, respectively.

Gardiner IJO 2012(22), s11-s15

MEDICATION RELATED WEIGHT GAIN

GENERAL CONCEPTS

- The medical literature is often contradictory regarding drug-induced weight gain
- Conditions treated may be associated with obesity (e.g. depression, diabetes mellitus, and hypertension)
- Changes in lifestyle brought on by these conditions
- Not every patient gains weight from medications associated with weight gain
- Some people actually lose weight on these drugs
- Some medications associated with weight gain may benefit eating disorders (ex: some SSRI's)

ANTIDEPRESSANTS

Antidepressants

May increase body weight (reports on body weight not always consistent):

- Some tricyclic antidepressants (tertiary amines)
  - Amitriptyline
  - Doxepin
  - Imipramine
  - Dosulepin
- Some selective serotonin reuptake inhibitors (e.g. paroxetine, citalopram)
- Some selective serotonin and norepinephrine re-uptake inhibitors (e.g., venlafaxine)
- Some irreversible monoamine oxidase inhibitors (e.g., isocarboxazid, phenelzine)
- Trazodone
- Mirtazapine
- Brexpiprazole

May decrease body weight:

- Bupropion
- Fluoxetine (variable)

Variable effects on body weight:

- Some tricyclic antidepressants (secondary amines)
  - Desipramine
  - Nortriptyline
  - Protriptyline
- Some selective serotonin reuptake inhibitors
  - Escitalopram
  - Sertraline
- Some serotonin and norepinephrine re-uptake inhibitors
  - Desvenlafaxine
  - Duloxetine
- Some irreversible monoamine oxidase inhibitors (i.e., tranylcypromine)
- Some other serotonergic agents
  - Vortioxetine

MOOD STABILIZERS/MIGRANE MEDS

Mood Stabilizers

May increase body weight:

- Gabapentin
- Divalproex
- Lithium
- Valproate
- Vigabatrin
- Cariprazine
- Carbamazepine

Variable/neutral effects on body weight:

- Lamotrigine (sometimes reported to decrease body weight)
- Oxcarbazepine

Migraine Medications

May increase body weight:

- Amitriptyline
- Gabapentin
- Paroxetine
- Valproic acid
- Some beta-blockers

May decrease body weight:

- Topiramate
- Zonisamide

ANTI-PSYCHOTICS

Antipsychotics

Most consistently increase body weight:

- Clozapine
- Olanzapine
- Chloropromazine
- Brexpiprazole
- Iloperidone
- Lithium
- Quetiapine
- Risperidone
- Sertindole
- Trifluoperazine
- Zotepine

Neutral/variable effects on body weight:

- Amisulpride
- Aripiprazole
- Asenapine
- Cariprazine
- Haloperidol
- Loxipine
- Lurasidone
- Ziprasidone
- Paliperidone
- Perphenazine

HYPNOTICS

Hypnotics

May increase body weight:

- Diphenhydramine

May have limited effects on body weight:

- Benzodiazepines
- Melatonergic hypnotics
- Trazodone

HORMONES

Hormones

May increase body weight:

- Glucocorticoids

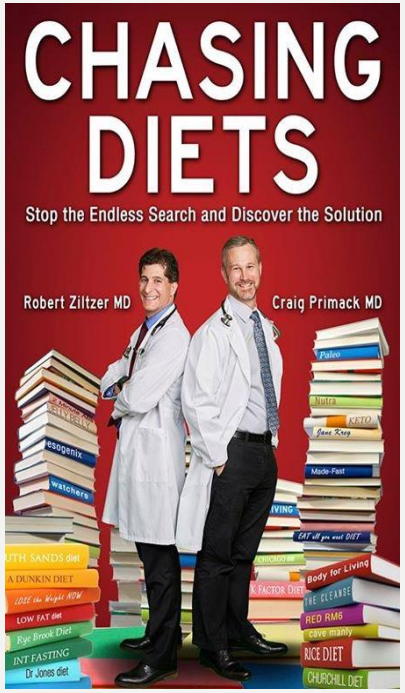
Variable effects on body weight:

- Progestin contraceptives
  - Injectable or implantable progestins may have greatest risk for weight gain
  - May be dependent upon the individual
- Testosterone
  - May reduce percent body fat and increase lean body mass, especially if used to replace testosterone deficiency in men

OBESITY: TREAT OR REFER

THANK YOU

- www. ScottsdaleWeightLoss.com
- DrPrimack@ScottsdaleWeightLoss.com
- www.DoctorPrimack.com
- IG:@DoctorPrimack



- Obesity Medicine Association
- www.ObesityMedicine.org
  - Clinician Finder
  - Pediatric Obesity Algorithm
  - 2 Conferences/year (spring and fall)
  - ABOM Review Course
  - OMAcademy