MANAGING METABOLIC MADNESS IN DIABETES Adiposity & Cardiometabolic Disease



Christine Kessler MN, CNS, ANP-BC, BC-ADM, FAANP

Metabolic Medicine Associates Journeys Weight Loss Clinic

CLASS OBJECTIVES

- 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 <u>HTN</u>, <u>dyslipidemia, Gerd</u>, 3 years & <u>prediabetes</u> (1 year), allergies
- Social: married, HVAC business, sedentary
- Surgical History: None
- Family Hx: HTN, DM and all are "heavy" (M, F, S); no cancer

<u>Relevant findings:</u>

• **BP**: 148/88, **BMI** 34.3, central adiposity, painful ROM right knee

• <u>LABS::</u>

- <u>TG</u>,g/dL; <u>TC</u> 236 mg/dL; <u>LDL</u> 134mg/dL;<u>HDL</u> 48 mg/dL;
- <u>AST</u> 67 u/L; <u>ALT</u> 102 u/L; <u>vitamin D</u> 34 ng/mL
- <u>FBG</u>: 94 mg/dL; <u>AIC</u>: 6.2
- <u>eGFR:</u> 72, <u>UACR</u>: 23

Meds: losartan, atorvastatin, metformin, omeprazole, cetirizine, melatonin, vitamins³

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: <u>https://apps.who.int/iris/handle/10665/353747</u> (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-fattyliver-disease (NAFLD) (also called, "Nonalcoholic steatohepatitis").
 - NAFLD is an important BIOMARKER for cardiometabolic disease (CMD)

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.

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

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

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 & treatable multifactorial, 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 <u>NOT</u>...

- 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

AIC %	mg/dL* mmol/L			
5	97 (76–120)	Dro-diabotos:		
6	126 (100–152)	5.7% to 6.4%		
7	154 (123–185)			
8	183 (147–217)	Diabetes:		
9	212 (170–249)	>/= 6.5%		
10	240 (193–282)			
П	269 (217-314)			
12	298 (240-347)			

THE NCEP ATP III DEFINITION OF METABOLIC SYNDROME 3 OR MORE OF THE FOLLOWING

	Risk Factor	Defining Level		
	Abdominal obesity Men Women	Waist circumference >102 cm (>40 in) >88 cm (>35 in)	Asians Europe	: 35 in. & 31.5 in. <u>an</u> : 37 in. & 31.5 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)		

MEASURING WAIST CIRCUMFERENCE

FYI: Waist circumference and obesity are NOT synonymous





irp.nih.gov

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

- ACC aligned with ADA and the OMA, TOS, & AMBS!
 - <u>Recent MACE data</u> show positive CV impact by GLP-1 agonists, SGLT2i, and metformin
 - <u>A focus on weight reduction and T2DM improvement</u> 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 <u>ORGAN</u>

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 spillover) & abnormal fat function

Overweight should be considered "pre-obesity"

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





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)





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.



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:
- In the morning....

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 <u>evening tendency</u> is associated with <u>elevated inflammatory</u> biomarkers (CRP, IL-6) and a greater cortisol stress response
 - <u>Increased cortisol</u> 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 <u>increase central</u> <u>adiposity & inflammatory biomarkers</u> in adolescent girls (Project Viva Study)



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



OBESITY RISK ABNORMAL ADIPOCYTE MASS AND FUNCTION ADIPOSITY-BASED COMPLICATIONS



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

-Ankle swelling

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



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*







The body will defend the fat mass

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



It is about <u>more</u> than numbers on a scale!

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

Desity 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	AACE/ACE	ОМА	ос
 Mention of nutrition, activity, behavioral intervention Details on available pharmacology for anti-obesity medications Obesogenic medications with options of other choices 	 Complication- specific treatment guideline Prevention reviewed Staged recommendatio ns for treatment ORC-centric obesity treatment based on pharmacology 	 Annually updated clinician tool Review of bias and stigma implications Podcast companions Top 10 messages of each section Obesity myths section 	 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"

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 <u>healthy weight.</u> *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)





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????
- <u>Exam</u>
 - 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)

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

LAB & PHYSICAL BIOMARKERS



• A1C

Vite and in D

What about getting a HOMA-IR score?

- T2 diabetes
- Depression
- Hypothyroidism
- infertility

• 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)

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.

<u>The calculation:</u>

Insulin uIU/mL (mU/L x Glucose (mg/dL) = HOMA-IR

Mark has a HOMA-IR of 4.1

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 <u>at least 7 hours</u> 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
- <u>Add fiber (water soluble & insoluble—IMPROVES microbiome—CV support)</u>
- **<u>Reduce fructose intake</u>** (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)
- <u>Meal replacement</u> 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)!

- <u>Suggest</u>: <u>Endurance</u>, 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)
- <u>After you eat (1-2 meals/day) walk/move for 10 minutes straight</u>

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—<u>2 to10 min bouts throughout the day</u>) JUST MOVE with intention!!!
 - <u>Resistance training</u> (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 in pregnancy</u>/ 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

Additional Medications that

may cause weight loss and used off label





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
- <u>Semaglutide 2.4mg</u> (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?)
- <u>Tirzepatide 15 mg</u> (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 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

<u>Class:</u> 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?

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

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

<u>Adv. effects:</u> 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?

Orlistat

<u>Class</u>: 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

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

Benefits: less expensive, <u>can use in CKD</u>

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

Naltrexone-bupropion (Contrave)

<u>Class</u>: Works on CNS hedonic (reward) pathway: satiety & reduction of cravings

<u>Action</u>: Naltraxone-an opioid antagonist- and Bupropion, an antidepressant – <u>Dosing</u>: 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

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

Benefits: Potential benefit for food addictions

Phentermine-topiramate ER(Qsymia)

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

<u>Action:</u> 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

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

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

<u>Benefits:</u> going generic, quicker weight –loss response; CAN give in children 12 years and Wean off by taking dose every other day for a week

<u>Liraglutide</u> 3.0 mg (Saxenda)/<u>Semaglutide</u> 2.4 mg (Wegovy)

<u>Class</u>: 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, 3.0 mg

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)

<u>Adv. effects</u>: 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.

Approved for 12 yrs and older

If not hungry—may not be thirsty. FLUIDS!

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 <u>comprised of 2</u> 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?

• <u>Oral</u>

- 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 <u>metabolic disease and BMI of 30-</u> <u>34.9 kg/m2.</u>
- BMI thresholds should be adjusted in the <u>Asian population such that a BMI ≥25</u> <u>kg/m2 suggests clinical obesity</u>, and individuals with <u>BMI ≥27.5 kg/m2 should be</u> <u>offered MBS.</u>
- 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 <u>multiple diet programs</u>, *but <u>always</u> regains her weight* **PMH**

HTN (stable), HLD, sleep apnea, hypothyroidism (treated), <u>NAFLD</u> *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 <u>okay</u> for Jenny?

phentermine

<u>orlistat</u>

phentermine-topiramate (Qsymia)

naltrexone-bupropion (Contrave)

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

semaglutide 1 or 2 mg (Ozempic)

<u>liraglutide</u> 1.6 mg (Victoza)

tirzepatide 15 mg (Mountjaro)

<u>SGLT2i</u>

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 <u>okay</u> for Jasmyne?



phentermine

<u>orlistat</u>

- phentermine-topiramate (Qsymia)
- naltrexone-bupropion (Contave)
- liraglutide 3mg/semaglutide 2.4 mg
- semaglutide 1 or 2 mg (Ozempic)
- <u>liraglutide</u> 1.6 mg (Victoza)
- tirzepatide 15 mg (Mountjaro)

<u>SGLT2i</u>

<u>pioglitazone</u>

Metformin

Vhat 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 <u>he feels hungry all of the time</u>—an hour after eating; stable family; he's motivated.

What Treatments could be tried?

So which drugs are <u>okay</u> for Roberto?



phentermine

<u>orlistat</u>

phentermine-topiramate (Qsymia)

naltrexone-bupropion (Contrave)

<u>liraglutide 3mg (Saxenda)/semaglutide 2.4 mg) Wegovy)</u>

semaglutide 1 or 2 mg (Ozempic)

liraglutide 1.6 mg (Victoza)

tirzepatide 15 mg (Mountjaro)

<u>SGLT2i</u>

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



This NP friend is doing great on her journey

Personal image of speaker

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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