MANAGING METABOLIC MADNESS IN DIABETES

Adiposity & Cardiometabolic Disease

https://mantracare.org/

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CLASS OBJECTIVES

1. Link the underlying pathophysiology of adiposity (obesity & overweight) to that of Type 2 Diabetes with relation to Insulin resistance and metabolic disruption.
2. Identify contributing risks factors for developing adiposity and glycemic impairment
3. Identify physical and laboratory biomarkers of adiposity, insulin resistance and Metabolic Syndrome
4. Discuss lifestyle interventions to help mitigate CVD risk in “diabesity”
5. Select appropriate diabetes and anti-obesity drugs for diverse patients with adiposity or diabesity.

MARK, (42) HOBBLES INTO YOUR EXAM ROOM

- **He c/o right knee pain (OA)**
- You have been treating his HTN, dyslipidemia, Gerd, 3 years & prediabetes (1 year), allergies
- **Social:** married, HVAC business, sedentary
- **Surgical History**: None
- **Family Hx**: HTN, DM and all are "heavy" (M, F, S); no cancer

- **Relevant findings:**
- **BP**: 148/88, **BMI** 34.3, central adiposity, painful ROM right knee
- **LABS**::
- TG,g/dL; TC 236 mg/dL; LDL 134mg/dL;HDL 48 mg/dL;
- AST 67 u/L; ALT 102 u/L; vitamin D 34 ng/mL
- FBG: 94 mg/dL; AIC: 6.2
- eGFR: 72, UACR: 23

Meds: losartan, atorvastatin, metformin, omeprazole, cetirizine, melatonin, vitamins

WHAT IS YOUR MAIN CONCERN FOR THIS PATIENT?

- You've decided to focus on the patient's weight issues
  - WHY now? What added lab or physical data do you require?
  - What drives your choice of weight loss treatment modality?
  - **Which AOM's would you choose and why?**
    - What are barriers to using anti-obesity medications (AOMs)?
    - Can you use some diabetes medications to for weight loss?
    - Are the off-label meds to use

Based on the prior talks—what would drug would you start with?

“Obesity is one of the greatest factors involved not only in the pathogenesis of type 2 diabetes (T2DM)—but also in the development of its complications.”

- World Health Organization

And obesity is becoming a problem in Type 1 DM!

World Health Organization, Regional Office for Europe. *WHO European Regional Obesity Report 2022*; World Health Organization, Regional Office for Europe: Geneva, Switzerland, 2022. Available online: https://apps.who.int/iris/handle/10665/353747 (accessed on 1 October 2022).

A NEW LOOK AT A SERIOUS METABOLIC "TWIN-DEMIC"

- For more than 3 decades, obesity and diabetes have led the way to ill health in the US.
- Obesity & overweight (adiposity) has the greatest impact on the development of T2DM & Metabolic Syndrome (Cardiometabolic Disease)
  - **Those with <u>obesity were three times likely</u> to develop T2DM vs without obesity compared (20% vs. 7.3%, respectively).**
- Both Obesity and T2DM increase the risk for **Non-alcoholic-fatty-liver-disease (NAFLD)** (also called, "Nonalcoholic steatohepatitis").
  - NAFLD is an important BIOMARKER for cardiometabolic disease (CMD)

https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. (Accessed 3/18/2023)

HOW COMMON IS THIS TWIN-DEMIC?

frontporchrepublic.com

- > 31 million Americans have T2DM
- Adiposity linked to 30-53% of new diabetes cases in the U.S. yearly
- Nearly 75% of US adults, > 20 years, are **overweight or obese**
- 43% of American adults are **obese** *(9%+ are morbidly obese)*
- 1 in 6 children are clinically **obese**
- T2DM is more common among Black, Hispanic/Latino, American Indian, Alaska Native, Pacific Islander or Asian American.
- Adiposity has a higher prevalence in South & Mid-West & *women of color*
- Obesity prevalence is lowest among Caucasian females
  - BUT this group has the **highest obesity-related Type 2 diabetes**.

http://stateofobesity.org/rates

https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. (Accessed 3/18/2023)

MORE CONCERNS ABOUT THE TWIN-DEMIC

- **It is estimated that:**
  - by 2030 > 50% of the adult population will be obese
  - by 2050, as many as 1 in 3 American adults will have diabetes
- **Currently, NAFLD is the LEADING cause of liver transplantation in this country. (BOTH adiposity & T2DM presents the highest risk for this disease)**

Folks, this is the REAL pandemic

The obese/ overweight phenotype is here to stay

https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. (Accessed 3/18/2023)

So, what's underlying the Obesity-Type 2 Diabetes link?

Abnormal fat mass and function leads to increased release of free fatty acid, and dysfunctional (inflammatory) adipokines……
Causing increased insulin resistance and beta-cell impairment

Lin S, Naseri T, Linhart C, et al. Trends in diabetes and obesity in Samoa over 35 years, 1978–2013. *Diabet Med*. 2017; **34**(5): 654- 661.;

THE DEFINITION OF OBESITY & ADIPOSITY?

There is NO real definition—but BMI is used as a screening tool

Obesity: BMI > 30
Overweight: BMI > 27 (with one complication**)**

Is it a good indicator? (maybe not in weight-lifters & sarcopenia)

- Fat vs lean mass
- Gender
- Ethnicity

Known: *the higher the BMI the higher the risk of CVD morbidity & death*

HERE'S ANOTHER DEFINITION OF OBESITY (ADIPOSITY)

Obesity is *a chronic, progressive, relapsing* & <u>treatable</u> multi-factorial, neurobehavioral, (inflammatory) disease:

- **It is caused by genetic, hormonal, epigenetic/environmental influences**
- **And leads to biological and anatomical abnormalities at both organ and cellular levels.**
-

Adiposity-Based Chronic Disease (ABCD)"

.

There is NO cure.

What Obesity is *NOT*…

- A character flaw
  - Nor is it a lack of willpower or a psychological or moral failing---- *NOT due to overeating!*
- A lifestyle choice
- AND, it is not JUST numbers on a scale

- Such beliefs create bias (medical, social, personal)— that then can impede treatment

Remember diagnosing diabetes

A1C %	mg/dL*	mmol/L
5	97 (76–120)	
6	126 (100–152)	
7	154 (123–185)	
8	183 (147–217)	
9	212 (170–249)	
10	240 (193–282)	
11	269 (217-314)	
12	298 (240-347)	

Pre-diabetes:
5.7% to 6.4%

Diabetes:
>/= 6.5%

THE NCEP ATP III DEFINITION OF METABOLIC SYNDROME

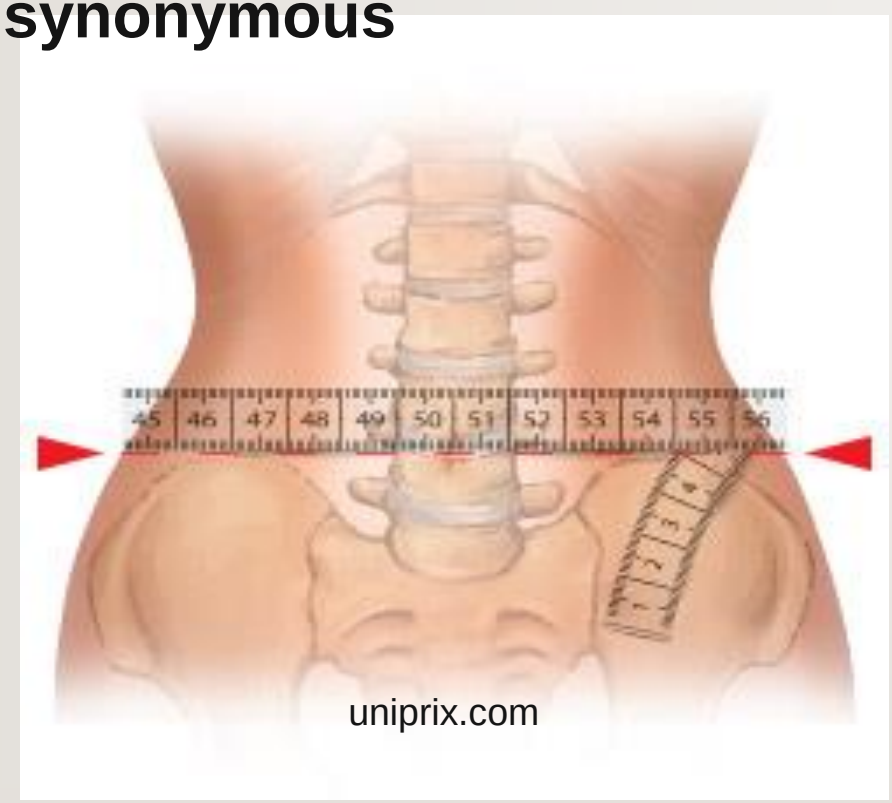
3 OR MORE OF THE FOLLOWING

Risk Factor	Defining Level
Abdominal obesitv Men Women	Waist circumference >102 cm (>40 in) >88 cm (>35 in)
Triglycerides	≥150 mg/dL (1.7 mmol/L)
HDL cholesterol Men Women	 <40 mg/dL (1.04 mmol/L) <50 mg/dL (1.29 mmol/L)
Blood pressure	≥130/ ≥85 mmHg
Fasting glucose	≥100 mg/dL (5.6 mmol/L)

Asians: 35 in. & 31.5 in.
European: 37 in. & 31.5 in.

MEASURING WAIST CIRCUMFERENCE

FYI: Waist circumference and obesity are NOT synonymous



uniprix.com

irp.nih.gov

BTW–WHO IS REALLY INTERESTED IN THIS TWIN-DEMIC?

- ACC aligned with ADA and the OMA, TOS, & AMBS!
  - Recent MACE data show **positive CV impact** by **GLP-1 agonists, SGLT2i, and metformin**
  - A focus on weight reduction and T2DM improvement has been shown to reduce risk of CVD morbidity & mortality, as well as progression of CKD (DKD)
  - **NOTE: it is NOT simply about better blood sugar or lowering numbers on a scale… it is something biohormonal…complicated…and brilliant!**
  - ***Treatment for both MUST start early in the Pre-disease state (prediabetes/ overweight)***

WHAT ARE WE *REALLY* TALKING ABOUT HERE?

FAT MASS!!

(Adipose Tissue!!)

Adipose tissue *DYSFUNCTION*
(adiposity)

The body will defend our fat mass

MORE POINTS WE SHOULD KNOW ABOUT FAT

Adipose Tissue is a ORGAN

It's essential for energy regulation
(energy storage and energy release)
(energy stored in fat as TGs and released as FFA)

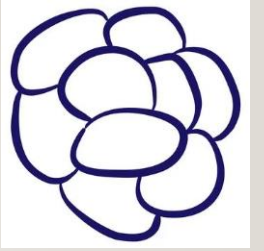
Like any organ, fat mass can become diseased & dysfunctional

Enlarged adipocytes (& mass), abnormal fat distribution (energy spill-over) **& abnormal fat function**

Overweight should be considered "pre-obesity"

Obesity Medical Association (OMA) - https://obesitymedicine.org/

Dysfunctional Fat



Adiposopathy (Sick fat): leads to metabolic disorders

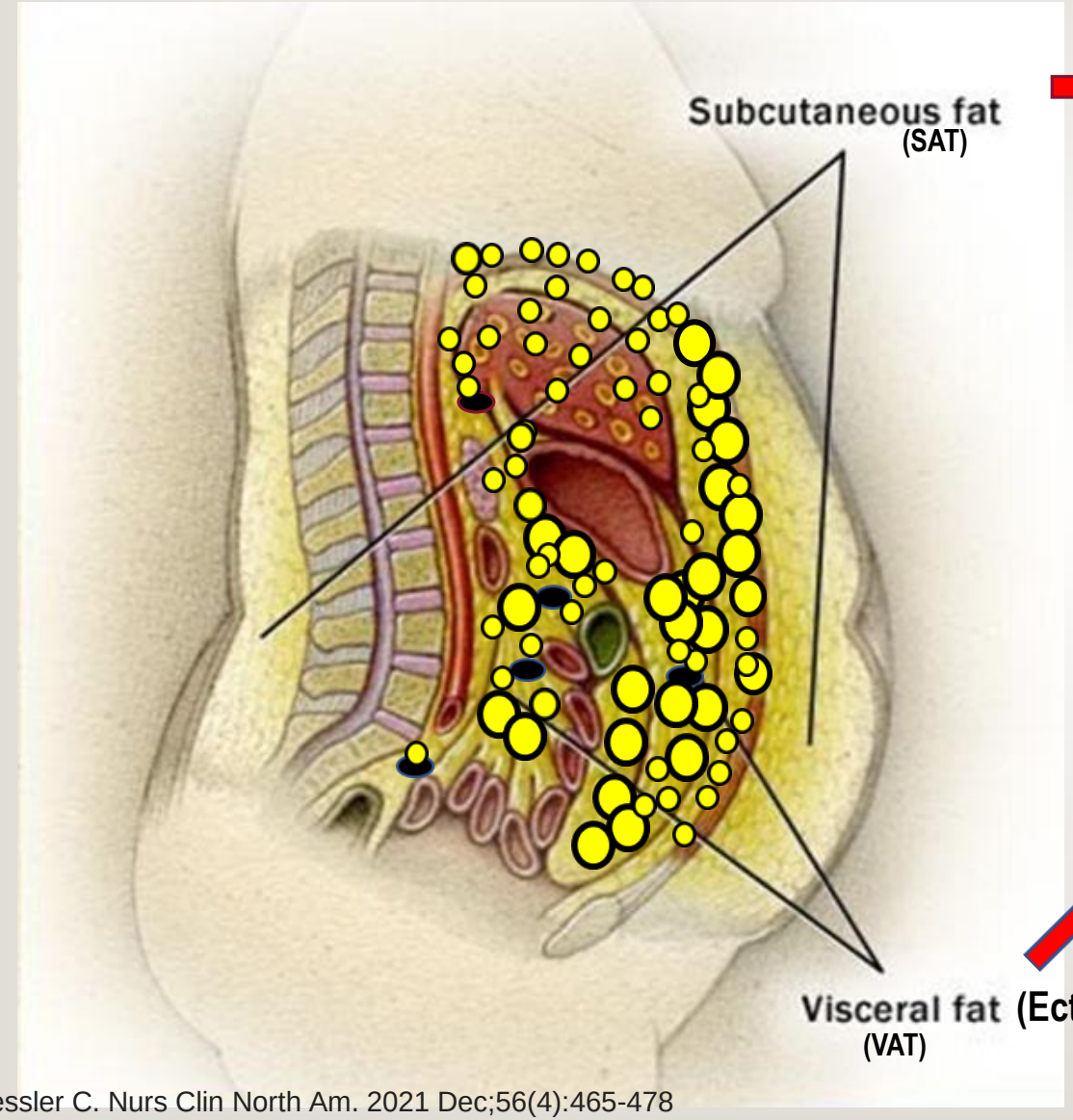
Due to pathogenic adipocytes (& ectopic fat) leading to immunopathies, endocrinopathies, increased free fatty acids (causing insulin resistance & beta cell failure)

Fat Mass Disease (FMD): leads to high mechanical forces

Due to weight or mass effect, (i.e, osteoarthritis, gerd, etc.)

Leads to > 230 complications & mortality risk

Adipogenesis: SAT versus VAT (*where fat is stored*)



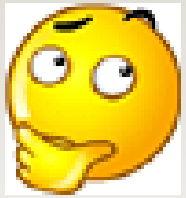
Adipocyte Hyperplasia

- ⬆ Adipogenesis
- ⬇ Adipocyte volume
- ⬆ Insulin sensitivity
- ⬇ inflammation

Adipocyte Hypertrophy

- ⬇ Adipogenesis
- ⬆ Adipocyte volume & hypoxia
- ⬆ Adipocyte necrosis
- ⬇ Insulin sensitivity
- ⬆ Low grade inflammation
- ⬆ Macrophage infiltration

- Kessler C. Nurs Clin North Am. 2021 Dec;56(4):465-478



WHY DO SOME PEOPLE HAVE GREATER RISK FOR ADIPOSITY?

Hint: it's the same for diabetes

GENETICS + ENVIRONMENT = BIOLOGY

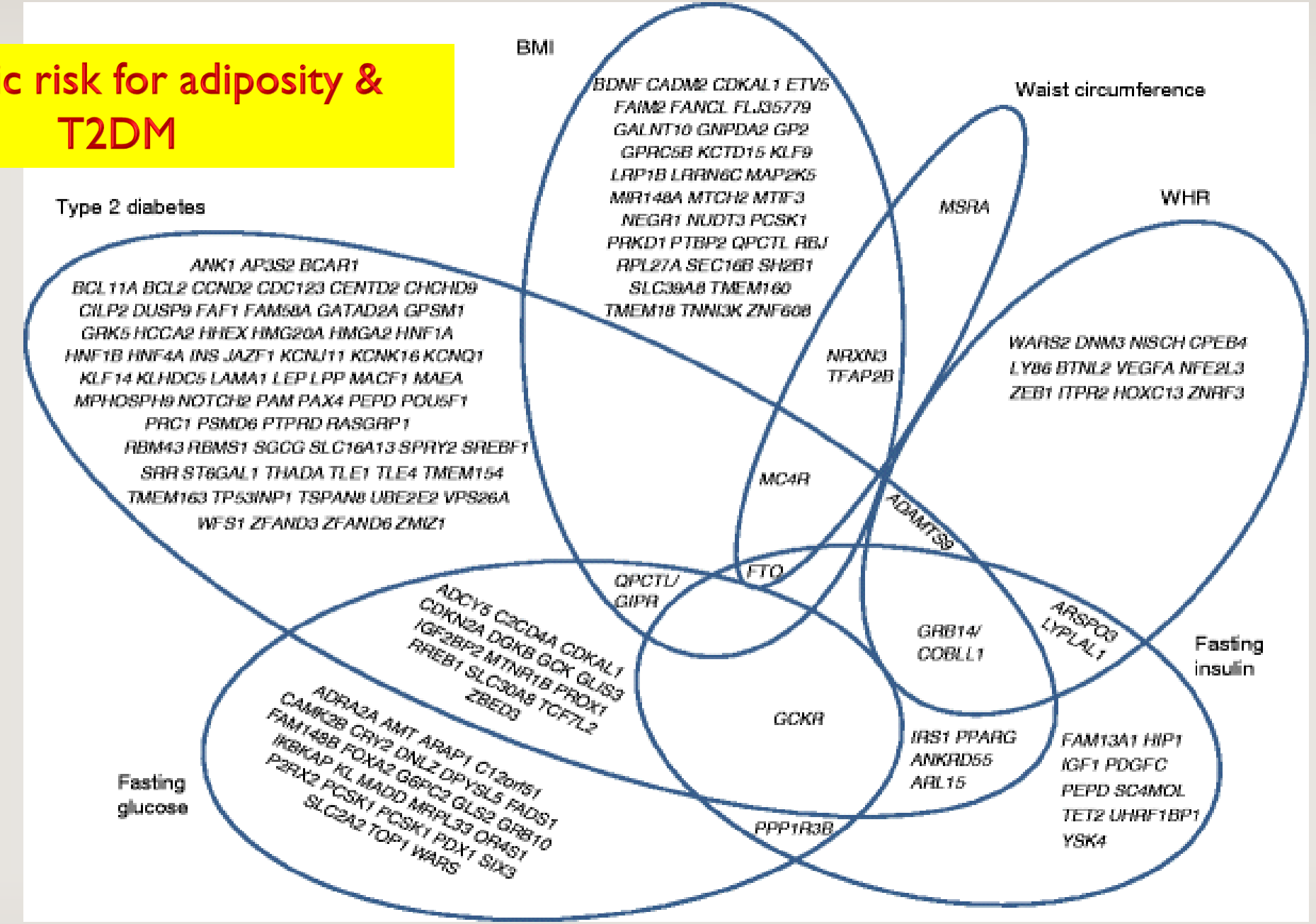
Polygenic risk + environment (epigenetics) =
Impaired ENERGY homeostasis bio-signaling

DNA is NOT destiny!

Having a greater risk for adiposity is not your fault

N Engl J Med. 2017;376(15):1492.

Polygenic risk for adiposity & T2DM



Grarup, N., Sandholt, C.H., Hansen, T. et al. Diabetologia (2014) 57: 1528. https://doi.org/10.1007/s00125-014-3270-4

EXAMPLES OF ENVIRONMENTAL TRIGGERS

- **Endocrine disrupting chemicals (EDCs)**
- Lack of nourishing sleep
- Stress (acute, chronic, & intrauterine)
- Poor diet (highly processed, high sugar, high fat, quality)
- **Shift work and evening chronotype**
- Various drugs (SSRIs, BB, antihistamines, psychotrophic drugs etc)
- *Microbiome dysbiosis*
  - *Leaky gut & the "turn on switch" for many chronic metabolic diseases*
  - *AFFECTED by ALL the ABOVE*

Mallappa RH, Rokana N, Duary RK, Panwar H, Batish VK, Grover S. Management of metabolic syndrome through probiotic and prebiotic interventions. *Indian J Endocrinol Metab*. 2012;16(1):20-27. doi:10.4103/2230-8210.91178

Stanley S et al. Physiol Rev. 2005;85:1131–1158. 2. Dietrich MO & Horvath TL. Nat Rev Drug Discov. 2012;11:675–691.

Feliciano EMC, Rifas-Shiman SL, et al. Chronotype, social jet lag, and cardiometabolic risk factors in early adolescence [published online September 16, 2019]. JAMA Pediatr. (accessed 9.23.2019) .

CHRONOTYPE AND ADIPOSITY/IR RISK

- Chronotype (“eveningness” vs “morningness”) influences several physiologic & metabolic processes
- What is ”chronotype” ***eveningness vs morningness:***
- <u>In the morning….</u>

  Are you a LARK? Chirp—Chirp…?

  Are you an OWL? Groan, yawn…”where’s the coffee?

de Punder K , Psychoneuroendocrinology. 2019 Mar;101:87-100

CHRONOTYPE & METABOLIC SYNDROME RISK

- An *evening tendency* is related to higher BMI and obesity risk.
  - An evening tendency is associated with elevated inflammatory biomarkers (CRP, IL-6) and a greater cortisol stress response
  - Increased cortisol and inflammatory responses correlate with increased BMI and central adiposity;
  - *The greater the cortisol response the greater the obesity risk*
- An evening chronotype (and poor sleep) has been found to increase central adiposity & inflammatory biomarkers in adolescent girls (Project Viva Study)

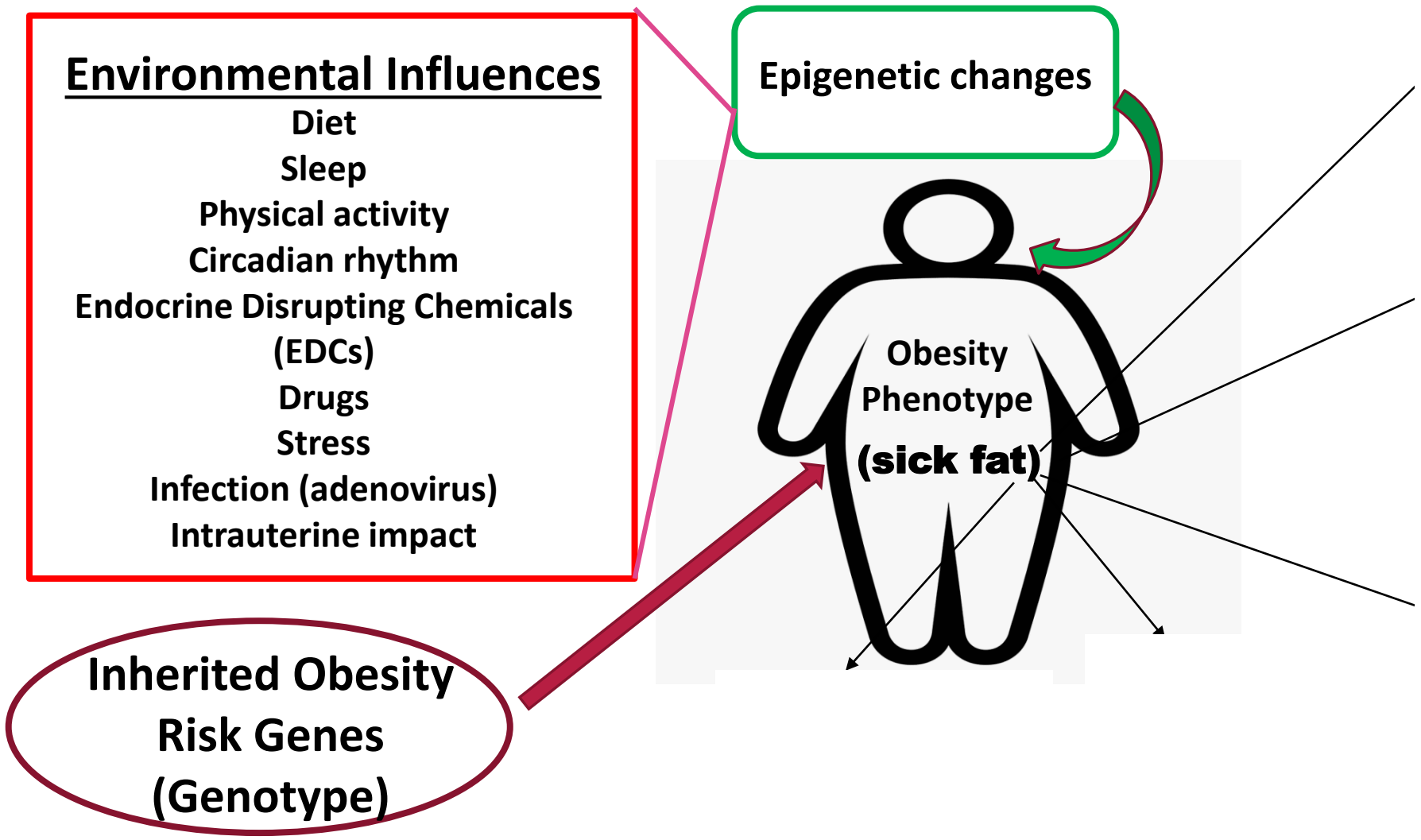
Feliciano. Pediatrics. 2018 Jul; 142(1): e20174085.
de Punder K , Psychoneuroendocrinology. 2019 Mar;101:87-100
N Engl J Med. 2017;376(15):1492.

Why does Obesity & Overweight Create such a concern?

It's the complications, worsened Morbidities, and Morbidity!

And it affects quality of life

OBESITY RISK ➡ ABNORMAL ADIPOCYTE MASS AND FUNCTION ➡ ADIPOSITY-BASED COMPLICATIONS



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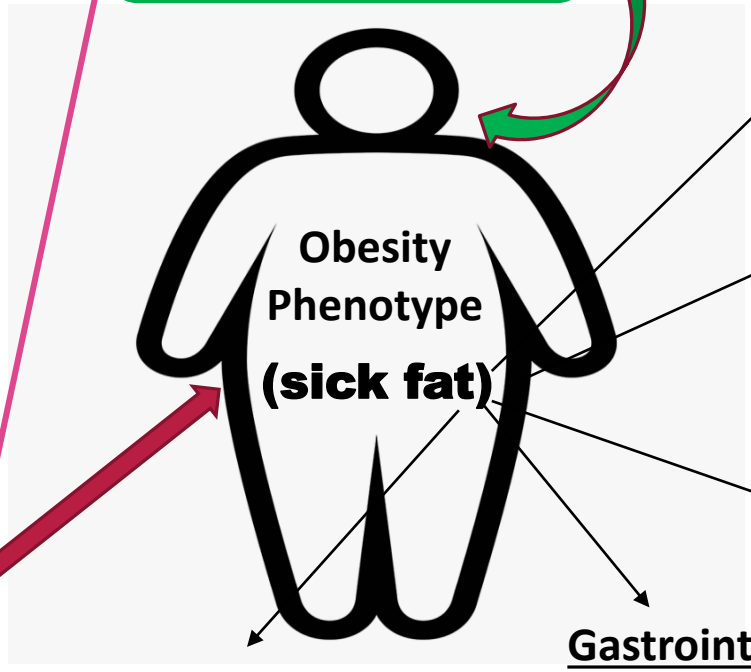
OBESITY RISK ➡ ABNORMAL ADIPOCYTE MASS AND FUNCTION ➡ ADIPOSITY-BASED COMPLICATIONS

Environmental Influences

Diet
Sleep
Physical activity
Circadian rhythm
Endocrine Disrupting Chemicals (EDCs)
Drugs
Stress
Infection (adenovirus)
Intrauterine impact

Epigenetic changes

Inherited Obesity Risk Genes (Genotype)



Neuro-psychological
-Early dementia
-Pseudotumor cerebri
-Stroke
-Depression, Anxiety
-Eating Disorders

Cardio-metabolic
-High blood pressure
-Dyslipidemia
-Heart attack
-Heart failure
-Insulin resistance
-Type 2 diabetes
-Hypothyroidism
CKD

Pulmonary
-Obstructive sleep apnea
-Hypoventilation syndrome
-Asthma

Reproductive
-Infertility, PCOS
-Erectile dysfunction

Vascular
-Ankle swelling

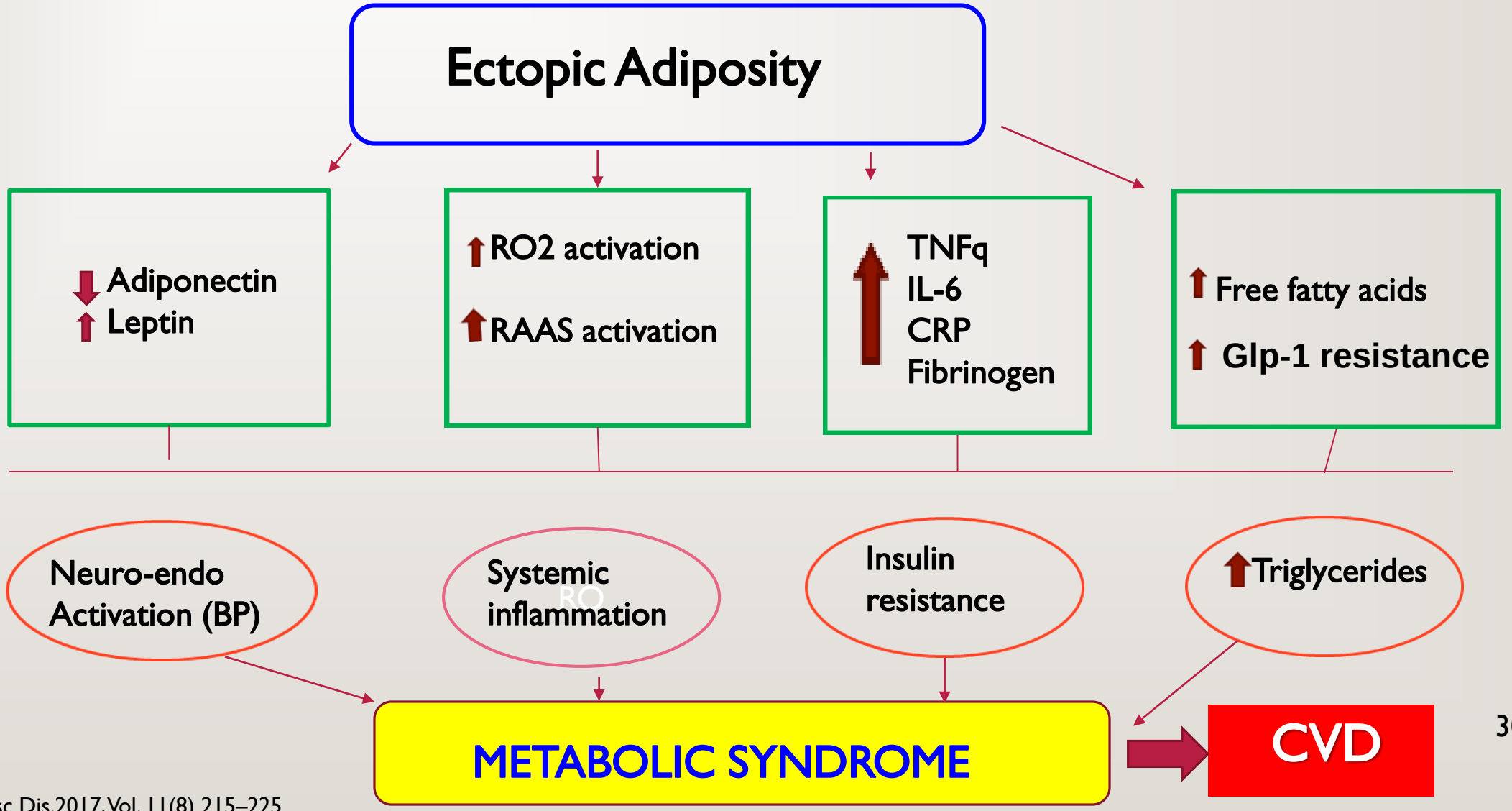
Gastrointestinal
-Fatty liver disease
-Cirrhosis
-Gallstones
-Reflux disease

Musculoskeletal
Osteoarthritis
Joint and back pain

Cancer
-Breast -Kidney
-Uterine -Prostate
-Cervix -Thyroid
-Colon -Esophagus
-Pancreas -Stomach
-Bladder -Lymphoma

Kessler C. Nurs Clin North Am. 2021 Dec;56(4):465-478.

VISCERAL ADIPOSE TISSUE (VAT)/ADIPOSOPATHY & METABOLIC SYNDROME/CMD



Ther Adv Cardiovasc Dis.2017,Vol. 11(8) 215–225

YOUR PATIENT EXPRESSES THE FOLLOWING

- I can eat and get hungry again soon after—I mean, I'm always hungry
- I crave carbs! Donuts are my crack cocaine!!
- **It's frustrating. I have been on lots of diets…lose weight… then start regaining again. What the heck??!**

Why do we REGAIN weight? *Metabolic Adaptation*

Most people who lose weight begin to regain within 1-4 years

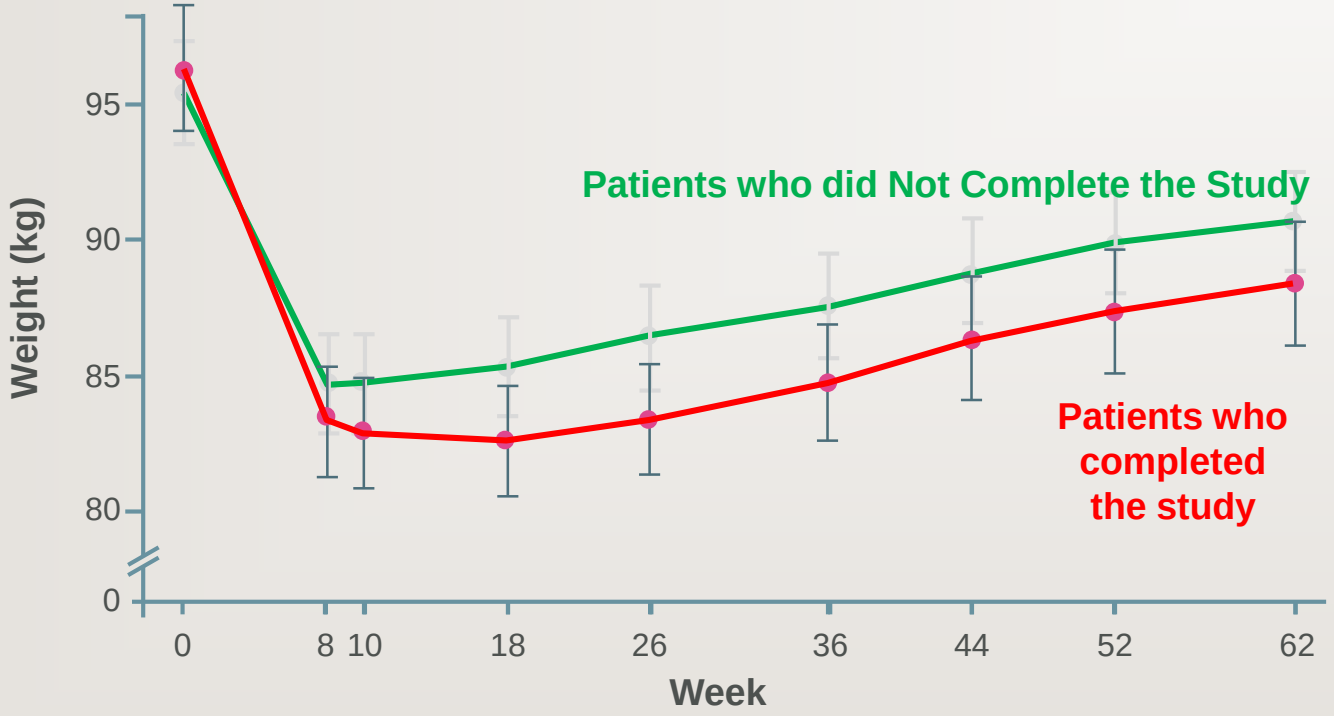
What a bummer!

Adapted from Sumithran P et al. *N Engl J Med.* 2011;365(17):1597-1604.

WHY DO WE REGAIN WEIGHT? *METABOLIC ADAPTATION*

Most people who lose weight begin to regain within 1-4 years

A genetic fat mass set-point



The body will defend the fat mass

↑ Hunger hormones

↑ Satiety hormones

↓ Resting metabolic rate

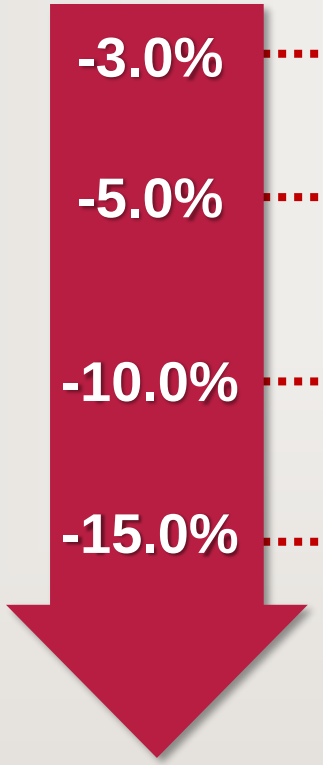
Adapted from Sumithran P et al. *N Engl J Med.* 2011;365(17):1597-1604.

TIME TO TREAT THIS DISEASE

WHAT IS THE WEIGHT TARGET?

SET REALISTIC GOALS WITH *MEANINGFUL* WEIGHT LOSS

How much weight loss helps reduce complications?



-3.0% Improved glycemic control: reduce risk for developing diabetes

-5.0% Improved glycemic control; Reduced BP & triglycerides, increased HDL, reduced NAFLD

-10.0% Greater improvements in above parameters; Reduced Knee/hip/spinal arthritis pain, reduces NASH, reduces sleep apnea 50%, reduced cancer risk; Reduces IR 50-60%

-15.0% Even greater improvements in above parameters, reduce CVD risk, and improve a variety of inflammatory conditions; Reduces IR

It is about more than numbers on a scale!

Jensen MD, et al. *J Am Coll Cardiol*. 2014;63(25 Pt B):2985-3023.

Obesity Management Guidelines

- Obesity Medicine Association (OMA)
- The Obesity Society (TOS)
- The American College of Cardiology (ACC)
- American Heart Association (AHA)
- The American Association of Clinical Endocrinology (AACE)
- American College of Endocrinology (ACE)
- The Canadian Adult Obesity Clinical Practice Guidelines

Obesitymedicine.org;
endocrinepractice.org
Obesity, diabetes mellitus, and cardiometabolic risk: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2023https://doi.org/10.1016/j.obpill.2023.100056

Current Algorithm/ Guidelines Comparison

ES

- Mention of nutrition, activity, behavioral intervention
- Details on available pharmacology for anti-obesity medications
- Obesogenic medications with options of other choices

AACE/ACE

- Complication-specific treatment guideline
- Prevention reviewed
- Staged recommendations for treatment
- ORC-centric obesity treatment based on pharmacology

OMA

- Annually updated clinician tool
- Review of bias and stigma implications
- Podcast companions
- Top 10 messages of each section
- Obesity myths section

OC

- Living document updated with emerging evidence
- Created with sections for primary care professions, persons living with obesity, and policy holders
- Prevention and treatment
- Only 3 medications approved in Canada

ORC, obesity-related complications and comorbidities.

Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100(2):342-362. Bays HE, et al. 2020. https://obesitymedicine.org/obesity-algorithm/ Accessed February 12, 2020. Garvey WT, et al. *Endocr Pract*. 2016;22(Suppl 3):1-203. Wharton S, et al. *CMAJ*. 2020;192(31):E875-E891.

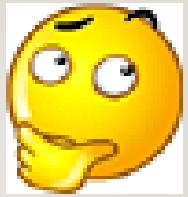
TREATMENT GOALS FOR ADIPOSITY

- Reduce fat mass excess
- *Improve patient health, quality of life, and body weight/ composition*
- Treat adipose tissue dysfunction, *(REDUCE sick fat)*
- Treating diseases d/t sick fat mass and adverse metabolic disease (i.e T2DM, CVD) and biomechanical problems related to excess fat mass.
  - *Reduce adiposity-related morbidities within 6 months*
- Avoid medications that produce weight gain (where possible)
- Have a clinic conducive for these patients.
- *Check the bias at the door*

Concern about "Sarcopenic Obesity"

Obesity Medical Association (OMA) https://obesitymedicine.org/

Is the patient ready to engage?



SO HOW DO YOU START THE CONVERSATION WITH A PATIENT ABOUT ADDRESSING WEIGHT?

Ask if it is okay to discuss meaningful ways to help achieve a healthy weight. *Avoid term Obesity*

There must be patient engagement

It's about HEALTHY weight and cardiometabolic health!

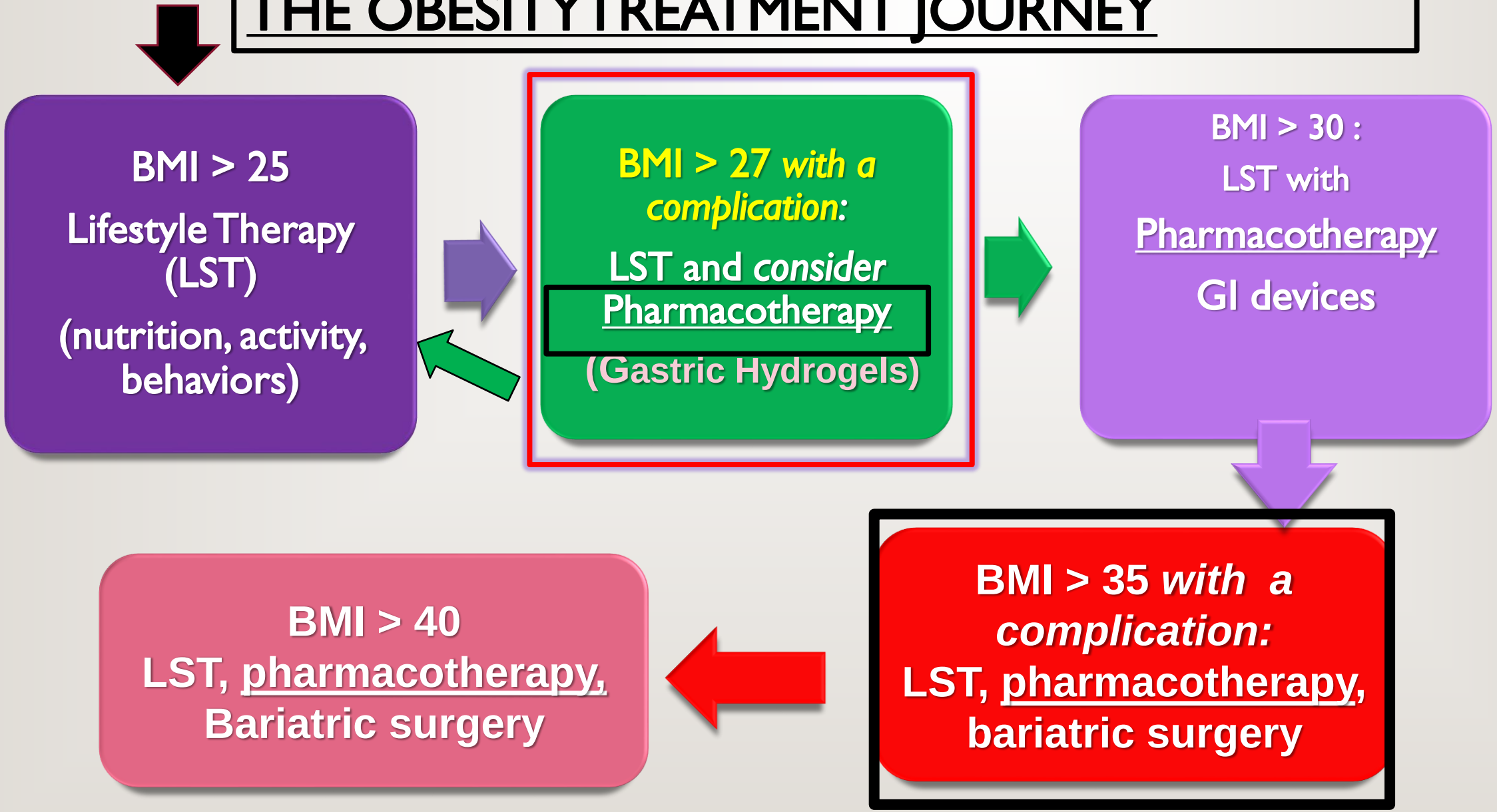
CONSIDERATIONS IN WEIGHT MANAGEMENT

- **Age, sex, ethnicity & risks related to weight**
- **Motivation**
  - Does patient perceive a need for weight loss?
  - Are they interested in pursuing weight loss interventions?
  - Are they confident?
  - Is their weight loss goals realistic
- **Weight loss history** *(look for weight ups and down variability)*
  - Perception of why there is excess weight
  - Prior attempts to lose weight (successes and failures)
- **Dietary history**
  - General food choices
  - Carb addiction, binging behaviors, triggers to eat, etc

E-bay (used shirt)

Weighing the Rx Options for adiposity (must consider IR & DM)

THE OBESITYTREATMENT JOURNEY



Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. CMAJ. 2020;192(31):E875–E891; Horn, Almandoz, & Look (2022) Postgraduate Medicine, 134:4, 359-375; endocrinepractice.org

WEIGHT LOSS ASSESSMENT PRIORITIES

HISTORY

- Weight loss trends (eg, yo-yo…)
- *SLEEP*
- **Obesigenic drugs (weight-inducing drugs and birth control pills!)**
- Activity level
- Related morbidities
  - Sleep quality, sleep apnea
  - CV risk (HTN, high lipids)
  - NAFLD
  - T2 diabetes
  - Depression
  - Hypothyroidism
  - infertility

LAB & PHYSICAL BIOMARKERS

- **Labs**
- CBC, Chemistry, (note GFR, UCAR & LFTs)
  - Lipids (esp. triglcerides)
  - **TSH**
  - A1C
  - Vitamin D
  - Uric acid????
- Exam
  - BMI **(BMI is a vital sign)**
  - Waist circumference for patients w/ BMI >25
    - >35 inches for women & >40 inches for men
  - Blood pressure (and other CV risk factors)

Endocr Pract 2016;22 Suppl 3:1-203

WEIGHT LOSS ASSESSMENT PRIORITIES

HISTORY

- Weight loss trends (eg, yo-yo…)
- *SLEEP*
- **Obesigenic drugs (weight-inducing drugs and birth control pills!)**
- Activity level
- Related morbidities
  - T2 diabetes
  - Depression
  - Hypothyroidism
  - infertility

LAB & PHYSICAL BIOMARKERS

- **Labs**

Oops!
Mark was on cetirizine

JCAR & LFTs)

- A1C
- Vitamin D

What about getting a HOMA-IR score?

- Exam
  - BMI **(BMI is a vital sign)**
  - Waist circumference for patients w/ BMI >25
    - >35 inches for women & >40 inches for men
  - Blood pressure (and other CV risk factors)

Endocr Pract 2016;22 Suppl 3:1-203

HOMA-IR
(HOMEOSTATIC MODEL ASSESSMENT FOR INSULIN RESISTANCE)

- It identifies presence and extent of insulin resistance
  - Healthy Range: 1.0 (0.5–1.4)
  - Less than 1.0 means you are insulin-sensitive which is optimal.
  - Above 1.9 indicates early insulin resistance.
  - Above 2.9 indicates significant insulin resistance.
- **The calculation:**
  - Insulin uIU/mL (mU/L x Glucose (mg/dL) = HOMA-IR

Mark has a HOMA-IR of 4.1

https://www.mdcalc.com/calc/3120/homa-ir-homeostatic-model-assessment-insulin-resistance. (accessed 4/11/23)

MORE ASSESSMENT AND TREATMENT FOCUS ON CMD/METS

- *Acanthosis nigricans* (insulin resistance)
- Central autonomic neuropathy?
    - **Pulse variability check**
    - Be aware they may not "feel" a heart attack (DOE?)
- **Treat CV risks (including glycemic control:**
- Treat dyslipidemia
- Treat hypertension *(CUT back dose when there is weight loss*)
- Smoking Cessation
- Reducing MetS/CMD biomarkers…reduces MACE!!

BTW-MetS with inflammatory biomarkers increases dementias

American Diabetes Association. *Diabetes Care*. 2017;40(Suppl 1):S1-S135.

WEIGHT LOSS INTERVENTIONS

- **Lifestyle interventions**
  - Targeted diets and eating plans
  - Increased activity
  - Psychotherapy---behavior changes
- **Approved Anti-obesity medications**
  - Phentermine
  - Orlistat
  - Naltrexone HCL-Buproprion HCL (*Contrave*)
  - Phentermine-topiramate ER (*Qsymia*)
  - Liraglutide 3 mg (*Saxenda*)
  - Semaglutide 2.4 mg (Wegovy)
  - *Tirzepatide (Mounjaro) not approved*

Gastric & Endoscopic interventions

Hydrogels (Plenity)
Intragastic balloons
Endoscopic sleeve gastroplasty
(Refer to GI for this)

Metabolic & Bariatric surgery (MBS)

Adjustable Gastric Band
Sleeve Gastrectomy
Gastric bypass (RYGB)
Duodenal switch
(Refer to bariatric surgeon)

Nourishing SLEEP

- Need at least 7 hours nourishing sleep! (genetic & environment impact)
- Sleep studies may be required also with weight loss strategies
- Discern ”chronotype” ***eveningness vs morningness***

Switch out weight-inducing meds

(if possible)

(Beta Blockers, Antipsychotics, Lithium, SSRIs, SNRIs, TCAs, trazadone, Antivirals (HIV), Antihistamines)

Need to change Mark’s cetirizine for other allergy Tx options

Verhaegen AA, Van Gaal LF. Drugs that affect body weight, body fat distribution and metabolism. 2-19 Feb 11. In:Feingold KR, Ahawalt B, Boyce A, et al., editors. Endotext (Internet) South Darmouth ()MA): MD Text com, Inc; 2000-2019. Available from: Https”??www.ncbi.nlm,nih,gov/books/NBK537590.

POINTS ABOUT WEIGHT LOSS DIETS

- **Adherence is key no matter the diet & portion control (care if on hypoglycemia-risk drugs)**
- Phenotype matters (yep—it's in your DNA)****
- **Calorie restriction!!**
- *The faster you start to lose weight the greater the adherence to treatment regimen*
- Add fiber *(water soluble & insoluble—IMPROVES microbiome—CV support)*
- **Reduce fructose intake** (*visceral fat promoter…think NAFLD)*
- ***Reduce excess refined carbohydrate intake*** *(raises TGs and other biomarkers)*
- **Reduce food additives** *(nitrates, phosphates & potassium bromate)*
- *FYI---studies show that people underestimate their caloric load by 1000 calories a day*
- **ADA recommends Mediterranean or DASH diet**

Am. J. Clin. Nutr. 2015;101:1320–1329; Diabetes Obes. Metab. 2018;20:858–871.

MORE DIETARY POINTERS FOR WEIGHT LOSS

- **Again—calorie reduction is key**
- ***Timing may matter…so can periotic fasting***
- **Intermittent fasting (alternated day or 5:2)** (500-600 cal/day)
- **Timed-block eating** (4, 6, 8 hours)

  Avoid late night eating; earlier is better
- Ketogenic diet (short-term…maybe short term—losing favor)
- LOW fat or LOW carb? (It's in your DNA)
- **Meal replacement with sufficient protein & fiber (powders, drinks, bars etc) Does it make an ENERGY difference?**

The BEST diet is safe, effective, and one to which the patient will adhere.

Am. J. Clin. Nutr. 2015;101:1320–1329; *Diabetes Obes. Metab.* 2018;20:858–871.

PHYSICAL ACTIVITY POINTS

Ensure cardiovascular-pulmonary safety for activity (CV eval)!

- ***Suggest: Endurance, resistance and flexibility training***
- Duration not as important as first thought
- Best time to do **aerobic exercise** (esp men) is in the morning; **weight lifting** best in late afternoon
- When walk—start small with intention and increase time involved (even 5 mins)
  - *Recommend walk 2 miles 3 to 4 x a week (each in under an hour)*
- After you eat (1-2 meals/day) walk/move for 10 minutes straight

Verboven K, Hansen D. Critical reappraisal of the role and importance of exercise intervention in the treatment of obesity in adults. Sports Med. 2021;51(3):379–389
http://sciencedrivennutrition.com/dieting-and-metabolism/ (accessed 5/14/2021;
Paley, C.A., Johnson, M.I. Abdominal obesity and metabolic syndrome: exercise as medicine?. BMC Sports Sci Med Rehabil 10, 7 (2018).

MORE EXERCISE POINTERS

- **What is currently suggested:**
- **Endurance** training (adjust intensity as needed and tolerated)
  - ***OKAY—2 to10 min bouts throughout the day) JUST MOVE with intention!!!***
  - **Resistance training** (isometric, weights) **good in older patients**
  - **Flexibility training** (stretching, modified yoga, Tai Chi) EXCELLENT

  - **Stand more, move more** (and include isotonic exercise more)
    - *Improves cardiopulmonary oxygen utilization*
    - *Improves insulin sensitivity (helps hyperglycemia & fatty liver!)*
    - ***Improves microbiome***
  - **JUST MOVE !!**

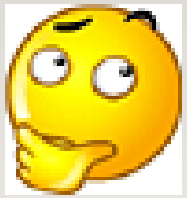
Verboven K, Hansen D. Critical reappraisal of the role and importance of exercise intervention in the treatment of obesity in adults. Sports Med. 2021;51(3):379–389
http://sciencedrivennutrition.com/dieting-and-metabolism/ (accessed 5/14/2021;
Paley, C.A., Johnson, M.I. Abdominal obesity and metabolic syndrome: exercise as medicine?. BMC Sports Sci Med Rehabil 10, 7 (2018).

POINTERS ON USING AOMS

- **They are for <u>life-long therapy</u>—USE WITH LIFESTYLE INTERVENTION…*lose ave. of 5-20+% (responders);***
- **Look at safety & contradictions------Consider AGE and sarcopenia**
- **Look at impact on underlying morbidities (T2DM, CVD, etc)**
- **COST realities—Medicare won't cover AOMs; <u>Medicaid *coverage varies per state*</u>**
- FYI---if drug not showing *4-5% weight loss in 12 to 16 weeks*—***consider stopping/change***
- **<u>Not used</u> in pregnancy/ breastfeeding!**
  - Or with other anti-obesity medications
  - **Or with OTC weight loss drugs/drinks, etc. (ASK about them!)**

Weight loss from any cause can lead to gall bladder issues

Horn, Almandoz, & Look (2022) Postgraduate Medicine, 134:4, 359-375



What FDA-approved Anti-obesity meds do we have & how do they work?

BTW– DO NOT use compounded OMAs

FDA approved

- Orlistat
- Phentermine
- Phentermine/Topiramate ER #
- Bupropion/Naltrexone XL
- Liraglutide 3mg #
- Semaglutide 2.4mg. #
- Setmelanotide
  *monogenic obesity**

Tirzepatide15 mg
(approval expected 2023)

Additional Medications that may cause weight loss and used off label

- Topiramate
- Zonisamide
- Bupropion
- Naltrexone
- Metformin
- GLP-1 RA
  - Dulaglutide
  - Exenatide
  - Liraglutide
  - Lixisenatide
  - Semaglutide
  - Tirzepatide — GIP/GLP-1 RA
  - Pramlintide — Amylin analogue
- SGLT2I
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin

Source & adaptation: A. Golden NP

A PEAK AT THE ANTI-OBESITY MEDICATIONS (AOM)
CONSIDER STARTING THEM WHEN WEIGHT PLATEAUS

- **Phentermine (Adipex-P, Suprenza, Lomaira) (3 to 5% wgt loss)**
  - Stimulant; Norepinephrine – releasing agent; short term use (3 months); avoid in CAD, HTN, tachy-dysrhythmias, glaucoma, hyperthyroidism
- **Orlistat (Xenical)** (3-5% wgt loss))
  - Lipase inhibitor; fat blocker; May block absorption of 160 meds; **GI upset**
- **Phentermine-topiramate ER (low dose) (Qsymia) (4 to 9% wgt loss)**
  - Stimulant & reduce appetite; GABA –receptor modulation; Avoid in CAD, HTN, Tachy; causes paresthesias; **teratogenic**
- **Naltrexone-bupropion (Contrave)** (may help carb addiction) **(5-7% wgt loss)**
  - Opioid antagonist; Dopamine & Norepinephrine reuptake inhibitor; risk seizures; **avoid in binge-eating disorder**; good for carbohydrate addictions

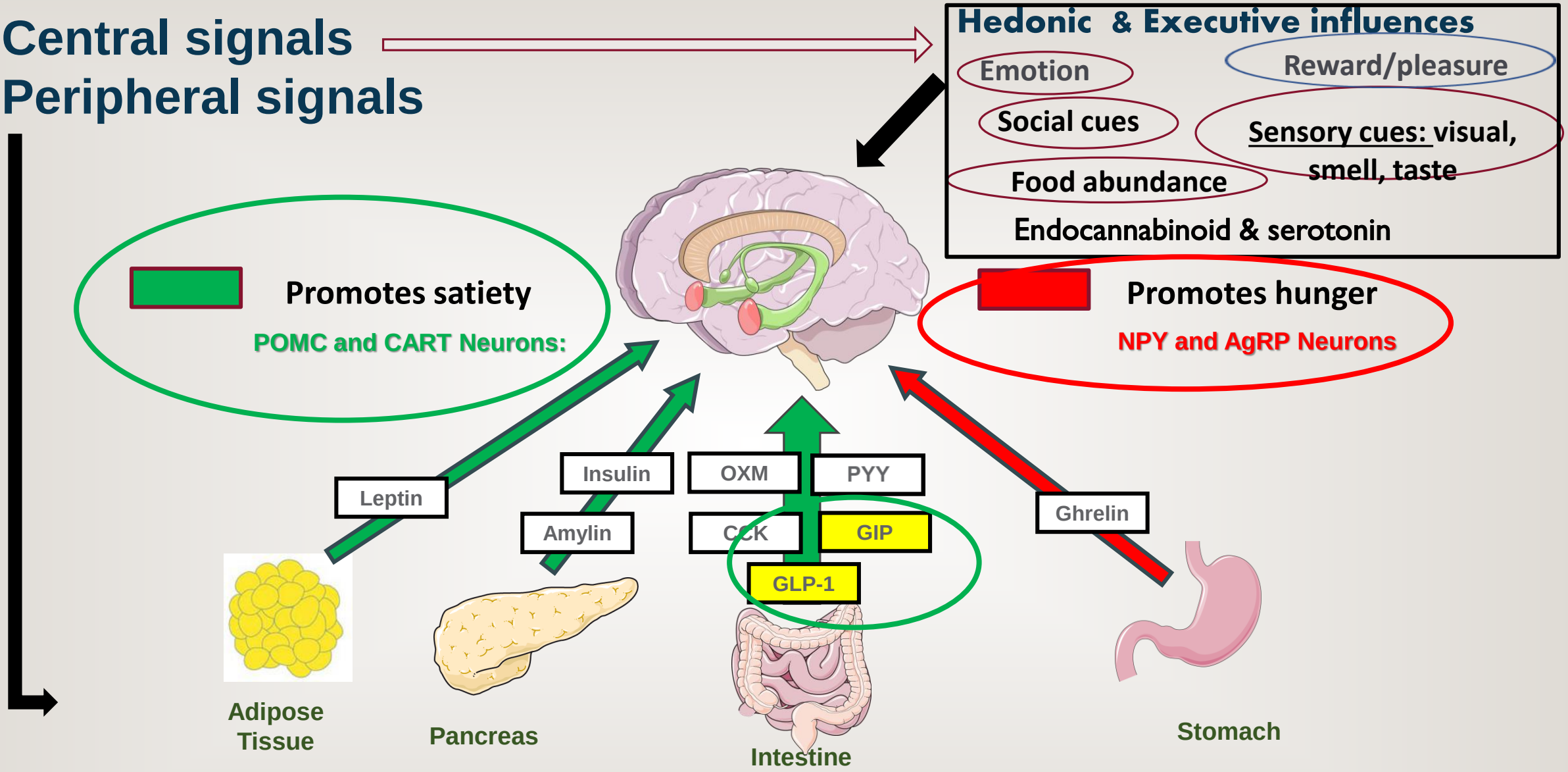
TIME TO PICK AN ANTI-OBESITY MEDICATION (AOM)

CONSIDER STARTING THEM WHEN WEIGHT PLATEAUS

- **Liraglutide 3mg (Saxenda)** (also reduces blood glucose) **(9% wgt loss)**
  - GLP-1 agonist; great for severe hunger; avoid in **thyroid medullary CA & pancreatitis; GI side effects**
- **Semaglutide 2.4mg (Wegovy)** (also reduces blood glucose) **(15-17% wgt loss)**
  - GLP-1 agonist; great with tandem T2DM: has **GI side effects. Avoid in medullary thyroid CA & pancreatitis. (*found increase in retinopathy?)***
- **Tirzepatide 15 mg (Mounjaro)** Also reduces blood glucose) (**20+% wgt loss)**
  - Same Considerations and Side effects as other GLP-1 agonists.; GIP synergizes GLP-1 affects.

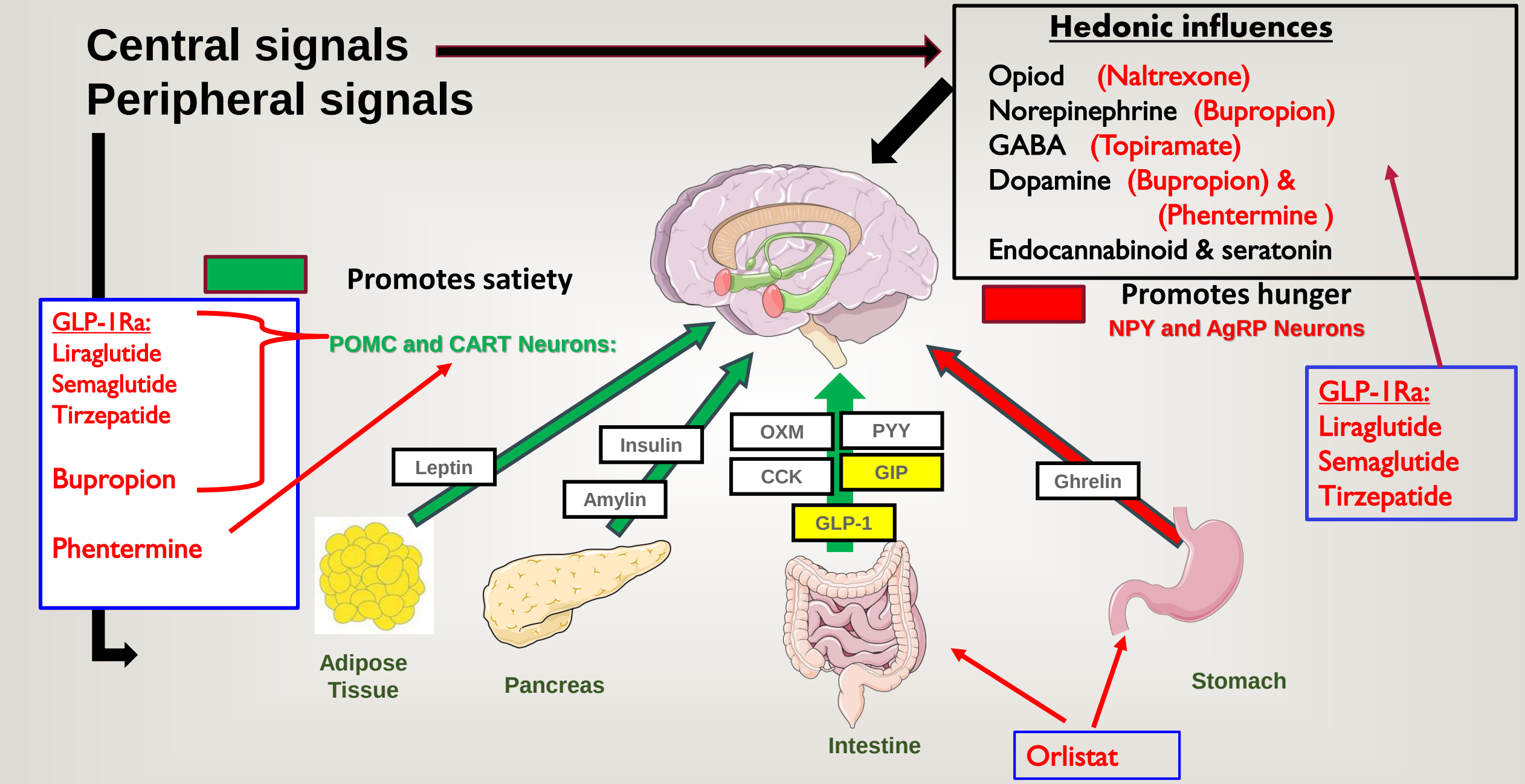
Can use liraglutide 1.6 mg, semaglitide 2.0 & tirzepatide 5 mg IF patient has DM/IR

Central signals
Peripheral signals



Central and peripheral control mechanisms of appetite regulation: These signals will promote hunger and food -seeking or increase satiety and a sensation of fullness.. In the arcuate nucleus of the hypothalamus*: NPY (neuropeptide Y), Agrp (Agouti-related protein), POMC (pro-opiomelanocortin/) CART neurons (cocaine- and amphetamine-related transcript neurons*). Peripheral hormones:; *.CCK = cholecystokinin. GLP-1 = glucagon-like peptide-1. OXM = oxyntomodulin. PYY = peptide YY.*

Kessler C. Nurs Clin North Am. 2021 Dec;56(4):465-478



Kessler C. Nurs Clin North Am. 2021 Dec;56(4):465-478

Phentermine

Class: stimulant—appetite suppressant *(use in 17 or 16 yrs & up)*

Most are Multidose: 8-37.5 mg (before or after); **Short or Long-acting** (4 to 12 hrs): *Phentermine, Diethylpropion, Phendimetrazine, Benzphetamine*

(AVOID long-acting and taking late in evening)

Label: Short term – longer if appropriate & safe….3 months?

Avoid: if hx of substance abuse, addiction, *CVD, severe HTN, anxiety, glaucoma*; (**Care with hyperthyroidism**)

Monitoring: check CV status at baseline, periodically and after D/C

Adv. effects: palpitations, tachycardia, increased BP, overstimulation, *tremor, insomnia*, HA

Benefit: INEXPENSIVE. Been around since the 1950's. Can be used as a "bridge drug"

Better exercise efficiency?

Bragg R, et al. *J Am Assoc Nurse Pract* 2016;28:107-15; Kahan S. *Am J Manag Care*. 2016;22:S186-S196

Orlistat

Class: lipase inhibitor (fat blocker) *(can use in 12 years and up)*

Action: blocks the digestion and absorption of fat in stomach & intestines

Dosing: 120 mg po tid **with meals (or within 60 mins)** (60 mg OTC: Alli)

Drug interactions: decreases fat-soluble agent absorption— **alters absorption & metabolism of nearly 160 drugs!!!**

Limit fat to < 30% with each meal

Adv. effects: Oily and frequent bowel movements, bowel urgency, fecal incontinence, greasy stools, cramps & flatulence, gallstones!

Benefits: less expensive, **can use in CKD**

FYI: don't use if you are not eating fat.

Naltrexone-bupropion (Contrave)

Class: Works on CNS hedonic (reward) pathway: satiety & reduction of cravings

Action: Naltraxone-an opioid antagonist- and Bupropion, an antidepressant –
Dosing: Up-titration dosing **(up to 2 tabs twice a day)**
Avoid in: **Seizure disorders*, severe HTN, eating disorders (eg BED),**
chronic opioid use; ETOH withdrawl, or MAO inhibitor use;
A high fat meal may increase systemic effects
Caution with use with CYP2D6 drugs
Black Box Warning: Suicidal Thoughts and Behaviors; and Neuropsychiatric Reactions

Adv. effects: Nausea, constipation, *headache, dizziness*, vomiting, *insomnia, dry mouth, increase in BP*, exacerbates underlying depression/anxiety

Benefits: **Potential benefit for food addictions**

Phentermine-topiramate ER(Qsymia)

Class: Stimulant and appetite suppressant. (Low-dose Combo, ER version drugs)

Action: Works in both the satiety-sympathomimetic (**phentermine**) & hedonic reward pathway--neurostabilizer (**topiramate**)

Dosing: up-titration doses (3.75mg/23mg x 2 wks; 7.5/46mg x 12 wks;11.25mg/69mg x 12 wks; 15mg/92mg

Avoid in: MAO-I use,Drug abuse,Tachy-dysrhythmias; Hyperthyroidism; *Severe menorrhagia*, Valvular heart disease, glaucoma

Adv. effects: **Paresthesias (with higher dose),insomnia, HA , dry mouth, acute myopia/glaucoma; cognitive impairment; metabolic acidosis; elevated creatinine; hypoglycemia; increased menstrual bleed It is teratogenic—cleft palate)**

Benefits: going generic, quicker weight –loss response; **CAN give in children 12 years and up**

Wean off by taking dose every other day for a week

Liraglutide 3.0 mg (Saxenda)/Semaglutide 2.4 mg (Wegovy)

Class: GLP-1R agonist; injectable---No need for have diabetes

Action: Potent satiety action (stimulates POMC and reduces Ghrelin activity);

Dosing: Daily (Saxenda) or Weekly (Wegovy) up-titration doses

Saxenda: 0.6 mg, 1.2 mg, 1.8 mg, 3.0mg

Wegovy: 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg

Avoid in: Medullary thyroid cancer history, multiple endocrine neoplasia type 2, pancreatitis (less risk of GB-related)

Adv. effects: Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM, increased lipase, increased heart rate, pancreatitis

Benefits: Potent satiety drugs, good weight loss**safe in CKD;** *Has Glycemic, CV and Neuro health benefits*;….But COSTLY.

If not hungry—may not be thirsty. FLUIDS!

Approved for 12 yrs and older

Bragg R, et al. *J Am Assoc Nurse Pract* 2016;28:107-15; Kahan S. *Am J Manag Care*. 2016;22:S186-S196

Liraglutide 3.0 mg (Saxenda)/Semaglutide 2.4 mg (Wegovy)

These GLP1-RAs cross the blood brain barrier to help reduce neurodegenerative disease & stroke.

They have pleiotropic effects on coronary arteries & reduce hepatic fat

GLP-1s may reduce efficacy of BCP

Stop Wegovy 2 months prior to attempting pregancy

Newer AOMs are coming….

Tirzepatide (Mounjaro) to be approved for weight loss….

Once weekly, injection, titrated dose that is comprised of **2 incretins (GIP & GLP-1 RA)** that appear to ***synergize*** each other.

Associated with ave. 15-20% weight loss (based on dose)
This hormone known to be successful in T2DM & found beneficial in CKD & NAFLD **(Not approved for latter)** (CVOT data pending)
Touting to become one of the best-selling AOM of all time….??

Not approved for < 18 yrs

JAMA. 2022;328(4):322; Anti-obesity drug discovery: advances and challenges. *Nat Rev Drug Discov* 21, 201–223 (2022).

So what about diabetes medication? Can any of them help with adiposity and metabolic syndrome?

Can you use them for weight loss without T2DM?

OVER 70 NON-INSULIN DIABETES DRUG OPTIONS

Which help CVD risk?

- **Oral**
  - **Biguanides (metformin)**
  - **Sulfonylureas**
  - **Meglitinides**
  - **Thiazolidinediones (TZD) (no weight help)**
  - **a-Glucosidase inhibitors (AGIs)**
  - **DPP-4 inhibitors**
  - **Sodium glucose cotransporter-2 (SGLT-2) inhibitors**
  - **D2 dopamine agonists**
- **Non-insulin injectable**
  - **GLP-1 Ra**
  - **GLP-1Ra:GIP**

And they can help with Pre-diabetes, IR, inflammation & NAFLD

Metabolic & Bariatric Surgery

CONTRAINDICATIONS

- Active Substance abuse
- Active psychiatric disease
- Active binging/bulimia
- Noncompliance
- Poor competence

*__Not a contraindication:__

- HgbA1c > 8%
- Age
- New Cancer diagnosis

HOW IT WORKS

Change in Microbiomes
Change in Incretins (Satiety & Hunger Hormones)

NOT “RESTRICTION”
NOT “MALABSORPTION”

LOW MORTALITY

2022 AMERICAN SOCIETY FOR METABOLIC AND BARIATRIC SURGERY (ASMBS) MAJOR UPDATES TO GUIDELINES FOR BARIATRIC SURGERY

- Metabolic and bariatric surgery (MBS) is recommended for a body mass index (BMI) ≥35 kg/m2, regardless of presence, absence, or severity of co-morbidities.
- MBS should be considered for individuals with metabolic disease and BMI of 30-34.9 kg/m2.
- BMI thresholds should be adjusted in the Asian population such that a BMI ≥25 kg/m2 suggests clinical obesity, and individuals with BMI ≥27.5 kg/m2 should be offered MBS.
- Long-term results of MBS consistently demonstrate safety and efficacy.
- Appropriately selected children and adolescents should be considered for MBS.

Eisenberg D et al. Surgery for Obesity & Related Disesase (2022) in press related October 20 (https://doi.org/10.1016/j.soard.2022.08.013)

CAN YOU GIVE AOMS **BEFORE AND/OR FOLLOWING** METABOLIC BARIATRIC SURGERY?

Case 2: Jenny

37 y/o Caucasian woman
BMI of 36 **;** Obesity since age 16—worse with birth of twins at 26
Successful with multiple diet programs, *but always regains her weight*
PMH
HTN (stable), HLD, sleep apnea, hypothyroidism (treated), NAFLD
NO diabetes (A1C 5.5) or depression/anxiety
Poor sleep
FMHx: *obesity and CV disease*
Social History: one glass of wine "muscato" nightly, *no use of illicit drugs.*
Craves carbs…sweets; HS snacking, no binging

IS SHE ON BCP?

Time for an AOM

So which drugs are okay for Jenny?

phentermine

orlistat

phentermine-topiramate (Qsymia)

naltrexone-bupropion (Contrave)

liraglutide 3mg (Saxenda)/semaglutide (Wegovy) 2.4 mg

semaglutide 1 or 2 mg (Ozempic)

liraglutide 1.6 mg (Victoza)

tirzepatide 15 mg (Mountjaro)

SGLT2i

pioglitazone (actos)

Metformin

What about bariatric surgery?

Case 3: Jasmyne

48 y/o Black Woman

BMI of 28. *(weight gain (visceral) since hysterectomy 2 yrs ago)*

Difficulty loosing weight and keeping it off

PMH

- *Depression and anxiety,*
- *HTN (uncontrolled),* HLD, *Graves disease (in remission); hx tachydysrhythmia*

Recent lab results

- Tg 191; *HgbA1C of 6.5 (new onset LADA); GFR 45 and UCAR > 30*

Social History: *no use of illicit drugs or ETOH excess.*

Hx of binge eating (nocturnal)

So which drugs are okay for Jasmyne?

phentermine

orlistat

phentermine-topiramate (Qsymia)

naltrexone-bupropion (Contave)

liraglutide 3mg /semaglutide 2.4 mg

semaglutide 1 or 2 mg (Ozempic)

liraglutide 1.6 mg (Victoza)

tirzepatide 15 mg (Mountjaro)

SGLT2i

pioglitazone

Metformin

What about bariatric surgery

Case 4: Roberto

12 y/o Salvadorian boy

BMI of 36- 72 Kg (higher weight began following fracture femur and long treatment of osteomyelitis at 8 years of age)

Elevated BP and TGs (134 g/dl); *A1C 6.1*

NAFLD

Says he feels hungry all of the time—an hour after eating; stable family; he's motivated.

What Treatments could be tried?

So which drugs are okay for Roberto?

phentermine

orlistat

phentermine-topiramate (Qsymia)

naltrexone-bupropion (Contrave)

liraglutide 3mg (Saxenda)/semaglutide 2.4 mg) Wegovy)

semaglutide 1 or 2 mg (Ozempic)

liraglutide 1.6 mg (Victoza)

tirzepatide 15 mg (Mountjaro)

SGLT2i

pioglitazone (actos)

Metformin

What about bariatric surge

NO

Realities about cost and access For weight loss treatment

Remember…We can win the battle of the bulge!

Personal image of speaker

This NP friend is doing great on her journey

And clobber the Twin-Demics

"AUNT CHRIS…AREN'T YOU DONE YET?"

Niece ASHLEY

Yes I am!

Personal image of speaker

Thank you all!

ckessler@maranatha.net

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