OBESITY:
Blame it on the Brain
Supporting the Need for Pharmacologic or Surgical Treatments

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Disclosure

Advisory Board: Boehringer Ingelheim; Currax; Lilly; Novo Nordisk

Consultant: Boehringer Ingelheim; Currax; Lilly; Novo Nordisk

Research Grant: Ethicon Endosurgery

Speaker's Bureau: Lilly; Novo Nordisk

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Objectives

- Identify the multiple influences and physiology of obesity.
- Compare the various treatment options for the morbidly obese patient including pharmacologic and surgical methods.
- Explain the biology of weight loss and why either pharmacologic or surgical interventions are needed for long term success.

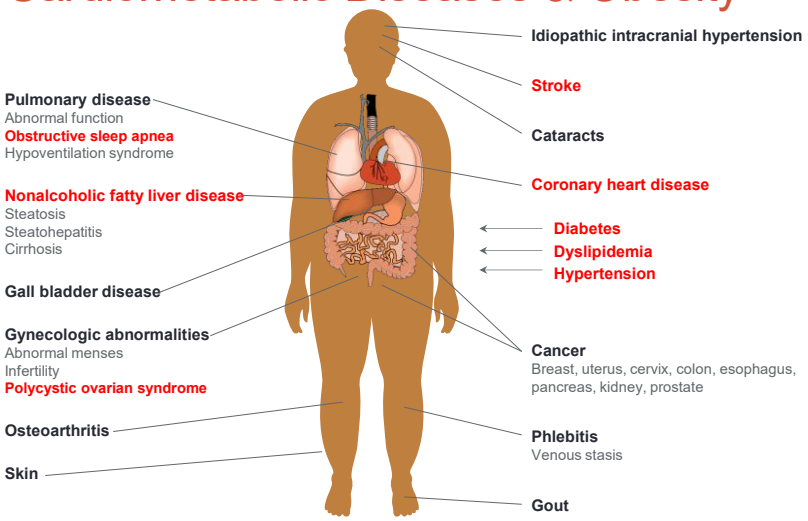
3

We Love to Lay Blame for OBESITY

- On the people with obesity (whom internalize that blame)
- On food companies
- On sugar (or fat, or artificial sweeteners, etc.)
- On urban planners
- **On the BRAIN**

4

Cardiometabolic Diseases & Obesity



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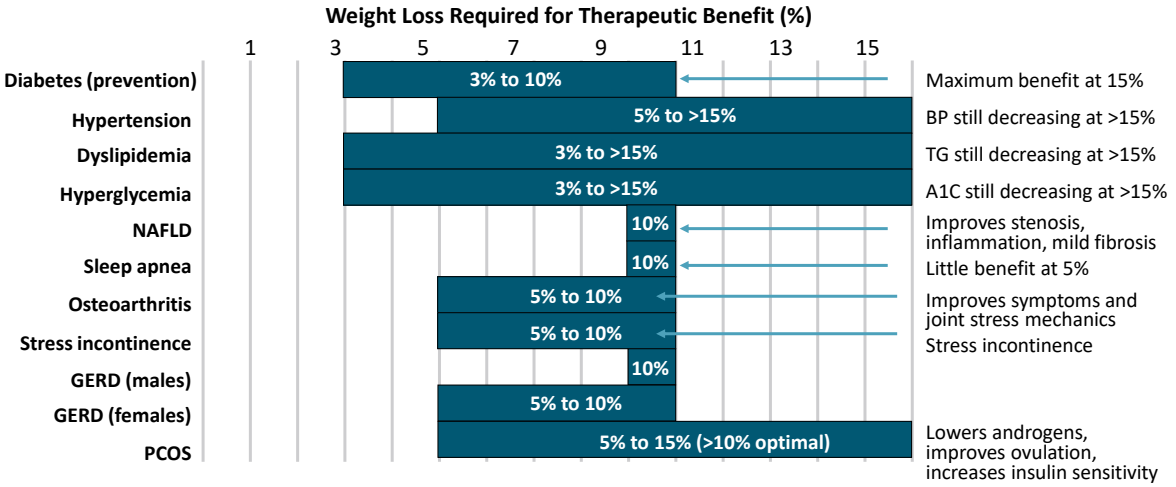
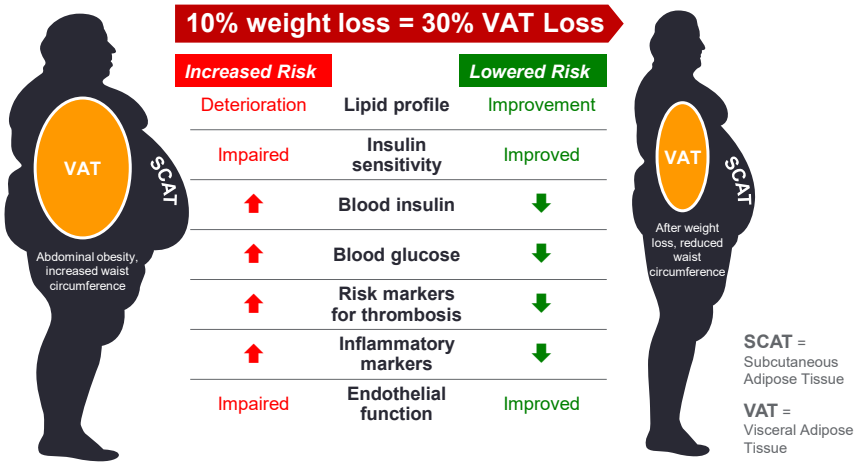
Therapeutic Weight Loss Reduces Complications



Cefalu. Diabetes Care. 2015;38:1567.

6

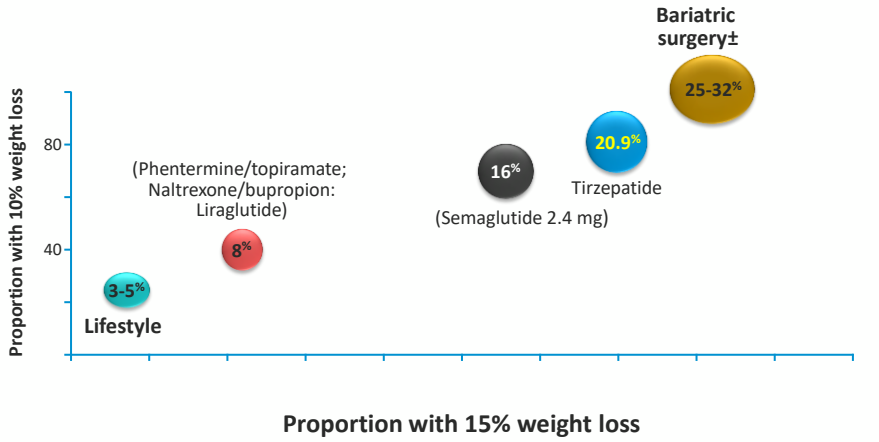
Why Is Modest Weight Loss Beneficial in Cardiometabolic Diseases?



Adapted from: Després J, et al. BMJ. 2001;322:716-720.

7

Efficacy of Existing Obesity Interventions



AoM, anti-obesity medications.
Bubble size represents mean % weight loss

Allison DB, et al. *Obesity*. 2012;20:330-342. [EQUIP]; Gadde KM, et al. *Lancet*. 2011;37:1341-1352. [CONQER]; Greenway FL, et al. *Lancet*. 2010;376:595-605. [COR-I]; Apovian CM, et al. *Obesity*. 2013;21:935-943 [COR-II]; Wadden TA, et al. *Obesity*. 2011;19(1):110-120. [COR-BMOD]; Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22. [SCALE]; Wadden TA, et al. *Int J Obes*. 2013;37:1443-1451. [SCALE MAIN]; Enebo LB, et al. *Lancet*. 2021;397(10286):1736-1748. [Cag + Sema]; Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989. [STEP 1]; Wadden TA, et al. *JAMA*. 2021;325(14):1403-1413. [STEP 3]; Rubino D, et al. *JAMA*. 2021;325(14):1414-1425. [STEP 4]; Ryan D. *Lancet Diabetes Endocrinol*. 2021;9(5):252-254. [STEP]; Sjöström L, et al. *N Engl J Med*. 2007;357:741-52; Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

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Obesity Is a Chronic Disease with a Complex Etiology[1-6]

Possible interrelated factors contributing to obesity:

Physiological[1-3]
- Altered levels of hormones and gastrointestinal peptides
- Altered homeostatic and reward system pathways
- Weight-positive medications
- Health conditions (IR, PCOS, DM, etc.)
- Sleep hygiene/quality

Behavioral[3]
- Physiologic "diet"
- Inactivity/sedentariness
- Emotional factors/ depression
- Lack of sleep
- Smoking cessation

Genetic[4]
- Epigenetics
- Mutations
- Single nucleotide polymorphisms

Environmental[5,6]
- Socioeconomic status
- Access to/affordability of food
- Built/physical environment
- Cultures
- Sociocultural attitudes
- Endocrine-disrupting chemicals

1. Lean MEJ et al. *Int J Obes (Lond)*. 2016;40:622-632. 2. Yu YH et al. *Obes Rev*. 2015;16:234-247.
3. National Heart, Lung, and Blood Institute. 2012.www.nhlbi.nih.gov/health/health-topics/topics/obe/causes#. Accessed July 14, 2016.
4. Moleres A et al. *Curr Obes Rep*. 2013;2:23-31. 5. Sharma AM et al. *Obes Rev*. 2010;11:362-370. 6. Chaput JP et al. *Obes Rev*. 2012;13:681-691.

9

Obesity Is a Complex Disease: Possible Causes

Genetic mutations leading to obesity remain to be elucidated[1,2]

High heritability of body weight as indicated by twin and adoption studies[2]

Multiple gene variations in key metabolic and homeostatic pathways may also contribute to obesity[1]

~5% of obesity cases may be due to single gene variations in[1]:
- *LEP, LEPR, POMC, MC4R*, and *PCSK1*

LEP=leptin; LEPR=leptin receptor; MC4R=melanocortin receptor 4; PCSK1=proprotein convertase subtilisin/kexin type 1; POMC=proopiomelanocortin.

1. Moleres A et al. *Curr Obes Rep*. 2013;2:23-31.
2. Chesi A et al. *Trends Endocrinol Metab*. 2015;26:711-721.

10

Possible Causes of Poor Weight Loss Maintenance

Adherence

One explanation for the poor long-term outcome of weight-loss diets relates to behavior:

Motivation to adhere to restrictive regimens typically diminishes with time

Hypothalamic Injury

Weight loss elicits biological adaptations that promote weight regain:

Specifically, a decline in energy expenditure (adaptive thermogenesis) and an increase in hunger

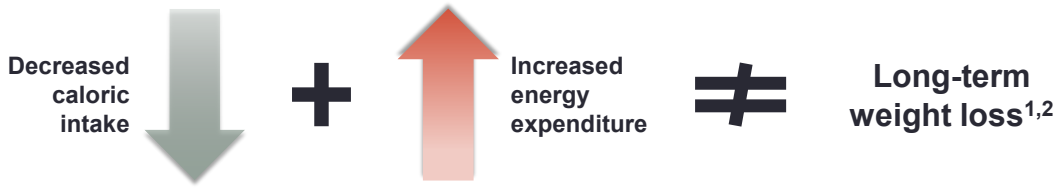
Ebbling CB, et al. JAMA. 2012 Jun 27;307(24):2627-34.

11

Regulation of Food Intake and Body Weight Regulation

12

Counting Calories Is Not Enough to Achieve Long-term Weight Loss



CNS pathways sense changes in weight and body energy stores and **exert opposing effects on energy balance** to promote homeostasis[3]

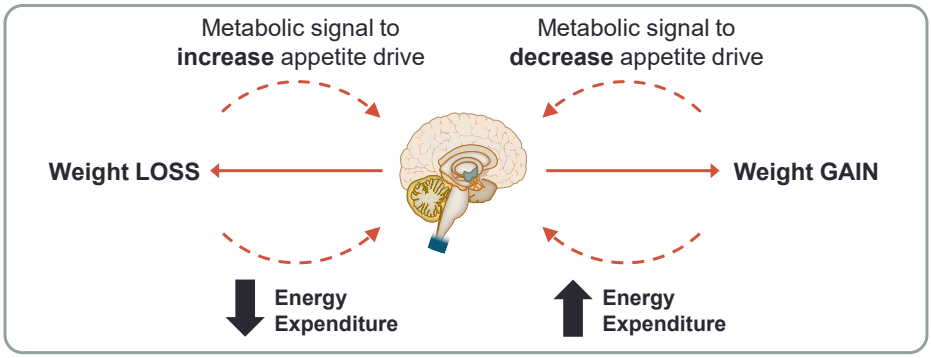
CNS=central nervous system.

1. Chaput JP et al. *Obes Rev*. 2012;13:681-691.
2. National Heart, Lung, and Blood Institute. 2012. www.nhlbi.nih.gov/health/health-topics/topics/obe/causes#. Accessed July 14, 2016.
3. Schwartz MW et al. *Diabetes*. 2003;52:232-238.

13

Homeostatic Regulation of Set Point Body Weight[1]

A homeostatic weight regulatory system prevents deviation from a body weight set point

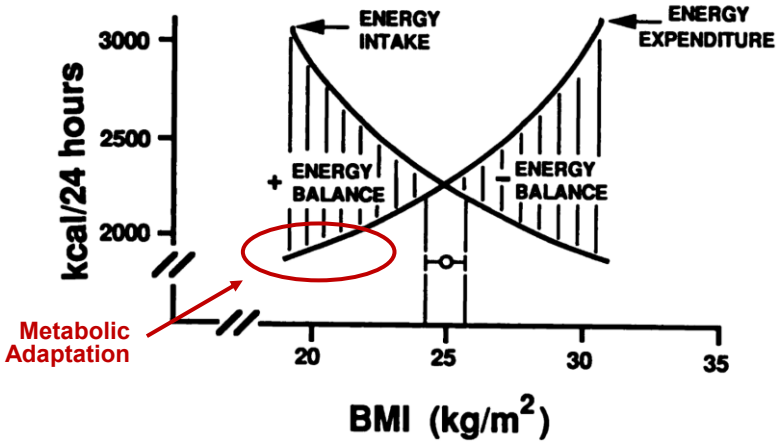


Deviation from this set point elicits a **physiological** compensatory mechanism controlling **food intake** and **energy expenditure**

1. Yu YH et al. *Obes Rev*. 2015;16:234-247.

14

Defense of a Body Fat Storage "Set Point"



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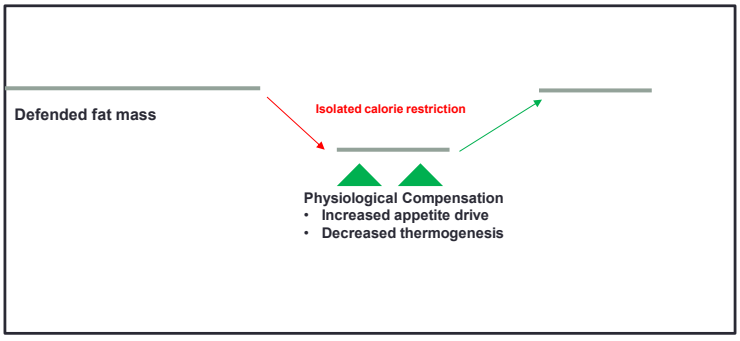
Counter-Physiologic Weight Loss: Caloric Restriction



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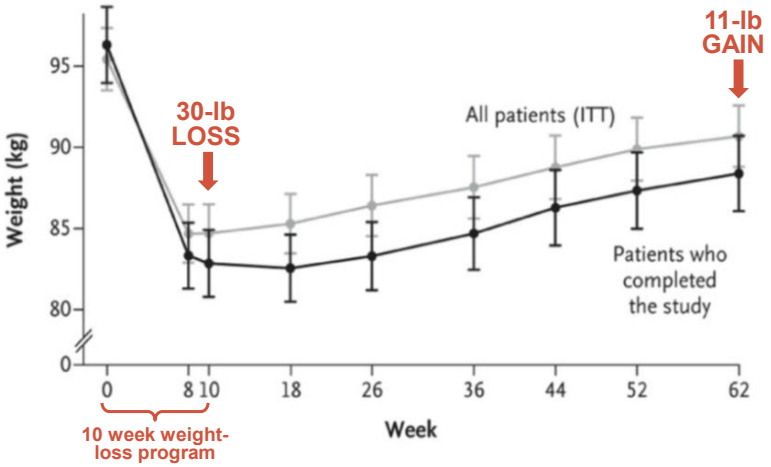
14% Weight Loss Led to Major **Hormonal** Adaptations Which Lasted for 1 Year

Changes in Weight from Baseline to Week 62



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

17

14% Weight Loss Produced Changes in 8 Hormones That Encourage Weight Regain

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

14% Weight Loss *Reduced:*	*Increased:*
• **Leptin - 65%** ↓ - Adipose hormone - Regulates appetite - Control of metabolism & energy homeostasis	• **Ghrelin** - Gastric hormone - Promotes hunger - Fat deposition
	• **Measures of appetite**

10-week, lifestyle-based weight loss intervention in healthy overweight and obese adults (n=34)

Led to sustained elevations in appetite stimulating hormone(s) and decreases in appetite suppressing hormones

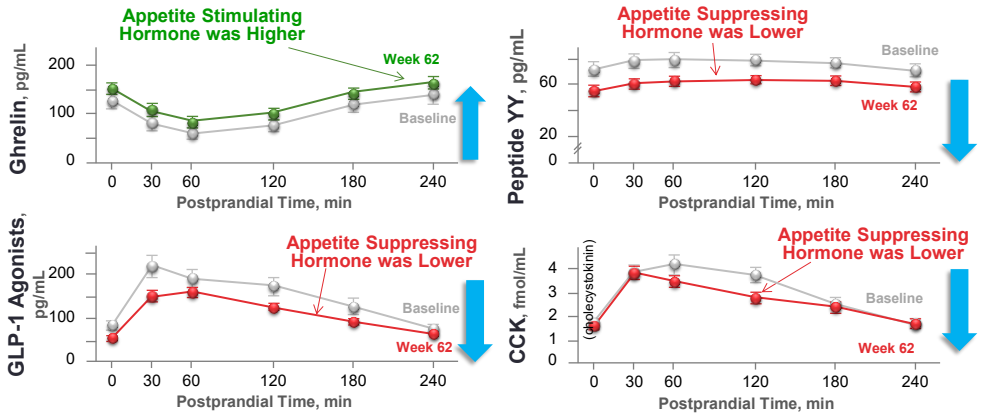
Net result of these hormonal changes is **WEIGHT GAIN**

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

18

Sustained Changes in Peripheral Signals for Up to One Year Following Weight Loss

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



10-week, lifestyle-based weight loss intervention in healthy overweight and obese adults (n=34) led to sustained elevations in appetite stimulating hormone(s) and decreases in appetite suppressing hormones

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

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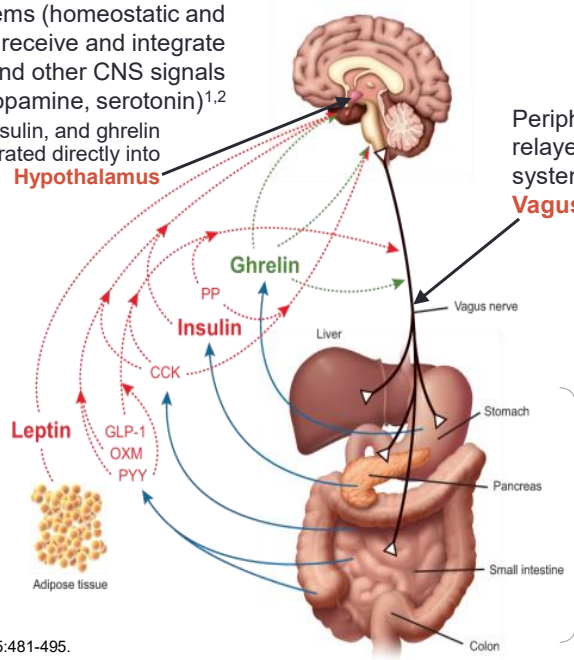
Complex Peripheral Signals are Integrated Into CNS Systems to Regulate Body Weight

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

Leptin, insulin, and ghrelin are integrated directly into **Hypothalamus**

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.

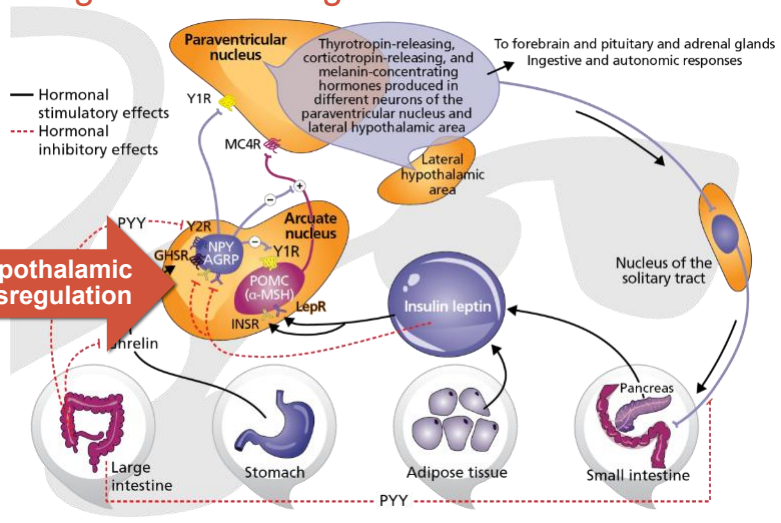
20

Hypothalamic **Dysregulation** Diminishes Signaling to Cortex and NTS, Leading to Greater Weight Gain

When damaged, the brain can't tell how much fat is stored or how much has been eaten

Brain becomes resistant to key hormone, leptin

Hypothalamic dysregulation



AGRP: agouti-related peptide
α-MSH: α-melanocyte-stimulating hormone
GHSR: growth hormone secretagogue receptor
INSR: insulin receptor;
LepR: leptin receptor
MC4R: melanocortin-4 receptor
NPY: neuropeptide Y
POMC: proopiomelanocortin
PYY: peptide YY
Y1R; neuropeptide Y1 receptor
Y2R: neuropeptide Y2 receptor

Apovian CM, Aronne LJ, Bessesen D et al. *J Clin Endocrinol Metab*. 2015;100:342-362.

21

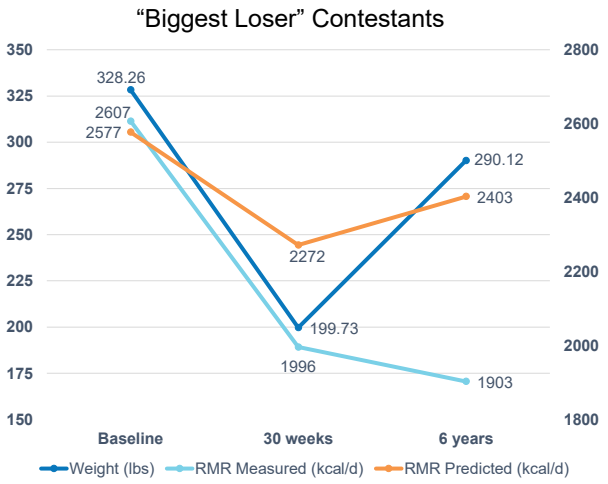
Metabolic Adaptation to Weight Reduction

- Reduction in resting metabolic rate greater than that predicted with weight loss alone
- Associated with degree of reduction in leptin levels greater than the percentage of weight loss alone
- Greater weight loss = greater metabolic adaptation
- Subject to individual variability
- Metabolic adaptation after weight loss has been demonstrated for up to 6 years.

Ravussin, E. and Ryan, D. H. Obesity, 2016. 24: 1607-1608.

22

Resting Metabolic Weight Decreases During Weight Loss and Weight Regain



Fothergill E, et al. Obesity (Silver Spring). 2016 Aug;24(8):1612-9.

N = 14
Competition = 30 weeks

Weight regain was not significantly correlated with metabolic adaptation at the competition's end (r = -0.1, P = 0.75)

Those maintaining greater weight loss at 6 years also experienced greater concurrent metabolic slowing (r = 0.59, P = 0.025)

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EAT LESS
MOVE MORE

24

The major problem – nearly all obesity treatment is not physiologically driven

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IMPLICATIONS FOR OBESITY TREATMENT

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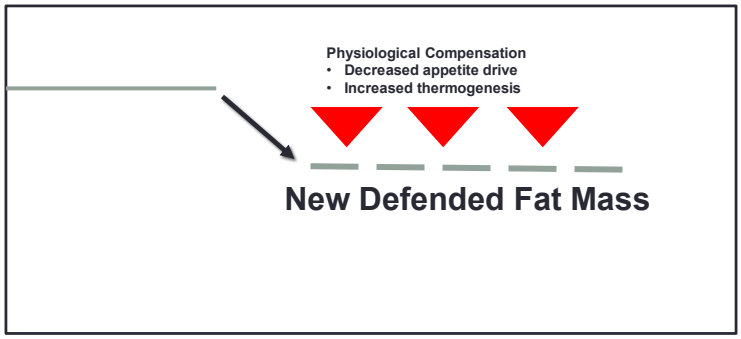
Physiologic Weight Loss:
Targeted Lifestyle Modification, Effective Medications, Surgery



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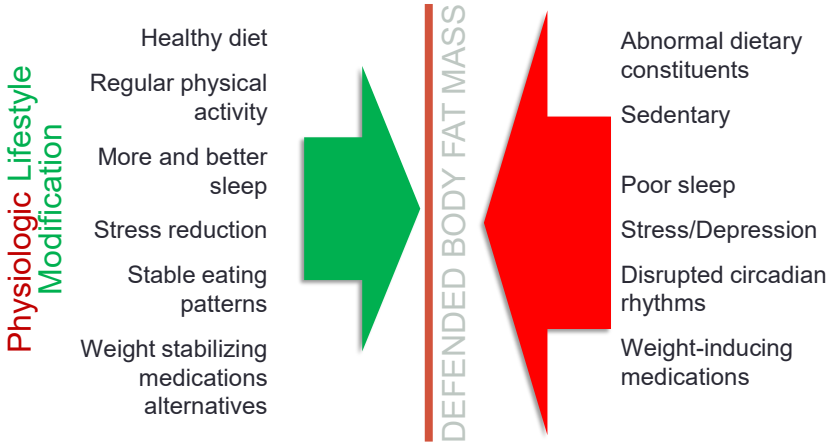
Battle of Physiologic Forces That Influence Fat Mass



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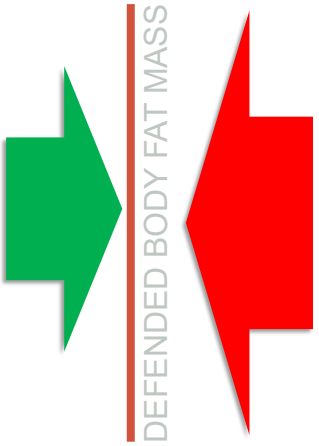
Battle of **Physiologic** Forces That Influence Fat Mass

Anti-Obesity Medications

Phentermine plus topiramate-ER *(3.75 mg/23 mg for 2 weeks, increased to 7.5 mg/46 mg, escalating to a max of 15 mg/92 mg; 1×/d*	Noradrenergic + GABA-receptor activator, kainite /AMPA glutamate receptor inhibitor causing appetite suppression
Bupropion/ naltrexone	Inhibitor of dopamine and noradrenaline reuptake + μ opiate antagonist
Liraglutide 3.0 mg **Sema 2.4 mg**	Glucagon-like peptide 1 (GLP-1) agonist



- Abnormal dietary constituents
- Sedentary
- Poor sleep
- Stress
- Disrupted circadian rhythms
- Weight-inducing drugs

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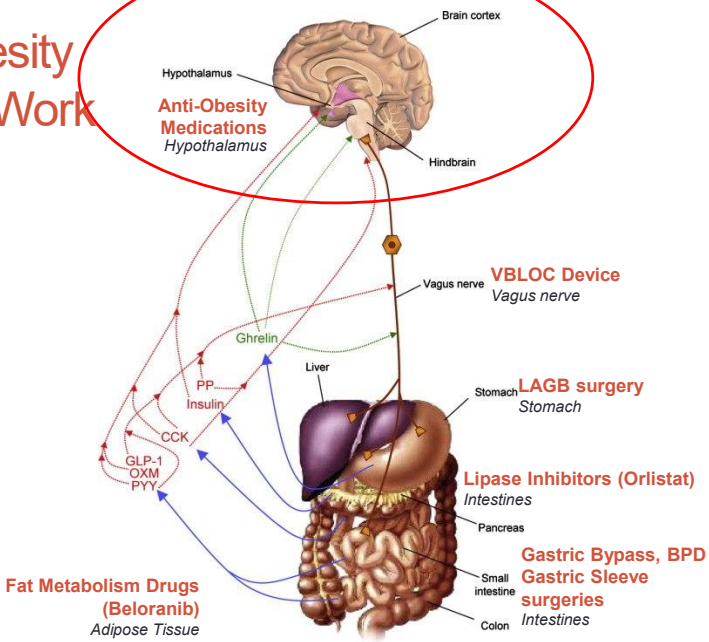
Where Obesity Treatments Work



a Department of Physiology, School of Medicine, University of Santiago de Compostela, San Franscisco s/n, 15782 Santiago de Compostea, A Corun˜a, Spain
b CIBER of Obesity and Nutrition (ISCIII), Spain Received 8 May 2007; revised 6 November 2007; accepted 12 November 2007

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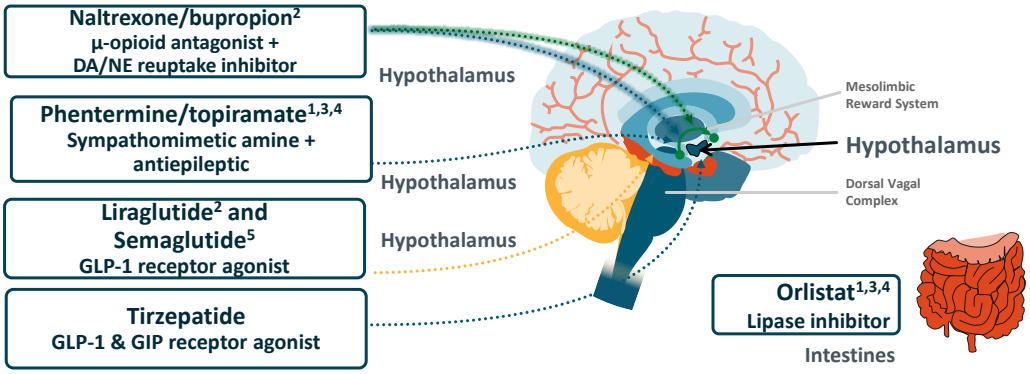
Current Obesity Pharmacotherapy for Long-term Use

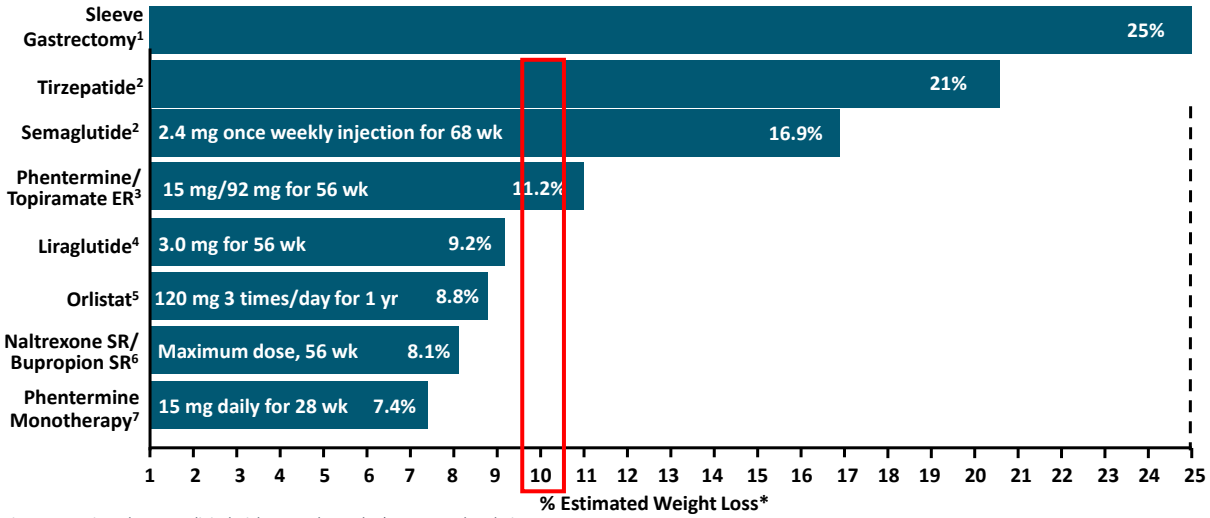
- Multiple pharmacotherapies with varying MoA currently approved in US for long-term treatment of obesity[1-4]



1. Yanovski. JAMA. 2014;311:74. 2. Apovian. J Clin Endocrinol Metab. 2015;100:342. 3. Kim. Clin Pharmacol Ther. 2014;95:53. 4. Dietrich. Nat Rev Drug Discov. 2012;11:675. 5. Christou. Obes Rev. 2019;20:805.

31

Efficacy of Current FDA-Approved Obesity Therapy



Direct comparisons between clinical trials cannot be made. *Per protocol analysis.
1. Mechanick. Endocr Pract. 2019;25(12):1346. 2. Wilding. NEJM. 2021;384:989. 3. Allison. Obesity (Silver Spring). 2012;20:330. 4. Pi-Sunyer. NEJM. 2015;373:11. 7. Finer. Int J Obes Relat Metab Disord. 2000;24:306. 6. Greenway. Lancet. 2010;376:595. 7. Aronne. Obesity (Silver Spring). 2013;21:2163.

Slide credit: clinicaloptions.com

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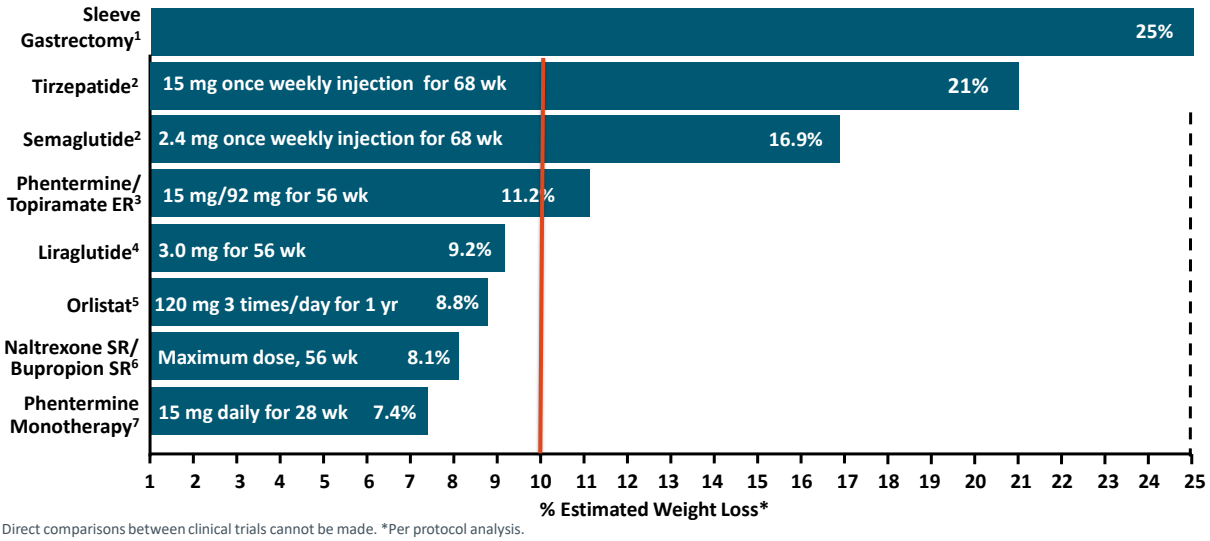
Efficacy of Current FDA-Approved Obesity Therapy



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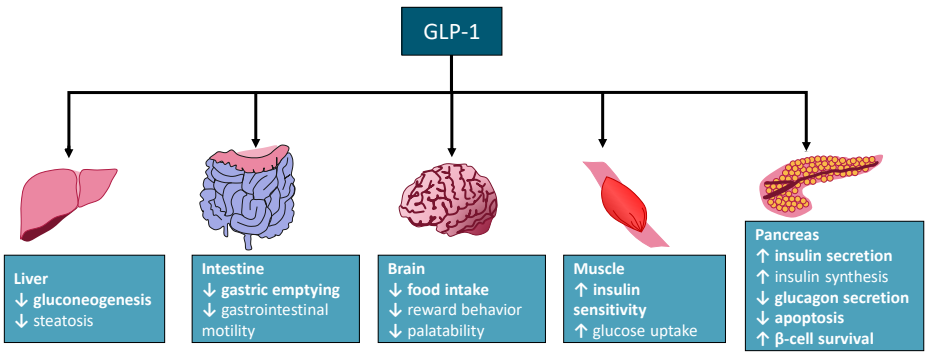
Regulation of Body Weight and Glucose Metabolism by GLP-1 Receptor Agonism



- The specific mechanism of action is multifactorial, with gut, brain, and systemic improvements in insulin sensitivity each contributing a finite fraction to the total efficacy

Müller. Nat Rev Drug Discov. 2022;21:201.

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Semaglutide (2.4 mg): Efficacy vs Placebo

5% Weight Loss	10% Weight Loss	15% Weight Loss	Average Weight Loss:
86.4% vs 31.5%	69.1% vs 12.0%	50.5% vs 4.9%	15.3 kg vs 2.6 kg

Wilding. NEJM. 2021;384:989.

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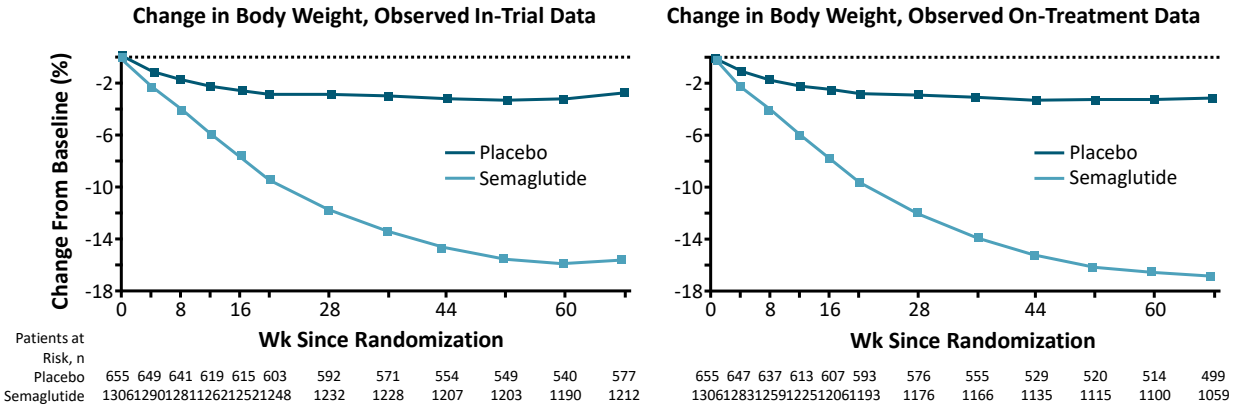
STEP 1 Trial: Body Weight Changes with Semaglutide

- Double-blind, placebo-controlled phase III trial in adults with BMI >30 kg/m^2 without diabetes (N = 1961)



Wilding. NEJM. 2021;384:989.

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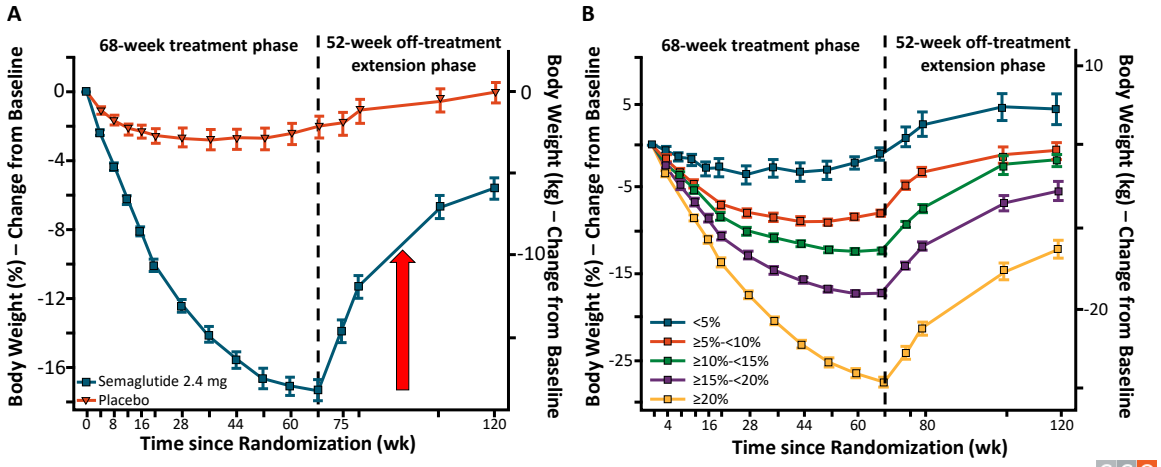
STEP 1 Trial Extension of Semaglutide 2.4 mg: Rational/Need to Treat as a Chronic Disease



Wilding. Diab Obes Metab. 2022:1.

Slide credit: clinicaloptions.com

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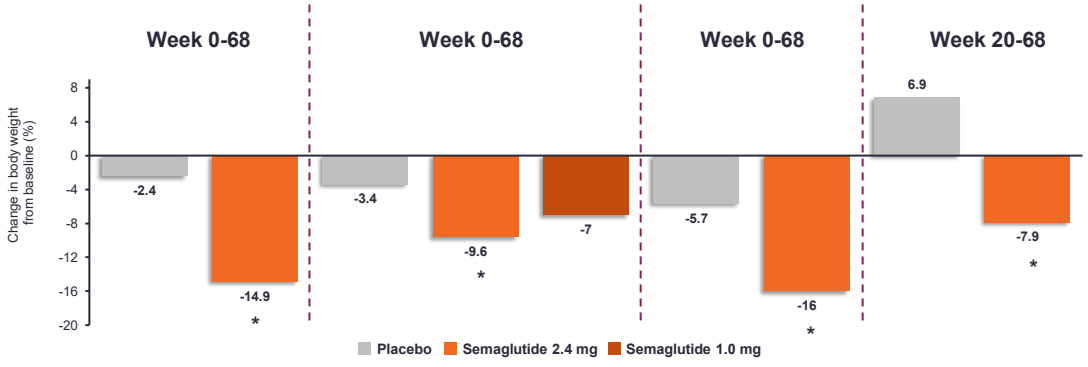
Semaglutide 2.4 mg: Mean Weight Loss (STEP Trials)

	STEP 1[1] N=1961	STEP 2[2] N=1210	STEP 3[3] N=611	STEP 4[4] N=902
	Weight management	Weight management in type 2 diabetes	Weight management with IBT	Sustained weight management*
Baseline BW	105.3 kg	99.8 kg	105.8 kg	96.1 kg



Primary endpoint. *Statistically significant vs placebo.
BW = body weight; IBT = intensive behavioral therapy

1. Wilding JPH et al. *N Engl J Med.* 2021;384(11):989-1002. 2. Davies M et al. *Lancet.* 2021;397(10278):971-84. 3. Wadden TA et al. *JAMA.* 2021;325(14):1403-13. 4. Rubino D et al. *JAMA.* 2021;325(14):1414-25.

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SELECT Trial: Cardiovascular Outcomes, August 2023

Randomised, double-blind, parallel-group, placebo-controlled trial

Semaglutide 2.4 mg **reduced risk of major adverse cardiovascular events (MACE) by 22%** in adults with overweight or obesity

- n = 17,604 adults
- ≥ 45 years
- BMI ≥27 kg/m^2
- with established CVD and no prior history of diabetes

Evaluated subcutaneous once-weekly semaglutide 2.4 mg vs placebo as an adjunct to standard of care for prevention of MACE, over a period of up to five years

https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=166301

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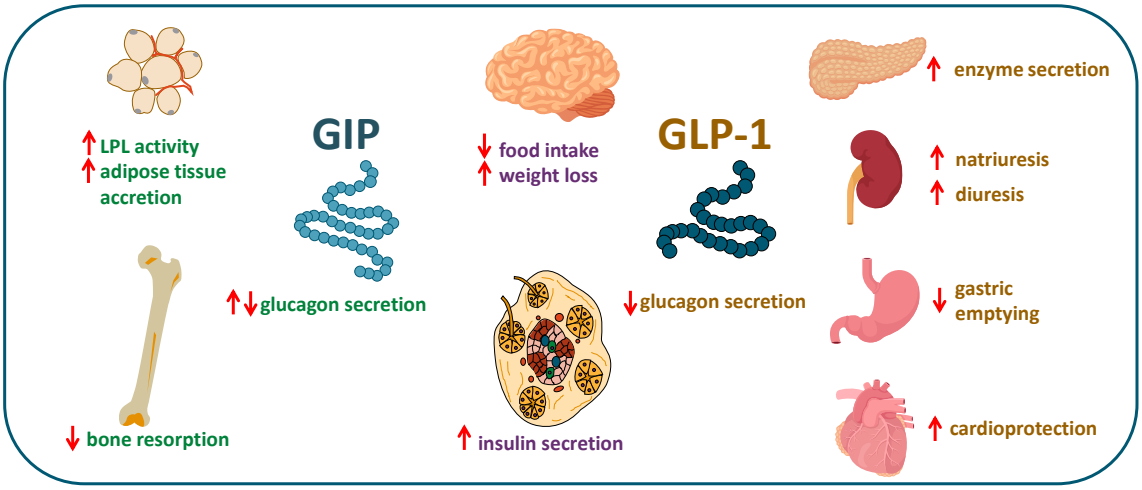
The Evolving GIP–GLP-1 Partnership in Metabolism



Baggio. J Mol Metabolism. 2020;46:101090.

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Tirzepatide: Novel Dual GIP and GLP-1 Receptor Agonist

- Tirzepatide is multifunctional 39 amino acid peptide based on native GIP peptide sequence and modified to bind to GIP or GLP-1 receptors
- Administered as once-weekly injection as half-life of 5 days
  - Starting dose 2.5 mg weekly, titrated at 2.5-mg increments monthly to max dose of 15 mg
- Demonstrated dose-dependent reduction in HbA1c (up to 2.4%) and body weight (up to 11.3 kg) in patients with T2D in phase I and II trials
- Contraindications and AEs similar to GLP-1 RAs
- Contraindications: personal or family history of MTC or MEN2
  - Precautions: pancreatitis, AKI, diabetic retinopathy, gallbladder disease
  - Adverse events: GI including nausea, vomiting, diarrhea, constipation, abdominal pain

Min. Diabetes Ther. 2021;12:143. Coskun. Mol Metab. 2018;18:3. Tirzepatide PI.

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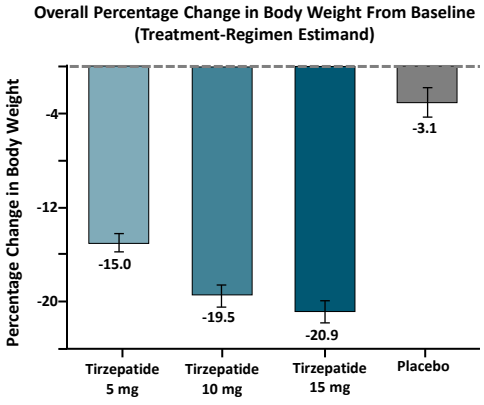
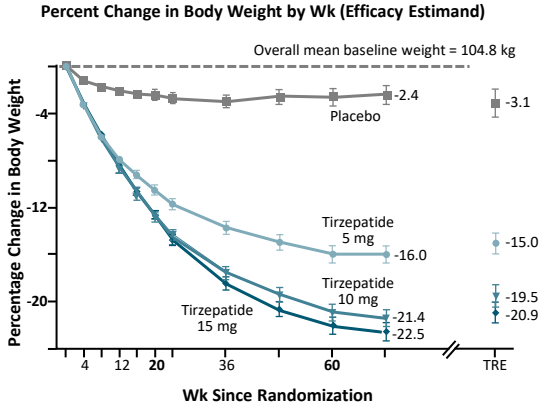
SURMOUNT 1: Weight Loss with Tirzepatide





Jastreboff. NEJM. 2022;387(3):205.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

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ABSTRACT

BACKGROUND

Obstructive sleep apnea is characterized by disordered breathing during sleep and is associated with major cardiovascular complications; excess adiposity is an etiologic risk factor. Tirzepatide may be a potential treatment.

METHODS

We conducted two phase 3, double-blind, randomized, controlled trials involving adults with moderate-to-severe obstructive sleep apnea and obesity. Participants who were not receiving treatment with positive airway pressure (PAP) at baseline were enrolled in trial 1, and those who were receiving PAP therapy at baseline were enrolled in trial 2. The participants were assigned in a 1:1 ratio to receive either the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo for 52 weeks. The primary end point was the change in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) from baseline. Key multiplicity-controlled secondary end points included the percent change in AHI and body weight and changes in hypoxic burden, patient-reported sleep impairment and disturbance, high-sensitivity C-reactive protein (hsCRP) concentration, and systolic blood pressure.

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GLP-1 Receptor Agonists: Side Effects and Precautions

Nausea[a-c]
- Most common side effect
- Diminishes with time in most patients

Pancreatitis[a-c]
- No causal relationship established
- Patients should be aware of symptoms of pancreatitis and stop taking incretin therapy if these symptoms occur
- If pancreatitis is confirmed, incretin treatment should not be restarted
- Consider other therapies in patients with a history of pancreatitis

Impairment of renal function[a-c]
- Some post-marketing reports
- Usually related to volume depletion/dehydration

Medullary thyroid tumors[a,c]
- Thyroid C-cell tumors observed in rodents
- Contraindicated in patients with a personal or family history of medullary thyroid cancer and patients with multiple endocrine neoplasia syndrome type 2 (MEN2)

a. Bydureon® [package insert] 2013[3]; b. Byetta® [package insert] 2013[4]; c. Victoza® [package insert] 2013.[5]

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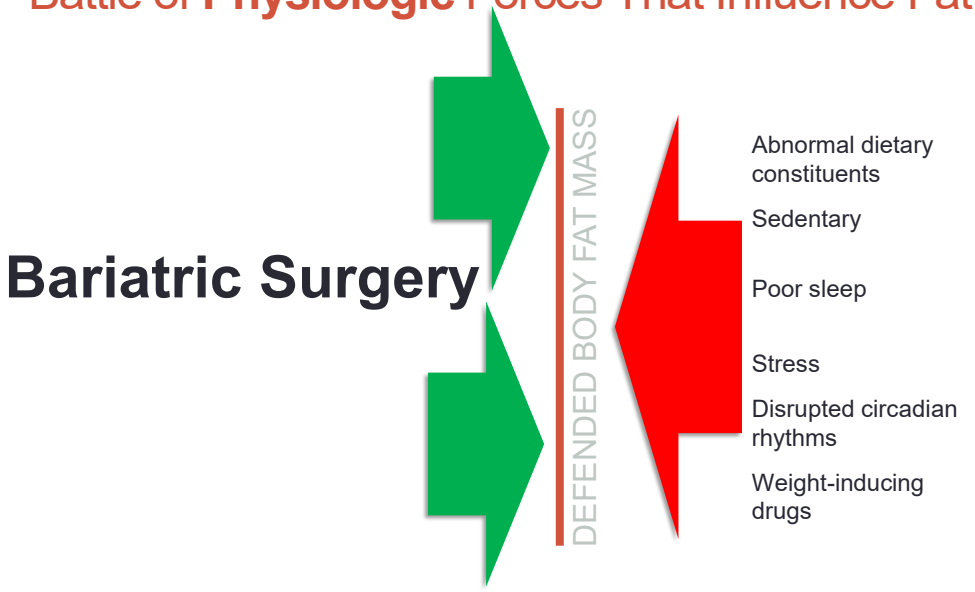
Battle of **Physiologic** Forces That Influence Fat Mass



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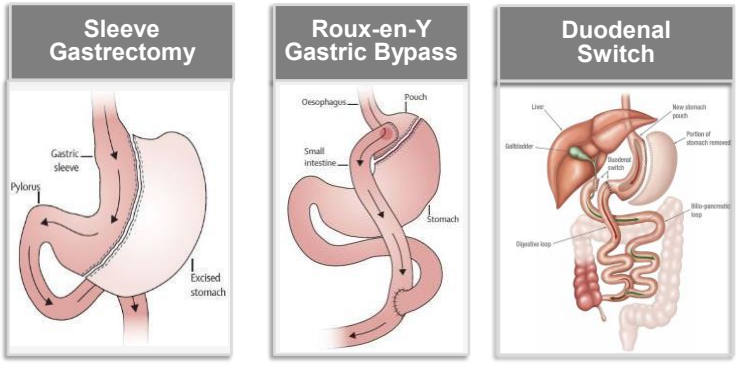
Most Common Bariatric Procedures



98% performed laparoscopically
Average length of stay – 1.2 days

Madsbad S, et al. *Lancet Diabetes Endocrinol*. 2014;2(2):152-64.
ASMBS. Estimate of Bariatric Surgery Numbers, 2011-2017. http://asmbs.org/resources/estimate-of-bariatric-surgery-numbers. Accessed Sept 17, 2018.

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Why Does Bariatric Surgery Work So Well?

Food Intake

- Changes in hunger and fullness via enhanced satiety leading to decrease in calorie intake
- Mean caloric intake 600-700 one month postop to 1000-1800 after first year
- Average reduction of 1800 kcal per day from pre-op intake sustained for several years

Potential Mediators of Decreased Food Intake

- Increased transit of food into mid-gut through gastric pouch

Mediators for Food Preferences

- Taste function domains
- Sensory-discriminative *(stimulus identification)*
- Hedonic *(ingestive motivation) altered brain responsivity to high calorie food cues*
- Physiological *(digestive preparation)*

Hormonal

- GLP-1 and PYY increase
- Ghrelin decreases

Change in Gut Microbiota

- Short chain fatty acids – calorie extraction/signals

Energy Expenditure

- Increase/Decreased basal metabolic rate after bariatric surgery – in gut?

Food Preferences Change

- Dumping syndrome?
- Conditioned food avoidance?

Calorie Malabsorption

- Exclusion of 10% of the bowel after RYGB unlikely to result in malabsorption

Neural

- Vagal and partial vagal transection

Change in Bile Acids

- Partly responsible for intestinal hypertrophy, anorexigenic hormone secretion and alterations in gut microbiota; activation of FXR signaling

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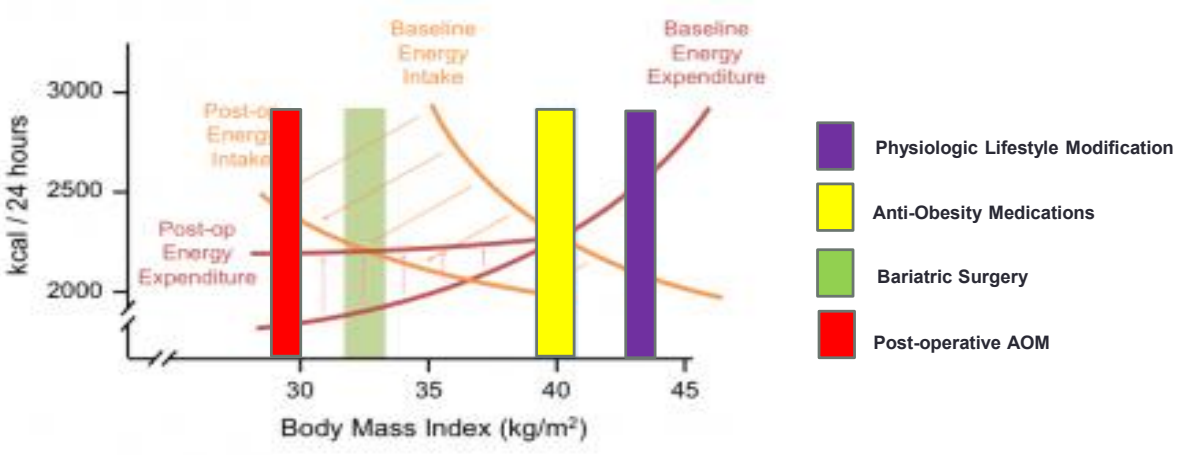
Physiologic Weight Loss:
Physiologic Lifestyle Modification, Effective Medications, Surgery



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Conclusion:

- The disease of obesity is a major driver of cardiometabolic diseases
- A modest weight loss of at least 5-10% does have significant metabolic benefits but greater weight loss → greater benefit.
- Obesity is a dysregulation of energy balance which is a function of the brain
- Physiologic lifestyle Modification, effective AO medications, and bariatric surgery are often required for physiologic compensation to a **NEW DEFENDED FAT MASS**