Obesity as a Chronic Disease: Treatment Using New Anti-Obesity Medications

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Intellihealth, Flyte Medical, New Canaan, CT

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Welcome

Today's Moderator

Linda Gigliotti, MS, RDN, CDCES, FAND

- Academy Foundation Board member
- Former Program Director, University of CA Weight Management Program
- Co-editor, *Health Professionals Guide to Obesity and Weight Management*

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Three-Part Webinar Series

New Anti-Obesity Medications and the Critical Role of Nutrition and the RDN

April 18th

Obesity as a Chronic Disease and Treatment Using New Anti-Obesity Medications

May 15th
The Role of the RDN to Optimize Short- and Long-term Use of Anti-Obesity Medications

June 4th
Anti-Obesity Medications: An Interdisciplinary Panel Discusses Cases

All webinars will be recorded for free on-demand viewing at eatrightpro.org.
These webinars do not provide CPE credit.

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This webinar series is made possible through a sponsorship from Eli Lilly and is supported by an educational grant provided by Novo Nordisk Inc. to the Academy Foundation.

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Planning Committee

Julia Axelbaum, RD, CSOWM, Weight Management DPG representative

Linda Gigliotti, MS, RDN, CDCES, FAND, Academy Foundation Board member

Carrie Snyder, MPH, RDN, CDCES, Diabetes DPG representative

Hope Warshaw, MMSc, RD, CDCES, BC-ADM, Academy Foundation Past-chair

Academy of Nutrition and Dietetics

Academy of Nutrition and Dietetics Foundation

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Affiliations & Disclosures

Donna Ryan, MD

Professor Emerita

Pennington Biomedical, Baton Rouge, LA

Investigator

POUNDS Lost, Look AHEAD, DPP, DASH studies

Advisor/consultant: Altimmune, Amgen, AstraZenica, Biohaven, Calibrate, Carmot, CinRX, Epitomee, Fractyl, Gila, Lilly, Novo Nordisk, Scientific Intake, Structure Therapeutics, Wondr Health, Xeno Bioscience, Zealand

Speaker's Bureau: Novo Nordisk, Lilly

Stock Options: Epitomee, Calibrate, Roman, Scientific Intake, Xeno

DSMB: setmelanotide (Rhythm, IQVIA) (2); tirzepatide (Lilly) (1)

6

Affiliations & Disclosures

Katherine H. Saunders, MD, DABOM

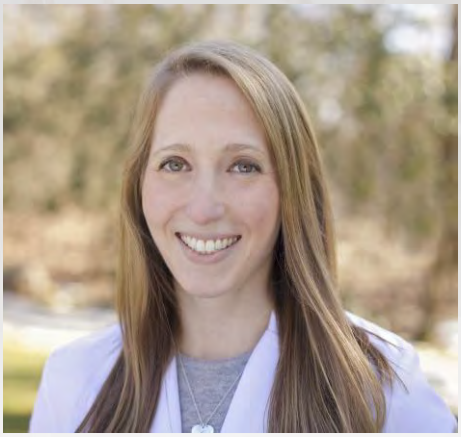
Clinical Assistant Professor of Medicine

Weill Cornell Medicine, New York, NY

Co-Founder, President

Intellihealth, Flyte Medical, New Canaan, CT

No disclosures



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Learning Objectives-

At the end of the presentation, attendees will be able to:

1. describe the etiology and pathogenesis of obesity;
2. discuss why obesity is a chronic disease;
3. communicate the physiology of weight loss and importance of safe weight loss; and
4. relate the rationale and principles for using medications as adjuncts to lifestyle intervention as a pathway to health benefits;

- Katherine to continue…

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What causes obesity and why does it harm us?

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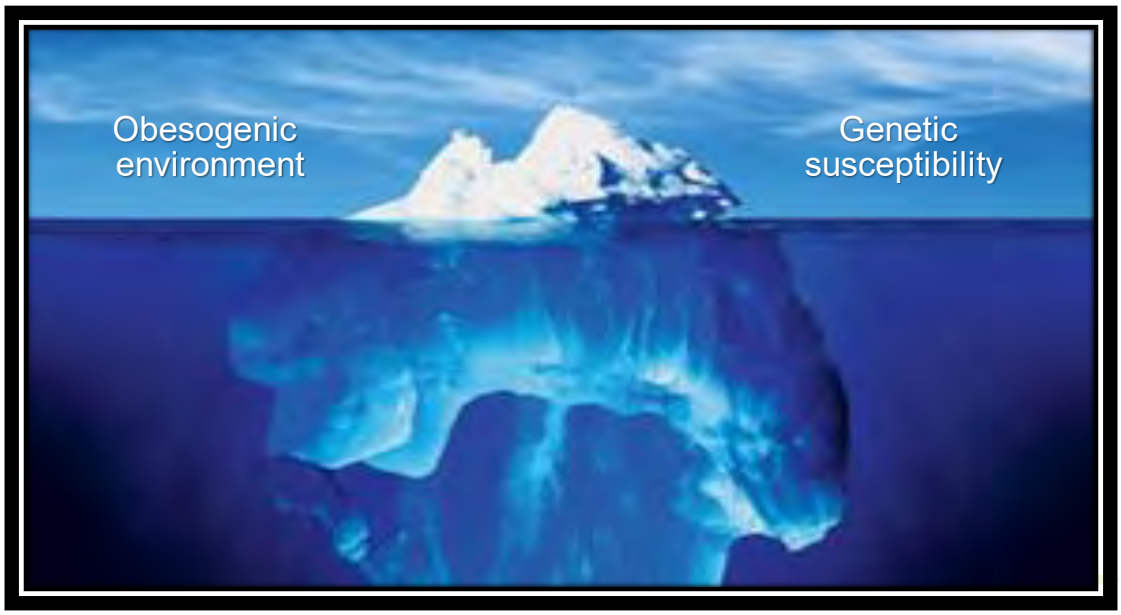
If Obesity Is a Disease, What Is the Etiology?



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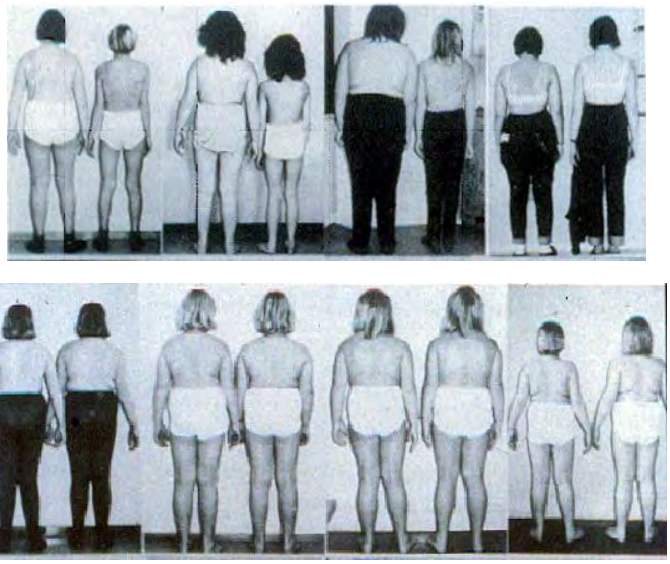
Genetic Contribution to Body Habitus



Borjeson M. *Acta Paediatr Scand*. 1976;65(3):279-287.

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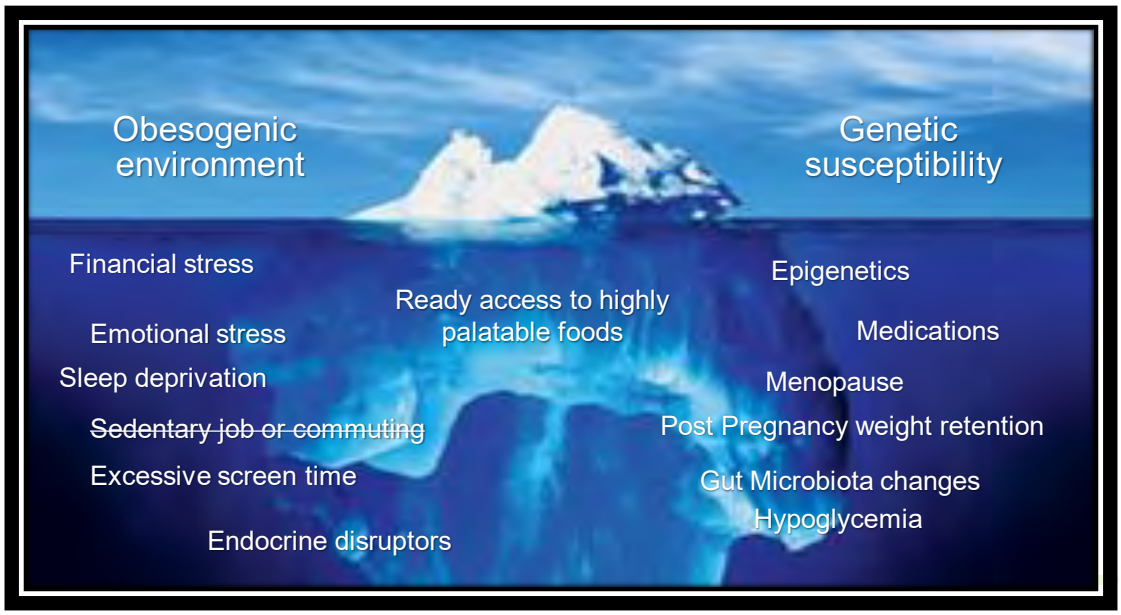
If Obesity Is a Disease, What Is the Etiology?



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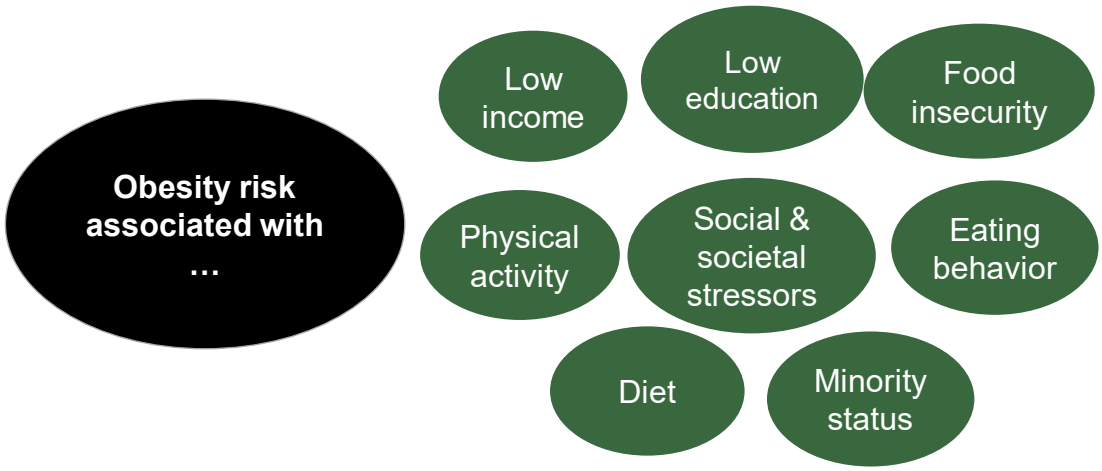
Obesity and Social Determinants of Health



US Centers for Disease Control and Prevention.

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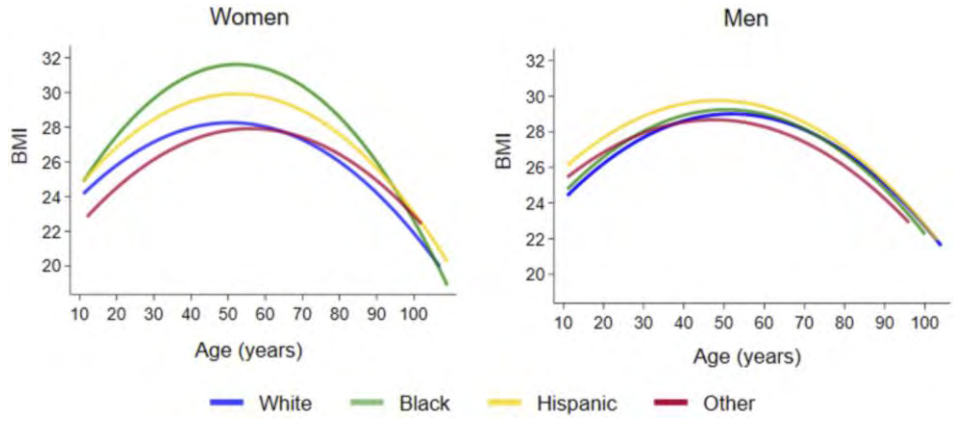
Most people gain weight over early and mid adulthood and lose weight (lean mass) beginning in mid-60's.



Yang, Y.C et al. Life-course trajectories of body mass index from adolescence to old age: Racial and educational disparities. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2020167118.

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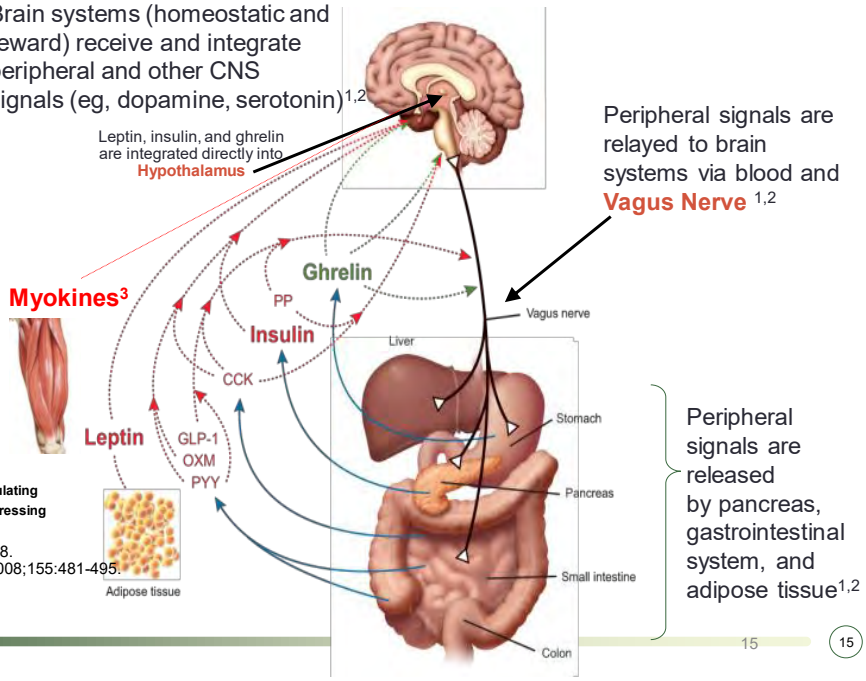
Complex Peripheral Signals are Integrated Into CNS Systems to Regulate Body Weight

Brain systems (homeostatic and reward) receive and integrate peripheral and other CNS signals (eg, dopamine, serotonin)[1,2]

Peripheral signals are relayed to brain systems via blood and **Vagus Nerve** [1,2]



Peripheral signals are released by pancreas, gastrointestinal system, and adipose tissue[1,2]

CNS, central nervous system
PfC, prefrontal cortex
NAc, nucleus accumbens
VTA, ventral tegmental area
PP, pancreatic polypeptide
CCK, cholecystokinin;
GLP-1, glucagon-like peptide 1
OXM, oxyntomodulin
PYY, peptide YY.
Primarily based on data from animal studies.

··· Appetite Stimulating
··· Appetite Suppressing

1. Yu JH et al. *Diabetes Metab J*. 2012;36(6):391-398.
2. Mendieta-Zerón H et al. *Gen Comp Endocrinol*. 2008;155:481-495.
3. Grannell A, et al. Muscles 2022, 1, 26–47.

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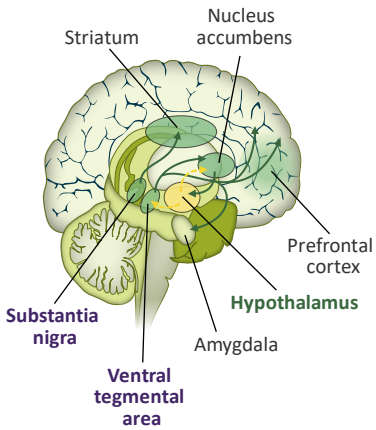
Integrated CNS Pathways Play a Key Role in Regulating Eating Behavior, Appetite, Cravings, and Body Weight

Homeostatic System
Hunger / Satiety

- Primarily driven by the arcuate nucleus of the **hypothalamus**
- Detection and integration of energy state information
  - Leptin, insulin
- Lateral hypothalamus projects to the VTA and receives input from the nucleus accumbens



Hedonic or Reward System

- Dopaminergic pathways from the **VTA or substantia nigra** to regions such as:
  - Striatum (movement, reward salience)
  - Nucleus accumbens (reward, addiction)
  - Prefrontal cortex (decision making, executive function)
  - Amygdala (memory, emotion)

CNS, central nervous system; VTA, ventral tegmental area.

Billes SK, et al. *Pharmacol Res*. 2014;84:1-11.

Definition of Obesity

In ICD codes, obesity is defined by the body mass index (BMI)

Formula: weight (kg) / [height (m)]^2

For adults age ≥20 years, BMI is interpreted using standard weight status categories. These apply to all body types and ages

Body Mass Index (BMI) Definitions	
BMI	**Weight Status**
Below 18.5	Underweight
18.5-24.9	Normal or Healthy Weight
25.0-29.9	Overweight
30.0 and above	Obesity

Obesity Classes		
Class	**BMI**	**Severity**
Class I	30.0-34.9	Mild
Class II	35.0-39.9	Moderate
Class III	≥40.0	Severe

CDC. About adult BMI. https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html
Arnett KD, et al. *J Am Coll Cardiol*. 2019;74:1376-1414.

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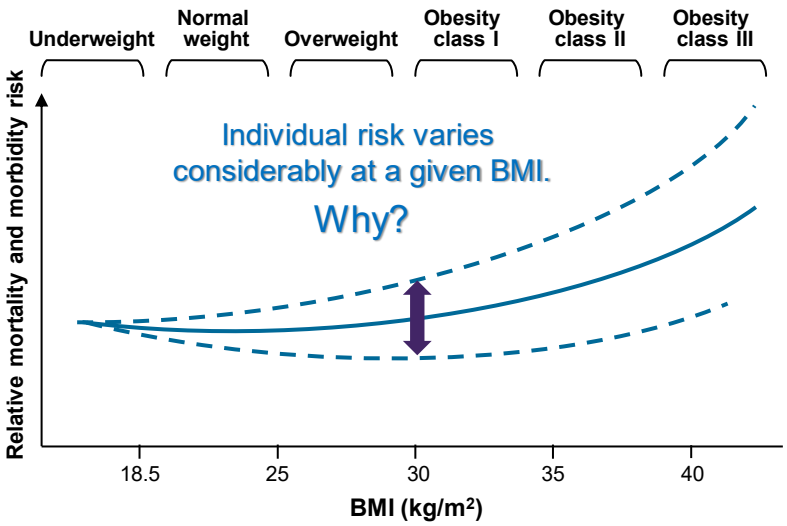
Limitations of BMI



Gonzalez-Muniesa P, et al. *Nat Rev Dis Primers*. 2017;3:17034.

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AMA June 14, 2023

- BMI is easy to measure and inexpensive.
- BMI does not directly assess body fat.
- AMA suggests that it be used in conjunction with other valid measures of risk
- **waist circumference**

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How to make a clinical diagnosis of obesity

Obesity is defined by the World Health Organization (WHO) as *excess abnormal body fat, which may impair health*

Body mass index (BMI) is a good population measure of body fat and an imperfect measure in individuals

For Europids:
Overweight BMI >25 kg/m^2
Obesity BMI >30 kg/m^2
Waist circumference: 35 inches for women & 40 inches for men

Jensen MD, et al. *Obesity.* 2014;22(S2):S1-S410.

For Asians:
Overweight BMI >23 kg/m^2
Obesity BMI >25 kg/m^2
Waist circumference: 31.5 inches
for women & 35 inches for men

WHO/IASO/IOTF, 2000.
(http://www.idi.org.au/obesity_report.htm)

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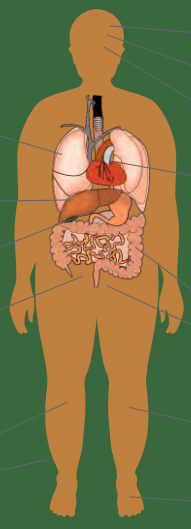
Comorbidities Associated with Obesity



Pulmonary disease
Abnormal function
Obstructive sleep apnea
Hypoventilation syndrome

Nonalcoholic fatty liver disease
Steatosis
Steatohepatitis
Cirrhosis

Gall bladder disease

Gynecologic abnormalities
Abnormal menses
Infertility
Polycystic ovarian syndrome
Urinary incontinence

Osteoarthritis

Skin

Idiopathic intracranial hypertension

Stroke

Cataracts

Coronary heart disease

Diabetes

Dyslipidemia

Hypertension

Cancer
Breast, uterus, cervix, colon, esophagus, pancreas, kidney, prostate

Phlebitis
Venous stasis

Gout

Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ.*Arch Med Sci*. 2013;9(2):191-200.

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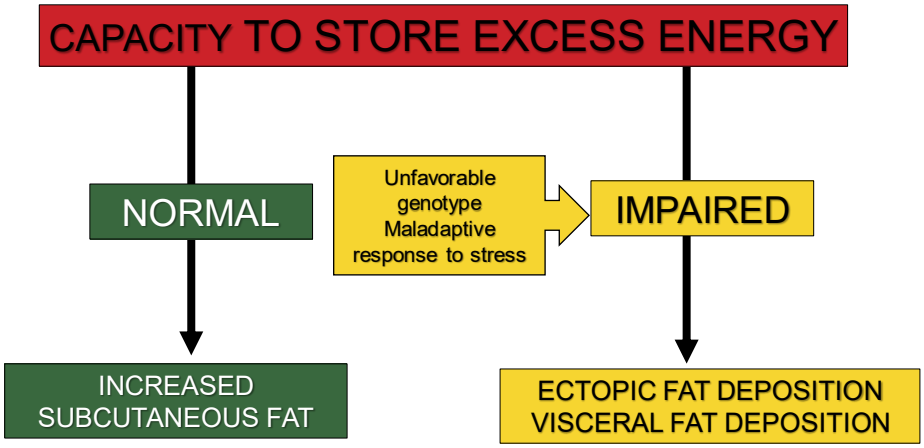
What happens when we exceed the capacity for normal storage of body fat or have impaired storage of healthy fat?



Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obesity Reviews. 2010 Jan;11(1):11-8.

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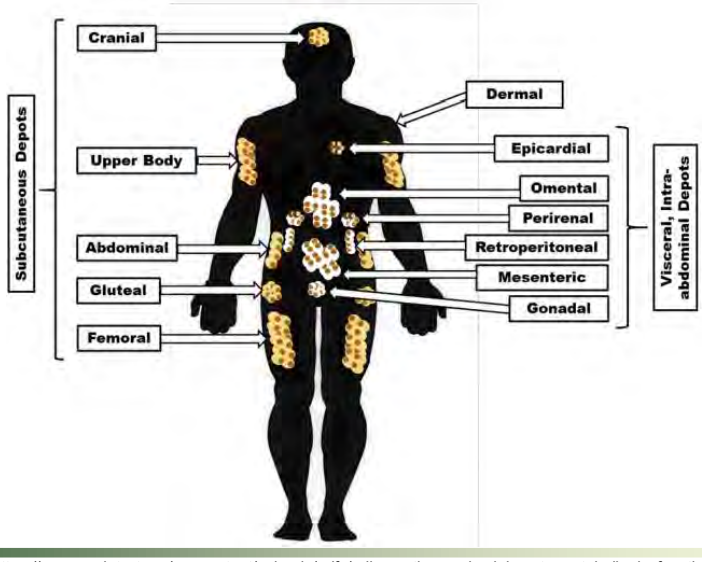
Subcutaneous, Visceral and Intra-abdominal fat depots



Richard AJ, et al. Endotext 2020 https://www.endotext.org/wp-content/uploads/pdfs/adipose-tissue-physiology-to-metabolic-dysfunction.pdf

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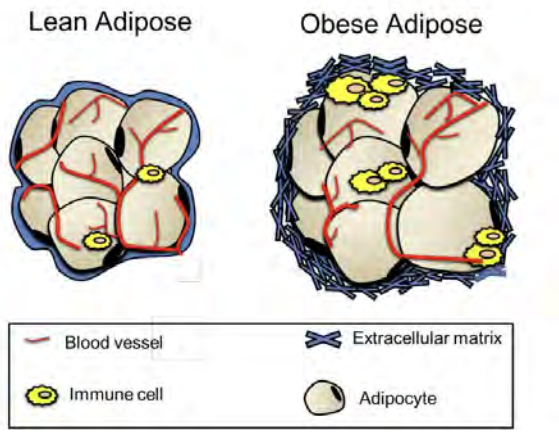
Metabolically unhealthy adipose tissue

- Large cell size
- Dense extracellular matrix
- Presence of inflammatory cells
- Helmet cells, dying fat cells

- Increased production of unfavorable cytokines
  - Pro-inflammatory
  - Pro-thrombotic
  - Pro-atherogenic
  - Pro-insulin resistance



Richard AJ, et al. Endotext 2020 https://www.endotext.org/wp-content/uploads/pdfs/adipose-tissue-physiology-to-metabolic-dysfunction.pdf

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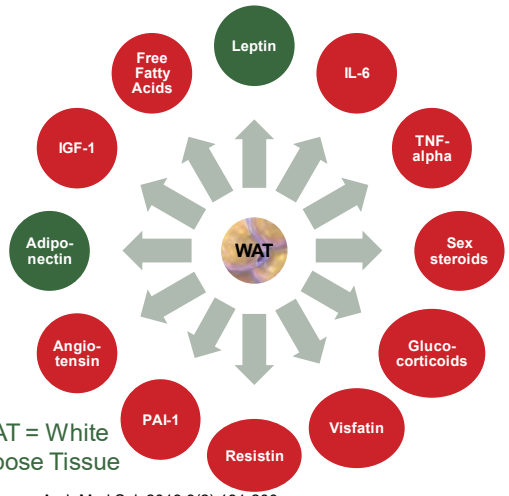
Important Secretory Products of White Adipose Tissue

- Visceral and ectopic white adipose tissue has a more UNFAVORABLE physiologic profile, produces more pro-inflammatory and pro-thrombotic cytokines.

LOCATION, LOCATION, LOCATION:

- Ectopic and visceral fat can have important local and regional effects



WAT = White Adipose Tissue

Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci. 2013;9(2):191-200.

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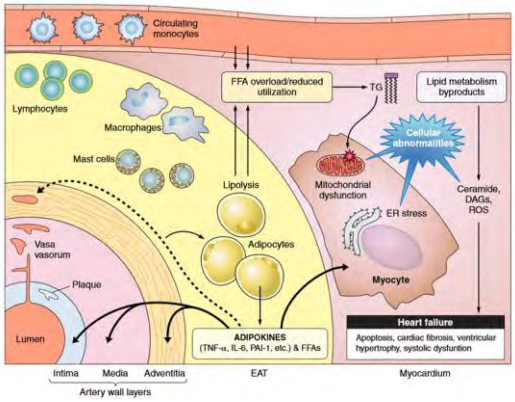
Location, Location, Location

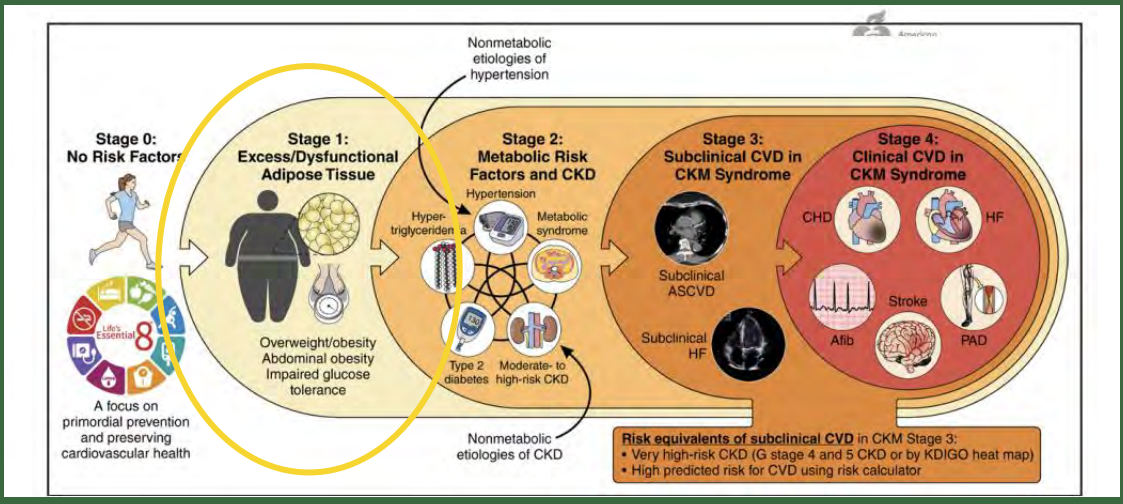
- Visceral and ectopic (muscle, liver, pancreas, epicardial) adipose tissue produces more pro-inflammatory and pro-thrombotic cytokines.

Role of epicardial adipose tissue in cardiovascular risk



Cherian S et al. Am J Physiol Endocrinol Metab. 2012;303:E937-E949.

Excess/Dysfunctional Adipose Tissue is a Driver of Cardiovascular Disease, Mediated Through CKM Syndrome



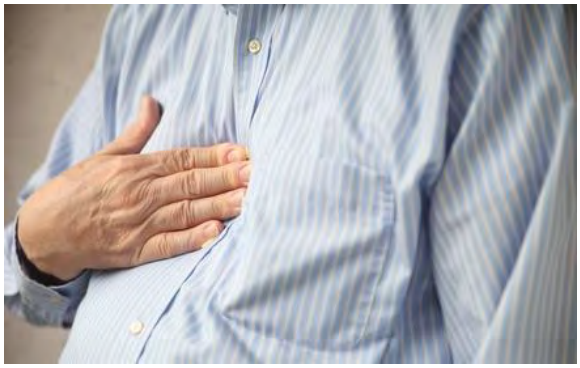
Ndumele CE, et al. Circulation. Circulation. 2023;148:1606–1635.

How does obesity drive other diseases?

Burden of excess fat – biomechanical effects

- Knee arthritis
- Obstructive sleep apnea
- GERD
- Urinary incontinence
- Others

Stigma



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Why can't we just eat less and exercise more? Why is obesity a chronic disease?

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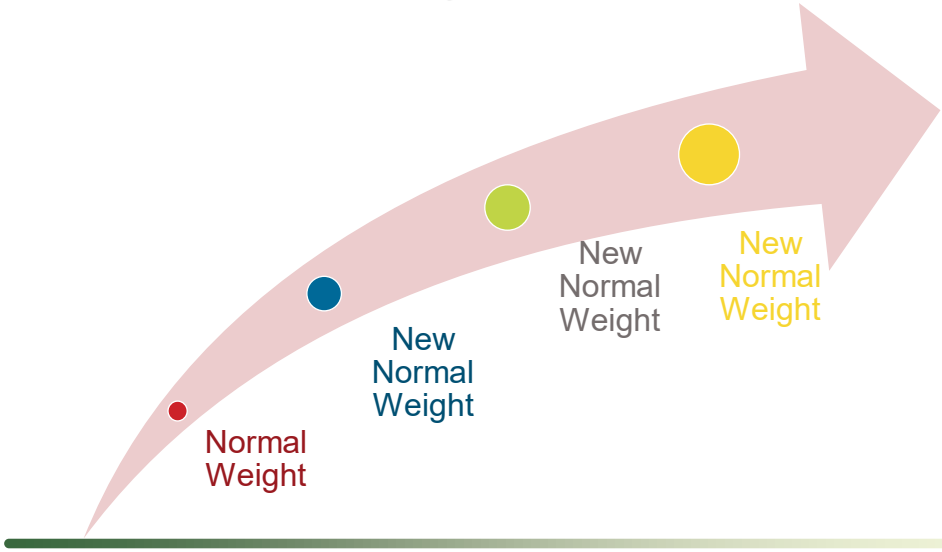
The Body Weight Set Point / Settling Point is the Reason Obesity is a Chronic Disease.



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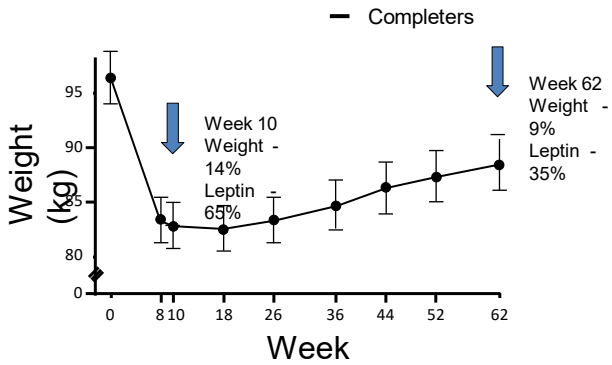
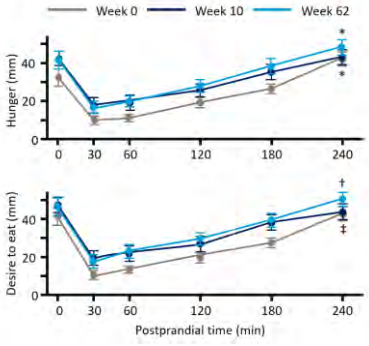
Biologic Responses to Weight Loss – Energy Intake



Average Weight and Leptin changes baseline to week 62.

The inpatient weight loss program was started at week 0 and completed at week 10; outpatient counseling continued until week 62.



Gut Hormone changes:

- Ghrelin
- PYY, CCK, GLP-1, insulin, amylin

Sumithran P, et al. *N Engl J Med.* 2011;365:1597-1604.

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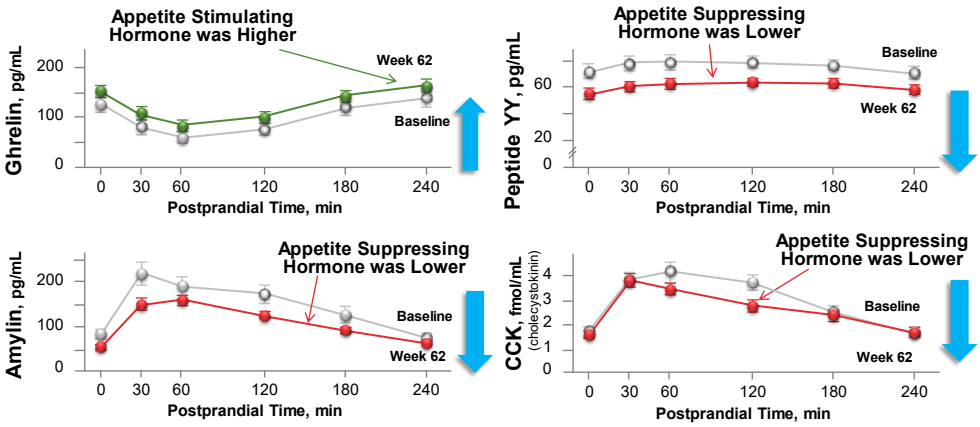
Changes In Appetite Signals After Weight Reduction

Mean fasting and postprandial levels of some peripheral signals at baseline and 62 weeks



Sumithran P, et al. *N Engl J Med.* 2011;365:1597-1604.

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Biologic and Physiologic Adaptations to the Weight Reduced State

- Alterations in appetite regulation[1]
  - ↑ Ghrelin (hunger hormone) and ↓ GLP-1, GIP, CCK, PYY, insulin, and amylin (satiety hormones)

- Alterations in energy expenditure[2,3]
  - ↓ Resting energy expenditure
  - ↑ Muscle efficiency
  - Related to ↓ leptin levels

1. Sumithran P et al. *N Engl J Med*. 2011;365:1597-1604. 2. Johannsen DL et al. *J Clin Endocrinol Metab*. 2012;97:2489-2496.
3. Ravussin E et al. *Obesity*. 2016;24:1607-1608.

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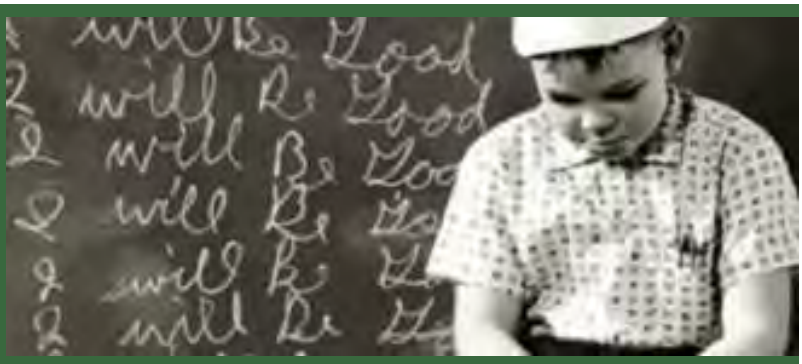
Changing our way of thinking: Obesity is less about will power and more about strong biologic forces making weight loss difficult and regain easy.



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Action needed: discuss the biology of weight regulation with your patients.

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How much weight loss is needed? What's the rationale for medications?

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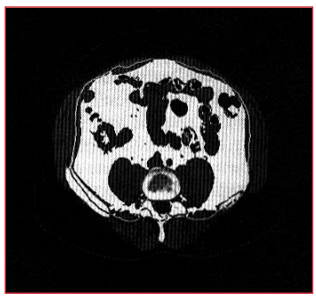
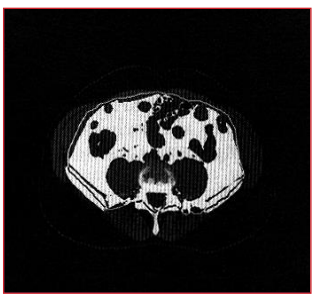
The good news: Weight loss seems to reduce visceral adipose tissue preferentially



Before weight loss
(95 kg, BMI 32)



After 10-kg–weight loss
(85 kg, BMI 29)

Després J-P. *Baillière's Clin Endocrinol*. 1994;8:629.

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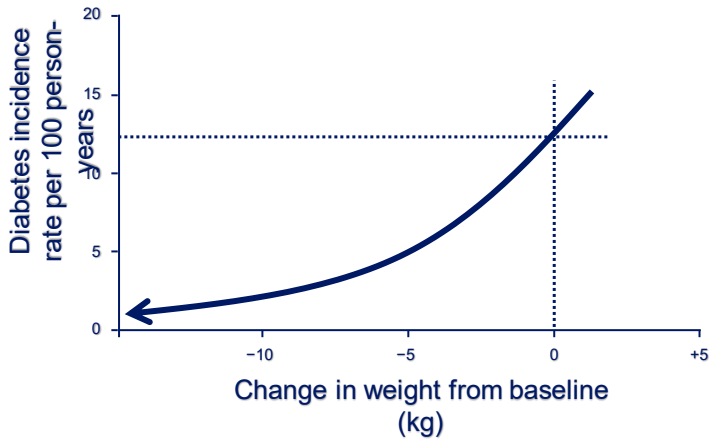
The DPP experience: Impact of modest weight loss on the risk of diabetes



Adapted from Hamman RF *et al. Diabetes Care* 2006;29:2102–7

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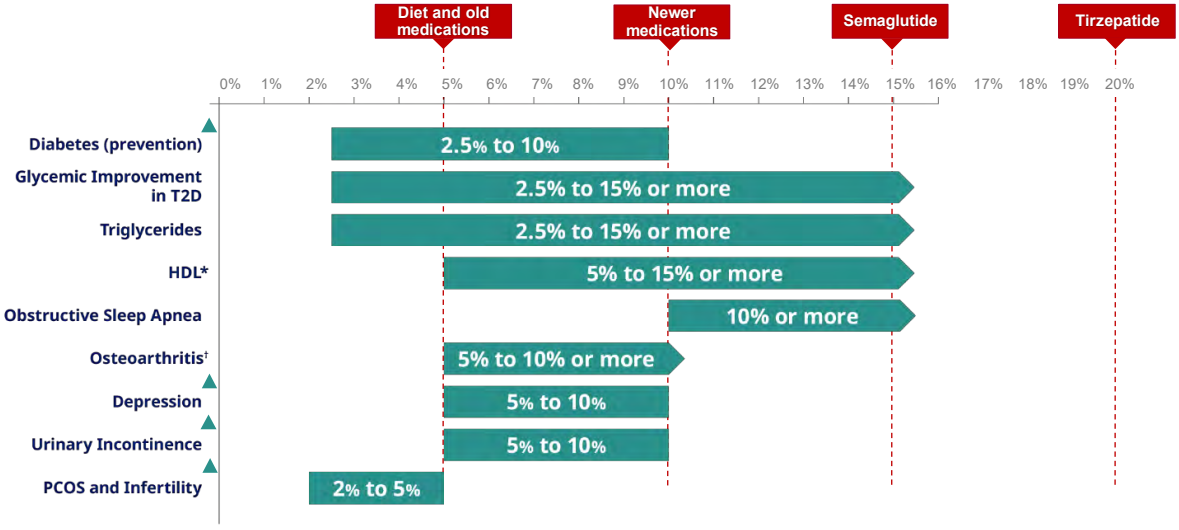
Modest Weight Loss Provides Clinical Benefits. More Weight Loss Provides More Clinical Benefit.[1-3]



1. Ryan DH, Yockey SR. *Curr Obes Rep*. 2017;6(2):187-194.
2. Garvey WT, Mechanick JI, Brett EM, et al. *Endocr Pract*. 2016;22(suppl 3):1-203.
3. Wing RR, Lang W, Wadden TA, et al. *Diabetes Care*. 2011;34(7):1481-1486.

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Multiple Mechanisms for Health benefits

Weight Loss Produces Health Benefits

Medications Have Weight-Independent Effects

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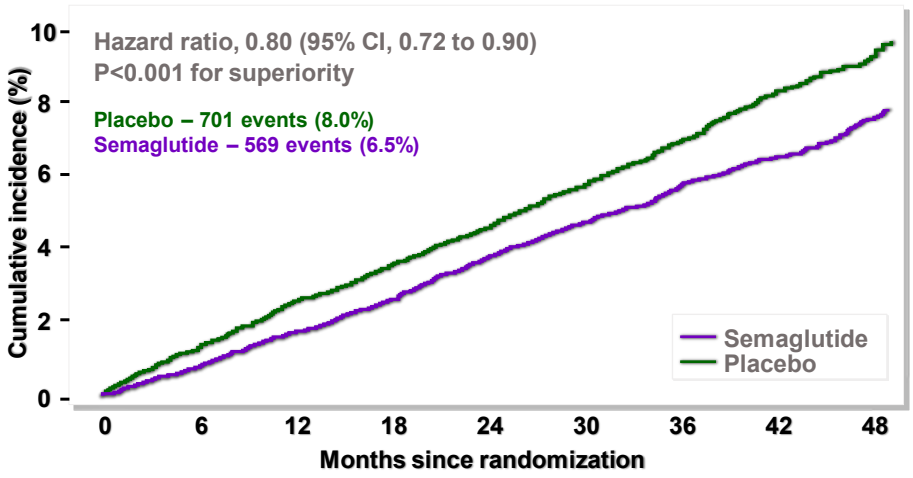
SELECT Trial – Cardiovascular Efficacy

CV Death, Nonfatal MI, or Nonfatal Stroke

Primary Cardiovascular Composite Endpoint



Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 2023;389:2221-2232.

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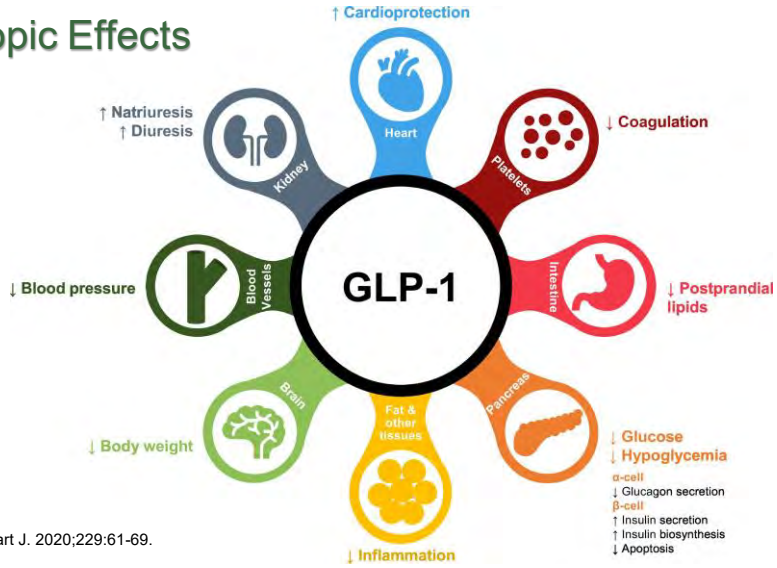
GLP-1 Has Pleiotropic Effects



Ryan DH, et al. Am Heart J. 2020;229:61-69.

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Influential study Results (and Promised results)

- SELECT: 20% reduction in MACE in persons with established CVD.[1]
- STEP HFpEF: Semaglutide (2.4 mg) in patients with heart failure and preserved ejection fraction led to larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than placebo.[2]
- FLOW: Study of semaglutide 2.4 mg in chronic kidney disease stopped early because it met pre-specified evidence of benefit.[3]
  - Prior, a post hoc analysis of the SUSTAIN-6 and LEADER trials, treatment with semaglutide or liraglutide slowed eGFR decline and reduced the risk of substantial loss of kidney function in patients with type 2 diabetes.[4]

1. **Lincoff AM.** Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 2023;389:2221-2232.
2. **Kosiborod NM, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity.** N Engl J Med 2023; 389:1069-1084.
3. https://www.hcplive.com/view/novo-nordisk-halts-semaglutide-kidney-outcomes-trial-for-early-efficacy
4. **Shaman AM, et al.. Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and LEADER.** ***Circulation*** **2022;145:575–585**

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Can weight loss be bad for you? Are there safety issues with weight loss *per se*?

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Patients may lose 5 pounds or more in the first week. This exceeds the energy deficit. Why?????

- Glycogen depletion causes water loss. Every molecule of glycogen is stored with 2 molecules of water.
- Fat is anhydrous.
- Initial weight loss is loss of both water and fat.
- Weight loss slows over time - liver glycogen is repleted.
- Over time, weight loss is reflective of the energy deficit.

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Consequences of Negative Energy Balance

- Acute Effects
- Reduction in insulin needs
  - Sulfonylureas and insulin pose danger of hypoglycemia
- Depletion of glycogen stores
  - Rapid water mobilization, diuresis
  - Diuretics may pose danger of hypotension
- Diuresis and electrolyte imbalance
  - Cardiac arrythmia
- Constipation

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Safety During Weight Loss

STOP OR REDUCE THE INSULIN SECRETAGOGUES FOR PATIENTS WHO ARE IN NEGATIVE ENERGY BALANCE

STOP OR REDUCE THE DIURETICS FOR PATIENTS WHO ARE LOSING WEIGHT RAPIDLY

MONITOR THE PATIENT AND INTERVENE IF LOSS IS TOO RAPID

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Consequences of Rapid Weight Loss

- Lack of high quality protein: heart failure and sudden death associated with starvation diets (maintain intake >500 kcal/d - >900 kcal/day is preferable - and use high quality protein source)
- Gall bladder disease
- Rapid reduction in glycemia may exacerbate retinopathy
- Loss of lean body mass

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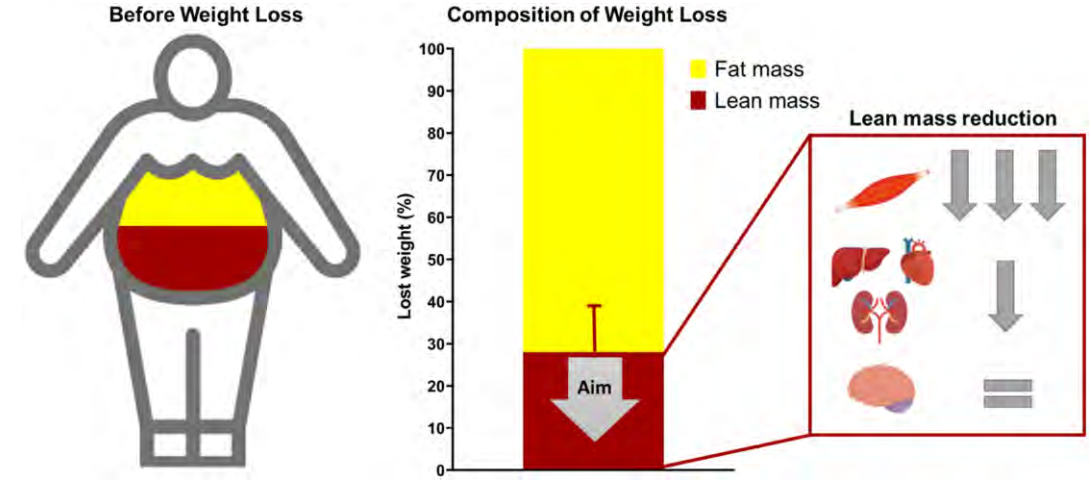
Weight Loss = Fat Loss + Lean Loss



Ostergaard B. et al. Beyond appetite regulation: Targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss. *Obesity (Silver Spring).* 2022; 30: 841–857.

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Anti-Obesity Medications and the Critical Role of RDNs

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Learning Objectives

At the end of the presentation, attendees will be able to:

1. describe the etiology and pathogenesis of obesity;
2. discuss why obesity is a chronic disease;
3. communicate the physiology of weight loss and importance of safe weight loss; and
4. relate the rationale and principles for using medications as adjuncts to lifestyle intervention as a pathway to health benefits;
5. **understand which anti-obesity medications (AOMs) are currently available**
6. **recognize which patients are good candidates for AOMs**
7. **describe the risks, benefits, considerations and barriers associated with AOMs**
8. **appreciate how RDNs are a critical part of the care team for patients on AOMs**

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Consider an Anti-Obesity Medication When….

	BMI ≥ 25 kg/m²	BMI ≥ 27 kg/m² with comorbidity or BMI ≥ 30 kg/m²	BMI ≥ 35 kg/m² with comorbidity or BMI ≥ 40 kg/m²
Diet, exercise, and behavioral modification for all patients with overweight and obesity →	Diet, exercise, behavioral modification	Diet, exercise, behavioral modification	Diet, exercise, behavioral modification
Consider pharmacotherapy for patients **unable to lose** weight and maintain weight loss with lifestyle interventions alone →		Pharmacotherapy	Pharmacotherapy
	Hydrogel devices	Some devices	Some devices Bariatric surgery

Prescribers: physicians, physician assistants, nurse practitioners, some pharmacists

Medications should not be prescribed in the absence of **behavioral counseling**

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Seven Medications are FDA-Approved

- **phentermine** (Adipex-P, Lomaira)*
- **orlistat** (Alli, Xenical)**
- **phentermine/topiramate ER** (Qsymia)**
- **naltrexone SR/bupropion SR** (Contrave)
- **liraglutide 3.0 mg** (Saxenda)**
- **semaglutide 2.4 mg** (Wegovy)**
- **tirzepatide** (Zepbound)

*other sympathomimetic amines also available – minimal data, prescribed less

**approved for pediatric populations

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The Oldest Med: Phentermine

- Brand names: **Adipex-P, Lomaira**
- Approved 1959 (short-term use = 3 months)
- Norepinephrine-releasing agent
- Dosing: 8, 15, 37.5 mg

Weight loss at 28 weeks

30 mg = 6.1%

15 mg = 5.5%

Lifestyle alone = 1.7%

Schedule IV controlled substance

Adverse events

- increased heart rate
- headache
- insomnia
- dry mouth

Caution

- pregnancy
- cardiovascular disease
- hyperthyroidism
- glaucoma

Aronne LJ, et al. Obesity (Silver Spring). 2013;21(11):2163-71.

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Orlistat

Brand names: **Alli** (OTC) 60 mg TID **Xenical** (Rx) 120 mg TID

- Approved 1999, lipase inhibitor

Adverse events: abdominal discomfort, steatorrhea, fecal urgency, fecal incontinence

Special considerations: constipation; psyllium fiber

Decreases absorption:

- vitamins A, D, E, K → take multivitamin
- meds → cyclosporine, levothyroxine, warfarin, antiepileptics

Yanovski SZ, et al. JAMA. 2014;311(1):74-86.

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Phentermine/topiramate ER

- Brand name: **Qsymia**
- Approved 2012
- **phentermine** = norepinephrine-releasing agent
- **topiramate** = neurostabilizer, approved for epilepsy (1996), migraines (2004)

Weight loss at 56 weeks

9.8% - 15/92 mg daily

7.8% - 7.5/46 mg daily

1.2% - lifestyle alone

Schedule IV controlled substance

Adverse events:

increased heart rate, headache, insomnia, paresthesia

Special considerations: migraines

Caution:

cardiovascular disease, hyperthyroidism, glaucoma, nephrolithiasis, pregnancy

Gadde KM, et al. Lancet 2011;377(9774):1341–52.

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Naltrexone SR/bupropion SR

- Brand name: **Contrave**
- Approved 2014

naltrexone = opioid receptor antagonist

- opioid dependency (1984)
- alcohol addiction (1994)

bupropion = dopamine and norepinephrine reuptake inhibitor

- depression (1985)
- smoking cessation (1997)

8/90 mg (1 tab) daily to 16/180 mg (2 tabs) BID

Weight loss at 56 weeks

6.1% = 16/180 mg (2 tablets) BID

1.3% = lifestyle alone

Adverse events: headache, nausea, vomiting,

constipation

Caution: pregnancy, pain, opioid use, seizures, uncontrolled hypertension

Special considerations: food cravings, addictive food behaviors, depression, desire to quit smoking or reduce alcohol consumption

Greenway FL, et al. Lancet. 2010;376(9741):595–605.

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Liraglutide 3.0 mg

Brand name: **Saxenda**

- Approved 2014
- **Victoza** = 1.8 mg daily, approved 2010 for diabetes, 2017 for cardiovascular risk reduction
- GLP-1 receptor agonist
- 0.6 – 3.0 mg subcutaneous injection once daily

Weight loss at 56 weeks

8.0% = 3.0 mg daily

2.6% = lifestyle alone

Pi-Sunyer X, et al. N Engl J Med. 2015;373(1):11–22.

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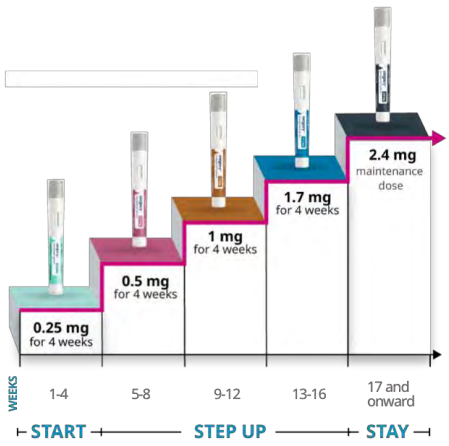
Semaglutide 2.4 mg

Brand name: **Wegovy**

- Approved 2021 for weight, **2024 for CV risk reduction**
- **Ozempic** = 1-2 mg weekly, approved 2017 diabetes, 2020 for CV risk reduction)
- GLP-1 receptor agonist
- 0.25 – 2.4 mg subcutaneous injection once weekly



Weight loss at 68 weeks

14.9% = 2.4 mg weekly

2.4% = lifestyle alone

Wilding JPH, et al. N Engl J Med. 2021; 18;384(11):989.

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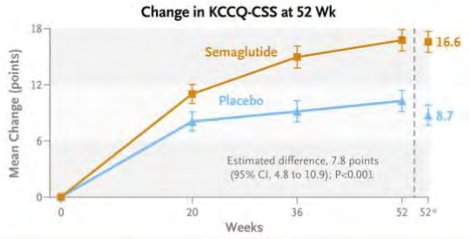
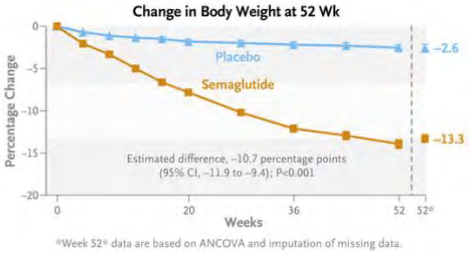
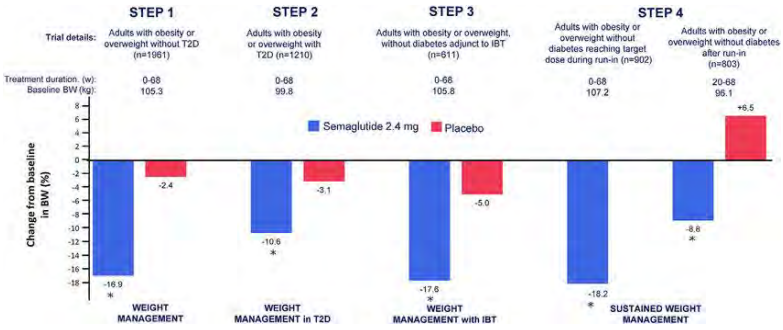
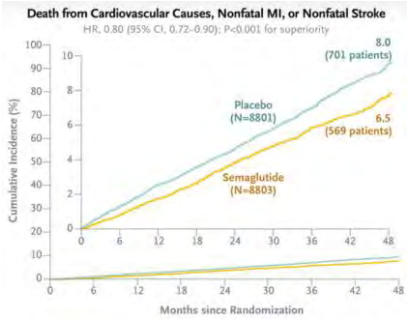
Semaglutide Trials





Week 52 data are based on ANCOVA and imputation of missing data.





Drucker DJ. Mol Metab. 2022;57:101351.
Lincoff AM, et al. N Engl J Med. 2023;389(24):2221-2232.
Kosiborod MN, et al. N Engl J Med. 2023;389(12):1069-1084.

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Tirzepatide

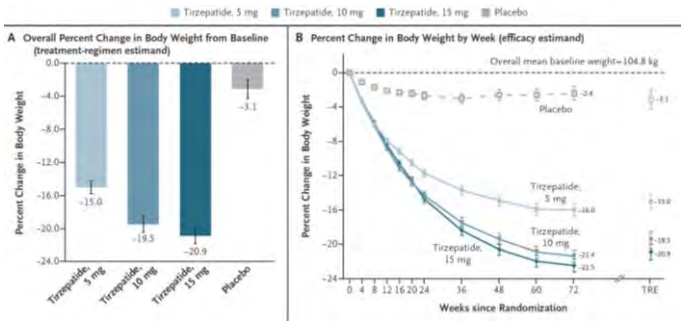
Brand name: **Zepbound**

- Approved 2023
- **Mounjaro** = same dosage, approved 2022 for diabetes
- GLP-1 /GIP co-agonist
- 2.5 – 15 mg subcutaneous injection once weekly

Weight loss at 72 weeks

22.5% = 15 mg weekly

2.4% = lifestyle alone



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Tirzepatide Trials

SURMOUNT PROGRAM

TIRZEPATIDE EVALUATED ACROSS A BROAD PATIENT POPULATION

Lilly

Phase 3 Study	Est. Read-out Date	Study Size (pts)	Studied Doses	Study Duration	Primary Endpoint	Key Inclusion Criteria
SURMOUNT-1 Weight Management in Participants with Obesity/Overweight*	✓	2,539	5/10/15 mg	72 weeks 12-year additional treatment period**	1) Percent change in body weight 2) Percentage of participants who achieve ≥5% body weight reduction	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with ≥1 weight-related comorbidity
SURMOUNT-2 Weight Management in Participants with Obesity/Overweight with T2DM	✓	938	10/15 mg	72 weeks		BMI ≥ 27 kg/m² with T2D (A1c 7-10%), treated with diet/exercise alone or any oral agent except DPP-4 inhibitors or GLP-1R agonists
SURMOUNT-3 Maximizing Weight Loss Following Intensive Lifestyle Program in Participants with Obesity/Overweight*	Mid-2023	806	MTD (10 or 15 mg)	84 weeks (incl. 12-wk intensive lifestyle lead-in)		BMI ≥ 30 kg/m² or ≥ 27 kg/m² with ≥1 weight-related comorbidity
SURMOUNT-4 Maintaining Weight Loss with Maximal Tolerated Dose Therapy in Participants with Obesity/Overweight*		783		88 weeks (incl. 36-wk open-label T2P lead-in)	Percent change in body weight from randomization (week 36) to week 88	
SURMOUNT-5 Comparing the Efficacy and Safety of tirzepatide to semaglutide 2.4mg in Participants with Obesity/Overweight	2025	~700	MTD (10 or 15 mg)	72 weeks	percent change in body weight from randomization to 72 weeks	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with ≥1 weight-related comorbidity
SURMOUNT-MMO Investigating the Effect of tirzepatide on the Reduction on Morbidity and Mortality in Adults With Obesity	2027	~15,000	MTD (10 or 15 mg)	Up to 5 years	Time to first occurrence of any component event of composite, all-cause death, nonfatal MI, nonfatal stroke, coronary revascularization, or heart failure events that results in hospitalization/urgent visits	BMI ≥ 27 kg/m2, individuals ≥40 years of age with established cardiovascular disease (CVD) or the presence of cardiovascular risk factors

Note: Separate on-going trials in Japan (SURMOUNT-J) and China (SURMOUNT-CN)
MTD = Maximum Tolerated Dose; BMI = Body Mass Index; T2DM = Type 2 Diabetes Mellitus; T2P = tirzepatide
* Participants without T2DM; ** For those with pre-diabetes at randomization

https://www.biochempeg.com/article/355.html

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GLP-1 and GLP-1 / GIP MEDICATIONS

Adverse events: nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain

Caution: pregnancy, gastroparesis, pancreatitis, medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2

Special considerations: type 2 diabetes, prediabetes, impaired glucose tolerance, cardiovascular risk, concomitant psychiatric medications,

GLP-1 / GIP medications (tirzepatide) are generally **more effective and more tolerable than GLP-1 medications (semaglutide, etc.)

****PATIENTS SHOULD NOTIFY THEIR CARE TEAM ABOUT MIND SIDE EFFECTS WAY BEFORE THEY EVOLVE INTO SERIOUS ADVERSE EVENTS**

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Overview of FDA-Approved Anti-Obesity Medications

Generic	Brand	Year approved	Mechanisms of action	Administration and timing	% TBWL	Secondary benefits
phentermine	Adipex, Lomaira	1959	Increases neurotransmitter, norepinephrine	Oral Daily to TID	6.1%	Can improve energy
orlistat	Xenical, Alli	1999	Blocks enzyme, lipase, that breaks down fat	Oral Daily to TID	2.9%	Can relieve constipation
phentermine/ topiramate ER	Qsymia	2012	Increases neurotransmitters, norepinephrine and GABA	Oral Daily	9.8%	Can improve migraines
naltrexone SR/ bupropion SR	Contrave	2014	Increases neurotransmitters including norepinephrine and dopamine	Oral Daily to BID	6.1%	Can treat depression, can aid in smoking cessation / alcohol reduction
liraglutide 3.0 mg	Saxenda	2014	Mimics glucagon-like peptide-1 (GLP-1)	Injectable Daily	8.0%	Can improve glucose, reduce cardiovascular risk
semaglutide 2.4 mg	Wegovy	2021	Mimics GLP-1	Injectable Weekly	14.9%	Can improve glucose, reduce cardiovascular risk
tirzepatide	Zepbound	2023	Mimics GLP-1 and GIP	Injectable Weekly	22.5%	Can improve glucose, reduce cardiovascular risk

BID = twice daily, TID = three times per day, TBWL = total body weight loss

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What does it meant to prescribe "off-label"?

- Use of medications for an **unapproved** indication or in an **unapproved** age group, dosage, or route of administration
- "From the FDA perspective, once the FDA approves a drug, providers generally may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient."

- **Examples:**
- metformin
- component of FDA-approved AOM (**topiramate, bupropion, naltrexone**)
- other med in a class of FDA-approved med (**Ozempic, Mounjaro, Rybelsus**)

https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label

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Which Factors Guide our Management?

1) **Any side effect, contraindication or drug-drug interaction?**
- phentermine → anxiety
- bupropion → seizure

2) **Could the medication improve another symptom or condition?**
- topiramate → migraines
- liraglutide, semaglutide → elevated glucose

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Which Factors Guide our Management?

3) **Anticipated effectiveness?**
- semaglutide → 14.9%
- orlistat → < 5%

4) **Patient's preference re: administration/timing?**
- bupropion/naltrexone → oral, twice daily
- semaglutide → subcutaneous injection, once weekly

5) **How expensive? Is there coverage?**
- phentermine → $11-50
- liraglutide, semaglutide, tirzepatide → >$1,000

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Consider Coverage and Cost

Medication	Monthly Cost*
phentermine	$9-36
orlistat	$49-64 (Alli) $732-997 (Xenical)
phentermine/topiramate ER	$168-276
naltrexone SR/bupropion SR	$515-848
liraglutide 3.0 mg	$1,303-1,738
semaglutide 2.4 mg	$1,303-1,781
tirzepatide	$1,032-1,579

*Prices from GoodRx.com (includes coupon discounts) – March 2023
Prices might be lower if mail-order pharmacies or drug-savings plans/coupons are used.

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What's Next?

- Prescribe medications with counseling on **food choices, physical activity** and **behavioral modifications**
- Assess **safety and effectiveness** ≥ monthly x 3 months then ≥ every 3 months
- **Continue** med if safe and effective (**≥ 5% at 3 months**)
- **Stop** if ineffective ("stopping rules") or safety/tolerability concern; **consider alternative** med or treatment approach **(remember: heterogeneity/variability)**

- **FOLLOW UPS: MD/NP/PA, RDN, other referrals (sequencing)**

Apovian CM et al. *J Clin Endocrinol Metab*. 2015;100:342-362.

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How are Medications Titrated?

- If weight loss and appetite control → **continue same dose**
- If weight plateau before goal / appetite not controlled → **increase dose or add another medication**
- If rapid weight loss / appetite oversuppressed / mild side effect → **reduce dose**
- If severe side effect / adverse event → **stop medication**

What is the goal?

- Discourage arbitrary numbers, unrealistic expectations
- Focus on health outcomes, reduction in health risks

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Pharmacotherapy is Long-Term

- Continued use promotes **sustained weight maintenance** by offsetting increased appetite and reduced energy expenditure
- Prepare patients for **weight plateaus**: natural course of weight loss; they DO NOT mean medications no longer working
- Once patient achieves desired weight, **reducing dose and/or frequency** of meds is a possible strategy requiring further study

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Set Patients up for Success

- Set the stage and **educate**
- Present **options, risks / benefits**
- Decide **together**

- Optimize **effectiveness and tolerability**
- **Prepare** for next steps
- Train to **administer** if rx injectable
- Check **understanding**

- Schedule **frequent check ins**
- Encourage **close communication** so mild side effects don't turn into major adverse events

- **Screen for disordered eating at the initial visit and at follow up appointments**

Dosage & titration:
Start LOW and go SLOWLY!

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Roadblocks and Strategies

COVERAGE
- Diagnosis codes
- Prior authorizations & appeals
- Programs: set formulary, rules
- MEDICARE: advocate for TROA (Treat and Reduce Obesity Act); new Wegovy CVD approval
- Switch to alternative medication

COST
- Savings cards, BUT check expiration date
- DO NOT recommended compounded meds
- Switch to alternative medication

SHORTAGES
- Fill scripts on time
- Request refills early
- Switch pharmacy depending on supply
- Switch to alternative medication

NOT ALL PATIENTS NEED GLP-1 MEDS!

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How can we encourage all patients on AOMs to work with RDNs?

"I know what to do. I'm just not doing it."

It's about so much more than food choices.

"I've worked with so many RDNs in the past."

This time will be different.

"I'm on medication now so I don't need nutritional counseling."

Nutritional counseling is a critical part of medical treatment:

- Learn how to eat differently on AOMs
- Mitigate side effects
- Prepare for set backs
- Optimize nutrition given smaller portions
- Strategize weight maintenance

Tips to prepare for RND meeting:

- Keep a food log for a few days
- Prepare questions

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How can RDNs help patients avoid side effects and improve adherence and safety?

Ask about appetite

- Ravenous?
- Oversuppressed?
- Difficult times of day?

Ask about side effects

- Mild symptoms?
- Moderate/severe symptoms?

Ask about AOM dose and frequency

- Differs from prescription?

Ask about physical activity

- Too much or too little?

Ask about energy, stress, sleep

- Good or bad changes?

Ask about relationship with food

- Disordered eating?
- Distress?
- Restriction?
- Effect on self esteem?

FEEL EMPOWERED TO NOTIFY THE PRESCRIBER!

- RDNs are CRITICAL members of the medical care team.
- Define red flags and decide on guardrails, mode of communication.

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What is the process to approve an anti-obesity medication?

In general, a product can be considered effective for weight management if after **one year of treatment** either of the following occurs:

- The difference in **mean weight loss** between the active-product and placebo-treated groups is **≥ 5%** and the difference is statistically significant
- The proportion of subjects who lose ≥ 5% of baseline body weight in the active-product group is **≥ 35%** is **approximately double** the proportion in the placebo-treated group, and the difference between groups is statistically significant

Improvements in **blood pressure, lipids, glycemia**, or other areas commensurate with the degree of weight lost are expected in patients treated with an effective weight-management product. Therefore, changes in common weight-related comorbidites should be factored into the efficacy assessment of investigational weight-management products.

https://www.fda.gov/media/71252/download

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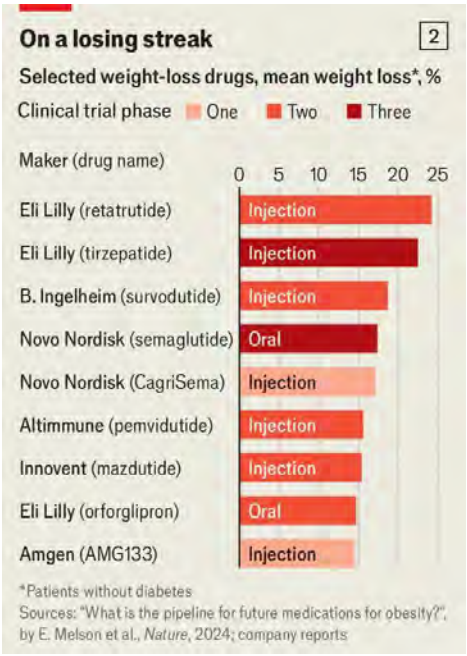
The pipeline is exciting

- ✓ **Injectable to oral**
- ✓ **Longer half lives (less frequent administration)**
- ✓ **Expanded indications**
- ✓ **Less focus on BMI**
- ✓ **Prevention of muscle loss**
- ✓ **Price decrease??**



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Summary

- There are seven main **FDA-approved** AOMs.
- Several other medications are prescribed **off-label** for obesity.
- Many factors inform **choice** of AOM(s).
- Patients on AOMs need a significant amout of **education and ongoing support**.
- RDNs are a critical part of the **care team**.
- Collaborate with your care team on **best practices**.

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THANK YOU

Academy of Nutrition and Dietetics webinar team

- Donna Ryan
- Linda Gigliotti
- Carrie Snyder
- Nicole Barrett
- Hope Warshaw
- Julia Axelbaum
- Jeanne Blankenship

RDN colleagues and friends

- Mary Van Nortwick
- Julie Schwartz
- Morgan Dickison
- Greta Kollmann
- Dana Cizinski
- Eleni Ottalagana
- Tori Campbell
- Janet Feinstein
- Rachel Lustgarten
- Ashley Kim
- Nina Crowley
- Lillian Craigs Dino

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Questions?

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Save the Date!

May 15th|noon-1:30 p.m. (Central time)
The Role of the RDN to Optimize Short- and Long-term Use of Anti-Obesity Medications

June 4th |noon-1:30 p.m. (Central time)
Anti-Obesity Medications: An Interdisciplinary Panel Discusses Cases

All webinars will be recorded for on-demand viewing

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