New Era of Anti-Obesity Medications

Michelle L. Look, MD, FAAFP, ABOM
Family Practice, Sports Medicine, Obesity Medicine
San Diego Sports Medicine Weight and Wellness Center
San Diego, CA

CONTINUING EDUCATION COMPANY

1

Disclosure

Advisory Board: Aadvark; Boehringer Ingelheim; Eli Lilly; Novo Nordisk

Speaker's Bureau: Eli Lilly

CONTINUING EDUCATION COMPANY

2

Learning Objectives

1. Recognize and prioritize obesity as a chronic, progressive relapsing disease that requires a comprehensive, long-term treatment approach.
2. Identify the goals of obesity treatment using pharmacotherapy.
3. Implement an evidence-based, stepwise, comprehensive treatment plan that includes pharmacotherapy.
4. Discuss how pharmacotherapeutic approaches can both enhance initial weight reduction and improve weight maintenance

3

Case Maria

54yo 5’6”, 192 lbs, BMI 31

PMHX: Prediabetes, Hyperlipidemia, Depression, Osteoarthritis of the knee

Presents for lab result follow up

4

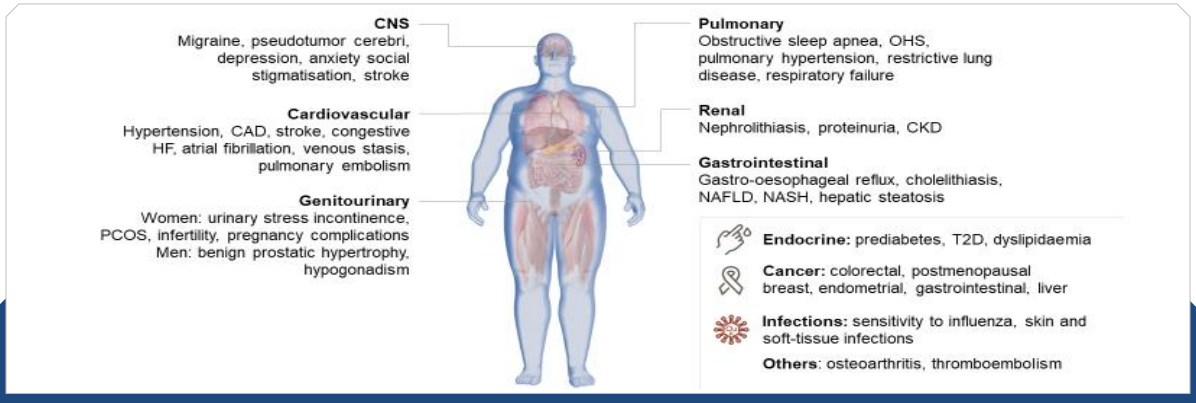
Maria Treat Obesity First

- Lab results: Abnormal liver enzymes AST/ALT 35/54,platelets 300, Fib-4 1.09, blood sugars elevated with a1c of 6.3%
- Meds
- Hyperlipidemia: Atorvastatin
- HTN: Metoprolol
- Depression: Lexapro
- Limited activity due to knee pain

What is your advice to Maria?

5

Obesity Is a **Multisystem Disease** Associated with Many Complications (>100!) Doesn't It Make Sense to Treat Obesity to Treat Them All?



CAD, coronary artery disease; CKD, chronic kidney disease; HF, heart failure; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OHS, obesity hypoventilation syndrome; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes

Slide courtesy of Lou Arrone, MD
Tsai AG, et al. *Ann Intern Med*. 2019;170(5):ITC33-ITC48; Sarma S, et al. *Diabetes Obes Metab*. 2021;23(suppl 1):3-16.

6

Maria

- Advise Maria that her weight is affecting her health
- Weight Loss Attempts: Weight watchers, Intermittent Fasting, Jenny Craig, Medifast, Fat burner supplement, hired personal trainer
- Knee pain: Orthopedic surgeon who told her her pain is due to her weight. Not a surgical candidate until she loses weight. Her knee hurts so much she is limited in her physical activity
- Frustrated

7

PwO Had Many Serious Weight Loss Attempts

Nearly 9 out of 10 PwO have made **between 1 and >15 serious attempts at weight loss** in their adult lifetime

Kaplan LM et al. *Obesity (Silver Spring).* 2018;26(1):61-69.

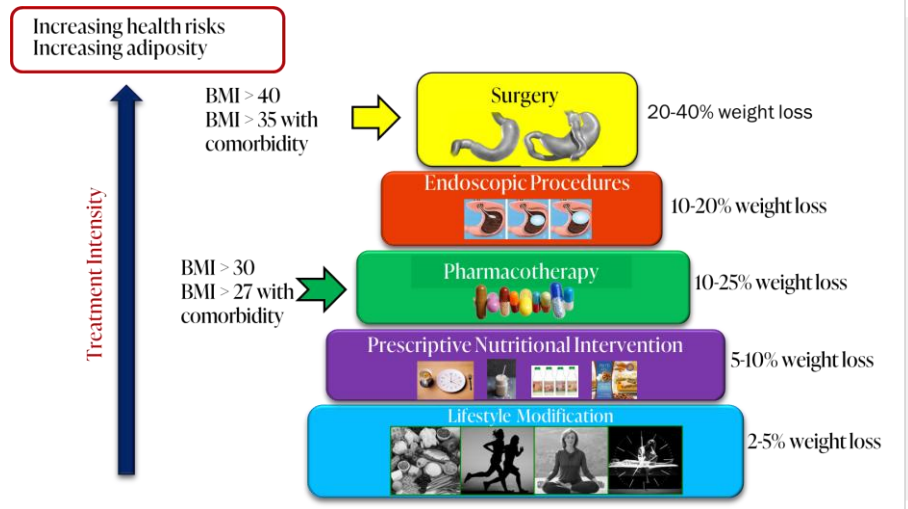
8

Understand and Recognize That:

- Most patients have tried to lose weight repeatedly
- Obesity is not just "personal responsibility"
- Obesity is a product of many factors
- Genetics and environment are paramount
- Our environment makes lifestyle change difficult

9

There Is a "Clear" Best Practice in Treating Obesity



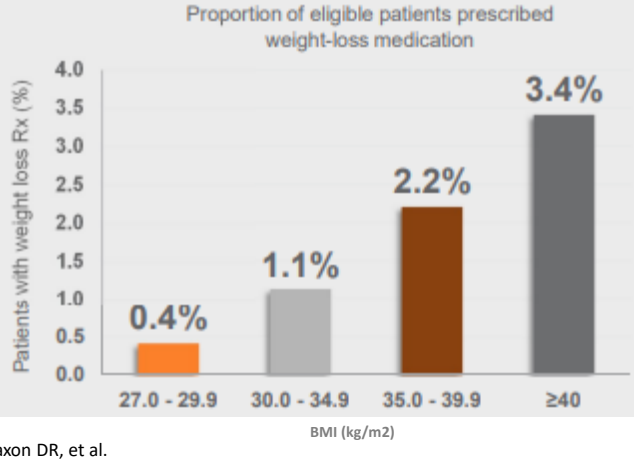
1. O'Neil PM, Birkenfield AL, McGowan B, et al. A randomized, phase II placebo-and active-controlled dose-ranging study of semaglutide for treatment of obesity in subjects without diabetes. Presented at the 100th Annual Meeting of The Endocrine Society, Chicago, Illinois; March 18, 2018. Abstract OR12-5 | 2. Lancet. 2011 Oct 22; 378 (9801): 1485—1492 | 3. JAMA Surg 2016 Nov 1;151(11):1046-1055 | 4. Obesity (Silver Spring). 2011 Jan; 19(1): 110-120 | 5. Obesity (Silver Spring). 2019 Jan; 27 (1):75-86

10

Anti-obesity Medication Prescriptions

Nearly 50% of US adults fit criteria for the use of anti-obesity pharmacotherapy, **but only <2%** received an anti-obesity medication prescription

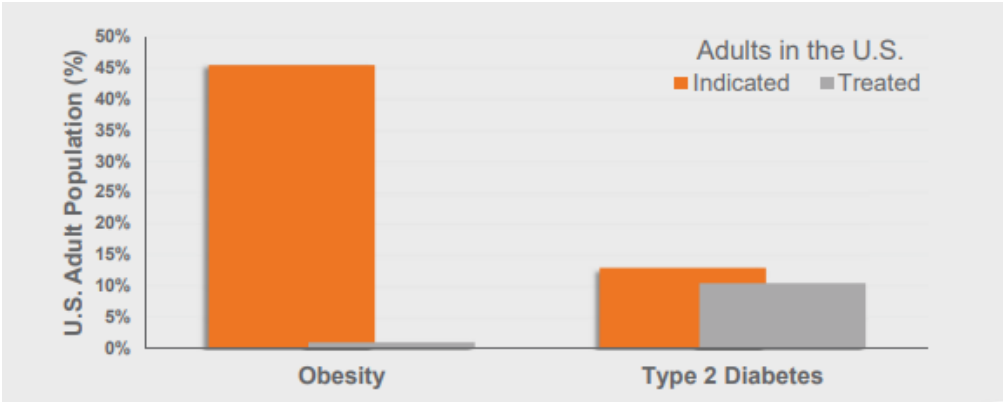
N = 2,248,407
82.3% female
median age 44.9 y
median BMI 37.2 kg/m²
Phentermine = 76.6% of all prescriptions



Heffron SP, et al. Circulation Research. 2020;126:1646–1665. Saxon DR, et al. Obesity (Silver Spring). 2019;27:1975–1981

11

Anti-obesity Medications Are Underutilized



CDC, National Center for Health Statistics, Division of Health Interview Statistics, data from the National Health Interview Survey.

12

Maria

- Interested in medication but husband says
- "Taking medication for weight loss is cheating"
- Just need to increase her activity
- Try harder?
- Activity is part of the treatment plan, but does not fix metabolic adaptation

13

Top Reasons Why PwO Do Not Seek Help with Their Weight Loss from HCPs

CHARACTERISTIC REASONS	PWO NOT SEEKING TREATMENT
PwO (n=823)	**%**
I believe it is my responsibility to manage my weight	44
I already know what I need to do to manage my weight	37
I do not have the financial means to support a weight loss effort	23
I do not feel motivated to lose weight	21
I am embarrassed to bring it up	15
HCPs (n=606)	**%**
They are embarrassed to bring it up	65
They do not feel motivated to lose weight	56
They do not believe that they can lose weight	55
They do not see their weight as a medical issue	55
They are not interested in losing weight	47

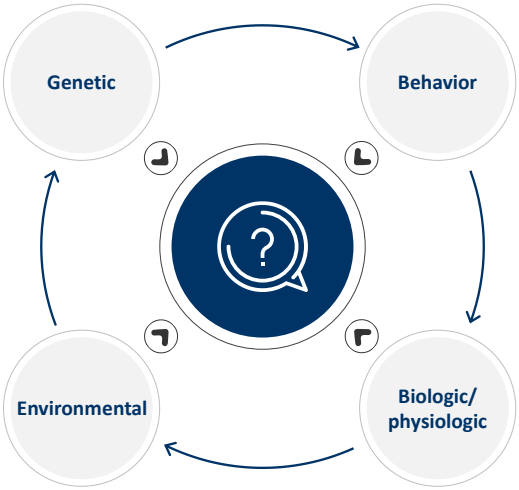
Kaplan LM et al. *Obesity (Silver Spring).* 2018;26(1):61-69.

14

Multifactorial Etiology

- Heritable traits
- Chromosomal abnormalities
- Protective and at-risk alleles for weight gain
- Race (ancestral admixture)
- Gene-gene interactions

- Endocrine disrupting chemicals
- Low macronutrient/high calorie foods
- Food availability
- Food quality
- Built environment
- Socioeconomic status
- Education



- Dietary preferences
- Physical activity
- Psychological factors
- Cultural factors
- Diurnal life patterns

- Altered microbiome
- GI/CNS regulation of hunger + satiety hormones
- Infection
- In utero environment/Birth weight
- Gender
- Age
- Concurrent diseases
- Medications causing weight gain

Golden A. Obesity. In A. Hollier (Ed.), Clinical Guidelines in Primary Care. 2016:281-285; Locke A, et al. Nature. 2015; 518(7538):197-206.

15

Metabolic Adaptation of Obesity

WEIGHT LOSS

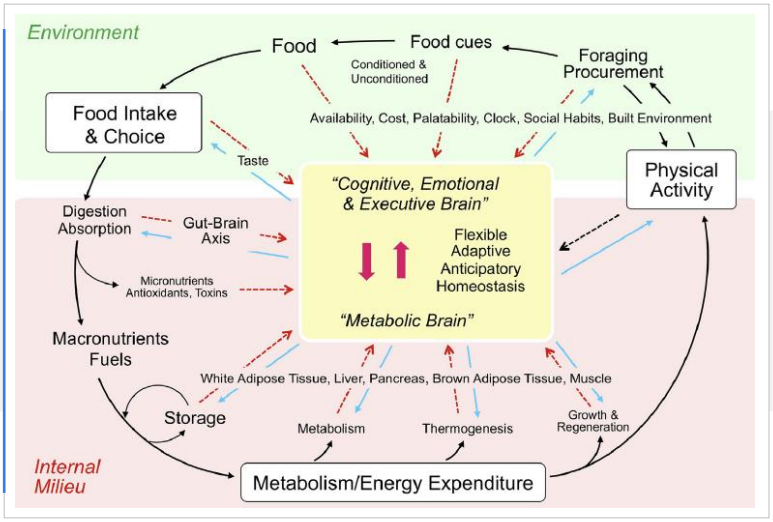
- **Reduced calories**
- **Increased Physical Activity**

Increased Hunger
Decreased Satiety
Decreased Total Energy Expenditure

WEIGHT GAIN

16

The System That Regulates Eating Is Complex



17

Components of Appetite

Hunger
Drive to consume

Satiety
End state of satisfaction
(between-meal inhibition)

Fullness
Physical feeling experienced in the gut

Wanting
Motivation to consume a specific food (craving)

Satiation
Negative feedback, leading to meal termination (within-meal inhibition)

Liking (hedonic)
Sensory pleasure elicited by contact with food

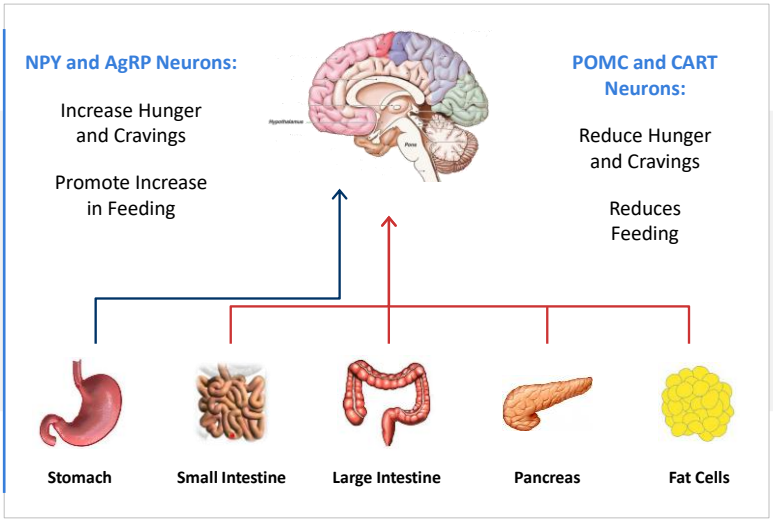
Prospective food consumption
How much an individual feels they would like to eat

Blundell et al. Obes Rev 2010;11:251–270; van Can et al. Int J Obes 2014;38:784–93

18

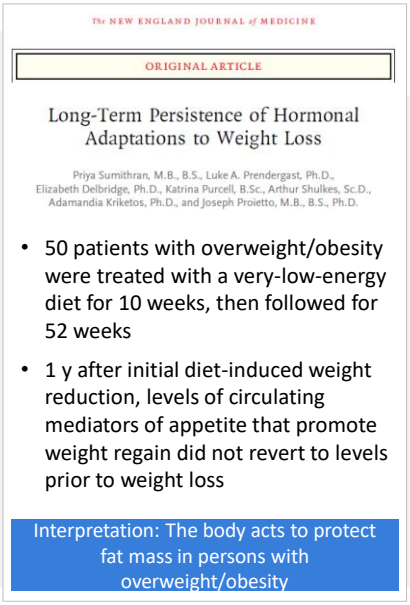
The Hypothalamus Centrally Regulates Weight But Is Influenced by Peripheral Signals

Parmar RM and Can AS. Physiology, Appetite, and Weight Regulation. StatPearls [Internet]. Updated August 29, 2022. Accessed October 31, 2022. https://www.ncbi.nlm.nih.gov/books/NBK574539/



AgRP = agouti-related peptide. CART = cocaine- and amphetamine-regulated transcript. NPY = neuropeptide Y. POMC = proopiomelanocortin

19


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

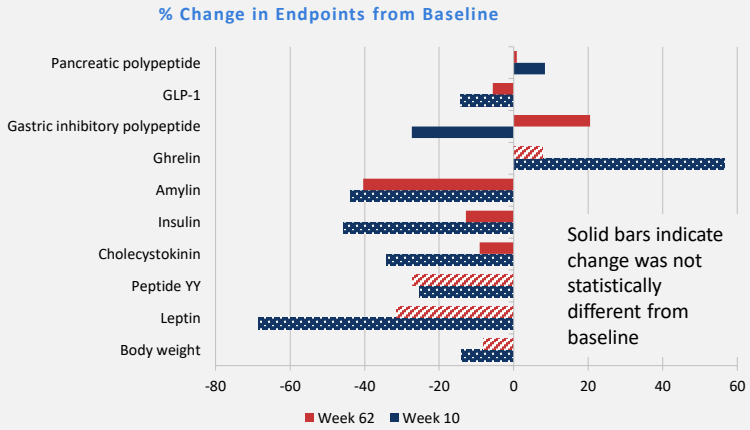
Long-Term Persistence of Hormonal Adaptations to Weight Loss

Priya Sumithran, M.B., B.S., Luke A. Prendergast, Ph.D., Elizabeth Delbridge, Ph.D., Katrina Purcell, B.Sc., Arthur Shulkes, Sc.D., Adamandia Kriketos, Ph.D., and Joseph Proietto, M.B., B.S., Ph.D.

- 50 patients with overweight/obesity were treated with a very-low-energy diet for 10 weeks, then followed for 52 weeks
- 1 y after initial diet-induced weight reduction, levels of circulating mediators of appetite that promote weight regain did not revert to levels prior to weight loss

Interpretation: The body acts to protect fat mass in persons with overweight/obesity

OBESITY…IT'S A CONSPIRACY



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

20

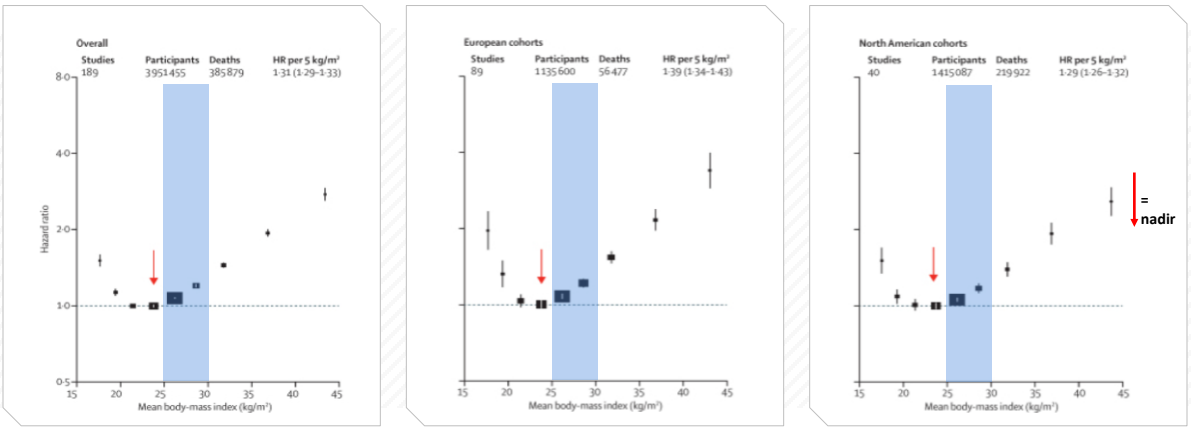
"Overeating Does Not Cause Obesity, Obesity Causes Overeating"

Lee, Kaplan, MD
Former President of The Obesity Society

21

Pre-obesity and All-cause Mortality

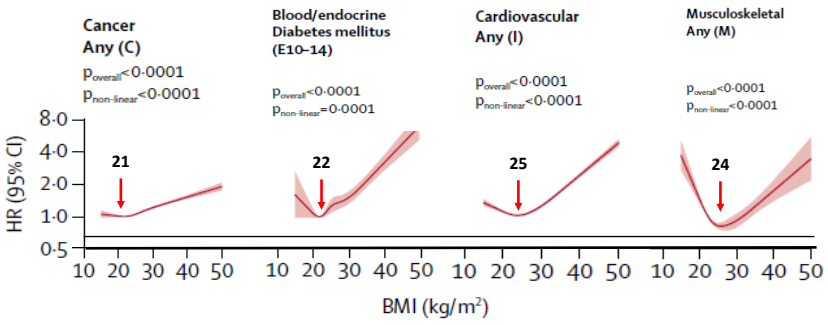
Association Between BMI and All-Cause Mortality Among Never-Smokers, by Region



22

Pre-obesity and Cause-specific Mortality

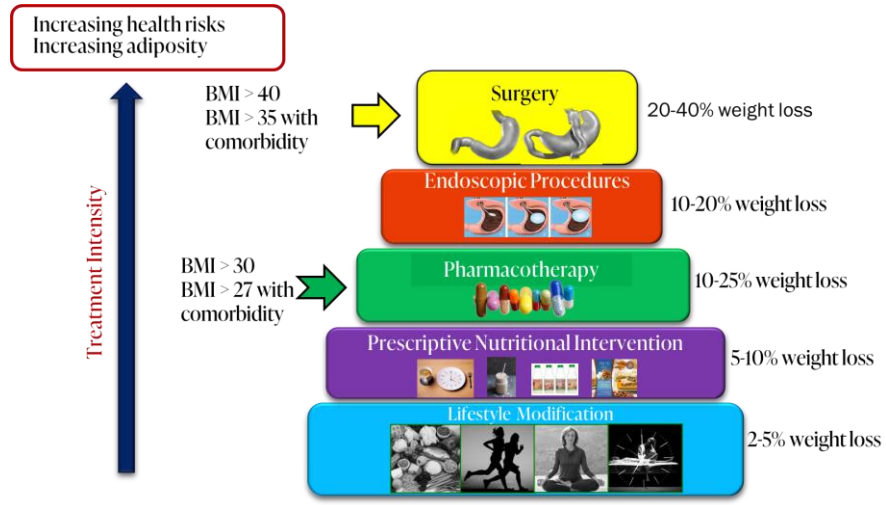
- Most causes of death have a J-shaped association with BMI
- The point of lowest risk (i.e., BMI change point) is between 21-25kg/m^2



1. Bhaskaran K, et al. Lancet Diabetes Endo. 2018;6:944-53.

23

There Is a "Clear" Best Practice in Treating Obesity

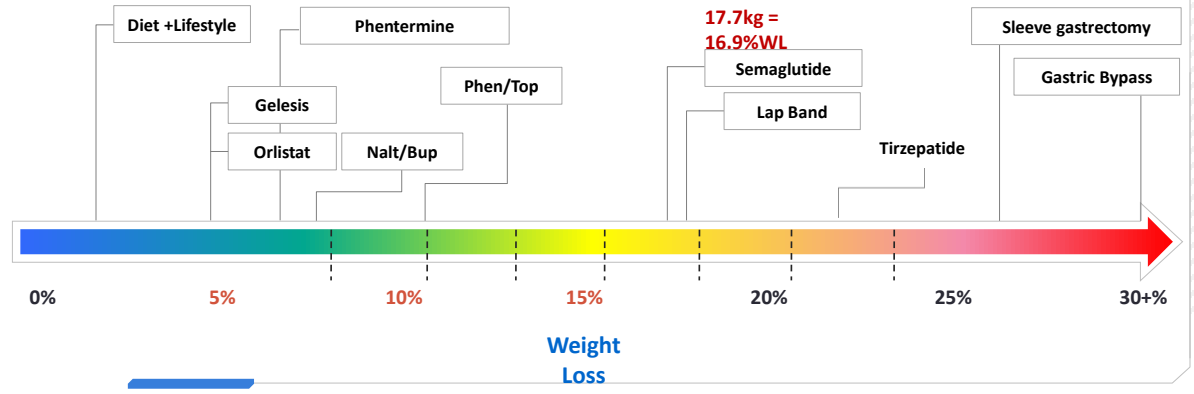


1. O'Neil PM, Birkenfield AL, McGowan B, et al. A randomized, phase II placebo-and active-controlled dose-ranging study of semaglutide for treatment of obesity in subjects without diabetes. Presented at the 100th Annual Meeting of The Endocrine Society, Chicago, Illinois; March 18, 2018. Abstract OR12-5 | 2. Lancet. 2011 Oct 22; 378 (9801): 1485—1492 | 3. JAMA Surg 2016 Nov 1;151(11):1046-1055 | 4. Obesity (Silver Spring). 2011 Jan; 19(1): 110-120 | 5. Obesity (Silver Spring). 2019 Jan; 27 (1):75-86

24

Current Treatment Landscape

New drugs and devices can reduce weight and weight-related comorbidities



After Aronne LJ. FDA VI-0521 EMDAC 2010.

25

FDA-Approved Medications for Chronic Weight Management

Agents	Mechanism of Action	Effect	Approval Date
Phentermine [Adipex-P, Lomaira, Fastin, Ionamin, Obenix]	▪ Modified amphetamine	**Appetite regulation**	1959
Orlistat [Xenical]	▪ Blocks the GI lipase enzymes that absorbs fat	Reduces fat absorption	1999
Phentermine/topiramate ER [Qsymia]	▪ Modified amphetamine ▪ Anticonvulsant medication already approved for prevention of migraine headaches and for seizure disorder	**Appetite regulation**	2012
Naltrexone/bupropion SR [Contrave[	▪ Opioid receptor blocker ▪ Increases dopamine/noradrenaline in the brain (already approved for depression and smoking cessation)	**Appetite regulation**	2014
Liraglutide [Saxenda]	▪ Mimics action of GLP-1 gut hormone	**Appetite regulation**	2014
Setmelanotide [Imcivree]	▪ Activates a specific neuro pathway (MC4R) in the brain (indication: obesity due to rare monogenetic forms of obesity)	**Appetite regulation**	2020
Semaglutide [Wegovy]	▪ Mimics action of GLP-1 gut hormone	**Appetite regulation**	2021
Tirzepatide [Zepbound]	▪ Mimics action of GLP-1/GIP gut hormones	**Appetite regulation**	2023

Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; April 2023. Contrave [package insert]. Brentwood, TN: Currax Pharmaceuticals LLC; November 2021. Xenical [package insert]. Montgomery, AL: H2-Pharma, LLC; November 2022. Qsymia [package insert]. Campbell, CA: VIVUS, Inc.; June 2023. Wegovy [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; July 2023. Phentermine [package insert]. Philadelphia, PA: Lannett Company, Inc.; April 2017. Imcivree [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; November 2023. Zepbound [package insert]. Indianapolis, IN: Eli Lilly and Company; November 2023

26

Setmelanotide: MC4 Receptor Agonist-Orphan Drug

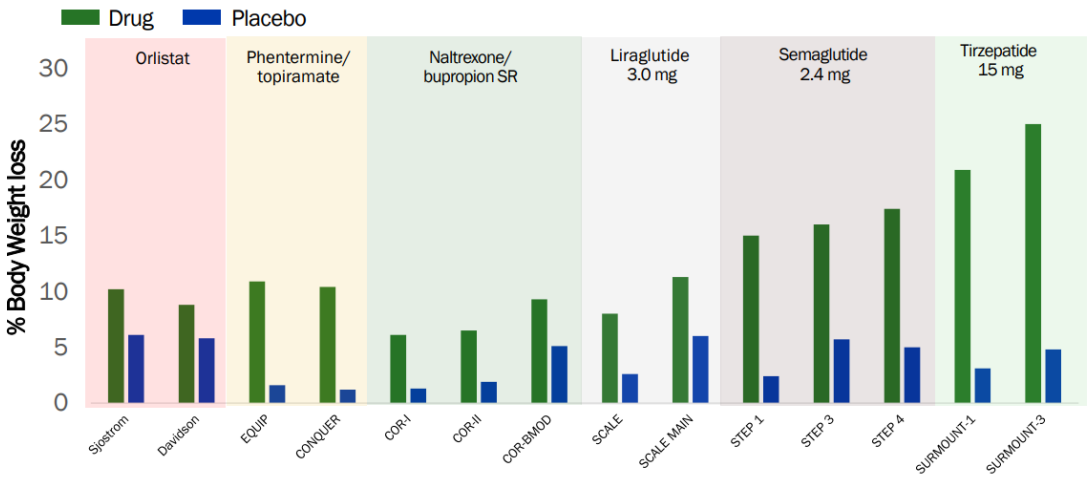
•Daily injection for people affected by rare genetic diseases known as Bardet-Beidl Syndrome or Alstrom Syndrome (Leptin receptor deficiency) and a few others.
•These disorders typically cause early childhood weight gain, diabetes and uncontrollable hunger

- POMC deficiency*
- 8/10 subjects (100%) achieved ≥10% weight loss at 1 y
- Common adverse events
  - Injection site reaction
  - Hyperpigmentation
  - Nausea, vomiting

- LEPR deficiency*
- 5/11 subjects (45%) achieved ≥10% weight loss at 1 year
- Common adverse events
  - Injection site reaction
  - Skin disorders
  - Nausea

27

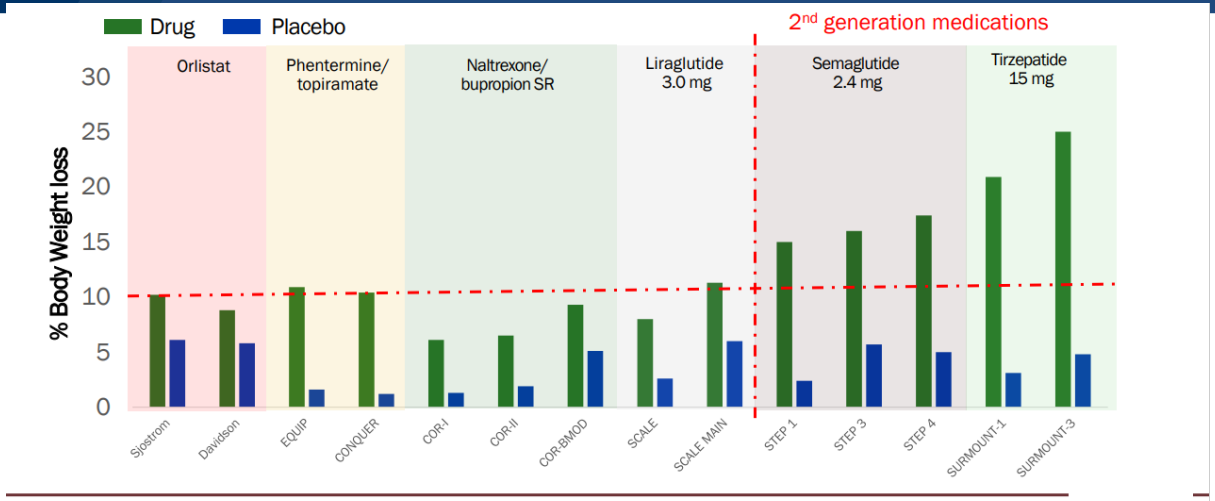
Percent Weight Loss (Drug vs Placebo)



Sjöstrom L, et al. Lancet. 1998;352(9123):167-172; Davidson MH, et al. JAMA. 1999;281(3):235-242; Allison DB, et al. Obesity (Silver Spring). 2012;20(2):330-342; Gadde KM, et al. Lancet. 2011;377(9774):1341-1352; Greenway FL, et al. Lancet. 2010;376(9741):595-605; Apovian CM, et al. Obesity (Silver Spring). 2013;21(5):935-943; Wadden TA, et al. Obesity (Silver Spring). 2011;19(1):110-120; Pi-Sunyer X, et al. N Engl J Med. 2015;373:11-22; Wadden TA, et al. Int J Obes (Lond). 2013;37(11):1443-1451; Wilding JPH, et al. N Engl J Med. 2021;384(11):989-1002; Wadden TA, et al. JAMA. 2021;325(14):140—1413; Rubino D, et al. JAMA. 2021;325(14):1414-1425; Jastreboff AM, et al. N Engl J Med. 2022;387(3):205-216; Wadden TA, et al. Nat Med. 2023;29(11):2909-2918.

28

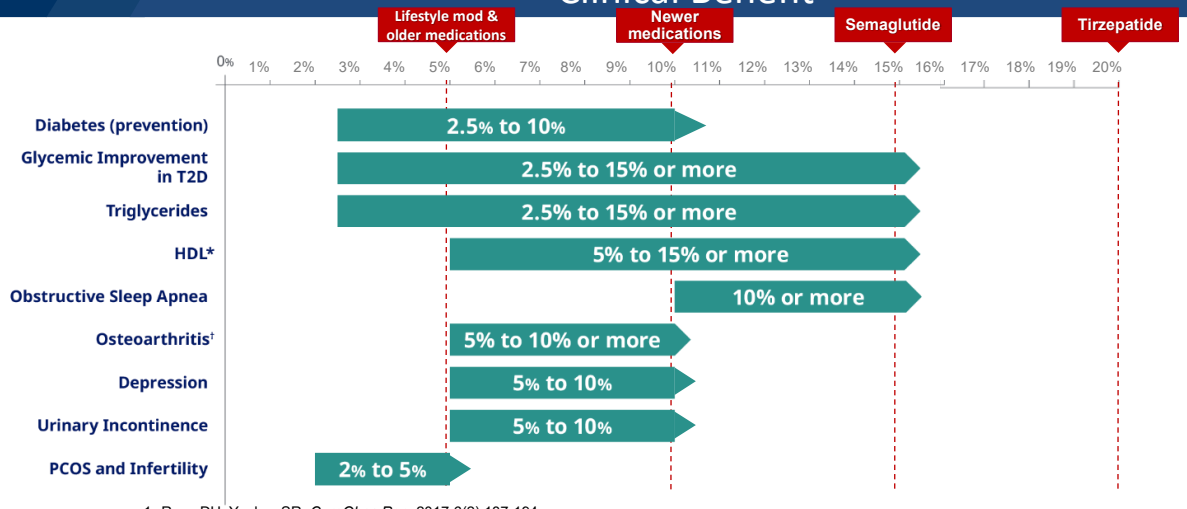
Percent Weight Loss (Drug vs Placebo)



Sjöstrom L, et al. *Lancet*. 1998;352(9123):167-172; Davidson MH, et al. *JAMA*. 1999;281(3):235-242; Allison DB, et al. *Obesity (Silver Spring)*. 2012;20(2):330-342; Gadde KM, et al. *Lancet*. 2011;377(9774):1341-1352; Greenway FL, et al. *Lancet*. 2010;376(9741):595-605; Apovian CM, et al. *Obesity (Silver Spring)*. 2013;21(5):935-943; Wadden TA, et al. *Obesity (Silver Spring)*. 2011;19(1):110-120; Pi-Sunyer X, et al. *N Engl J Med*. 2015;373:11-22; Wadden TA, et al. *Int J Obes (Lond)*. 2013;37(11):1443-1451; Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002; Wadden TA, et al. *JAMA*. 2021;325(14):140–1413; Rubino D, et al. *JAMA*. 2021;325(14):1414-1425; Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216; Wadden TA, et al. *Nat Med*. 2023;29(11):2909-2918.

29

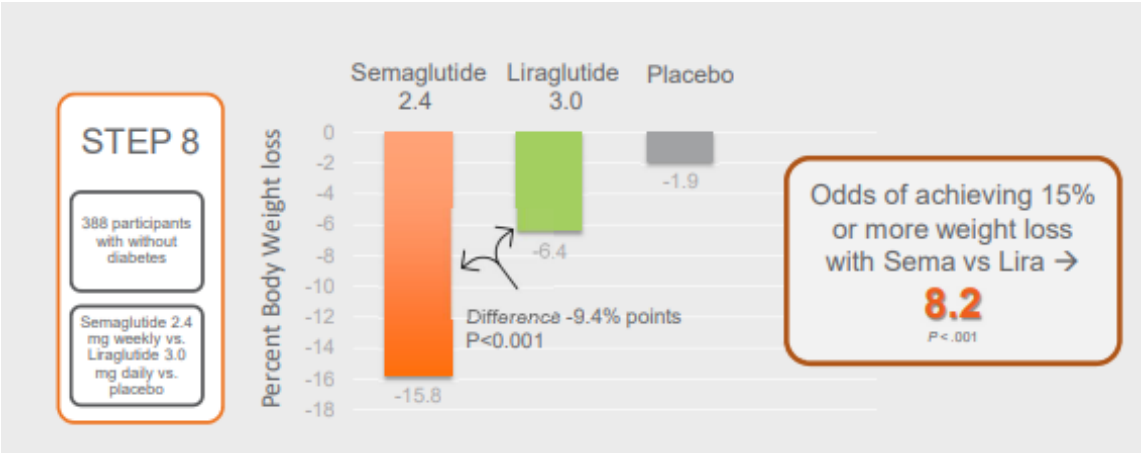
Important: More Weight Loss Provides More Clinical Benefit[2]



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.

30

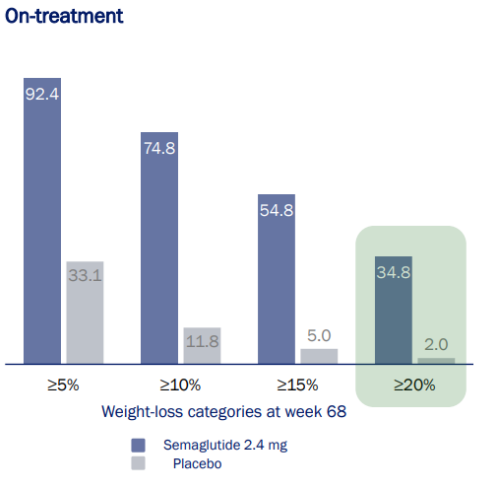
Not All GLP 1 RA Are the Same.. Sema vs Lira



Rubino DM, et al. JAMA. 2022 Jan 11;327(2):138-150

31

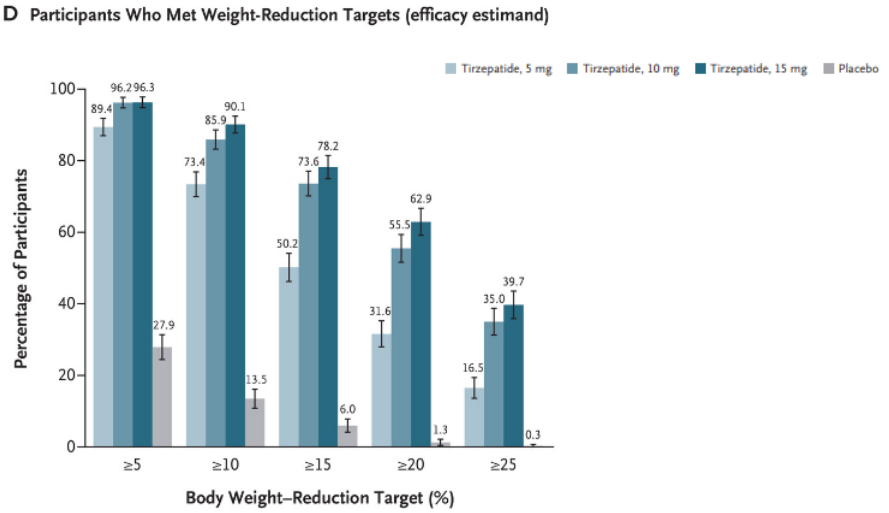
STEP 1 Semaglutide 2.4 mg Categorical Weight Loss



Wilding JPH, et al. N Engl J Med. 2021;384:989-1002

32

SURMOUNT-1 Tirzepatide Categorical Weight Loss



Jastreboff AM, et al. New Engl. J. Med. 2022;387(3):205-216

33

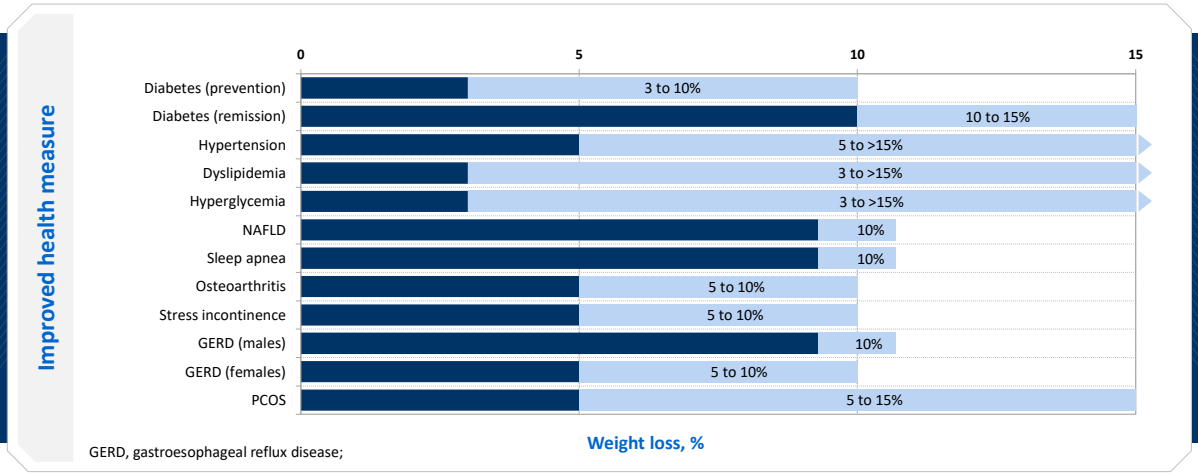
The World Is About to Change….

'A Game Changer': Drug Brings Weight Loss in Patients With Obesity
The New York Times

R&D
The "Medical Bypass": New drugs to strike obesity

34

Small Amounts of Weight Loss Can Lead to Meaningful Health Improvements[1,2]

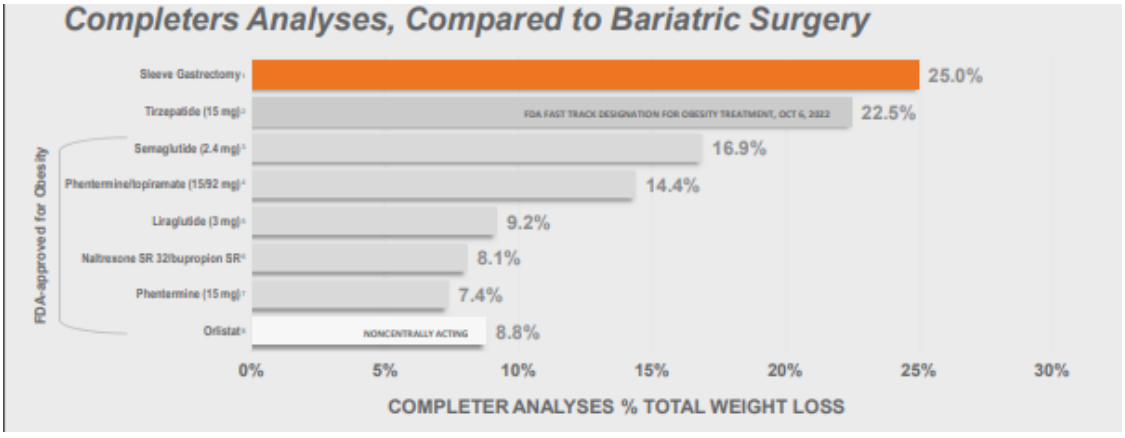


GERD, gastroesophageal reflux disease;

1. Cefalu W, et al. Diabetes Care. 2015;38:1567–1582; 2. Lean MJ, et al. Lancet. 2018;391:541–551.

35

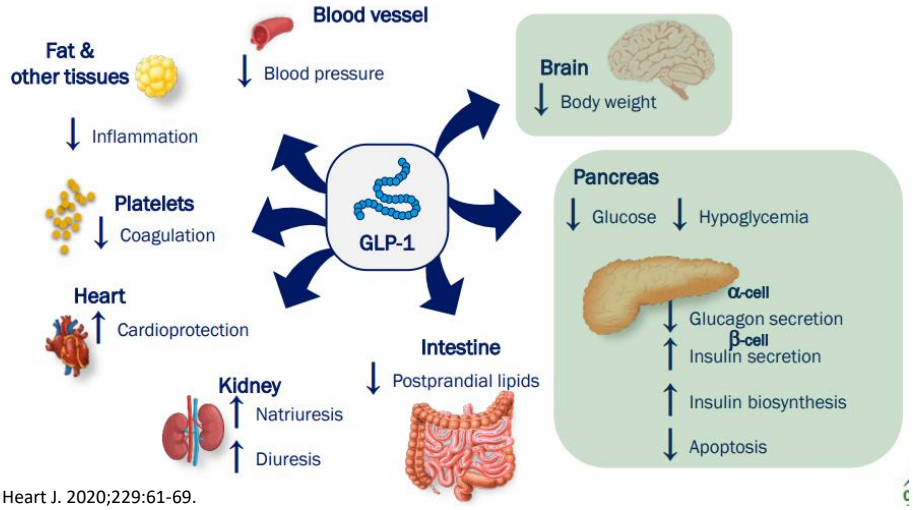
Efficacy Approaching Bariatric Surgery Levels



1. Mechanick JI, Apovian C, et al. *Endocr Pract.* 2019 Dec;25(12):1346-1359.
2. Jastreboff AM, et al. *N Engl J Med.* 2022 Jul 21;387(3):205-216.
3. Wilding JPH, et al. *N Engl J Med.* 2021 Mar 18;384(11):989.
4. Allison DB, et al. EQUIP Trial. *Obesity (Silver Spring).* 2012 Feb;20(2):330-42.
5. Pi-Sunyer X, et al. *N Engl J Med.* 2015 Jul 2;373(1):11-22.
6. Aronne LJ, et al. *Obesity (Silver Spring).* 2013 Nov;21(11):2163-71.
7. Greenway FL, et al. COR-I Trial. *Lancet.* 2010 Aug 21;376(9741):595-605.
8. Finer N, et al. *Int J Obes Relat Metab Disord.* 2000 Mar;24(3):306-13.

36

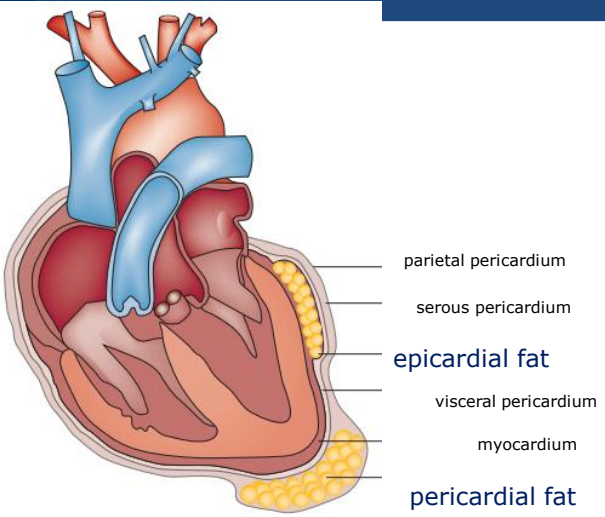
Pleiotropic Effects of GLP-1



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

37

Epicardial Fat Correlation with CV Morbidity



Epicardial fat correlates with and or predicts:

- Heart failure
- Insulin resistance
- The metabolic syndrome
- Atrial fibrillation
- Coronary atherosclerosis
- Fatty liver disease

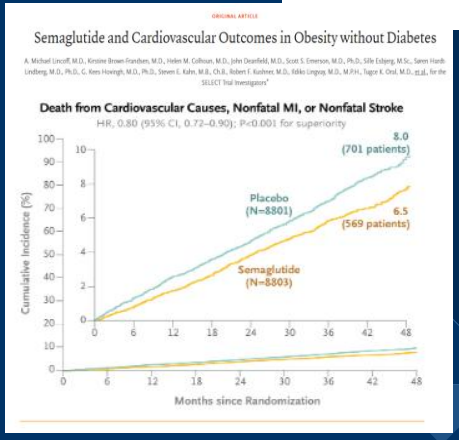
Iacobellis G. NATURE REVIEWS | ENDOCRINOLOGY VOLUME 11 | JUNE 2015

38

For Immediate Release:
March 08, 2024

FDA NEWS RELEASE

FDA Approves First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults with Obesity or Overweight



Beneficial Effects of Semaglutide 2.4mg on Cardiovascular Risk vs. Placebo

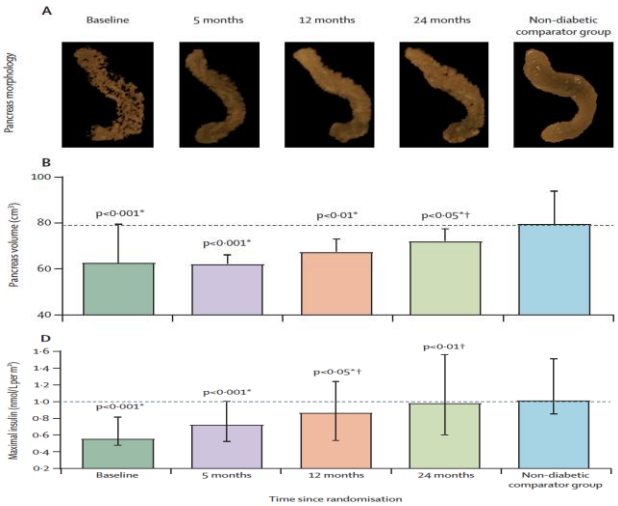
20%
relative risk reduction in MACE-3 events
(statistically significant)

MACE, major adverse cardiovascular events; MI, myocardial infarction

•. Lincoff, et. Al. NEJM 2023 Dec 14;389(24):2221-2232. doi: 10.1056/NEJMoa2307563. Epub 2023 Nov 11.

39

The Effect of Fatty Pancreas on Insulin Secretion (DIRECT Study)



Ahmad Al-Mrabeh Lancet, 2020

40

Tongue Fat and Its Relationship with OSA

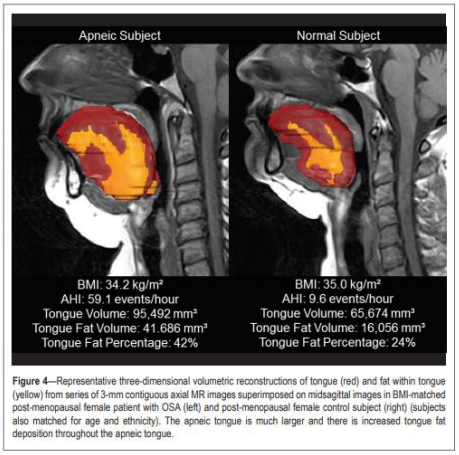


Figure 4—Representative three-dimensional volumetric reconstructions of tongue (red) and fat within tongue (yellow) from series of 3-mm contiguous axial MR images superimposed on midsagittal images in BMI-matched post-menopausal female patient with OSA (left) and post-menopausal female control subject (right) (subjects also matched for age and ethnicity). The apneic tongue is much larger and there is increased tongue fat deposition throughout the apneic tongue.

Tongue Fat and its Relationship to Obstructive Sleep Apnea

Andrew M. Kim, BS[1]; Brendan T. Keenan, MS[1]; Nicholas Jackson, MPH[1]; Eugenia L. Chan, BA[1]; Bethany Staley, RPSGT, CRC[1]; Harish Poptani, PhD[3]; Drew A. Torigian, MD, MA[3]; Allan I. Pack, MBChB, PhD[1,2]; Richard J. Schwab, MD[1,2]

[1]Center for Sleep & Circadian Neurobiology, University of Pennsylvania, Philadelphia, PA; [2]Division of Sleep Medicine, Department of Medicine, University of Pennsylvania, Philadelphia, PA; [3]Department of Radiology, University of Pennsylvania, Philadelphia, PA

Study Objectives: The objective of this study was to determine whether tongue fat is increased in obese sleep apneics compared to obese subjects without sleep apnea. We hypothesized that excess fat is deposited in the tongue in obese patients with sleep apnea.
Design: Case-control design.
Setting: Academic medical center.
Patients: We examined tongue fat in 31 obese controls (apnea-hypopnea index, 4.1 ± 2.7 events/h) and 90 obese apneics (apnea-hypopnea index, 43.2 ± 27.3 events/h). Analyses were repeated in a subsample of 18 gender-, race-, age-, and BMI-matched case-control pairs.
Interventions: All subjects underwent a MRI with three-point Dixon magnetic resonance imaging. We used sophisticated volumetric reconstruction algorithms to study the size and distribution of upper airway fat deposits in the tongue and masseter muscles within apneics and obese controls.
Measurements and Results: The data supported our *a priori* hypotheses that after adjustment for age, BMI, gender, and race, the tongue in apneics was significantly larger (P = 0.001) and had an increased amount of fat (P = 0.002) compared to controls. Similar results were seen in our matched sample. Our data also demonstrate that within the apneic and normal tongue, there are regional differences in fat distribution, with larger fat deposits at the base of the tongue.
Conclusions: There is increased tongue volume and deposition of fat at the base of tongue in apneics compared to controls. Increased tongue fat may begin to explain the relationship between obesity and obstructive sleep apnea.
Keywords: obstructive sleep apnea, tongue fat
Citation: Kim AM, Keenan BT, Jackson N, Chan EL, Staley B, Poptani H, Torigian DA, Pack AI, Schwab RJ. Tongue fat and its relationship to obstructive sleep apnea. *SLEEP* 2014;37(10):1639-1648.

41

ORIGINAL ARTICLE

Effect of Weight Loss on Upper Airway Anatomy and the Apnea–Hypopnea Index

The Importance of Tongue Fat

Stephen H. Wang[1,2*], Brendan T. Keenan[2*], Andrew Wiemken[2], Yinyin Zang[2], Bethany Staley[2], David B. Sarwer[3], Drew A. Torigian[4], Noel Williams[5], Allan I. Pack[2,6], and Richard J. Schwab[2,6]

[1]Albert Einstein College of Medicine, Bronx, New York; [2]Center for Sleep and Circadian Neurobiology, [4]Department of Radiology, [5]Department of Surgery, and [6]Division of Sleep Medicine, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and [3]Center for Obesity Research and Education at the College of Public Health at Temple University, Philadelphia, Pennsylvania

Abstract

Rationale: Obesity is the primary risk factor for obstructive sleep apnea (OSA). Tongue fat is increased in obese persons with OSA, and may explain the relationship between obesity and OSA. Weight loss improves OSA, but the mechanism is unknown.

Objectives: To determine the effect of weight loss on upper airway anatomy in subjects with obesity and OSA. We hypothesized that weight loss would decrease soft tissue volumes and tongue fat, and that these changes would correlate with reductions in apnea–hypopnea index (AHI).

Methods: A total of 67 individuals with obesity and OSA (AHI ⩾ 10 events/h) underwent a sleep study and upper airway and abdominal magnetic resonance imaging before and after a weight loss intervention (intensive lifestyle modification or bariatric surgery). Airway sizes and soft tissue, tongue fat, and abdominal fat volumes were quantified. Associations between weight loss and changes in these structures, and relationships to AHI changes, were examined.

Measurements and Main Results: Weight loss was significantly associated with reductions in tongue fat and pterygoid and total lateral wall volumes. Reductions in tongue fat were strongly correlated with reductions in AHI (Pearson's rho = 0.62, $P < 0.0001$); results remained after controlling for weight loss (Pearson's rho = 0.36, $P = 0.014$). Reduction in tongue fat volume was the primary upper airway mediator of the relationship between weight loss and AHI improvement.

Conclusions: Weight loss reduced volumes of several upper airway soft tissues in subjects with obesity and OSA. Improved AHI with weight loss was mediated by reductions in tongue fat. New treatments that reduce tongue fat should be considered for patients with OSA.

Keywords: obstructive sleep apnea; upper airway; weight loss; apnea–hypopnea index

American Journal of Respiratory and Critical Care Medicine Volume 201 Number 6 | March 15 2020

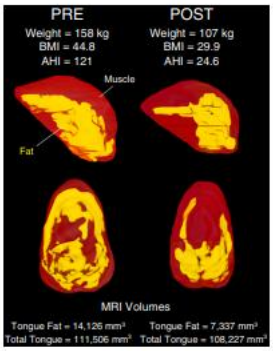


Figure 3. Change in tongue fat volume with weight loss. Three-dimensional reconstruction of tongue (red) and tongue fat (yellow) derived from axial magnetic resonance imaging (MRI; T1-weighted, spin echo, 3-mm slice thickness) and Dixon fat-only MRI (3-mm slice thickness), demonstrating loss of tongue fat between baseline and a 6-month follow-up visit in the same male subject with apnea as shown in Figure 2. The tongue is defined as the genioglossus muscle, and tongue fat is defined as all fat within the genioglossus. AHI = apnea–hypopnea index; BMI = body mass index.

42

HEALTH

FDA approves weight loss drug Zepbound to treat obstructive sleep apnea

UPDATED DECEMBER 22, 2024 · 5:10 PM ET

Juliana Kim

The Food and Drug Administration has authorized the use of Zepbound for adults with obesity and moderate to severe obstructive sleep apnea.
Getty Images/iStockphoto

The weight loss drug Zepbound has become the first prescription medication approved to treat obstructive sleep apnea.

Source NPR.org

Improved Sleep Apnea (OSA)

50.2%

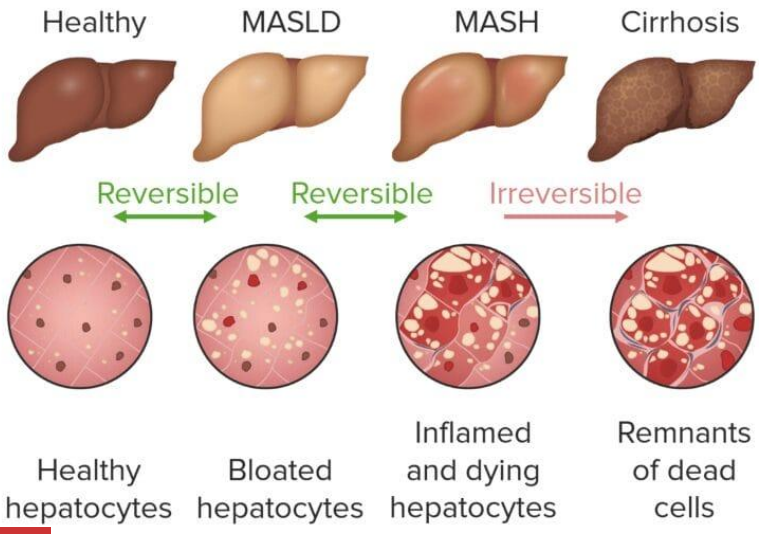
Achieved OSA Disease Resolution

Zepbound significantly reduced the apnea-hypopnea index (AHI) by **25 to 29 events/hour** from baseline in clinical trials.

Malhotra, A, et al. NEJM.2024;391(13); 1193-1205

43

Effect of Fat on the Liver



Elaine Shao, MD; Na Li, MD, PhD
Department of Gastroenterology, Hepatology, and Nutrition
The Ohio State University Wexner Medical Center

44

The New York Times

A Common Weight Loss Drug Can Treat Severe Liver Disease, F.D.A. Says

Wegovy has been approved for use among the growing number of Americans who have MASH.

45

200+ complications are associated with obesity including:

- Type 2 diabetes
- Heart or cardiovascular disease
- Cancer
- Arthritis
- Urinary incontinence
- Infertility
- Depression
- Anxiety

Source: Yuen MM et al. A Systematic Review and Evaluation of Current Evidence Reveals 195 Obesity-Associated Disorders (OBAD). Presented at: Obesity Week 2016; October 31–November 4, 2016; New Orleans, LA. Poster T-P-3166.

46

Obesity Pipeline Has Tripled in Size Over The Last Year

47

Emerging Anti-obesity Pharmacological Therapies: A New Paradigm

Category	Mechanism	Drug	Route	Development Stage	Weight Loss	Weeks
	GLP-1 RA	Semaglutide	SC	Approved '21	15.2%	104
	GLP-1/GIP RA	Tirzepatide	SC	Approved '23	21%	72
	GLP-1 RA	Semaglutide (SNAC)	Oral	Phase 3	17.4%	68
Hormonal	GLP-1 RA and Amylin RA	Cagri Sema	SC	Phase 3	–	–
	GLP-1/Glucagon RA	Survodutide Pemvidutide Cotadtide efinopegdutide	SC	Phase 2	14.9% - - -	46 - - -
	GLP-1/ GIP/Glucagon RA	Retatrutide	SC	Phase 2	24.2%	48
	GLP-1 small molecule RA	Danuglipron Orforglipron	Oral	Phase 2	- 14.7%	- 36
Monoclonal antibody	Activin type II RA	Bimagrumab	SC	Phase 2	–	–

RA, receptor agonist; SC, subcutaneous

Slide courtesy of Robert Kushner, MD

48

The Third Generation Drug Pipeline is Rich and Diverse

There are three ways to reduce weight of a human: (1) cause the human to eat less (appetite suppression), (2) fail to store energy in food as fat or (3) cause the stored energy to be used less efficiently. A final approach to obesity involves no change in weight but instead looks to preserve muscle mass. We count 66 separate drug mechanisms that fall into one of these categories.

Appetite Suppressants (138 Agents)		Energy Storage Blockers (24 agents)	Energy Usage Efficiency (40 agents)	Muscle Preservants (16 agents)
Cannabinoid Agonist	IRS2 modulator	Acarbose	Adenosine A3 Agonist	Activin receptor II inhibitor
DAT Antagonist	Leptin sensitizer	Delta-5-Desaturase	Adipocyte Biology: IL-22	IGF-2 Fusion Protein
Duodenum Masker	MAS/Angiotensin System	GIP inhibitor	Adipogenesis: GPR75	Myostatin inhibitor
GDF15 analogue	Melanocortin 4 Agonist	HDAC11 inhibitor	AMPK activator	SARM
Ghrelin Inverse Agonist	Mucin Enhancer	INHBE Modulator	Apelin Receptor Agonist	Testosterone Replacement
GLP-1 Receptor Agonist	NPYR2 Agonist	Lipase Inhibitors	FGF21 agonist	
GLP-2 Receptor Agonist	Nutrient receptor agonists	LPL Activator	Glucagon RA	
Glucagon Receptor Agonist	PTP1B inhibitor	MGAT2	Inflammation: NLRP3	
Incretin: Amylin Analogue	Psychedelic	Microbiome modulators	IP6K Modulator	
5-HT2A receptor agonist	PYY Agonist	mir-515-5p modulator	Lipolysis Agonists	
GPR40 receptor antagonist	Serotonin 6 Antagonist	Mots-c Modulator	MAP/ERK modulator	
Gut Blocker	Serotonin-2c Agonist	RASP Modulator	mir-22-3p modulator	
IGF-1 Agonist	Taste Receptor: TASR2	SLC13A5 protein inhibitors	Mitochondrial Uncoupler	
		SPTBN1	Nuclear Rec: ERR Agonist	
		VEGF Inhibitor	SCD-1 Inhibitor	
			SHIP1 agonist	
			Sirt1 Activator	
			THRB Agonist	

Source: Stieffel Banking investment analysis

49

Maria: New Era in the Treatment of Obesity

- Maria returns requesting a prescription for “injection obesity medication”
- Family helping her to pay cash for GLP-1RA: For 6 months
- Would we give HTN medications for 6 months and stop?

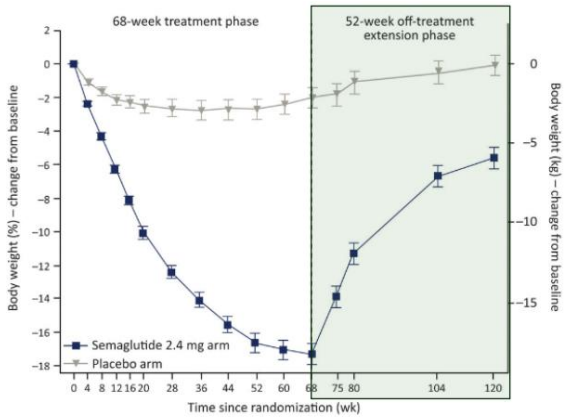
50

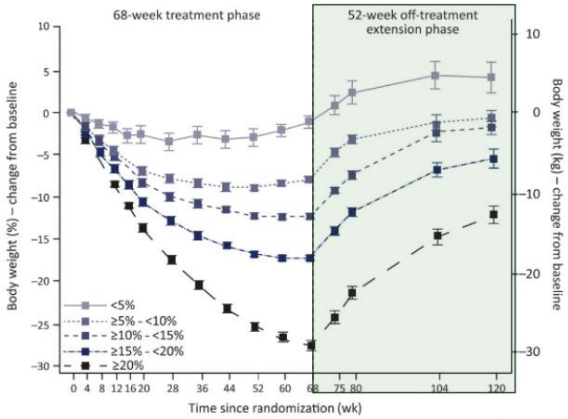
OBESITY: NOT a Description But a Disease

Craig Primack, OMA President 2020

51

The STEP 1 Trial Extension of Semaglutide 2.4 mg

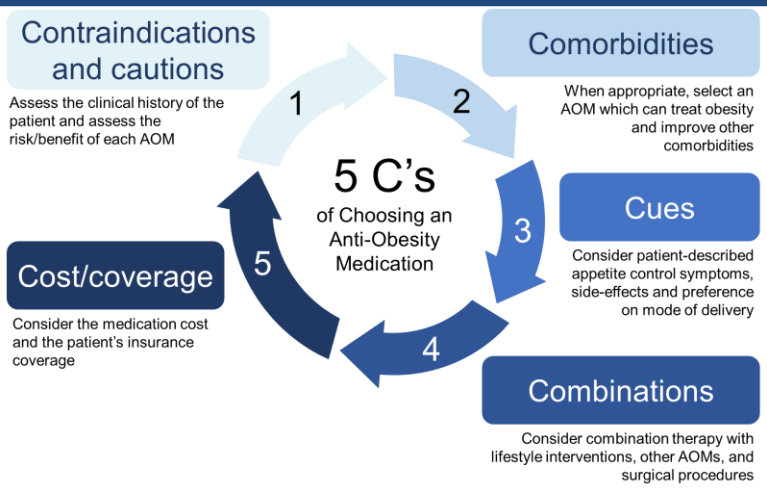




N=327 patients

52

5 C's of Choosing an Anti-obesity Medication



- AOM, anti-obesity medication.

- Deborah B. Horn, Jaime P. Almandoz & Michelle Look (2022) What is clinically relevant weight loss for your patients and how can it be achieved? A narrative review, Postgraduate Medicine, 134:4, 359-375, DOI: 10.1080/00325481.2022.2051366

53

Barriers to Obesity Treatment

- Access to comprehensive obesity care
  - Supply shortages of drug
  - Shortage of HCP to provide care
- Employers who have covered AOM are now removing coverage
- Patients who have been receiving AOM, transition to medicare and no longer have access

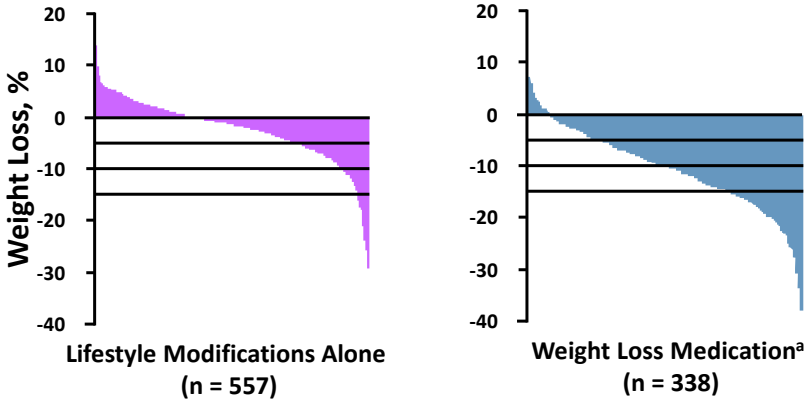
Image by macrovector on Freepik

54

Individual Responses to Weight Loss Medication Vary

- [a] Phentermine/topiramate ER 7.5/46 mg/day.

Vertical bars signify outcomes for individuals who completed a 56-week study



- AACE Obesity Resource Center. http://obesity.aace.com/weight-loss-medications.

55

Change in BW% With or Without IBT Nearly the Same

STEP 1 16.9%
STEP 3 17.6%

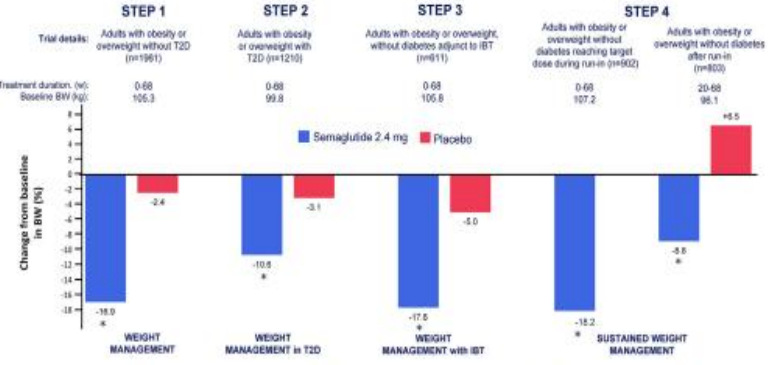


Figure 3: Weight loss in the STEP trials with semaglutide. Data represent the trial product estimand, assuming the medication has been taken as assigned. *Statistically significant vs placebo. BW, body weight; IBT, intensive behavioral therapy. Data are from [84–87].

Drucker, DJ, GLP-1 physiology informs the pharmacotherapy of obesity Molecular Metabolism Volume 57, March 2022,https://doi.org/10.1016/j.molmet.2021.101351

56

Progress

PRESIDENT DONALD J. TRUMP

The WHITE HOUSE

FACT SHEETS

Fact Sheet: President Donald J. Trump Announces Major Developments in Bringing Most-Favored-Nation Pricing to American Patients

The White House | November 6, 2025

ADVANCING MOST-FAVORED-NATION (MFN) PRICING: Today, President Donald J. Trump announced the latest in a series of the most significant actions ever taken by our Federal government to lower prescription drug prices, unveiling agreements with pharmaceutical manufacturers Eli Lilly and Company and Novo Nordisk to dramatically reduce the prices Americans pay for some of the world's most popular drugs.

- Need for OM to be a standard benefit, not a carve out
- Need for adiposity not BMI to be used as an indication for OM and bariatric treatment

57

The Future Is Bright
Obesity As a Treatable Disease

- Like Hypertension
- Like Depression
- When the disease is treatable, the pathophysiologic mechanisms understood, bias and stigma can change

58