



DELIVERING **VALUE** SERIES

A New Frontier: The Impact of Anti-Obesity Drugs

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Agenda

- **Presentation**

- **Srividya Kidambi, M.D., MS**, *Associate Professor and Chief, Division of Endocrinology and Molecular Medicine, Froedtert & The Medical College of Wisconsin*

- **Panel**

- **Dr. Kidambi**
- **Kevin Mead**, *Obesity National Account Director, Novo Nordisk, Inc.*

Moderated by **Dave Osterndorf**, *Strategic Consultant, BHCG & Chief Actuary, Centivo*

- **Panel**

- **Sara King, PharmD**, *Senior Manager, Clinical Account Executive, Navitus Health Solutions*
- **Emma Holmi, PharmD**, *Clinical Account Executive, Navitus Health Solutions*

Moderated by **Dave Osterndorf**





Obesity and Weight Management

Vidya Kidambi, MD, MS

Professor & Division Chief

Division of Endocrinology and Molecular Medicine



Objectives

Science of obesity and weight loss

- Implications of obesity on health
- Lifestyle strategies for weight loss
 - Dietary Management
 - Physical Activity
- Medical management of weight loss
- Surgical options

Subsets of patients with obesity

Deranged endocrine and immune responses



Sick Fat Disease (SFD) (Adiposopathy)

Endocrine/metabolic:

- Elevated blood glucose
- Elevated blood pressure
- Dyslipidemia
- Other metabolic diseases

Abnormal and pathologic physical forces



Fat Mass Disease (FMD)

Biomechanical/structural:

- Stress on weight-bearing joints
- Immobility
- Tissue compression (i.e., sleep apnea, gastrointestinal reflux, high blood pressure, etc.)
- Tissue friction (i.e., intertrigo, etc.)

Causes

Primary

- Dietary
- Social and behavioral
 - Economic factors
 - Cost of food
 - Gym Membership
 - Two jobs
 - Binge eating
 - Lack of Sleep
 - Psychological factors
 - Stress
 - Low-self esteem
- Sedentary lifestyle
- Genetic/Family

Secondary

- Medications
- Neuroendocrine causes (hormones)
 - Hypothyroidism
 - Hypothalamic
 - Cushing's syndrome
 - PCOS
 - Hypogonadism
 - GH deficiency
 - Depression
- Genetic
 - Real "genes"
 - Prader-Willi
 - Melanocortin 4 receptor def
 - Bardet-Biedl Syndrome

Drugs causing weight gain

Antidepressants/psychotropic

- SSRI
- Mood Stabilizers
 - Clozapine
 - Lithium
 - Olanzapine
 - Quetiapine
 - Risperidone
- Tricyclics
- Valproic acid, carbamazepine
- Mirtazapine
- Gabapentin
- Pregabalin

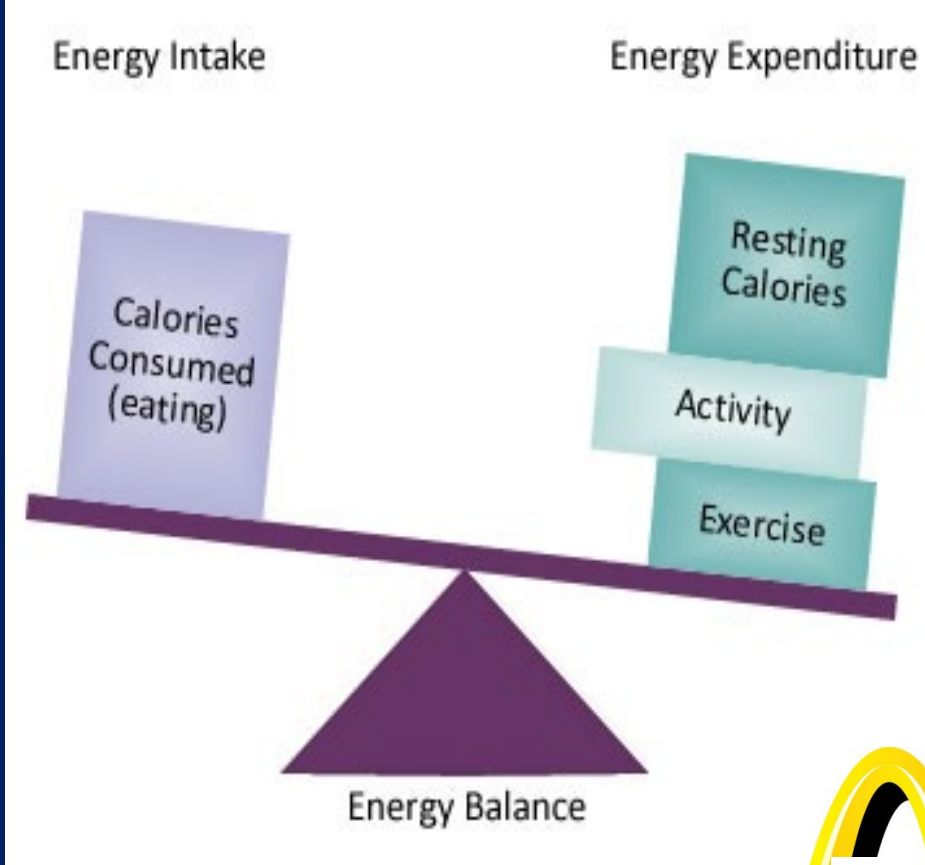
Hypoglycemic agents

- Sulphonylureas
- Meglitinides
- Insulin
- Thiazolidinediones

Others

- Glucocorticoids
- Beta-blockers
- Dihydropyridines
- Anti-histamines
- Estrogens/progestins
- Anti-retrovirals

But in the end...



2017- 2018
estimate of
obesity in the US

~ 42% of adults
~19.3% of youths

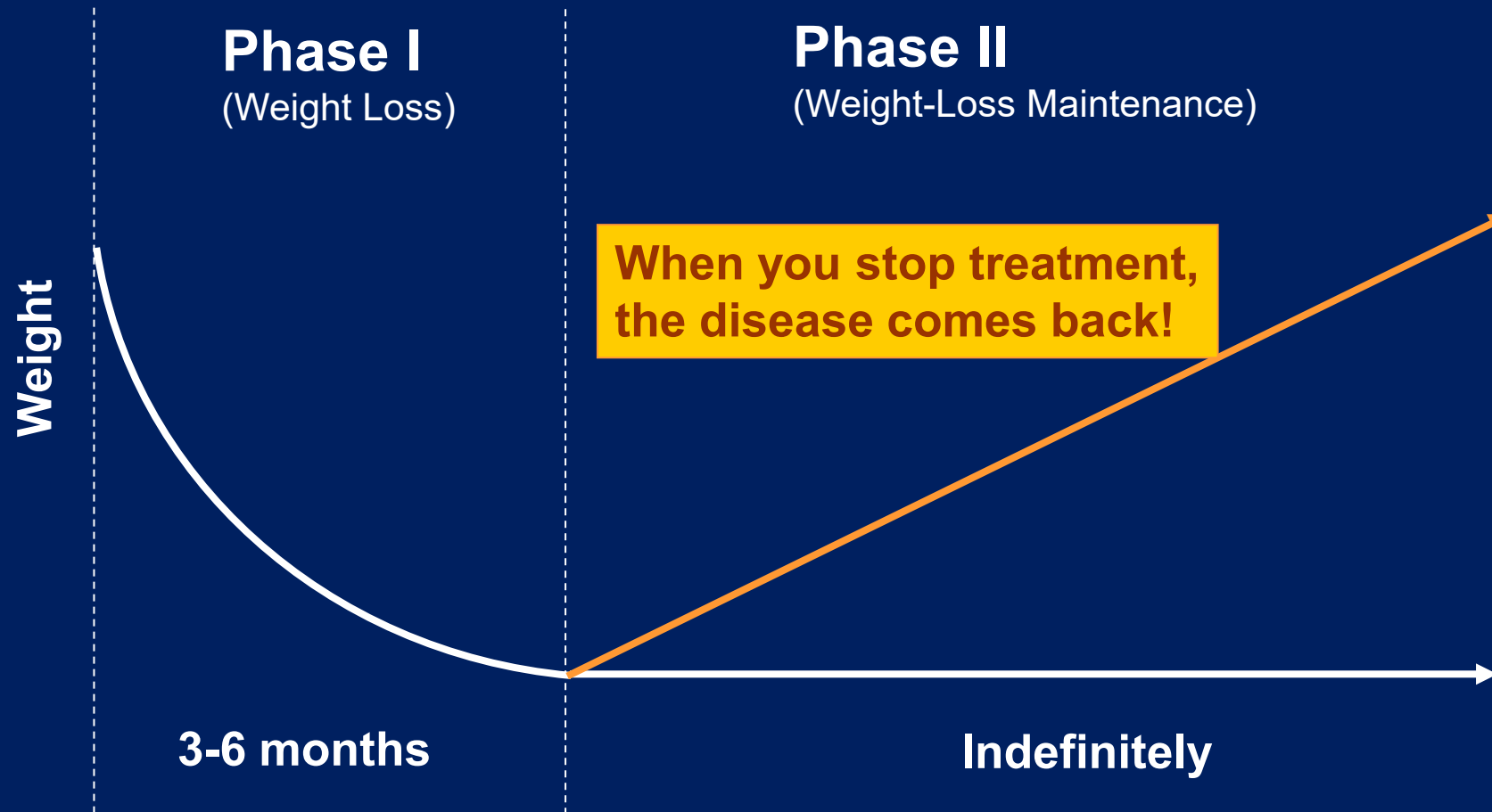


Benefits of treating obesity as a disease: weight reduction results in ...

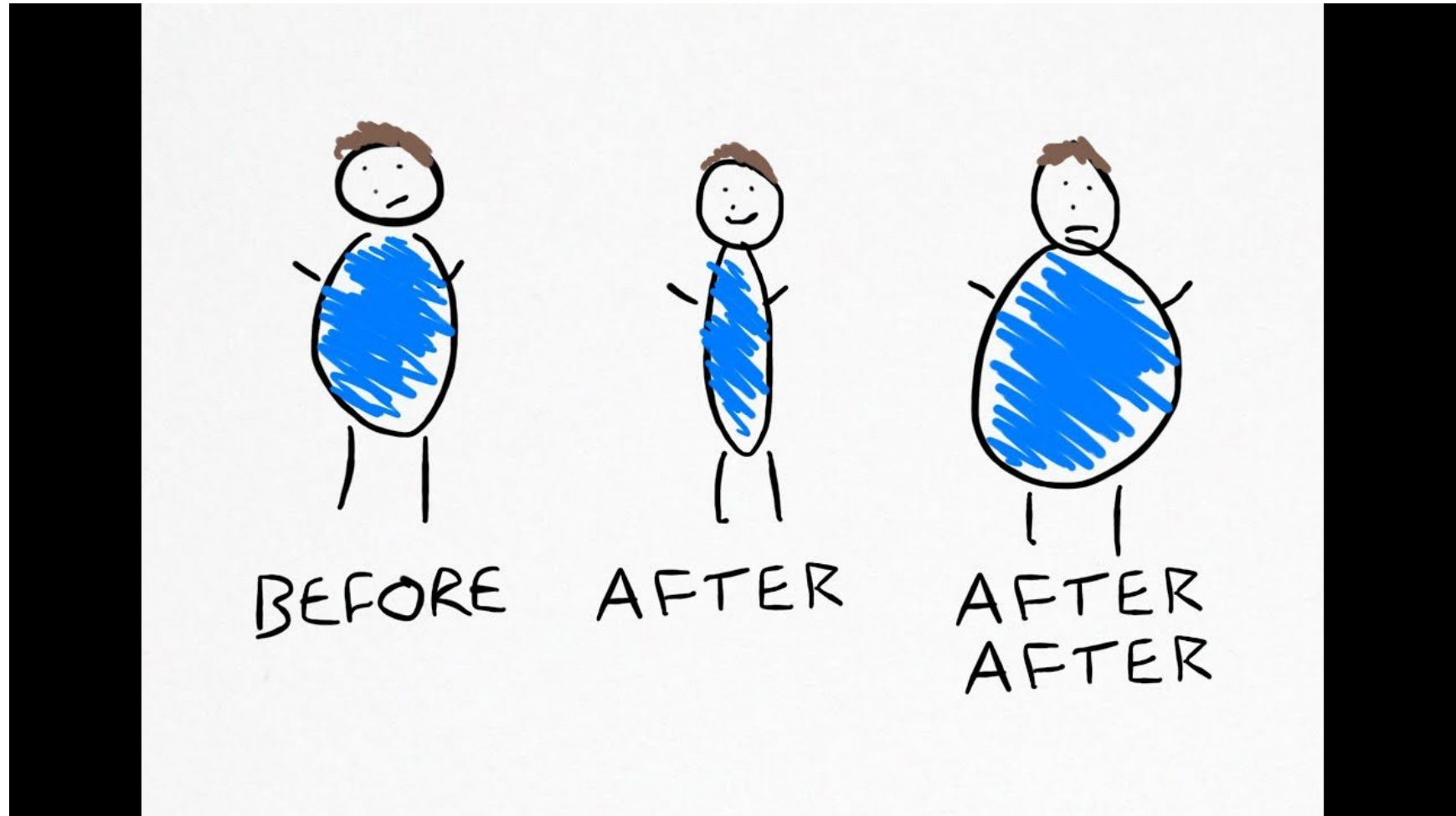
- Improved diabetes control, cholesterol, and blood pressure levels
- Reduced disability and premature mortality
- Improves obstructive sleep apnea and osteoarthritis
- Reduced onset of certain cancers, improved response to cancer treatments, and reduced the onset/recurrence of new cancers
- Improved polycystic ovary syndrome, improved obesity related gynecologic and obstetric disorders
- Improved testosterone levels in men with low testosterone levels
- Improve quality of life, improved body image, and improved symptoms of some psychiatric disorders



Phases of Obesity Treatment

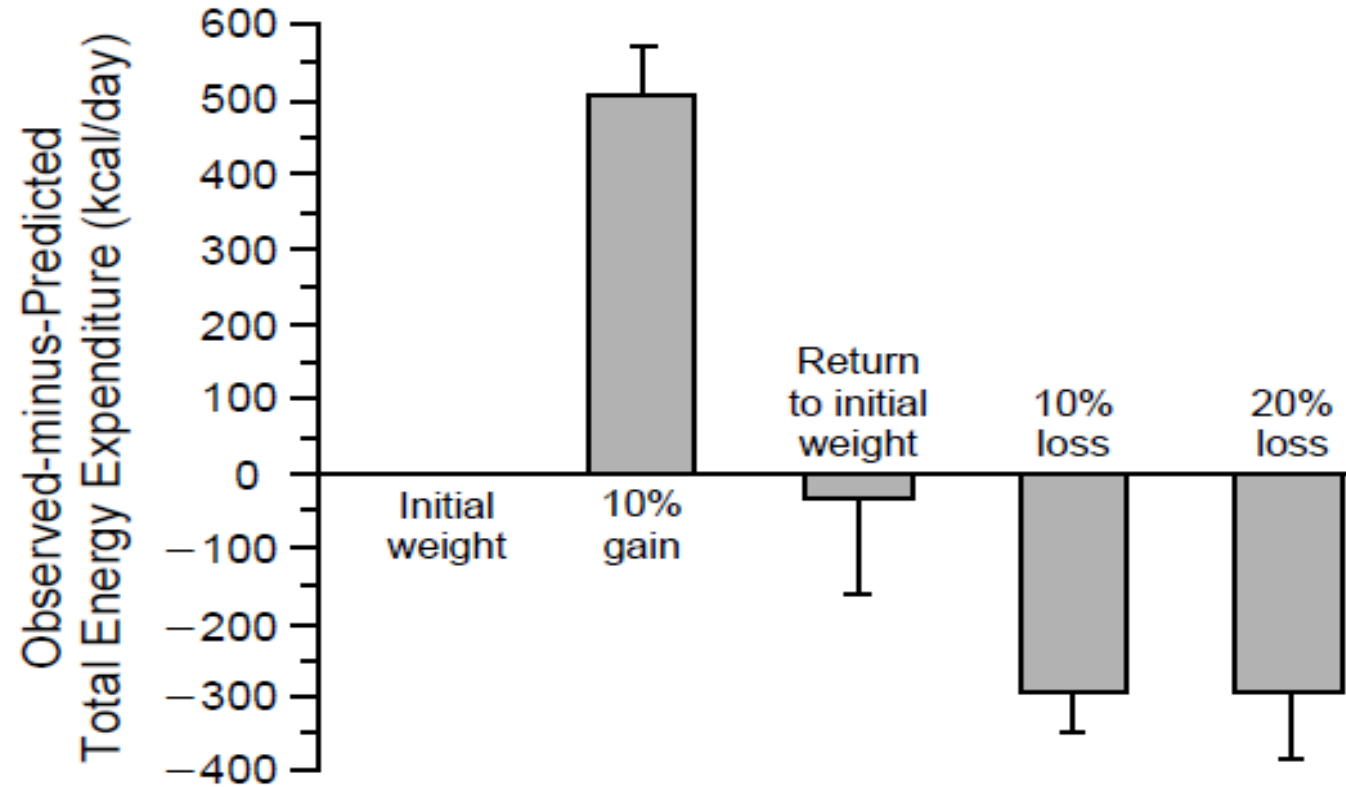


Metabolic adaptation



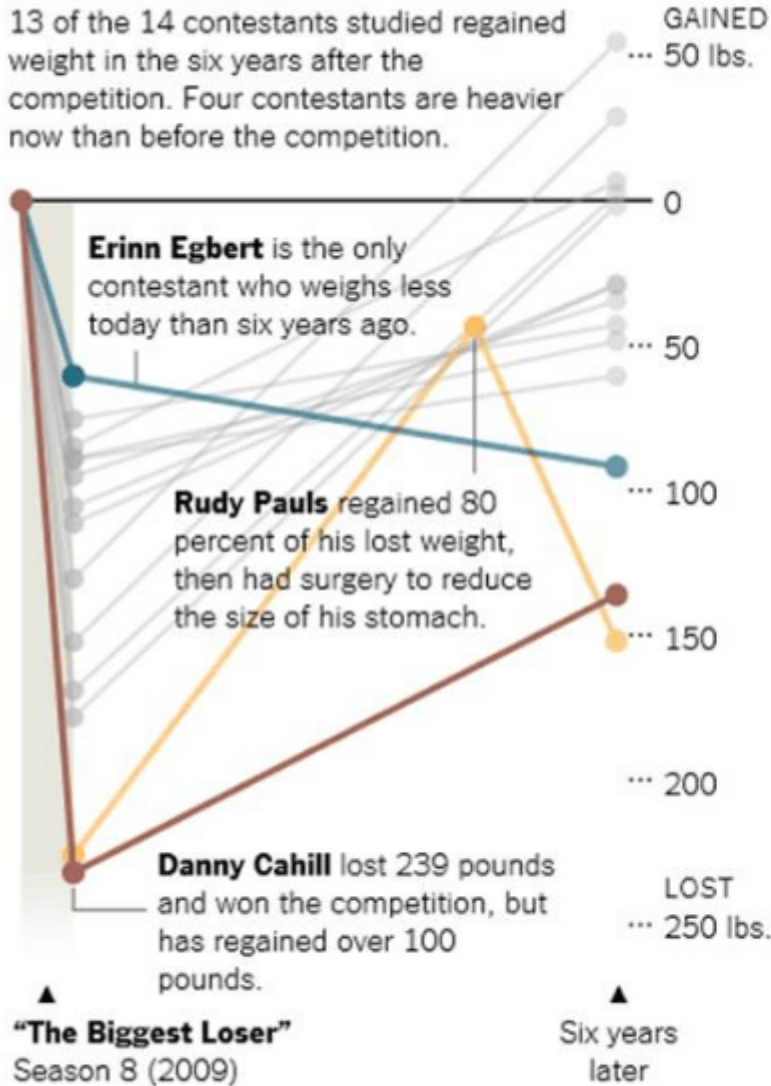
Do I have it?

Decrease in energy expenditure with weight loss



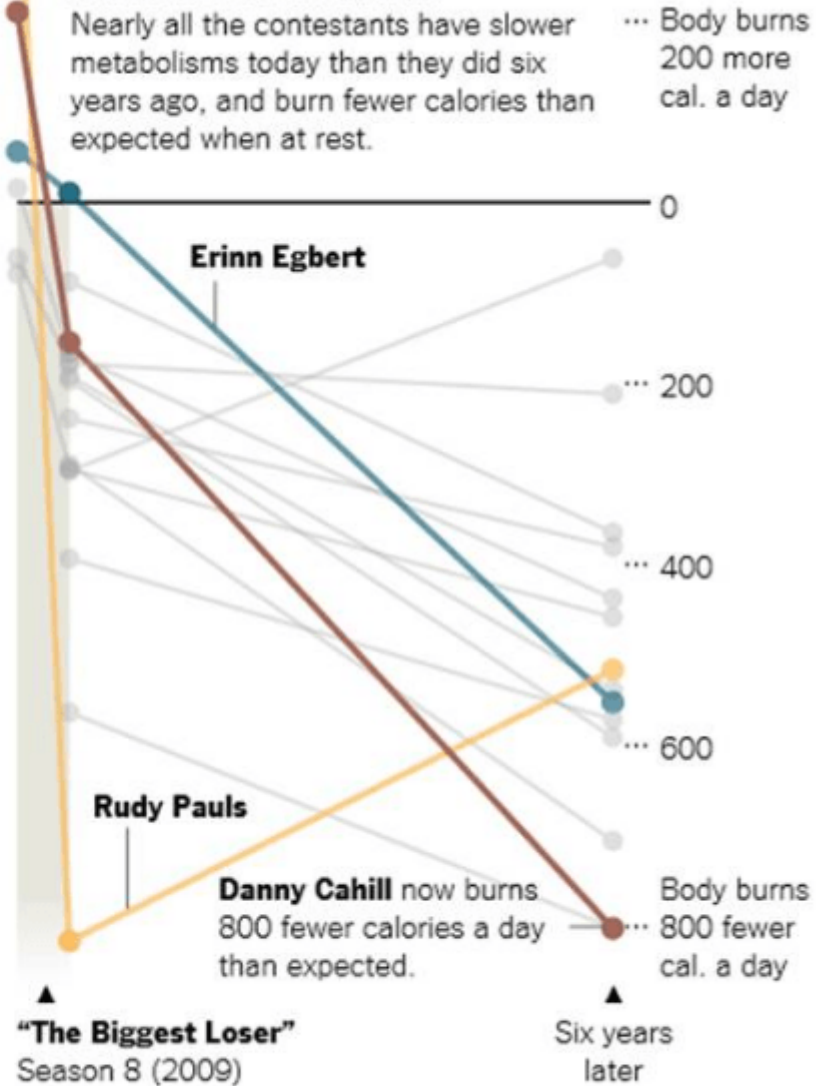
REGAINING LOST WEIGHT

13 of the 14 contestants studied regained weight in the six years after the competition. Four contestants are heavier now than before the competition.



A SLOWING METABOLISM

Nearly all the contestants have slower metabolisms today than they did six years ago, and burn fewer calories than expected when at rest.



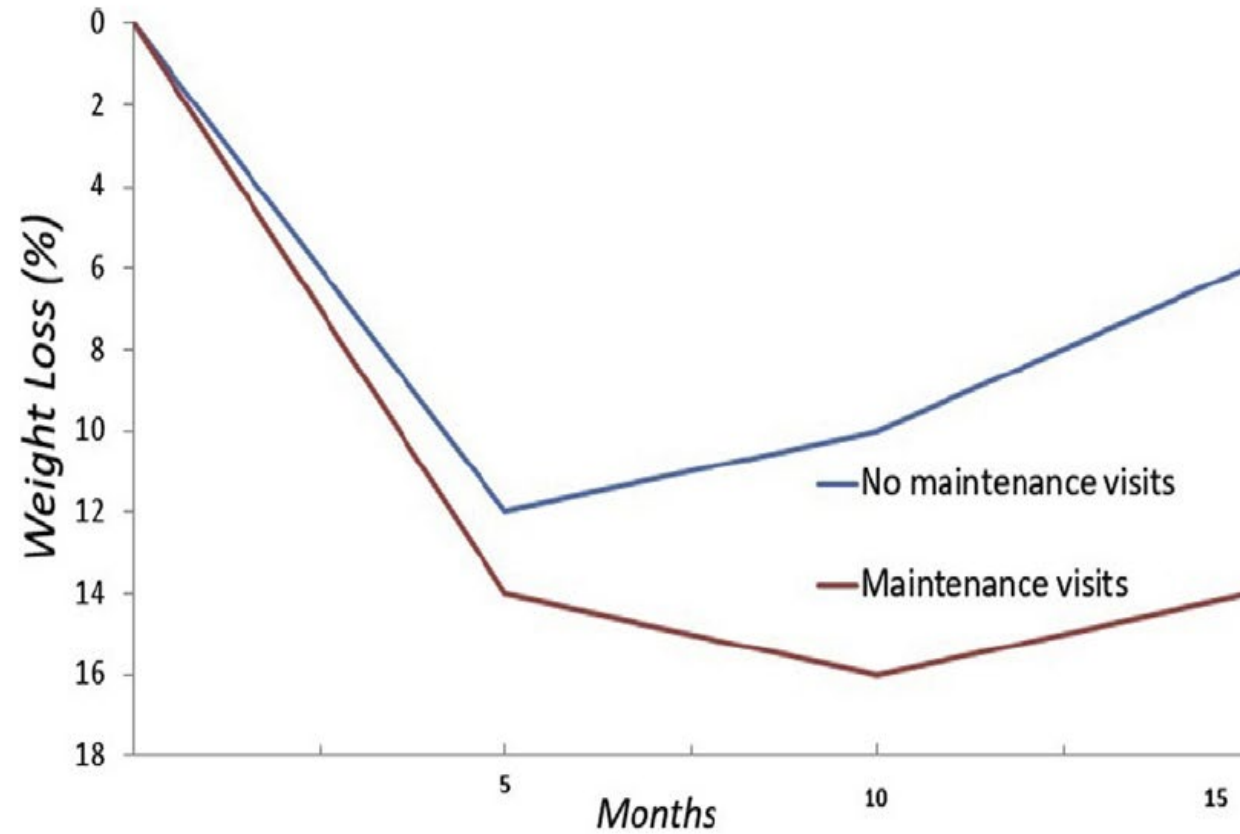
Sources: Obesity; individual contestants

By The New York Times

Physiological changes after diet-induced weight loss

Increase energy storage
↓ Energy expenditure
↓ Fat oxidation
↓ Thyroid hormones
↑ Cortisol
Increase food intake
↑ GIP
↓ Leptin
↓ PYY
↓ Amylin
↓ Insulin
↑ Ghrelin

Weight Management Programs with a focus on maintenance of lost weight demonstrate improved long-term weight loss



Surgery



Pharmacotherapy



Lifestyle Modification



Any 'diet' is better than no diet...

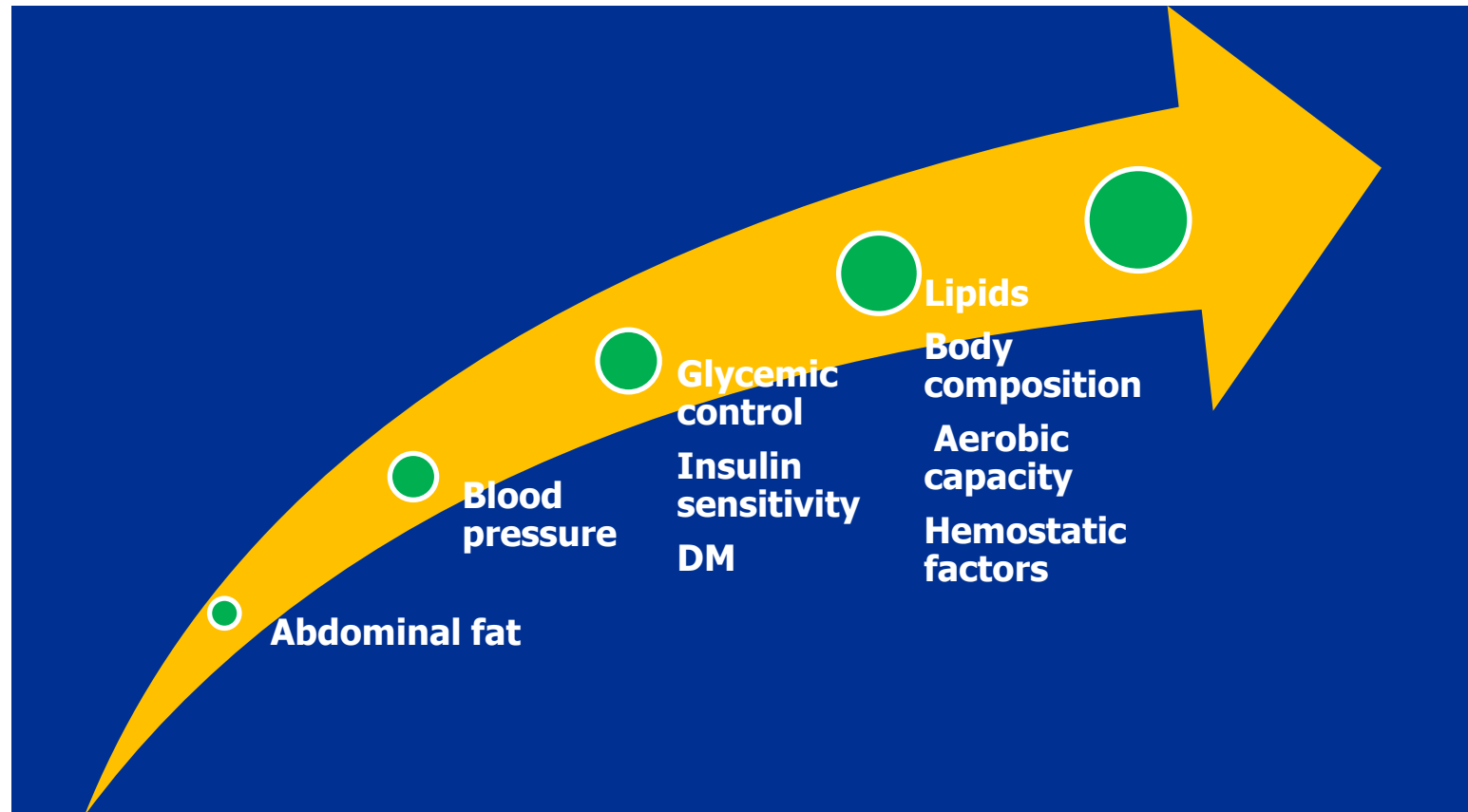
- Under-reporting of calorie consumption
- Men lose more weight than women
- Metabolic rate declines by 2% per decade (100 kcal/day)

Choice of dietary therapy remains uncertain....

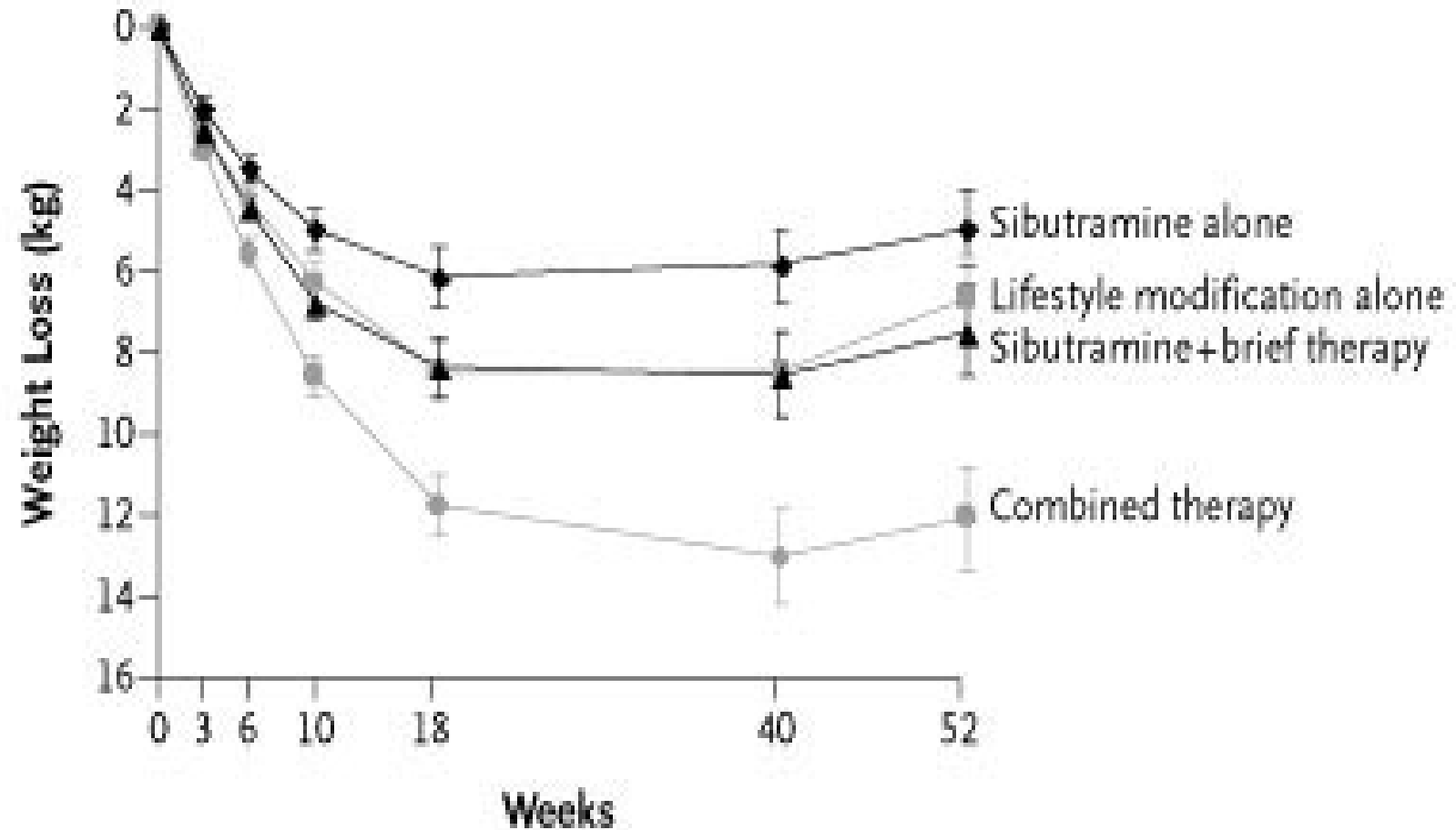
- Total calories vs. macronutrient composition
- Meal replacements/pre-packaged meals
 - Lack of variety
- Fad diets
 - Unsustainable

Exercise Therapy

- Maintaining long-term weight loss
 - A dose-response relationship
- Preserving lean body mass while dieting



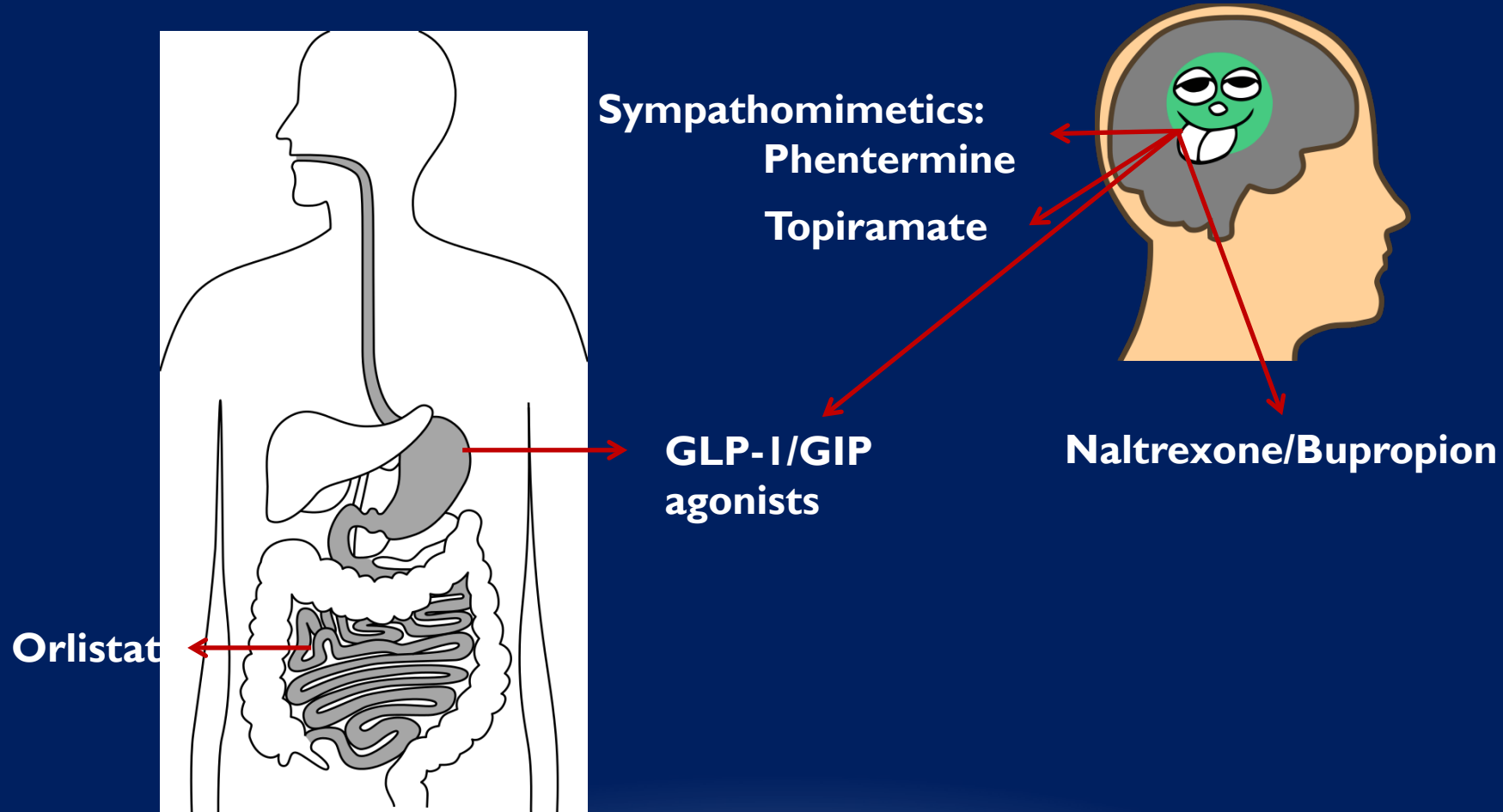
Weight loss medications should be used in combination with efforts at lifestyle modification



Indications for drug therapy

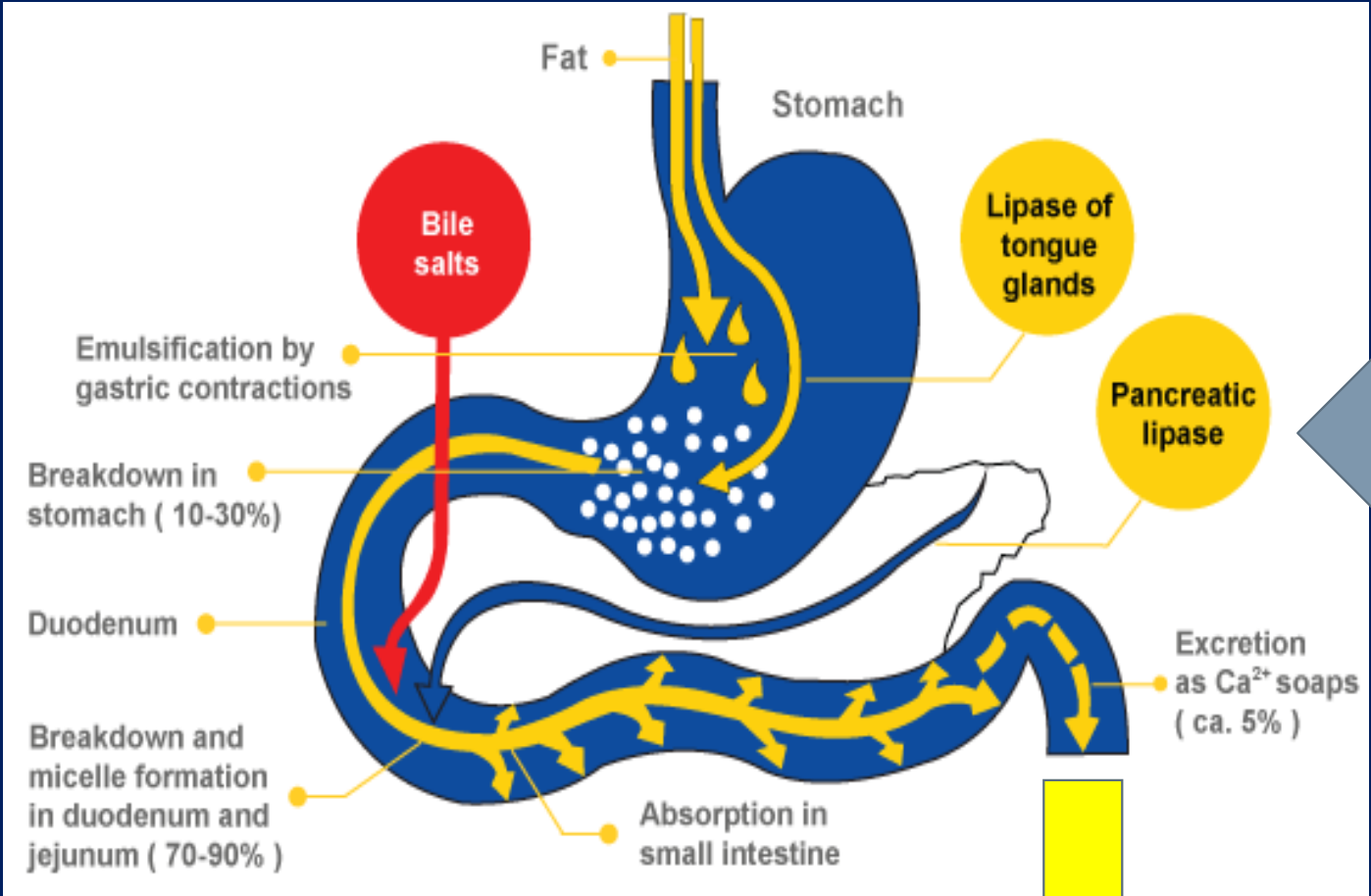
- BMI > 30 kg/m², who have failed to achieve weight loss goals through diet and exercise alone
- BMI of 27 to 29.9 kg/m² with comorbidities
- When bariatric surgery is being considered

Currently approved anti-obesity drugs



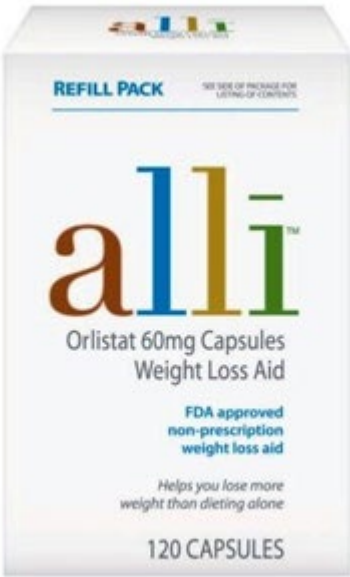
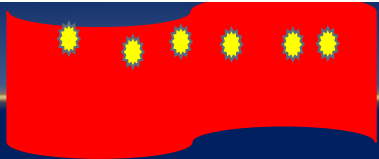
Orlistat: Mechanism of Action

Orlistat, 1999



Average wt loss= 10%
70% lost ≥5%
40% lost ≥10%

Fecal excretion





Phentermine, 1959

- Belong to stimulant class of drugs
 - Reduces appetite
- Efficacious but side-effects limit use
- Typically restricted to 12-week use
- Not indicated in those with CVD, HTN
 - Migraines
 - High thyroid conditions

**Average weight loss:
3.6 kg to 10.0 kg.**

Phentermine-Topiramate, 2012

Reduce hunger
8-10% weight loss
Risk during pregnancy



- Cannot be used in patients with heart disease or uncontrolled HTN
- Dry mouth, increase in HR, depression/anxiety, kidney stones, increased creatinine, non-anion gap acidosis
- Labs every 4 weeks

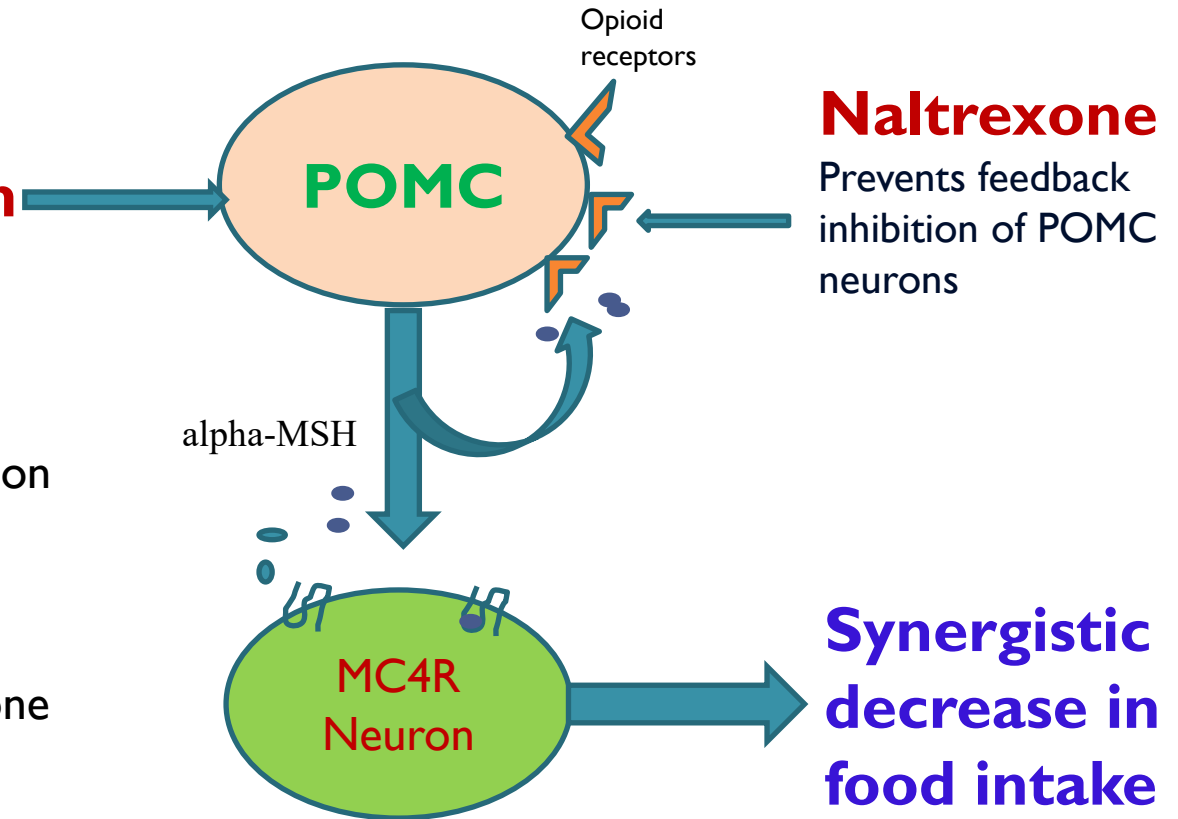
Bupropion-Naltrexone, 2014



Average wt loss= 7%
52% lost \geq 5%
28% lost \geq 10%

Exact mode of action
unknown-
? Norepinephrine
? Dopamine
? Role for naltrexone

Bupropion



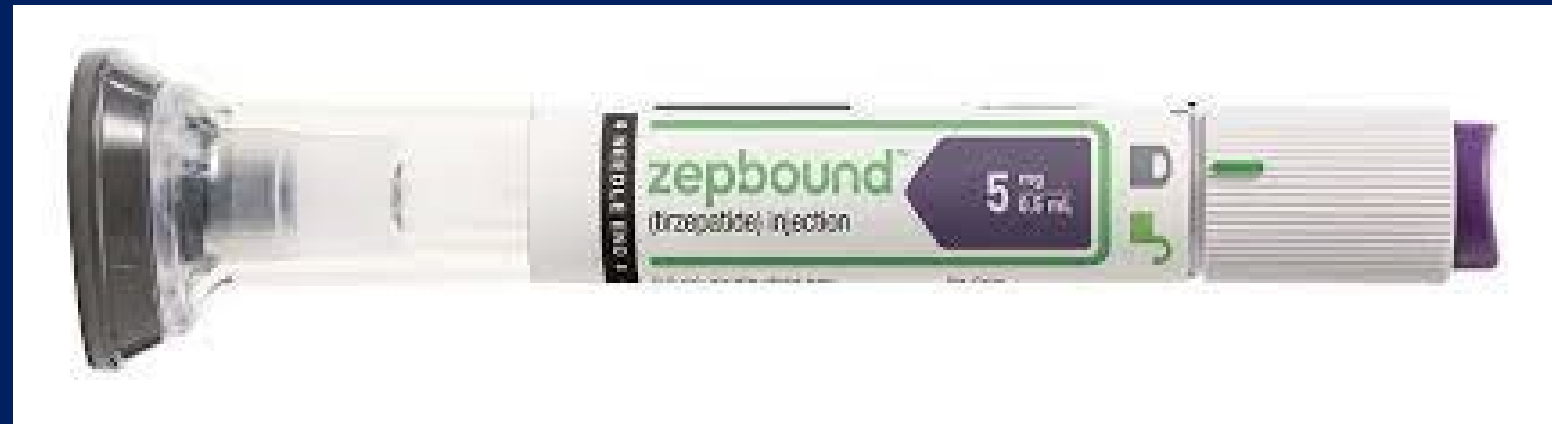
Liraglutide, 2014



Semaglutide, 2021



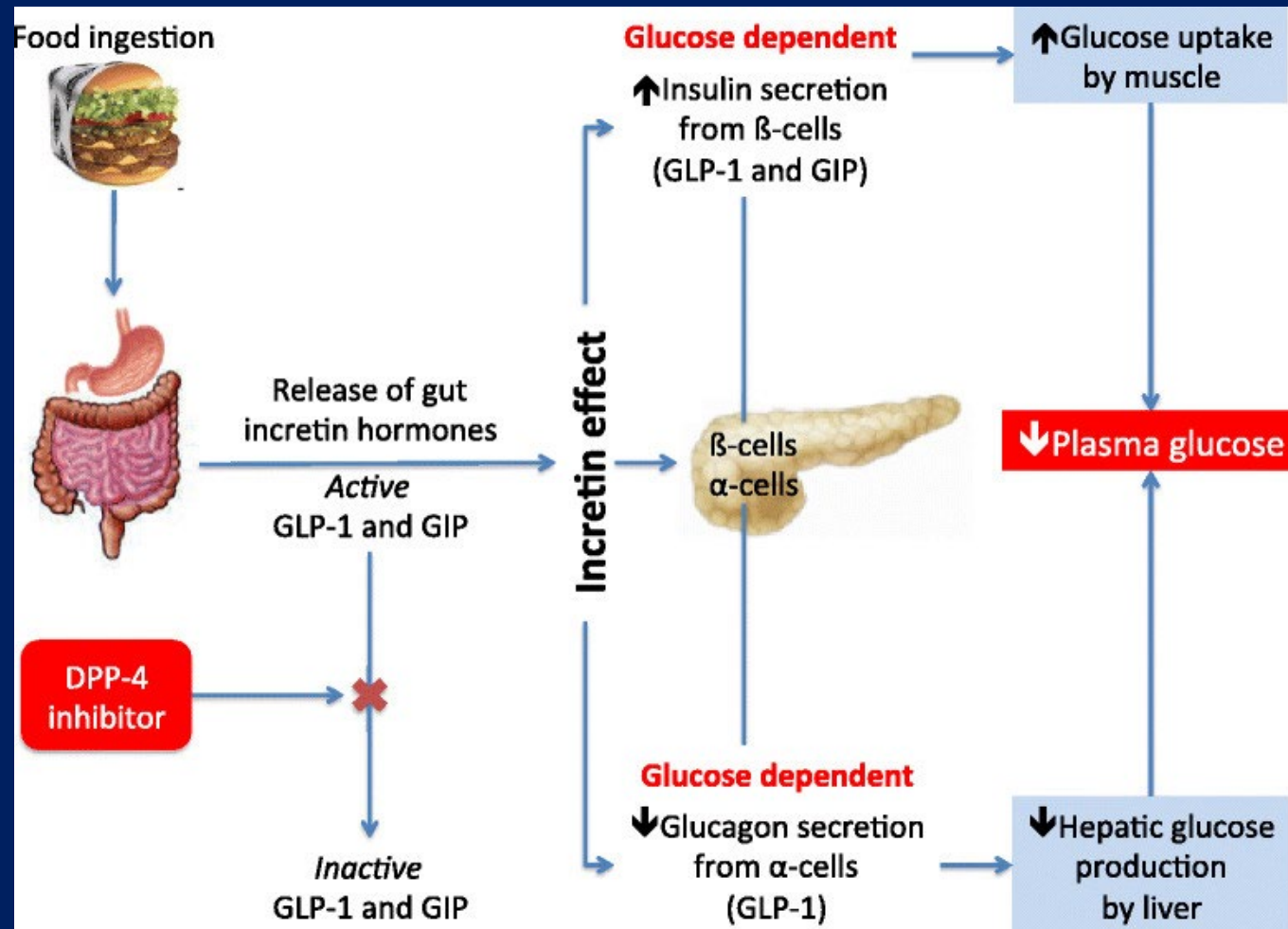
Tirzepatide, 2023



❖ Synthetic analogues of GLP-1/GIP hormone

Glucagon-Like Peptide-1 (GLP-1) & Gastric inhibitory Polypeptide (GIP): Natural Gut Hormones

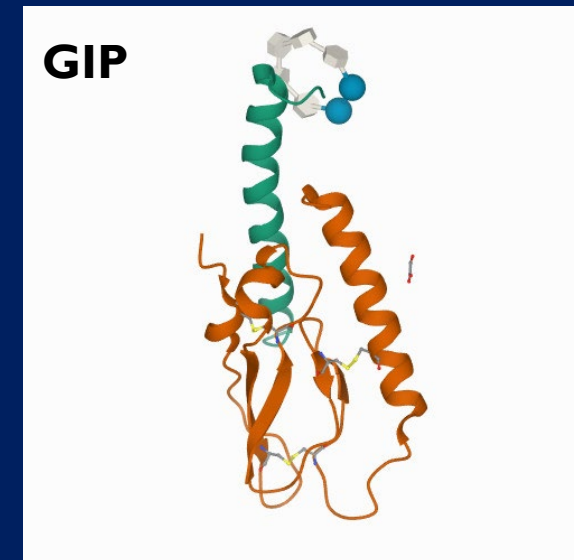
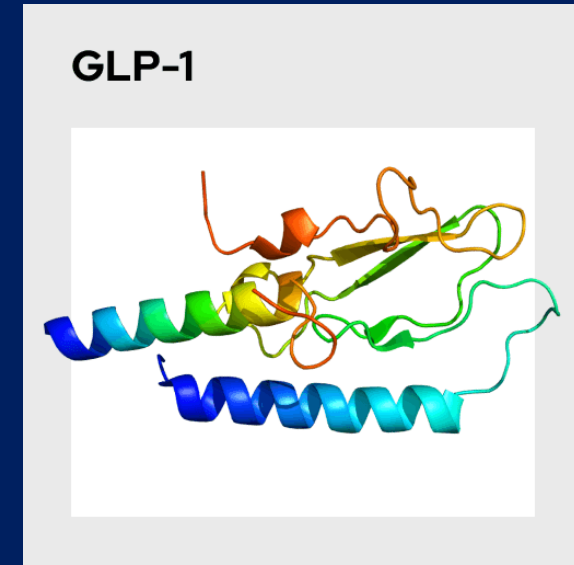
- Produced by intestinal cells
- Stimulate insulin release after oral intake of calories – lowering blood sugars
- Reduce glucagon (hormone that raises blood sugar)



GLP-1/GIP Receptor Agonists- Mimicking a Natural Hormone

- Agonists mimic GLP-1/GIP's effects.
- Injected once or weekly, depending on the medication.

Tirzepatide is a newer GLP-1 agonist which targets both GLP-1 and GIP receptors, mimicking two gut hormones. This dual action may offer enhanced benefits for blood sugar control.



GLP-/GIP agonists

Dose escalation is needed for all the medications

GLP-I Agonist	Commercial Name	Approved for Diabetes (Year)	Approved for Obesity (Year)	Scheduled
Exenatide	Byetta	2005	Not Approved	Twice daily
Liraglutide	Victoza	2010	2014 (Saxenda)	Daily
Exenatide- ER	Bydureon	2012	Not Approved	Weekly
Albiglutide	Tanzeum	2014	Not Approved	Weekly
Dulaglutide	Trulicity	2014	Not Approved	Weekly
Lixisenatide	Adlyxin	2016	Not Approved	Daily
Semaglutide (injection)	Ozempic	2017	2021 (Wegovy)	Weekly
Semaglutide (oral tablets)	Rybelsus	2019	Not Approved	Daily
Tirzepatide	Mounjaro	2022	2023 (Zepbound)	Weekly



Tirzepatide is a newer agonist which targets both GLP-I and GIP receptors, mimicking two gut hormones.

This dual action may offer enhanced benefits for blood sugar control.

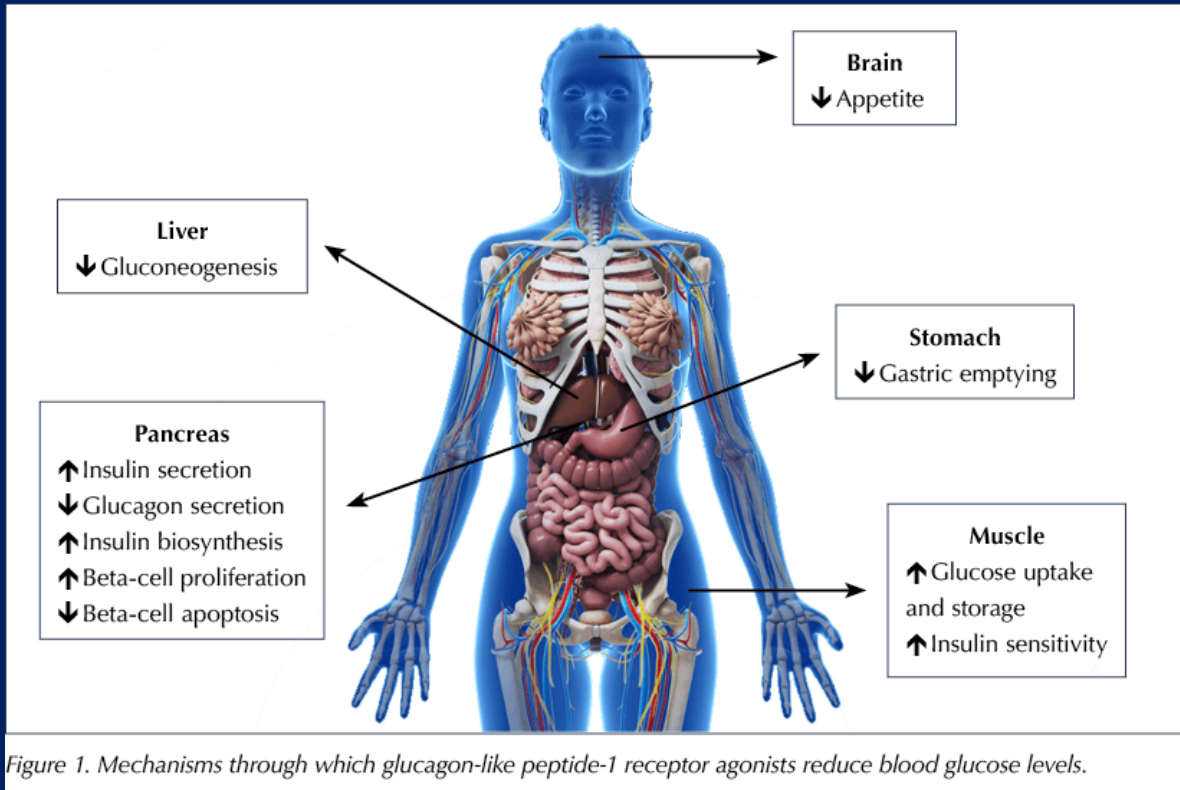
HbA1C lowering with GLP-1/GIP agonists (diabetes trials)

Medication (Brand Name)	Trial Name	Average A1c Reduction	Average Weight Reduction
Liraglutide (Victoza)	LEAD-6	-1.20%	-3.0 kg (6.6 lbs)
Dulaglutide (Trulicity)	AWARD-11	-1.80%	-4.7 kg (10.4 lbs)
Semaglutide (Ozempic)	SUSTAIN-FORTE	-2.20%	-6.9 kg (15.2 lbs)
Tirzepatide (Mounjaro)	SURPASS-2	-2.46%	-12.4 kg (27.3 lbs)

Weight lowering with GLP-1/GIP agonists (obesity trials)

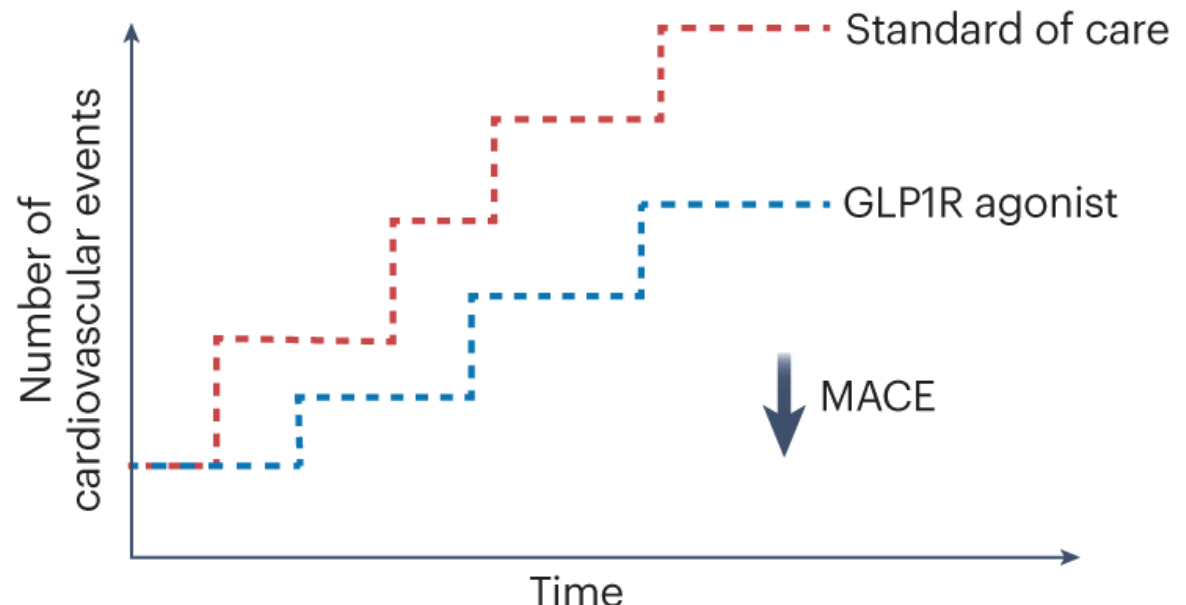
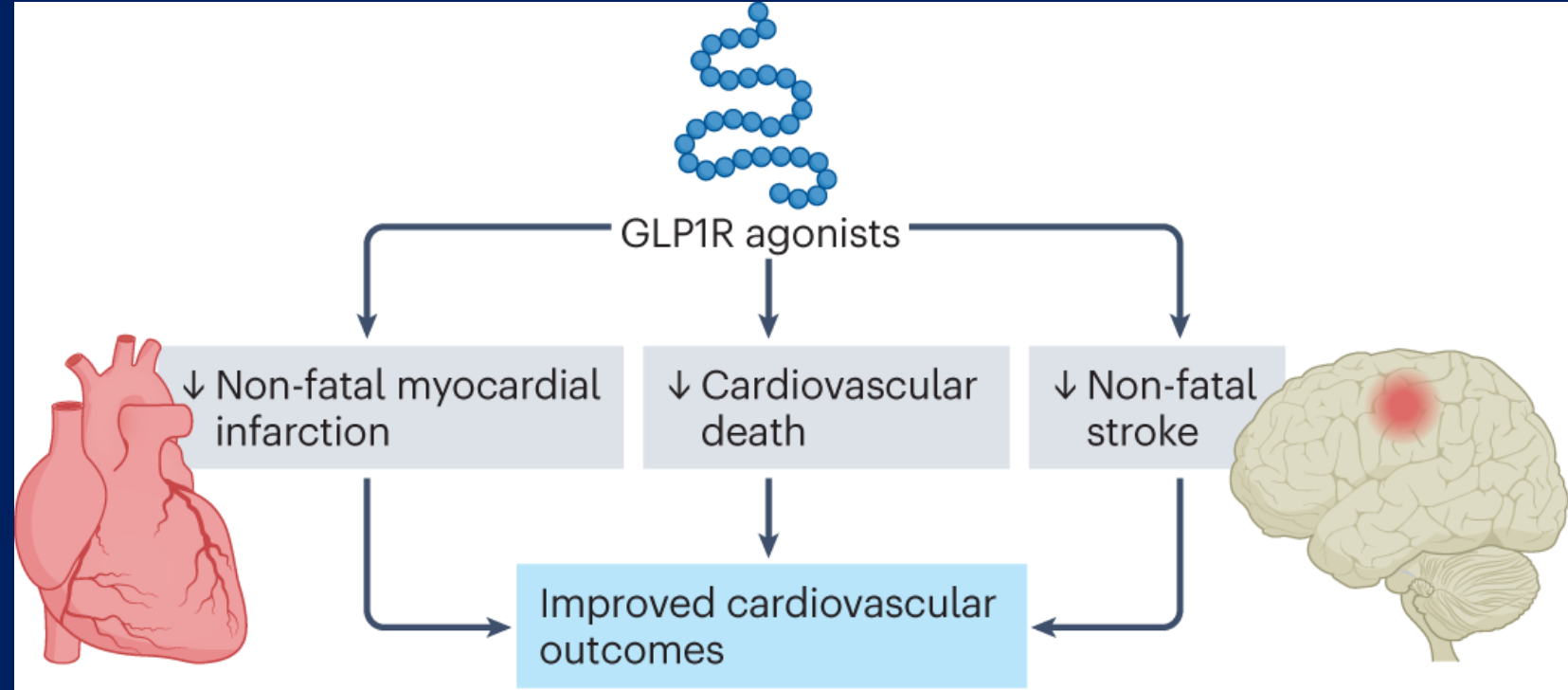
Medication (Brand Name)	Trial Name	Average Weight Reduction
Liraglutide (Saxenda)	Liraglutide Effect and Action in Weight-Loss (LEAW)	-5.4 kg (11.9 lbs)
Semaglutide (Wegovy)	STEP 1	-15.3 kg (33.7 lbs)
Tirzepatide (Zepbound)	SURMOUNT 4	-18.8 kg (41.4 lbs)

Benefits of GLP-1/GIP Receptor Agonists



- Improve blood sugar control.
- Promote weight loss.
 - Reduce hunger
 - Increase satiety
- Reduce cardiovascular risk.
- Improve kidney health

GLP1R/GIP agonists reduce MACE.



Understanding the Side Effects: What to Expect with GLP-1/GIP Agonists

Most common: nausea, vomiting, diarrhea, constipation
(usually improve with time).

Less common: headache, stomach pain, dizziness.

Do not use in patients with personal or family history of medullary thyroid cancer and MENII

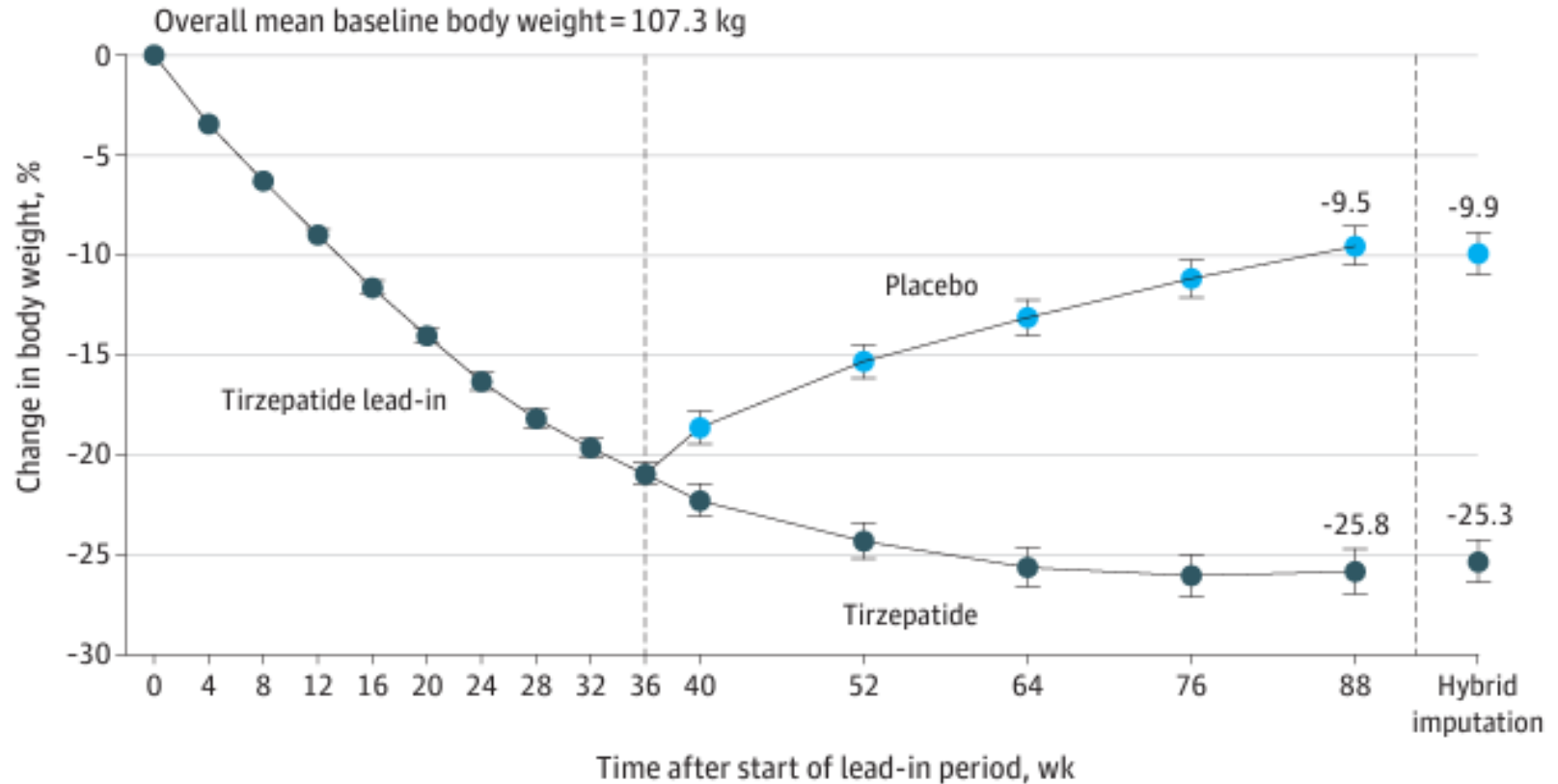
Risk of pancreatitis –

Some studies suggest a small possible increase, especially soon after starting treatment, others haven't found a clear link.

One need to weigh risks and benefits in whom these drugs are being considered and has had pancreatitis.

Stopping tirzepatide – SURMOUNT 4

A Percent change in body weight (week 0-88)



No. at risk

Tirzepatide lead-in 670 666 669 668 667 667 669 663 659 670

Tirzepatide

335 333

328

317

310

310

335

Placebo

335 330

317

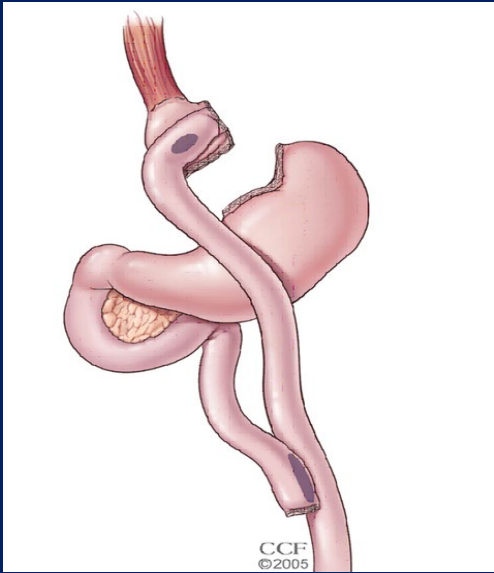
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292

289

335

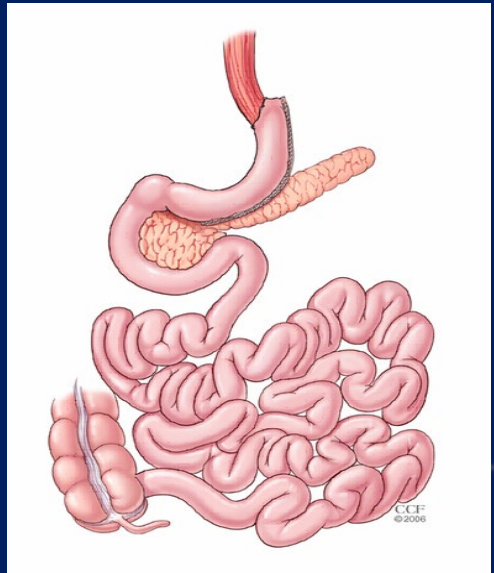
Gastric Bypass



LONG-TERM MORTALITY AFTER GASTRIC BYPASS SURGERY

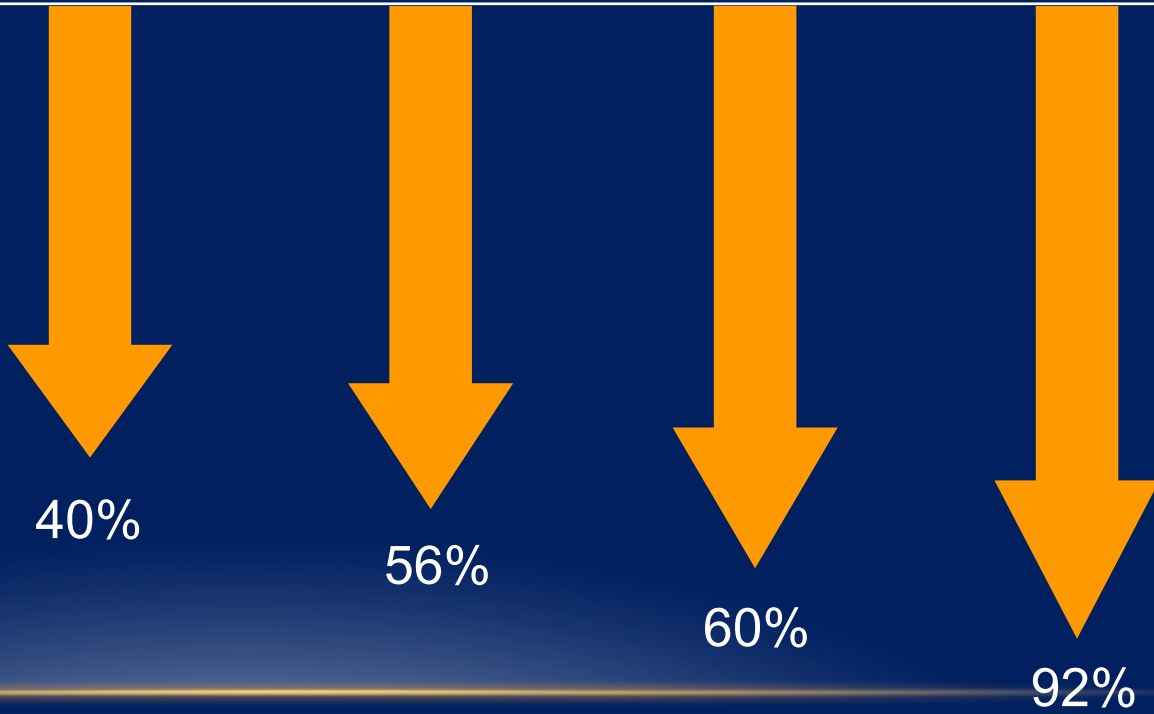
(N=7928 VS. 7925)

Sleeve Gastrectomy



% reduced/10,000 person-yr

All Cause Mortality Coronary Artery Disease Cancer Diabetes



Adams TD, et al. NEJM 2004;357:753

Thank You!

