Brigham and Women's Hospital
Founding Member, Mass General Brigham

Obesity
Focus on Weight Loss Medications

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Zeb Ijaz Saeed, MD

The Center for Weight Management and Wellness (CWMW) at Brigham and Women's Hospital offers comprehensive, multidisciplinary care for patients seeking treatment of their overweight and obesity. Dr. Zeb Ijaz Saeed is a board-certified obesity medicine specialist who is committed to advancing the care and outcomes of individuals living with obesity and diabetes.

Dr. Saeed has contributed to NIH-funded research focused on identifying novel biomarkers for diabetes secondary to acute and chronic pancreatitis and pancreatic cancer, as well as being involved in a study identifying new genetic causes of rare and atypical forms of diabetes. She is currently involved in clinical trials evaluating pharmacologic therapies aimed at improving cardiometabolic health in individuals with obesity and/or diabetes.

Disclosures

- Research support (Site-PI) by Amylyx Pharmaceuticals, Kailera therapeutics and Eli Lilly.

- Advisory consultation completed with Sanofi

Objectives

Upon completion, participants will be able to:

- Recognize obesity as a **chronic, multifactorial disease** with strong biological underpinnings.

- Review updated guidelines on the **classification** of obesity

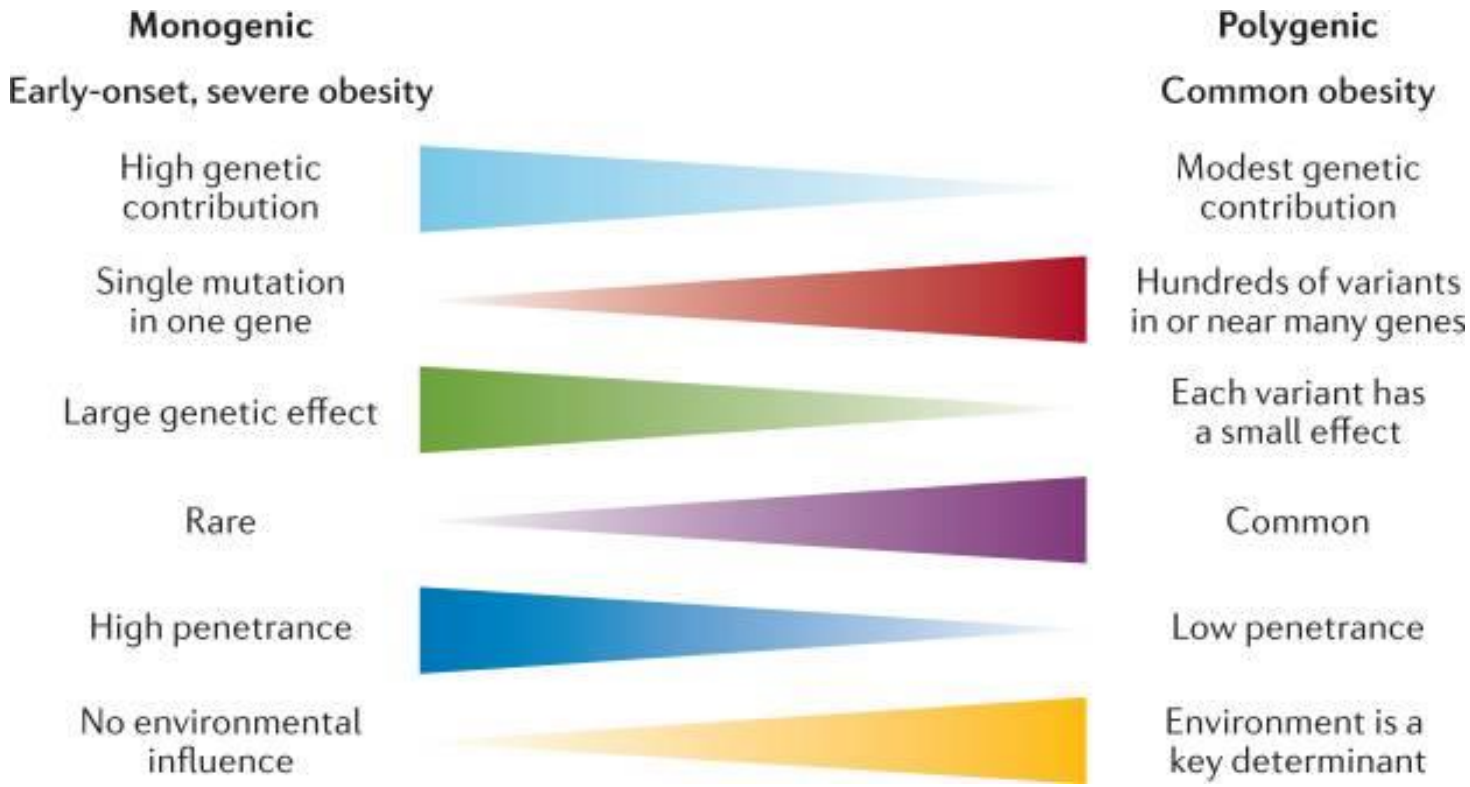
- Understand the **pharmacologic options** for obesity management including oral and injectable options and **apply them to use in clinical practice**

- Analyze the **pleiotropic metabolic effects of nutrient-stimulated hormone (NuSH)** therapies and their implications for cardiometabolic health.

Obesity and Overweight is a multifactorial, biologically rooted disease with strong genetic underpinnings.

Biology of Obesity - Genetics

- Obesity is not simply about willpower or lifestyle choices
- Chronic disease
- Complex interplay of genetics and environment
- Heritability: 40% and 70%



Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. Nat Rev Genet. 2022

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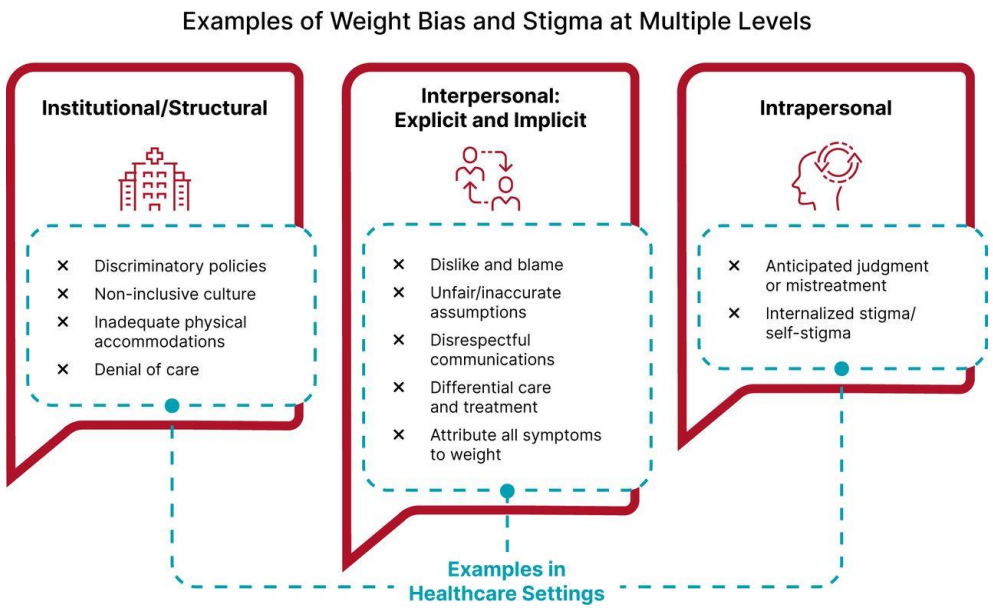
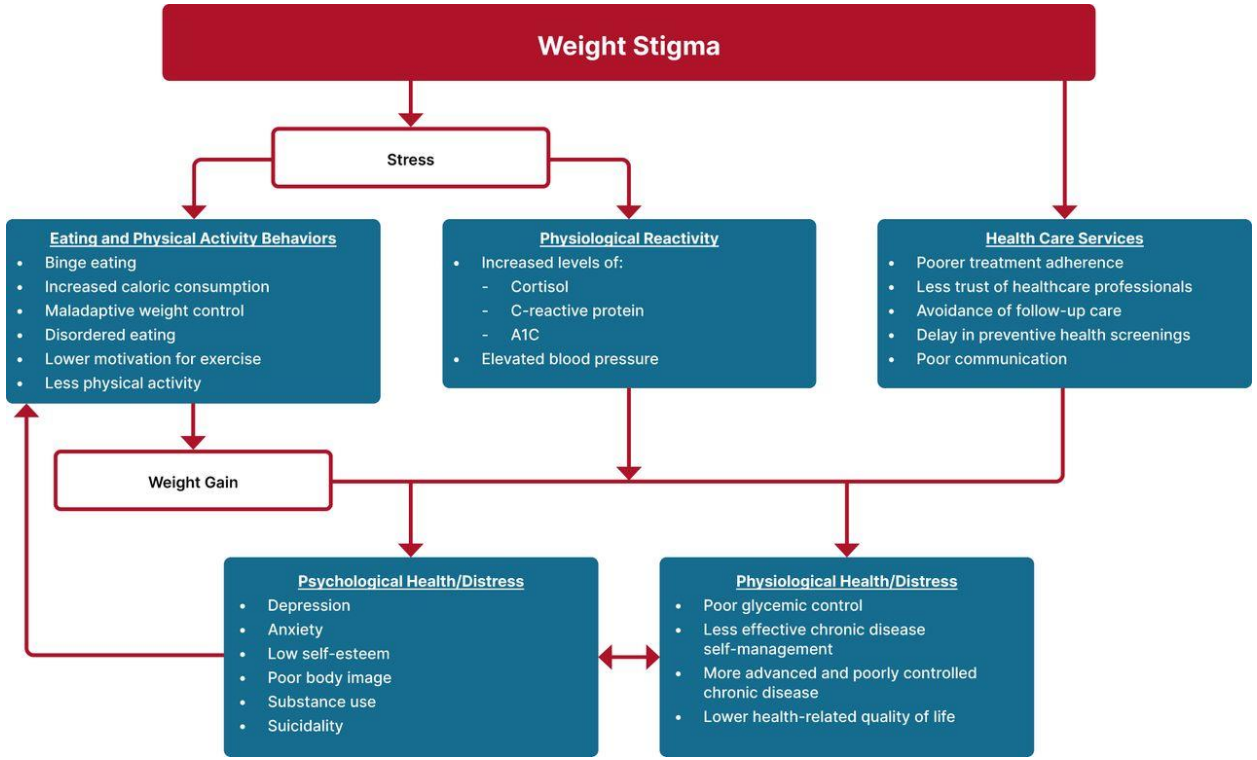
Importance for recognition of biology of obesity

Awareness of weight bias and stigma:
69% women with obesity report experiencing weight bias from doctors, and 52% from nurses.

People-first/people-centered language





Puhl RM, Phelan SM, Nadglowski J, Kyle TK. Overcoming Weight Bias in the Management of Patients With Diabetes and Obesity. Clin Diabetes. 2016 Raveendhara R Bannuru - Weight stigma and bias: standards of care in overweight and obesity—2025: BMJ Open Diabetes Research & Care 202;

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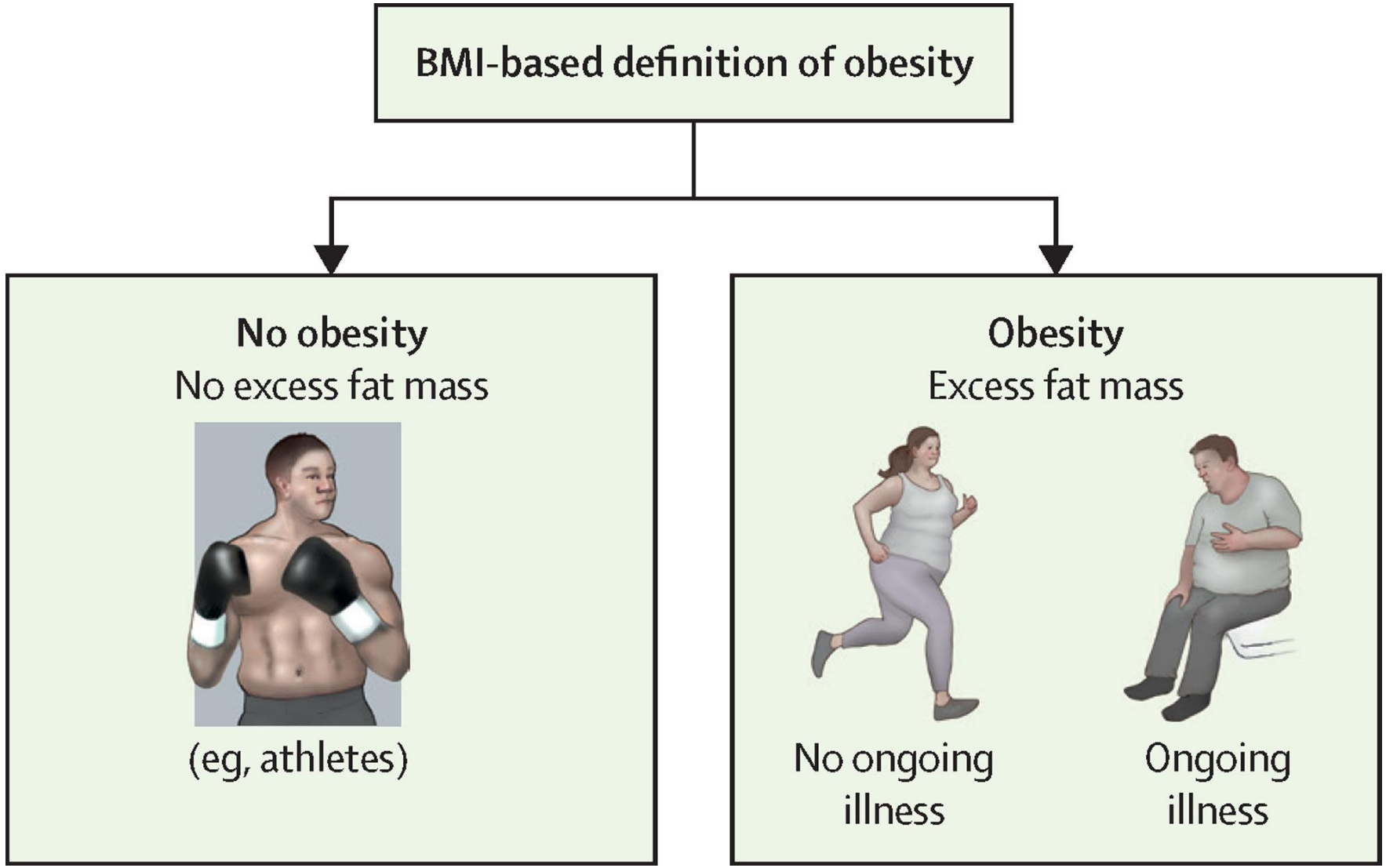
Updated Classification of Obesity

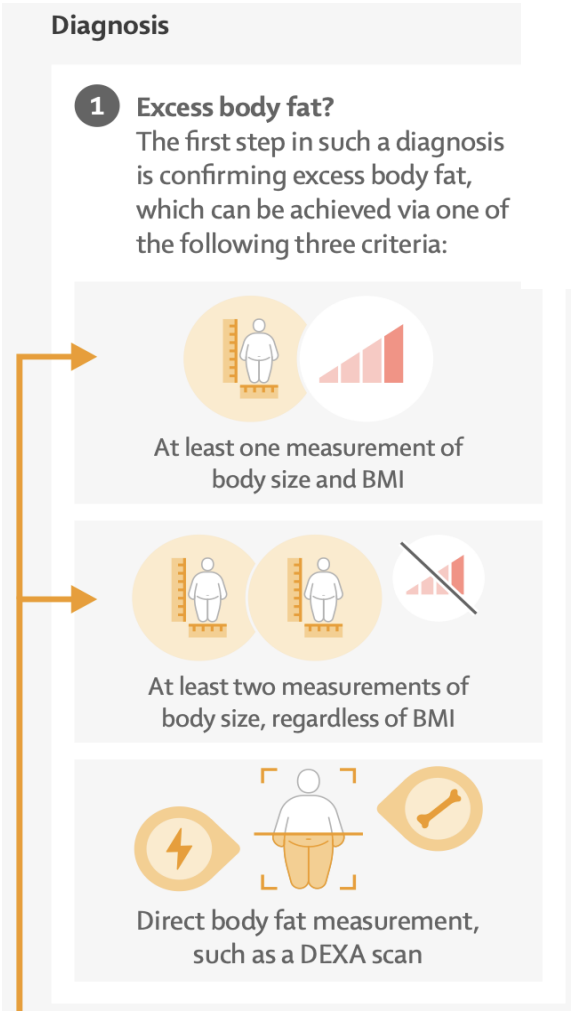
BMI pitfalls

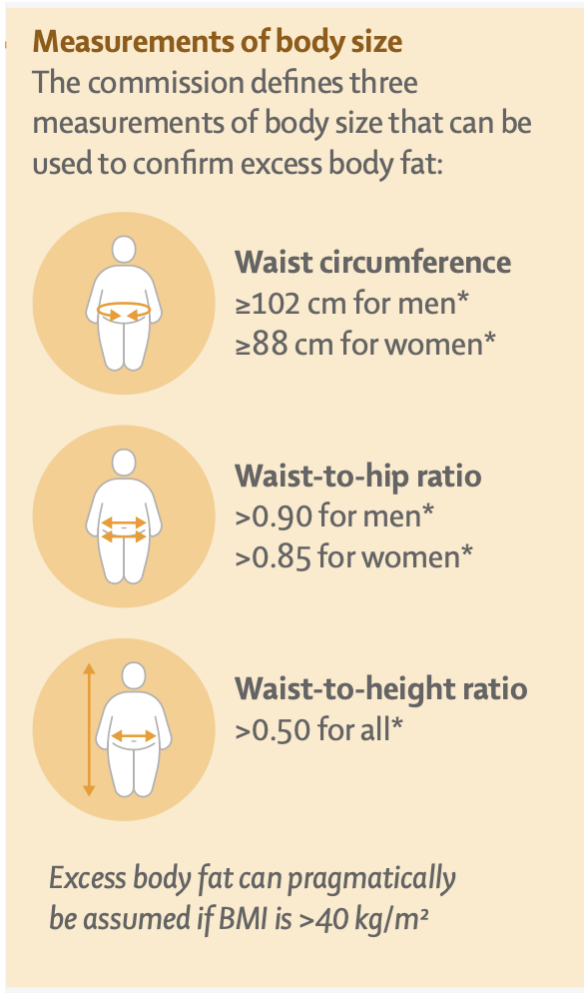


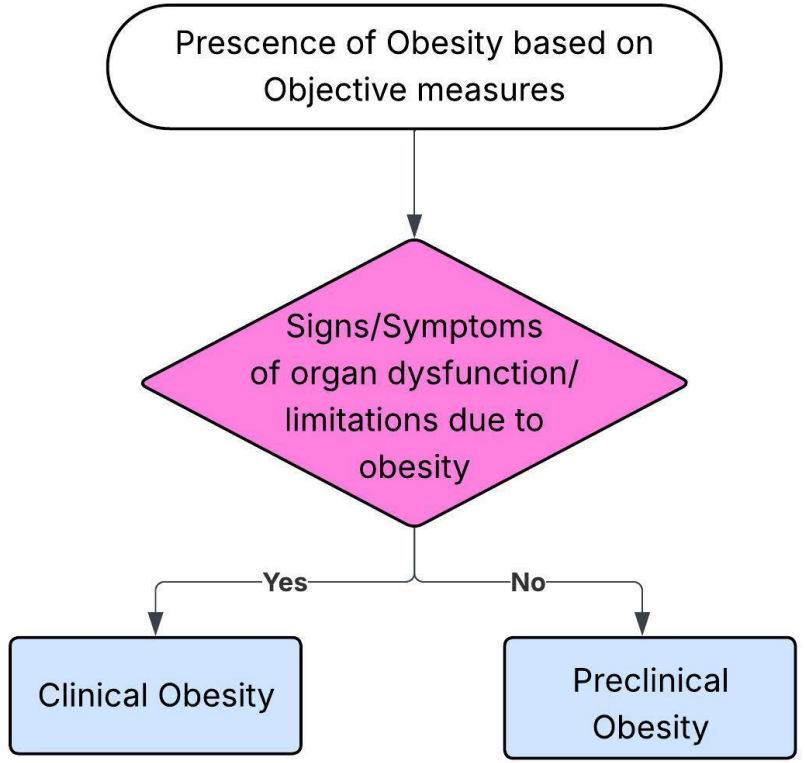
Francesco R et al., The Lancet Diabetes & Endocrinology, Volume 13, Issue 3, 221 - 262

New Proposed Definition of Obesity: BMI pitfalls

BMI may under and over diagnose obesity

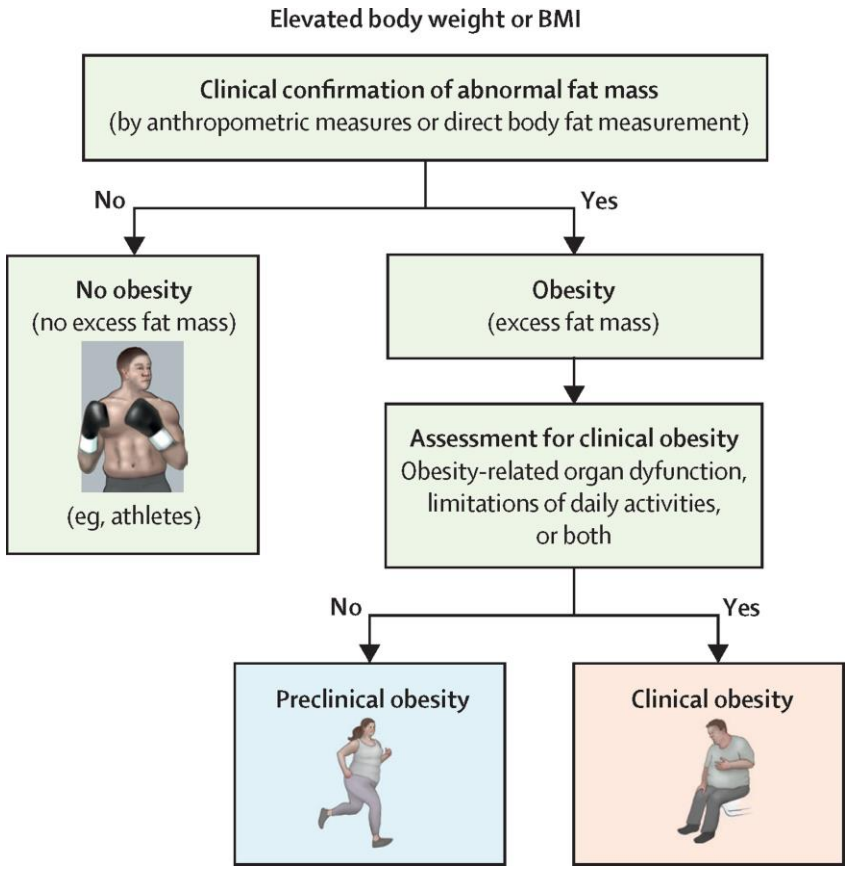


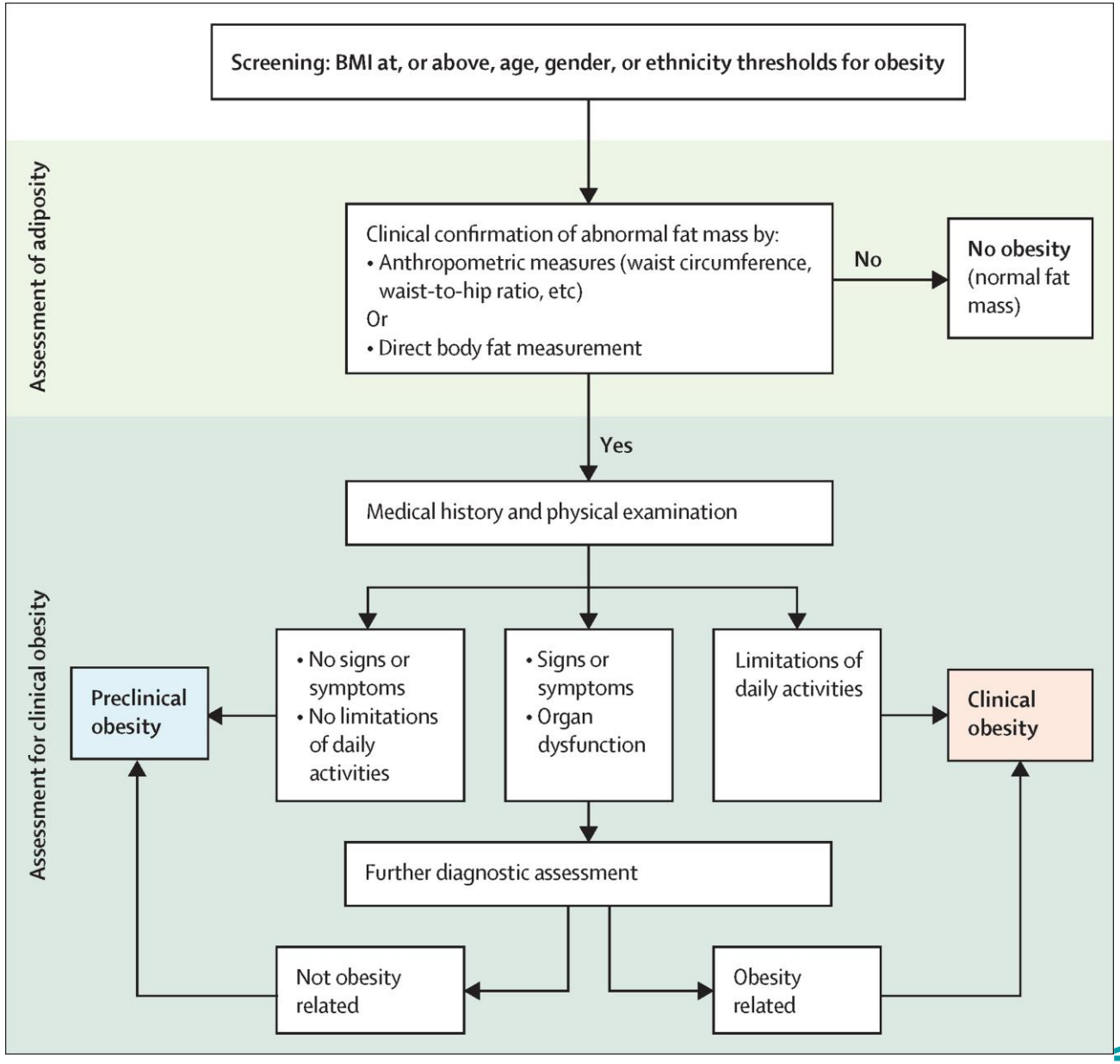




Francesco R et al., The Lancet Diabetes & Endocrinology, Volume 13, Issue 3, 221 - 262

Classification of Obesity





Francesco R et al., The Lancet Diabetes & Endocrinology, Volume 13, Issue 3, 221 - 262

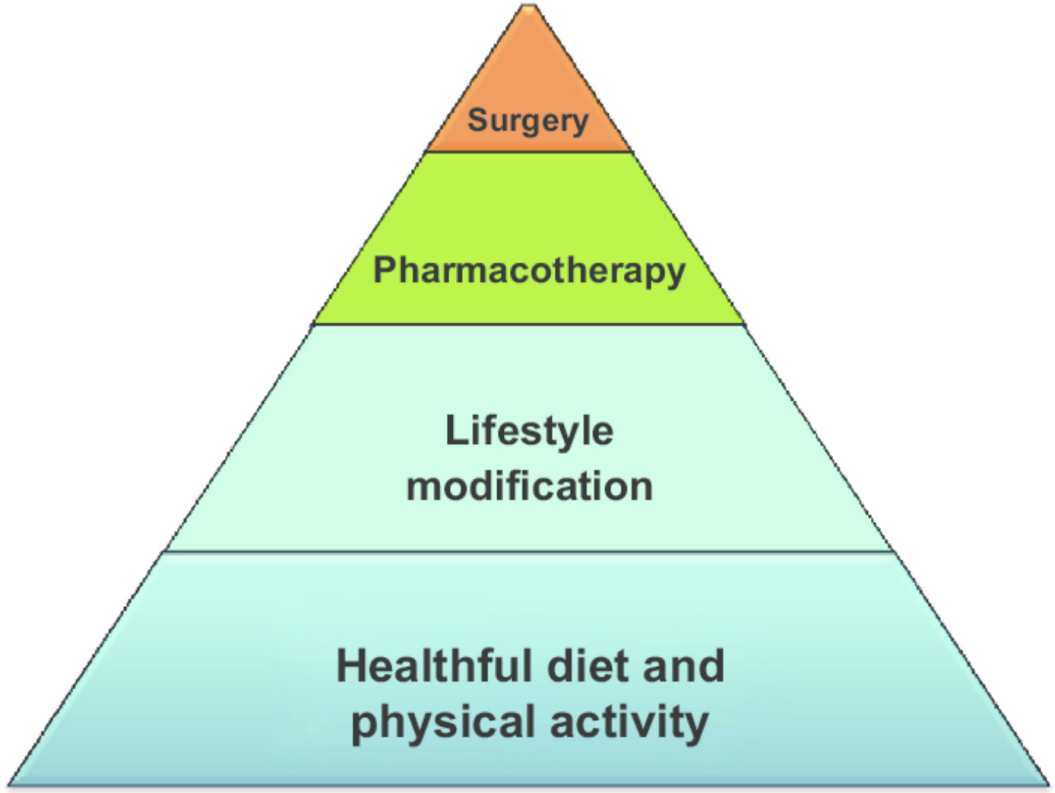
Treatment of Obesity is multi-faceted, inter-disciplinary and longitudinal

Pyramid of weight management

Lifestyle modifications
No single dietary pattern superior
Key→ Consistency

Mediterranean diet : MASH and cardiovascular risk reduction
DASH: benefit for hypertension

Exercise: Mild weight loss.
150 -300mins of moderate-intensity aerobic exercise every week
AND
resistance training at least 2 sessions per week



Wimalawansa, S. (2013). "Visceral adiposity and cardiometabolic risks: Epidemic of abdominal obesity in North America." Research Reports in Endocrine Disorders 3: 17-30.

Stone T, DiPietro L, Stachenfeld NS. Exercise Treatment of Obesity. . Availablerom:https://www.ncbi.nlm.nih.gov/books/NBK27896 1/

Anti-Obesity Medications

	BMI Category (kg/m^2)				
Treatment	**25-26.9**	**27-29.9**	**30-34.9**	**35-39.9**	**≥40**
Diet, Physical Activity, Behavior	**With co-morbidities**	**With co-morbidities**	**+**	**+**	**+**
Pharmaco-therapy		**With co-morbidities**	**+**	**+**	**+**
Surgery			**With type 2 diabetes**	**With co-morbidities**	**+**

If lifestyle does not yield results, escalate to pharmacotherapy→ Avoid clinical inertia

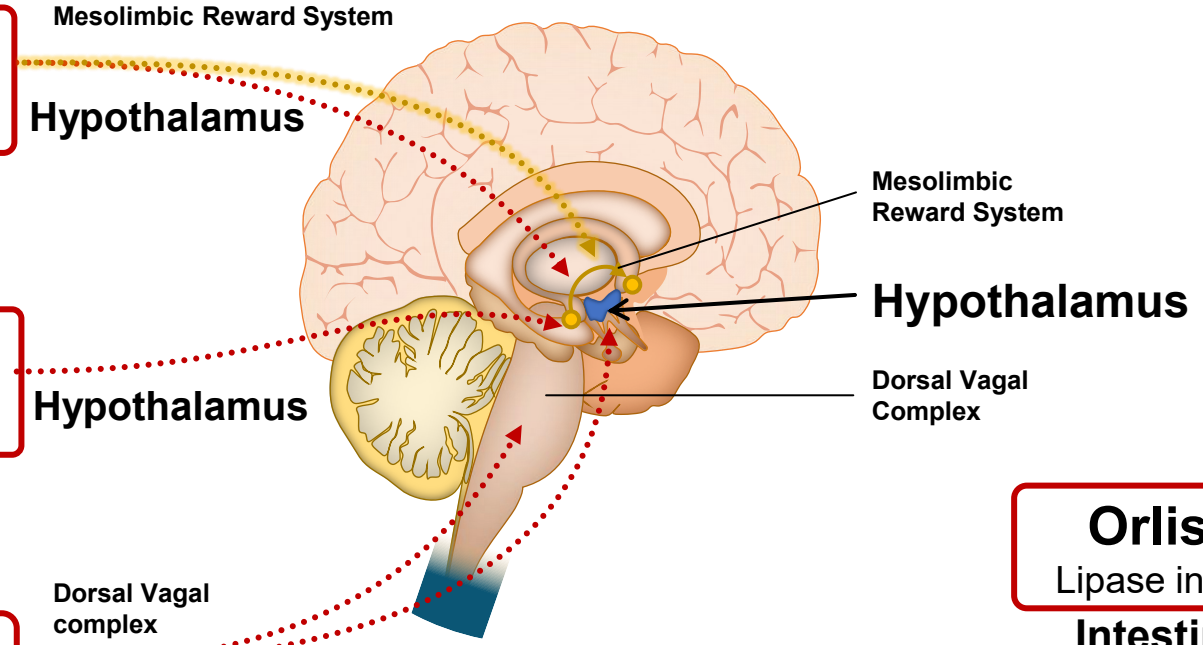
The Practical Guide to the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 2000. Table 3, page 25

Current Obesity Pharmacotherapy
Where They Work and Mechanisms of Action

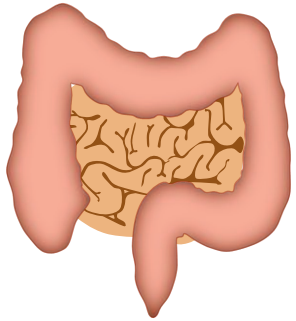
Naltrexone/bupropion
μ-opioid antagonist +
DA/NE reuptake inhibitor

Phentermine/topiramate
Sympathomimetic amine + antiepileptic

Liraglutide, Semaglutide, Tirzepatide, Orforglipron
GLP-1 receptor agonists



Orlistat
Lipase inhibitor
Intestines



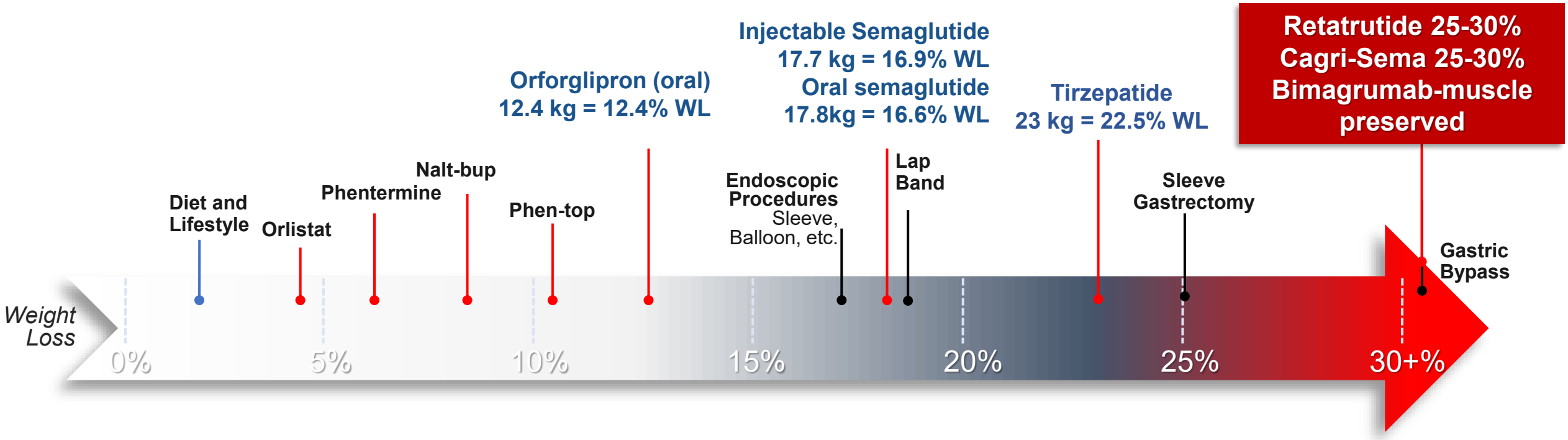
5-HT2c=serotonin; DA=dopamine; GLP-1=glucagon-like peptide-1; MOA=mechanism of action; NE=norepinephrine.

1. Yanovski SZ et al. *JAMA*. 2014;311:74-86.
2. Apovian CM et al. *J Clin Endocrinol Metab*. 2015;100:342-362.
3. Kim GW et al. *Clin Pharmacol Ther*. 2014;95:53-66.
4. Dietrich MO et al. *Nat Rev Drug Discov*. 2012;11:675-691.

Current Treatment Landscape

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

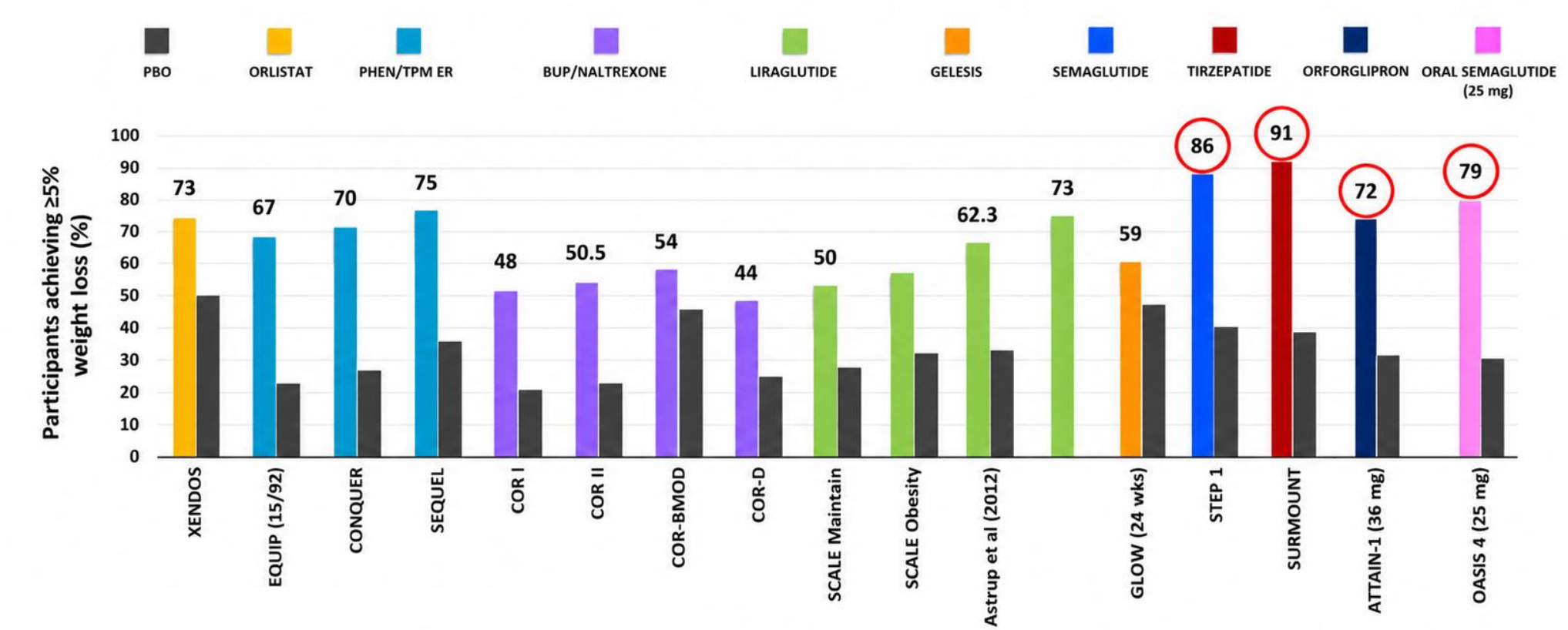
This is not the grand finale
More effective meds in development



Bariatric surgery currently provides the best results – newer drugs are catching up

After Aronne LJ. FDA VI-0521 EMDAC 2010.

Pharmacotherapy Increases Magnitude and Likelihood of Weight Loss Particularly Newer Drugs



ITT; SEQUEL, some changes have been derived from reported data.

Modified by L.J. Aronne. Pucci A, et al. *Can J Car*diol. 2015;31(2):142-152.
Astrup A, et al. *Int J Obes* (Lond). 2012;36(6):843-854.
Wilding JPH, et al. N Engl J Med. 2021 Mar 18;384(11):989-1002.
Jastreboff AM, Aronne LJ, et al. N Engl J Med. 2022 Jul 21;387(3):205-216.
Wharton S, et al. Engl J Med. 2025 Nov 6;393(18):1796-1806.
Wharton S, et al. N Engl J Med. 2025 Sep 18;393(11):1077-1087.

Phentermine Monotherapy

Approved by the FDA for **short term use** (up to 12 weeks) approved in children ≥17 years and adults

Mechanism of action:	**Sympathomimetic --> NE and DA release in CNS→ appetite suppression**
Doses available:	Long acting (once a day) - Capsules 15mg, 30mg, 37.5mg - Tablets : 37.5mg Short acting (Three times a day) - Tablets: 8mg
Placebo-subtracted weight loss:	~ 8% long term use. TWL 10-12%
Contraindications:	Cardiovascular disease, uncontrolled hypertension, hyperthyroidism, anxiety/agitation, glaucoma, substance use disorder
Side effects:	Dry mouth, insomnia, dizziness, irritability, increased blood pressure and heart rate
Cost considerations:	Cheap with coupons: $10 -30 per month

Kang JG, et ak . Randomized controlled trial to investigate the effects of a newly developed formulation of phentermine diffuse-controlled release for obesity. Diabetes Obes Metab. 2010

Phentermine- Topiramate

FDA approved for long-term management of weight for adults and children 12 and older

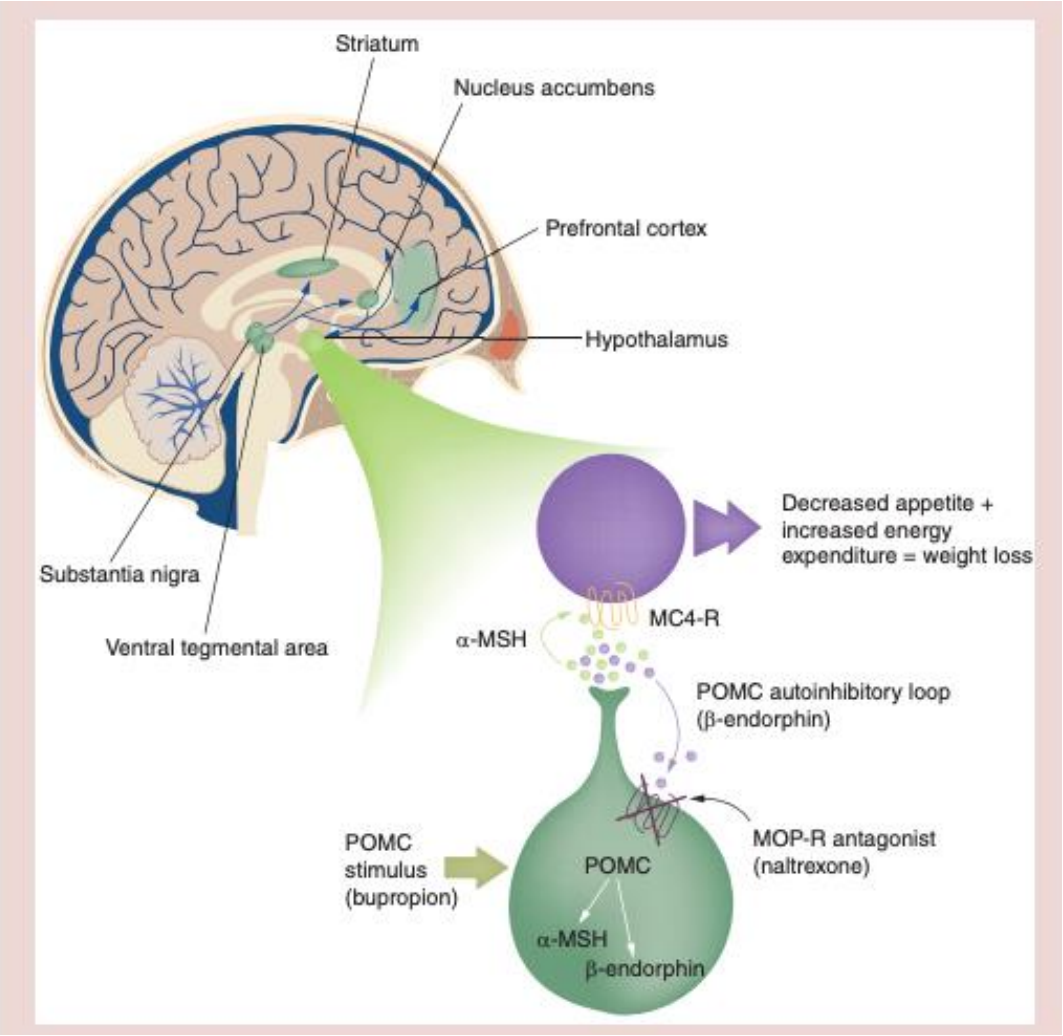
Mechanism of action:	**Sympathomimetic→ NE release in hypothalamus→ Appetite suppression Topiramate→ modulation of GABA receptors, carbonic anhydrase inhibitor and glutamate antagonist → affects satiety and changes taste sensation**
Doses available:	3.75 mg phentermine / 23 mg topiramate (initial dose only for 14 days) 7.5 mg phentermine / 46 mg topiramate (recommended dose) 11.25 mg phentermine / 69 mg topiramate (escalation dose) 15 mg phentermine / 92 mg topiramate (maximum dose)
Effectiveness:	**CONQUER trial: 56 weeks Phase III RCT.** (-7.8% and -9.8% weight loss compared to -1.2% placebo): -8.8% Placebo subtracted weight loss 5% weight loss : 62, 70 and 21%, respectively
Contraindications:	CVD, glaucoma, hyperthyroidism, **teratogenic (reliable contraception)**
Side effects:	Dry mouth, paresthesia, constipation, insomnia, dizziness, and dysgeusia. Serious but less common side effects include mood changes, cognitive impairment, and increased heart rate. RTA and increased risk of renal stones (calcium phosphate)
Cost considerations:	Expensive!! $200-400 per month without insurance coverage

Gadde KM, Allison DB, Ryan DH, et al. Effects of Low-Dose, Controlled-Release, Phentermine Plus Topiramate Combination on Weight and Associated Comorbidities in Overweight and Obese Adults (CONQUER): A Randomised, Placebo-Controlled, Phase 3 Trial. Lancet (London, England).

Bupropion-Naltrexone

FDA approved for long-term management of weight for age 17 and above, can help with smoking cessation

Mechanism of action	Naltrexone, an opioid antagonist Bupropion, a norepinephrine-dopamine reuptake inhibitor.
Mode of delivery	Oral twice a day
Effectiveness	Average weight loss of **5–6%** can be enhanced with intensive lifestyle intervention.
Contra indications:	Chronic opioid use, uncontrolled hypertension, seizure disorder, anorexia or bulimia
Side effects:	Nausea, constipation, headache, vomiting, increased blood pressure and heart rate
Cost consideration	Expensive!! $400-600 per month without insurance coverage



Apovian CM. Naltrexone/bupropion for the treatment of obesity and obesity with Type 2 diabetes. Future Cardiol. 2016

Potential Actions of GIP and GLP-1

Based on Preclinical and Clinical Research

- GLP-1 Receptor Agonism
- GIP Receptor Agonism
- Indirect Action

GLP-1 Receptor Agonism

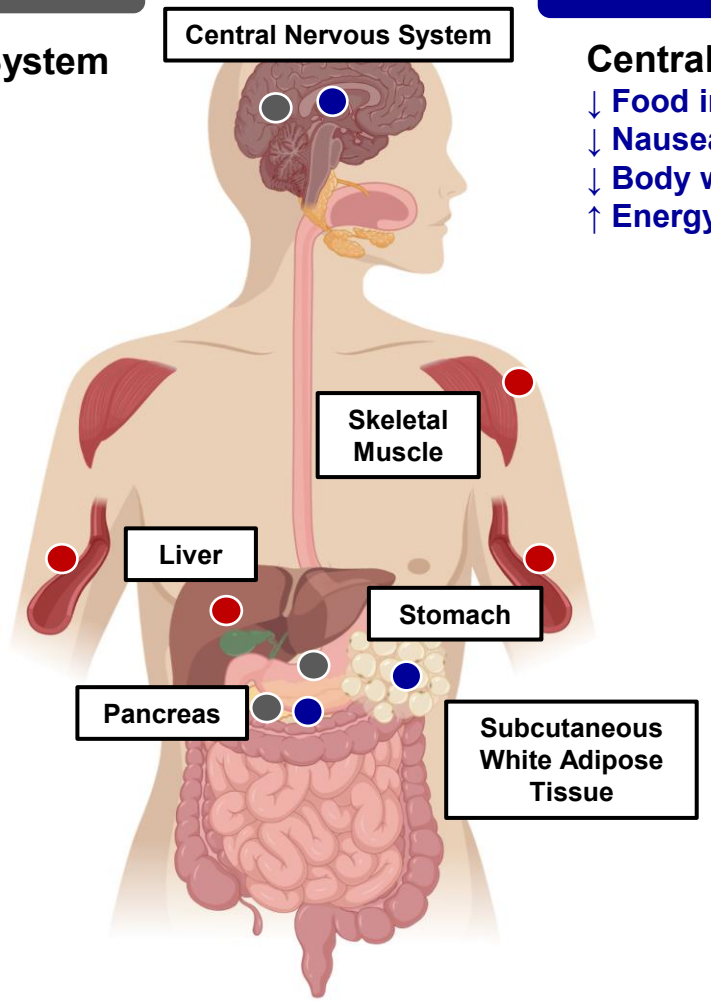
Central Nervous System
↑ Satiety
↓ Food Intake
↑ Nausea
↓ Body Weight

Pancreas
↑ Insulin
↓ Glucagon

Stomach
↓ Gastric Emptying

Systemic
↓ Hyperglycemia

Liver
↑ Insulin Sensitivity
↓ Hepatic Glucose Production
↓ Ectopic Lipid Accumulation



GIP Receptor Agonism

Central Nervous System
↓ Food intake
↓ Nausea
↓ Body weight
↑ Energy expenditure

Pancreas
↑ Insulin
↑ Glucagon (glucose dependent)

Subcutaneous White Adipose Tissue
↑ Insulin Sensitivity
↑ Lipid Buffering Capacity
↑ Blood Flow
↑ Storage Capacity
↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia, Dietary Triglyceride

Skeletal Muscle
↑ Insulin Sensitivity
↑ Metabolic Flexibility
↓ Ectopic Lipid Accumulation

GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1
Adapted from: Samms RJ, et al. Trends Endocrinol Metab. 2020;31(6):410-421

Liraglutide

FDA approved children ≥12 years and adolescents, same dosing as adults

Mechanism of action:	**GLP1-RA--> hypothalamic neurons-→ increase satiety Decrease gastric emptying → increase satiety**
Doses available:	0.6mg SQ QD x 1 week→ 1.2mg QD x 1 week→ 1.8mg QD x 1 week→ 2.4mg x 1 week→ 3mg QD thereafter
Placebo-subtracted weight loss:	4-5% TWL : 8%
Contraindications:	Personal or family history of medullary thyroid cancer or Type 2 Multiple Endocrine Neoplasia syndrome
Side effects:	Nausea, vomiting, bloating, fullness, diarrhea, constipation, dyspepsia, abdominal pain, fatigue
Cost considerations:	Expensive!! $ 400-1000 per month without insurance coverage

Astrup A et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes (Lond). 2012

Semaglutide Injectable

FDA approved in children ≥12 years and adolescents and adults
FDA approved for reducing the risk of major adverse cardiovascular events in adults with established cardiovascular disease and obesity or overweight.
FDA approved for the treatment of adults with MASH (Metabolic Dysfunction–Associated Steatohepatitis) and fibrosis (stage F2–F3), without cirrhosis

Mechanism of action:	**GLP1-RA--> hypothalamic neurons-→ increase satiety Decrease gastric emptying → increase satiety**
Doses available:	0.25mg SQ Q1W x 4 weeks → 0.5mg SQ Q1W x 4 weeks-→ 1.0 mg SQ Q1W X 4 weeks → 1.7mg SQ Q1W x 4 weeks → 2.4 mg SQ Q1W ; can increase to **7.2mg SQ (STEP-UP trial)**
Effectiveness:	Average weight loss 15-16% of body weight 2.4mg dose , 18.7% with 7.2mg dose Placebo-subtracted weight loss: 11.9%
Contraindications:	Personal or family history of medullary thyroid cancer or Type 2 Multiple Endocrine Neoplasia syndrome
Side effects:	Nausea, vomiting, bloating, fullness, diarrhea, constipation, dyspepsia, abdominal pain, fatigue, dizziness, headache, worsening depression, increase in lipase, and rarely renal insufficiency ?? Pancreatitis; worsening diabetic retinopathy; NAION?
Cost considerations:	$199-399/month without insurance coverage

Wilding JPH, et al . STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021

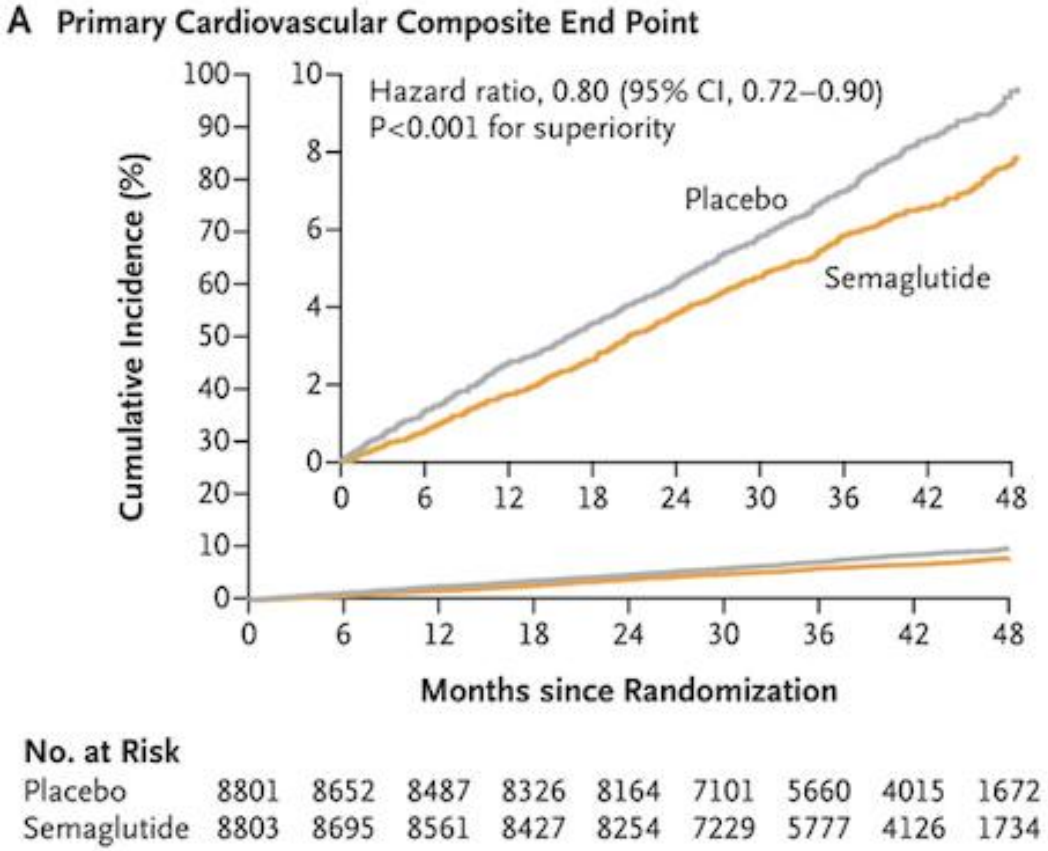
SELECT Trial: Cardiovascular Outcomes, August 2023

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

Semaglutide 2.4 mg reduced risk of major adverse cardiovascular events (MACE) by 20% 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

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



Lincoff AM, et al. SELECT Trial Investigators. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023

SELECT Trial: Diabetes Prevention Results

SELECT: Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity

Risk of HgbA1c ≥ 6.5%
- Reduced 73%, NNT = 12

Risk of HbA1c ≥ 5.7% (prediabetes) among those with baseline ≤ 5.7%
- Reduced 67%, NNT 3.4

Table 2. Primary and Secondary Time-to-First-Event Efficacy End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary cardiovascular composite end point†	569 (6.5)	701 (8.0)	0.80 (0.72 to 0.90)	<0.001
Confirmatory secondary end points‡				
Death from cardiovascular causes	223 (2.5)	262 (3.0)	0.85 (0.71 to 1.01)	0.07
Heart failure composite end point§	300 (3.4)	361 (4.1)	0.82 (0.71 to 0.96)	NA
Death from any cause	375 (4.3)	458 (5.2)	0.81 (0.71 to 0.93)	NA
Supportive secondary end points¶				
Cardiovascular expanded composite end point‖	873 (9.9)	1074 (12.2)	0.80 (0.73 to 0.87)	NA
Cardiovascular composite end point with death from any cause**	710 (8.1)	877 (10.0)	0.80 (0.72 to 0.88)	NA
Nonfatal myocardial infarction	234 (2.7)	322 (3.7)	0.72 (0.61 to 0.85)	NA
Nonfatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74 to 1.15)	NA
Hospitalization or urgent medical visit for heart failure	97 (1.1)	122 (1.4)	0.79 (0.60 to 1.03)	NA
Coronary revascularization	473 (5.4)	608 (6.9)	0.77 (0.68 to 0.87)	NA
Unstable angina leading to hospitalization	109 (1.2)	124 (1.4)	0.87 (0.67 to 1.13)	NA
Glycated hemoglobin level ≥6.5%††	306 (3.5)	1059 (12.0)	0.27 (0.24 to 0.31)	NA
Nephropathy composite end point‡‡	155 (1.8)	198 (2.2)	0.78 (0.63 to 0.96)	NA
Glycated hemoglobin level ≥5.7% among patients with baseline glycated hemoglobin <5.7%§§	623 (21.3)	1501 (50.4)	0.33 (0.30 to 0.36)	NA

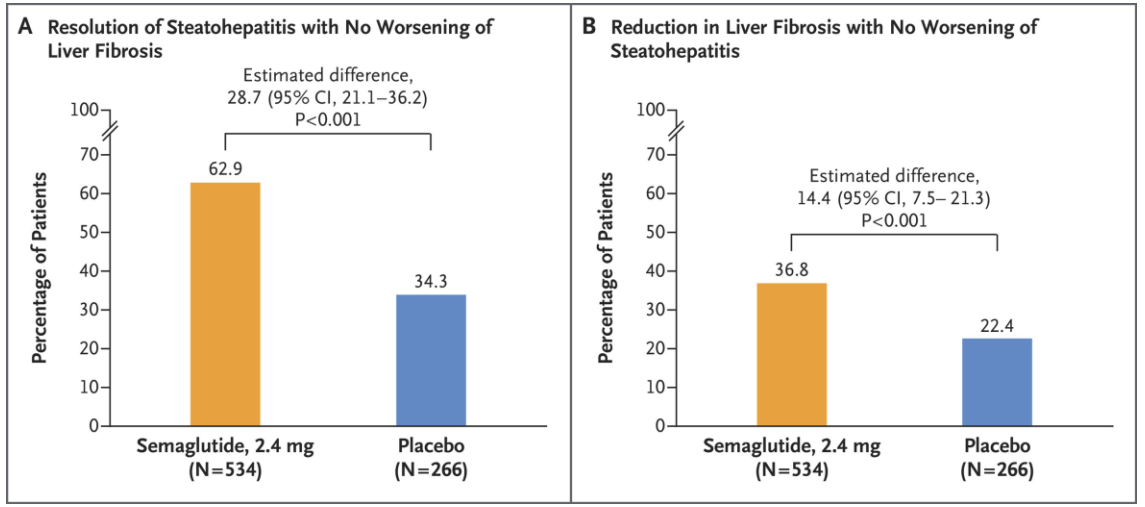
Lincoff AM, et al. N Engl J Med. 2023 Dec 14;389(24):2221-2232.

Semaglutide now approved in the US for MASH F2-F3 fibrosis

ESSENCE trial

- Phase 3 Multi-Center RCT
- Semaglutide vs Placebo
- Biopsy-confirmed MASH and moderate to advanced fibrosis (stage F2 or F3) – *55.9% had T2D and mean BMI was 35*

- **Primary Outcomes:**
  - Steatohepatitis resolution: 62.9% vs 34.3%
  - Fibrosis improvement: 36.8% vs 22.4%
- **Weight Loss**
  - 10.% vs 2.0% body weight reduction



Subgroup	Semaglutide 2.4 mg (N)	Placebo (N)	EDP (95% CI)	Semaglutide 2.4 mg Prop. responders	Placebo Prop. responders
Type 2 diabetes status at baseline					
Yes	296	151	24.42 (14.30; 34.53)	60.1	35.7
No	238	115	33.98 (22.65; 45.31)	66.5	32.5

FDA Approves Treatment for Serious Liver Disease Known as 'MASH'

Sanyal AJ, et al. N Engl J Med. 2025 Jun 5;392(21):2089-2099.

Semaglutide Oral

FDA approved for weight management in adults only
FDA approved for reducing the risk of major adverse cardiovascular events in adults with established cardiovascular disease and obesity or overweight

Mechanism of action:	**GLP1-RA--> hypothalamic neurons-→ increase satiety Decrease gastric emptying → increase satiety**
Doses:	1.5mg PO daily x 4 weeks → 4mg PO daily x 4 weeks→9mg PO daily x 4 weeks→25mg PO daily To be taken on empty stomach with nothing to eat for 30 mins after
Effectiveness:	Placebo-subtracted weight loss: 11.4%
Contraindications:	Personal or family history of medullary thyroid cancer or Type 2 Multiple Endocrine Neoplasia syndrome
Side effects:	Nausea, vomiting, bloating, fullness, diarrhea, constipation, dyspepsia, abdominal pain, fatigue, dizziness.
Cost considerations:	$149-299/month without insurance coverage

Wharton, S. et al OASIS 4 Study Group. Oral Semaglutide at a Dose of 25 mg in Adults with Overweight or Obesity. N Engl J Med. 2025

Tirzepatide

FDA approved for weight management in adults only
FDA approved for adults with moderate-severe OSA with BMI ≥30 kg/m^2

Doses available:	2.5mg SQ Q1W x 4 weeks → 5mg SQ Q1W x 4 weeks-→ 7.5mg SQ Q1W X 4 weeks → 10mg SQ Q1W x 4 weeks → 12.5 mg SQ Q1W-→ 15mg SQ Q1W
Effectiveness:	Average weight loss 22-23% with highest dose
Contraindications:	Personal or family history of medullary thyroid cancer or Type 2 Multiple Endocrine Neoplasia syndrome
Side effects:	Nausea, vomiting, bloating, fullness, diarrhea, constipation, dyspepsia, abdominal pain, fatigue, dizziness, headache, worsening depression, increase in lipase, and rarely renal insufficiency ?? Pancreatitis; worsening diabetic retinopathy
Cost considerations:	$299-499/month without insurance

Jastreboff AM et al. SURMOUNT-1 Investigators. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022

Tirzepatide reduced sleep apnea severity by up to nearly two-thirds in adults with obstructive sleep apnea (OSA) and obesity

SURMOUNT-OSA Study 1 – Participants Not on PAP Therapy		
	Efficacy Estimand Results at 52 Weeks	**Treatment-Regimen Estimand[ii] Results at 52 Weeks**
Primary Endpoint – Change in AHI from Baseline		
Tirzepatide*	**-27.4**	**-25.3**
Placebo	**-4.8**	**-5.3**
Secondary Endpoint – Percent Change in AHI from Baseline		
Tirzepatide*	**-55.0 %**	**-50.7 %**
Placebo	**-5.0 %**	**-3.0 %**
Secondary Endpoint – Percent Change in Body Weight from Baseline		
Tirzepatide*	**-18.1 %**	**-17.7 %**
Placebo	**-1.3 %**	**-1.6 %**

**Tirzepatide MTD is maximum tolerated dose of 10 mg or 15 mg once-weekly. The starting dose of 2.5 mg tirzepatide was increased by 2.5 mg every four weeks until maximum tolerated dose was achieved. Participants who tolerated 15 mg continued on 15 mg as their maximum tolerated dose. Participants who tolerated 10 mg but did not tolerate 15 mg continued on 10 mg as their maximum tolerated dose.*

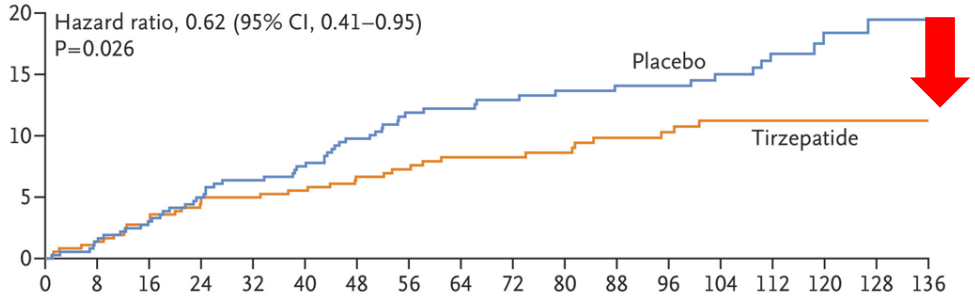
Apnea-hypopnea index (AHI)

Malhotra A,et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. N Engl J Med. 2024

Heart Failure Risk : Tirzepatide reduces worsening HF

- **Tirzepatide: Reduced incidence of composite of adjudicated death from CV causes or a worsening HF event and quality of life and improved HF symptoms in people with obesity and HFpEF with or without T2D**

Death from CV causes or worsening HF event



-38%

- SUMMIT Trial
  - N= 731 (352 w T2D, *17% on baseline SGLT-2i*)
  - Follow-up: 52 weeks
  - Study population: HFpEF EF≥50 +/- T2D+ BMI ≥ 30
  - Primary outcome:
    - CV death or worsening HF event
    - Change in KCCQ score - Increased by 19.5 points vs 12.7 points in placebo

Packer M, et al. N Engl J Med. 2025 Jan 30;392(5):427-437

Tirzepatide Diabetes Prevention: SURMOUNT-1 extension study

Population: 1032 adults with obesity/overweight + prediabetes

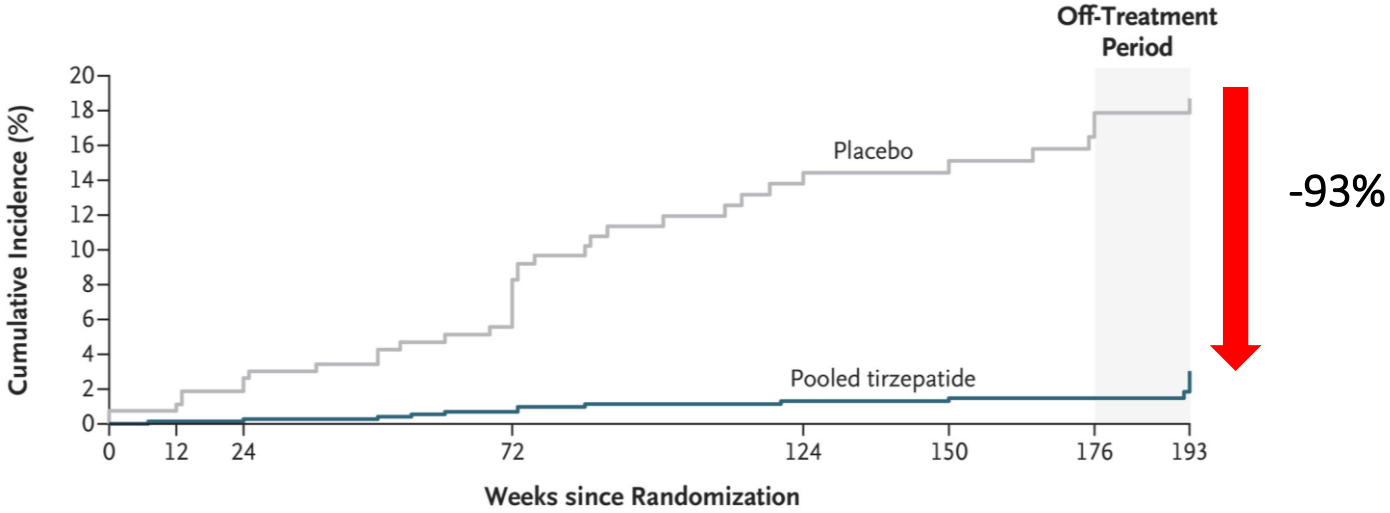
Treatment duration: 176 weeks + 17-week off-treatment follow-up

Risk of progression to diabetes:

During treatment:
→ HR **0.07** (**93% lower risk**)

After stopping treatment:
→ HR **0.12** (**88% lower risk**)

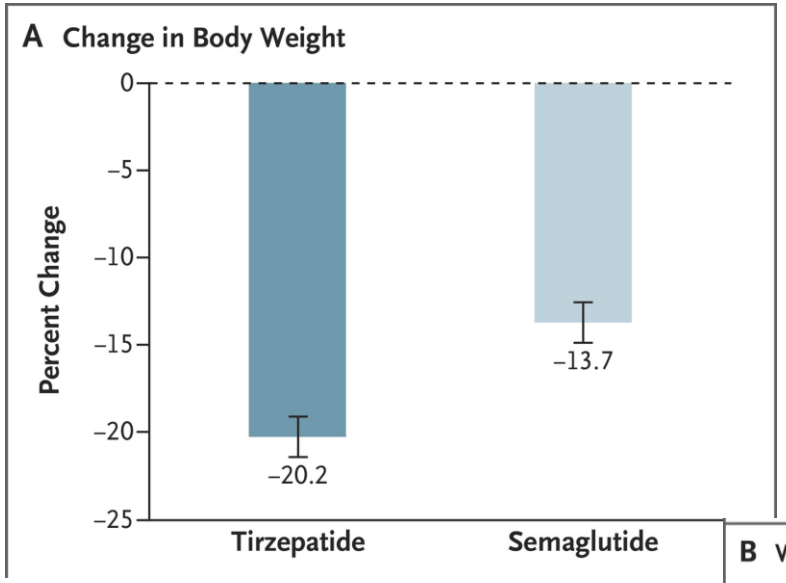
Incidence of Diabetes

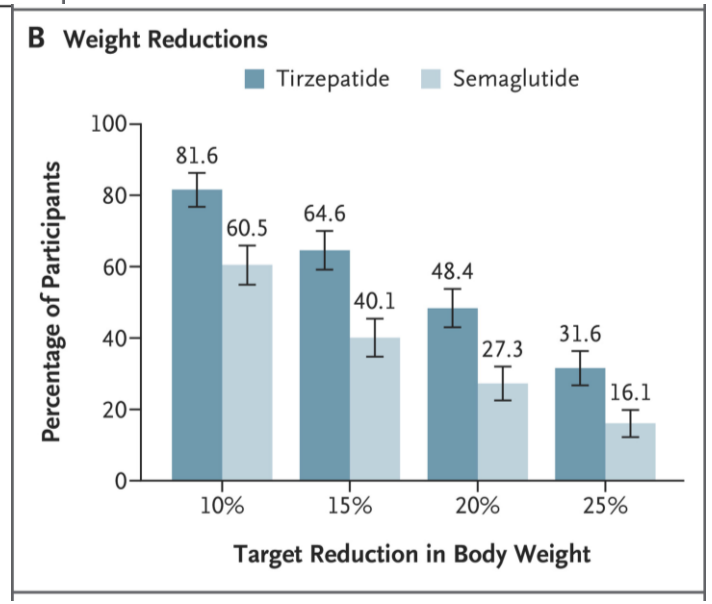


Jastreboff AM, et al. N Engl J Med. 2025 Mar 6;392(10):958-971

SURMOUNT-5: Tirzepatide Superior to Semaglutide for Weight Loss

- Open-label RCT
- Adults with obesity but without diabetes
- 1:1 semaglutide or tirzepatide
- 72 weeks follow up





Aronne LJ,. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity. N Engl J Med. 2025

Orforglipron

FDA approved for adults with obesity or overweight with ≥1 weight-related comorbidity.

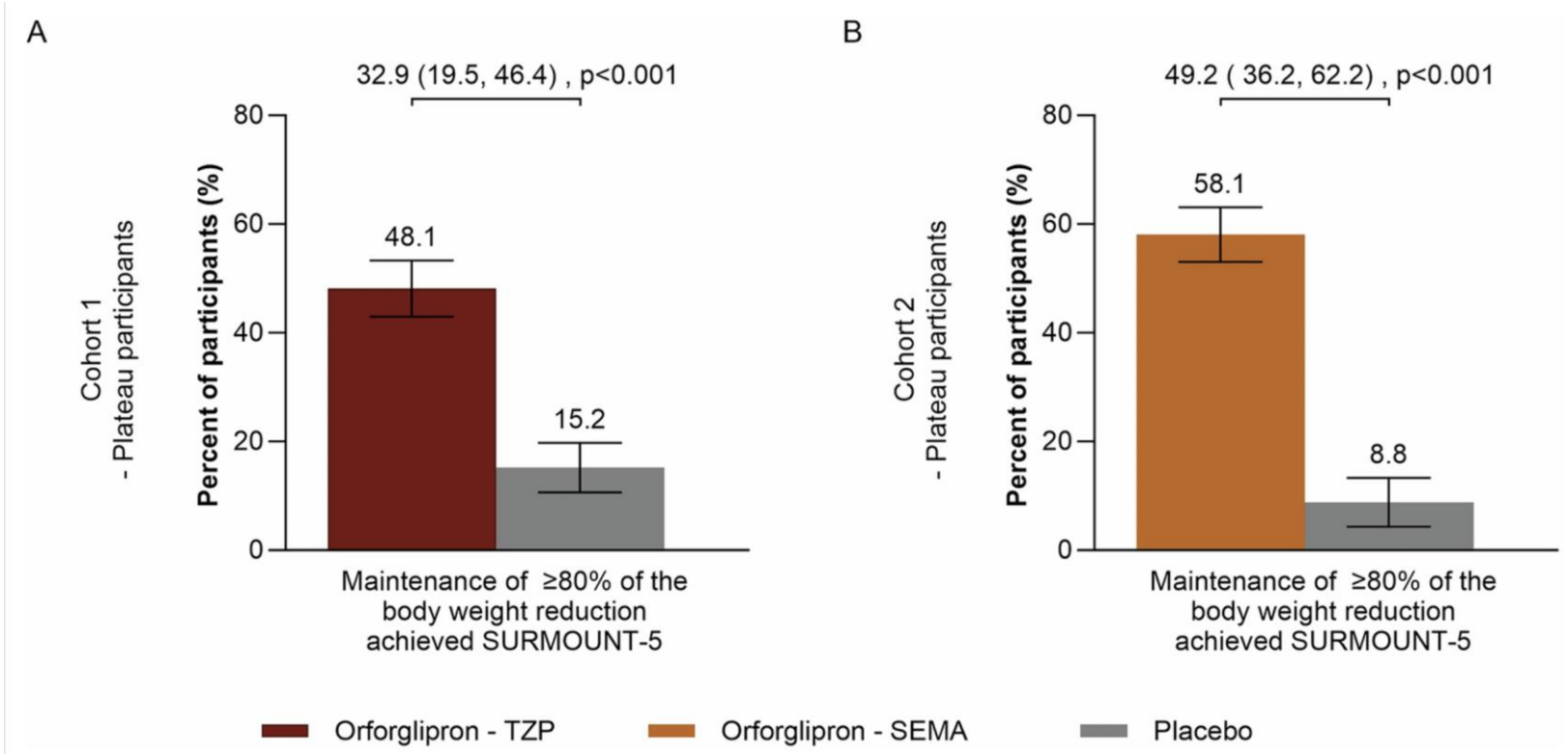
Mechanism of action:	Small-molecule, non-peptide GLP-1 receptor agonist
Doses available:	0.8mg PO QD x 1 month→ 2.5mg PO QD→ 5.5mg PO QD→ 9mg /14.5/17.2mg PO QD (maintenance doses) **Can be take with or without food** **Max dose 9mg if taken with strong CYP3A4 inhibitor**
Placebo-subtracted weight loss:	9.1% TWL (Treatment-regimen estimand): 11.2%
Contraindications:	Personal or family history of medullary thyroid cancer or Type 2 Multiple Endocrine Neoplasia syndrome
Side effects:	Nausea, vomiting, bloating, fullness, diarrhea, constipation, dyspepsia, abdominal pain, fatigue
Cost considerations:	$149-299/month without insurance coverage

Wharton S, et al. N Engl J Med. 2025 Nov 6;393(18):1796-1806..

ATTAIN-MAINTAIN

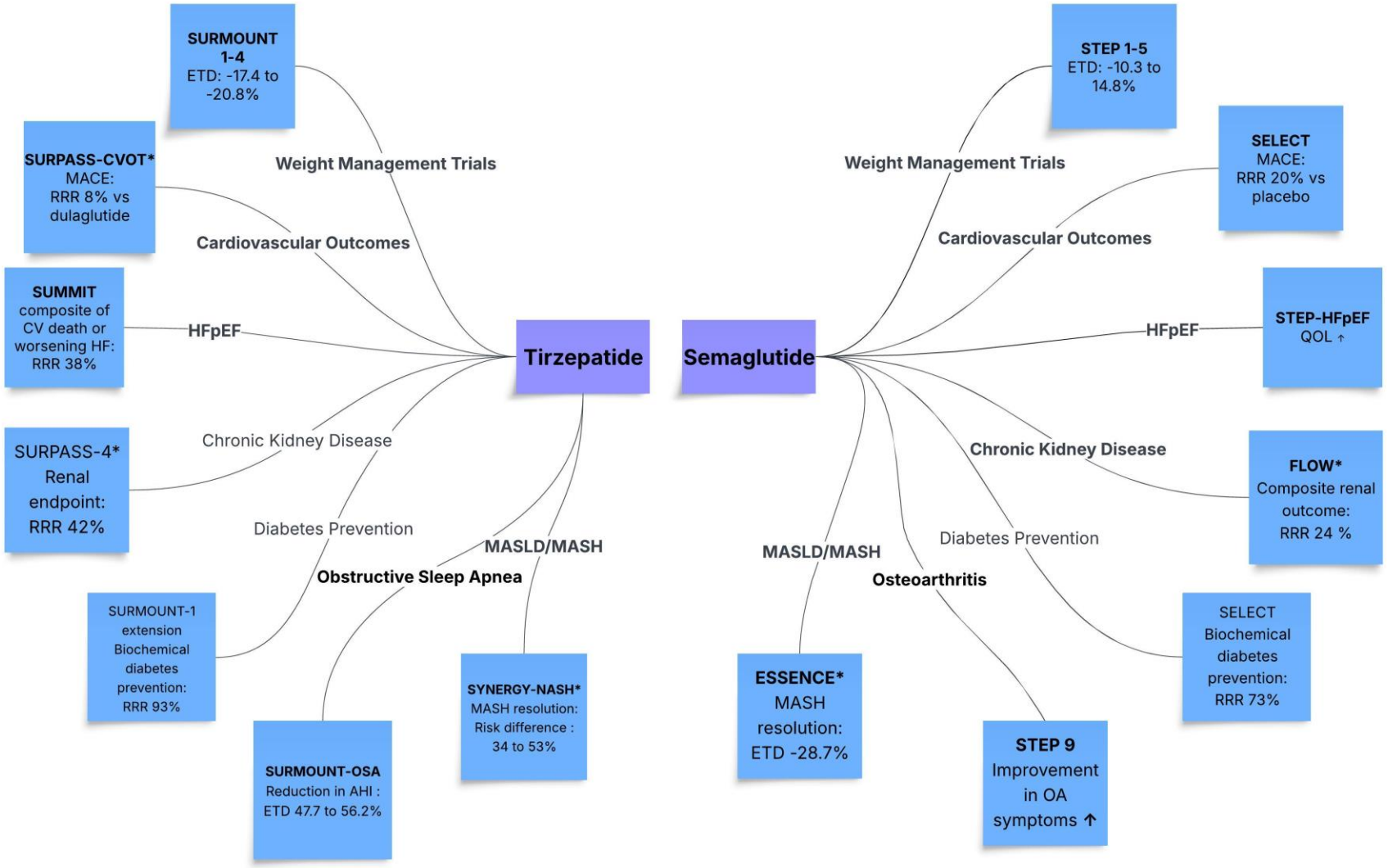
- Can patients who have already lost substantial weight on injectable incretins maintain that weight by switching to an oral GLP-1?
- 52-week maintenance study: 376 participants from SURMOUNT-5

Maintenance of ≥ 80% of body weight reduction



- Aronne LJ, et al. Nat Med. 2026 May 13. doi: 10.1038/s41591-026-04386-7.

Summary – Pleotropic Effects



Accepted-In press Current Atherosclerosis Reports,, Saeed, ZI et al

Polling Question #1

A 52-year-old man with obesity (BMI 37 kg/m²) and moderate obstructive sleep apnea (AHI 18) presents to discuss treatment options. He has been unable to tolerate CPAP despite multiple attempts and is interested in pharmacologic therapy to improve both his weight and sleep apnea.

Which of the following obesity medications is currently FDA approved for the treatment of moderate-severe obstructive sleep apnea in adults with obesity?

Polling Question #1

Which of the following obesity medications is currently FDA approved for the treatment of moderate-severe obstructive sleep apnea in adults with obesity?

a) Phentermine-topiramate
b) Oral Semaglutide
c) Injectable Semaglutide
d) Tirzepatide

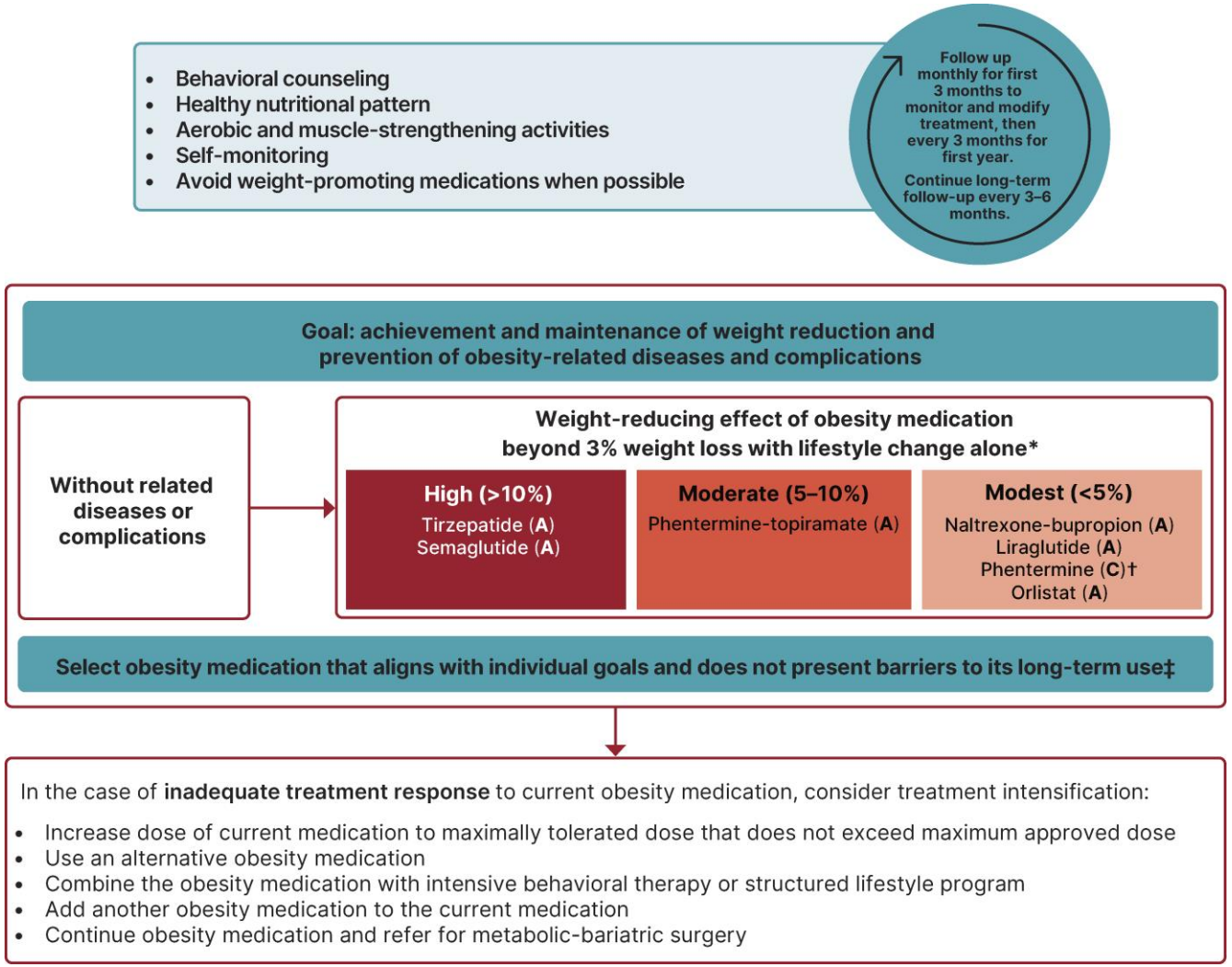
Polling Question #1

Which of the following obesity medications is currently FDA approved for the treatment of moderate-severe obstructive sleep apnea in adults with obesity?

a) Phentermine-topiramate
b) Oral Semaglutide
c) Injectable Semaglutide
d) **Tirzepatide**

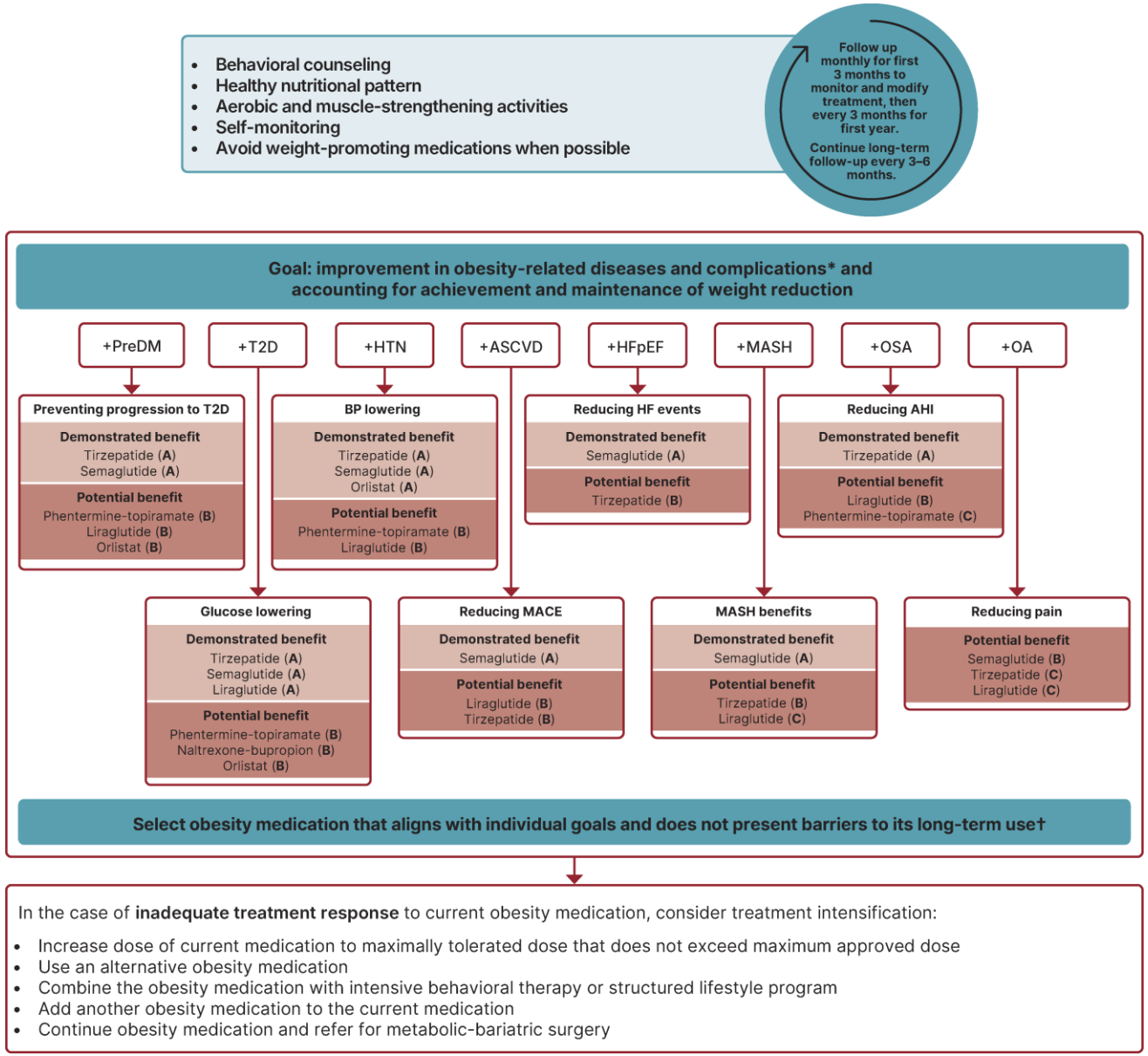
Prescribing Guide

Prescribing AOMs- Person Centered Approach: PreClinical Obesity



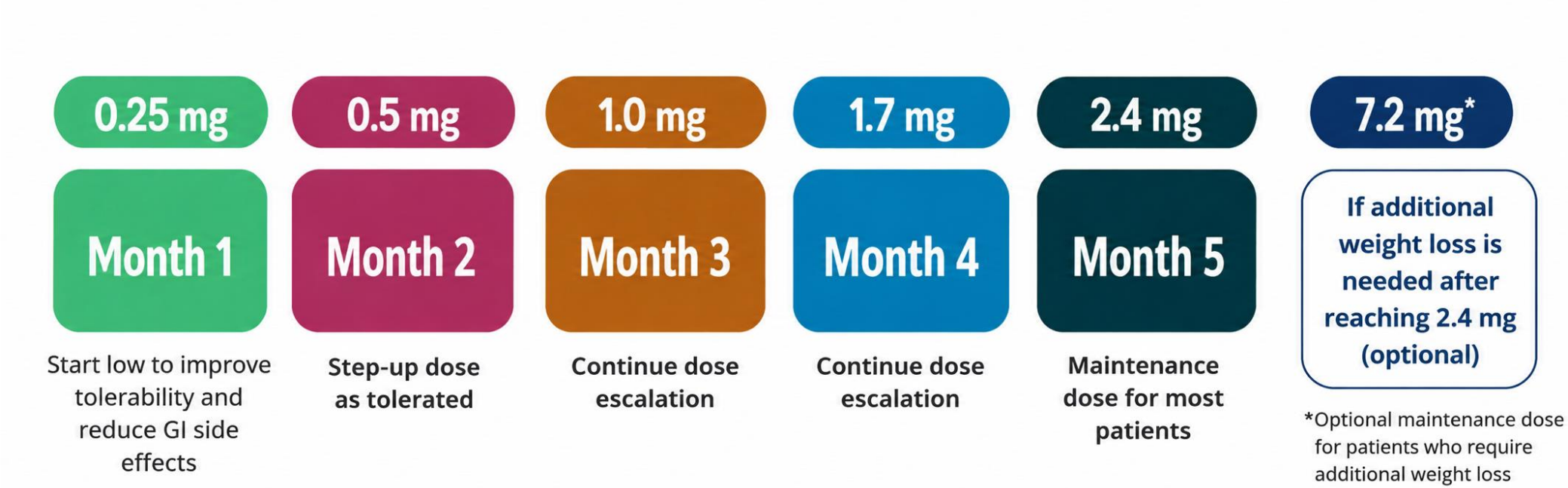
Diabetes, Obesity, and Cardiometabolic CARE. 2026;1(1):5-36. doi:10.2337/doci25-0008

Prescribing AOMs- Person Centered Approach: Clinical Obesity



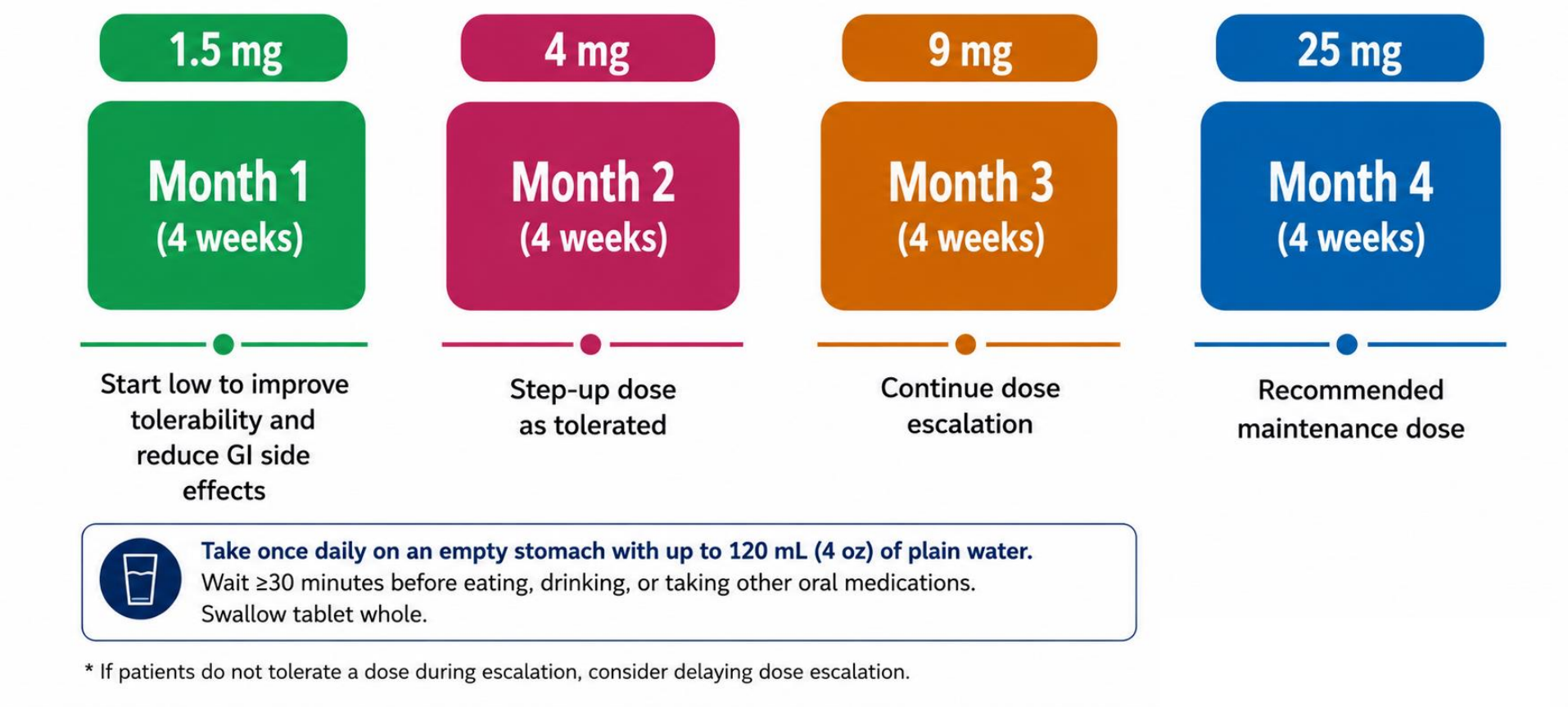
Diabetes, Obesity, and Cardiometabolic CARE. 2026;1(1):5-36. doi:10.2337/doci25-0008

Injectable SemaglutideTitration



Tirzepatide Titration

Oral Semaglutide Titration



Orforglipron Titration

SIDE EFFECTS for GLP-1RAs

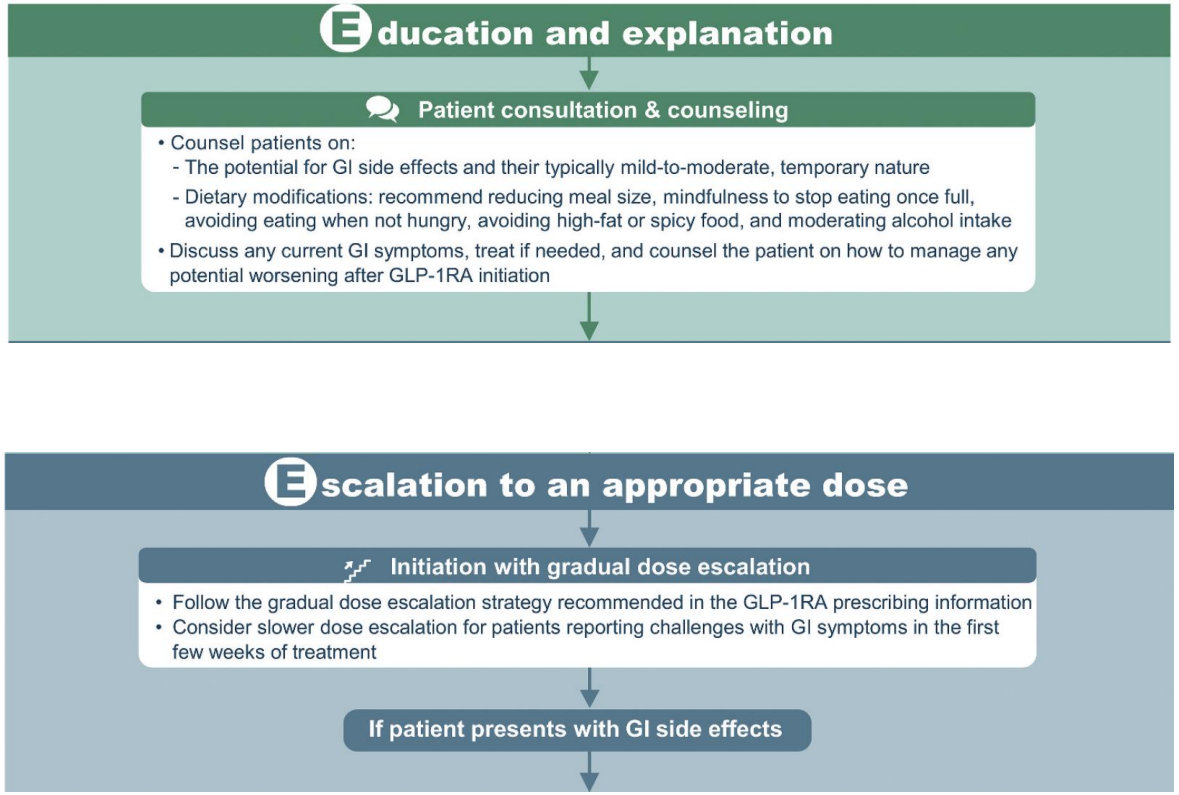
	SCALE (Liraglutide 3.0, placebo %)	STEP-1 (Semaglutide 2.4, placebo,%)	SURMOUNT-1 (Tirzepatide 5/ 10/ 15, placebo %)	OASIS-4 (Oral semaglutide 25mg, placebo %)	ATTAIN-1 (Orforglipron 36mg , placebo %)
Nausea	40.2/ 14.7	44.2/ 17.4	24/ 33/ 31/ 9.5	46.6 / 18.6	33.7/ 10.4
Vomiting	16.3/ 4.1	24.8/ 6.6	18.7/ 21/ 23/ 7	30.9 / 5.9	25.0 / 9.3
Diarrhea	20.9/ 9.3	31.5/ 15.9	8.3/ 10.7/ 12.2/ 1.7	17.6 / 8.8	23.1 / 9.6
Constipation	20.0/ 8.7	23.4/ 9.5	16.8/ 9.7/ 11.3/ 4/2	20.1 / 9.8	20.4 / 8.2
Dyspepsia	9.5 / 3.1	10.3/ 3.5	8.9/ 9.7/ 11.3/ 4.2	18.1 / 8.8	14.0 / 5.0
Abdominal pain	5.2/ 3/5	10.0/ 5.5	4.9/ 5.3/ 4.9/ 3/5	7.4/3.9	7.8 / 3.5
Cholelithiasis	0.8/ 0.4	1.8/ 0.6	1.1/ 1.4/ 0.6/ 0.9	NR	1.5 / 0.8
Gallbladder disorders		2.6/ 1.2		2.5/1	0.8/0.4
Cholecystitis acute	0.5/0.4		0.2/ 0..6/ 0.2/ 0	NR	0.5/0.1
Pancreatitis acute	0.2/ 0	0.2/ 0	0.2/ 0.2/ 0.2/ 0.2	0 / 0	0.3 / 0
Injection site hematoma	5.7/ 7.5		Reaction 2.9/ 5.7/ 4.6/ 0.3	N/A (oral)	N/A (oral)

Mitigating Side Effects

- **START LOW AND GO SLOW**
- Nausea most frequent side effect

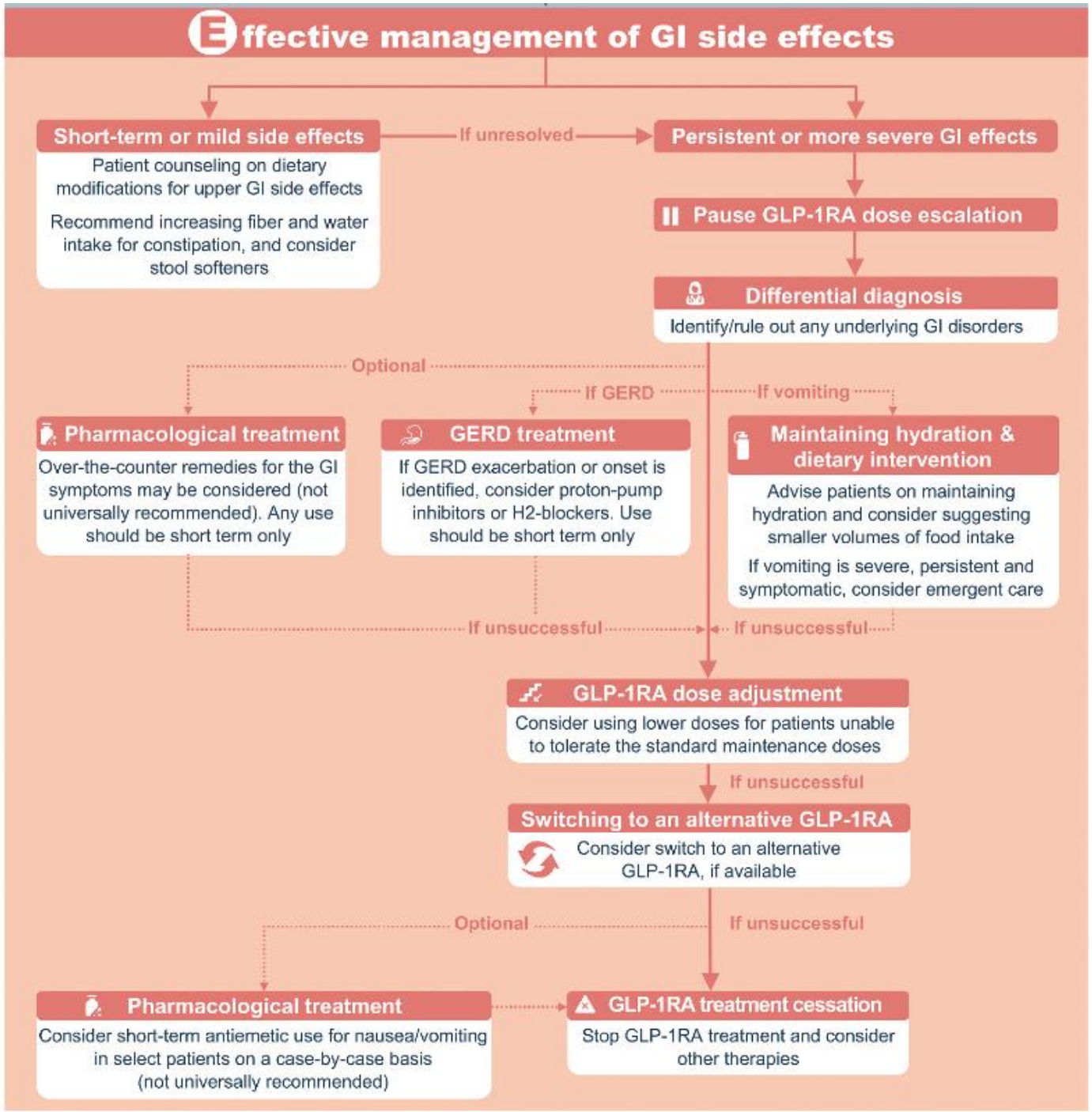
- Prevalence highest during
  first 4-5 weeks of treatment
  - Gastric emptying also slowest
  - Last 8 days from onset

- Constipation - onset in first 16 weeks
  - may last longer than other GI SEs



Gorgojo-Martínez JJ, et al. J Clin Med.2022 Dec 24;12(1):145.
Wharton S et al; Postgraduate Medicine 2022; 134:14-19

Effectively Managing GI side effects



Gorgojo-Martínez JJ, et al. J Clin Med.2022 Dec 24;12(1):145.

Tips to navigate GLP1RA and GIP/GLP1RA shortages

Switch as needed

Low Potency	Medium Potency (Level1)	Medium Potency (Level 2)
• Liraglutide 0.6 mg • ORAL Semaglutide 1.5mg	• Liraglutide 1.2 mg • Semaglutide 0.25 mg • ORAL semaglutide 4 mg	• Liraglutide 1.8 mg • Semaglutide 0.5 mg • Tirzepatide 2.5 mg • Oral Semaglutide 9 mg

High Potency	Very High Potency	Highest Potency
• Liraglutide 2.4 mg and 3 mg • Semaglutide 1.7mg • Tirzepatide 5 mg • Oral Semaglutide 9 mg	• Semaglutide 2.4 mg • Tirzepatide 7.5 and 10 mg • Oral Semaglutide 25mg	• Tirzepatide 12.5 mg and 15mg

Adapted from Whitley HP, Trujillo JM, Neumiller JJ. Clin Diabetes. 2023 Summer;41(3):467-473.
Special Report: Potential Strategies for Addressing GLP-1 and Dual GLP-1/GIP Receptor Agonist Shortages

Tips to navigate GLP1RA and GIP/GLP1RA shortages

Use lower doses if a prolonged period has lapsed since use

Medication	Last dose taken	Manufacturer Recommendations for resuming treatment
Liraglutide	1.8 mg	Resume at 1.2 mg or 0.6 mg if >one week missed
Semaglutide	1.7/2.4mg	If 2 or more consecutive doses are missed, reinitiate dosage escalation at a lower dosage
Tirzepatide	≥ 5 mg	If ≤ 2 doses are missed, reinitiate at the same dose (provided dose adequately tolerated If ≥ 3 doses are missed, reinitiate at 5mg once weekly
Semaglutide PO Orforglipron PO	9 or 25 mg 9mg /14.5/17.2mg	If < 7 doses are missed, reinitiate at same dose (if adequately tolerated) If ≥ 7 doses are missed, consider re-initiating at lower dose Decision can be informed based on patient's prior GI tolerability

Novo Nordisk. Victoza (liraglutide) prescribing information. Bagsvaerd, Denmark, Novo Nordisk, July,2022, Ozempic (semaglutide) injection prescribing information, Plainsboro, NJ.

Whitley HP, Trujillo JM, Neumiller JJ. Clin Diabetes. 2023 Summer;41(3):467-473.

Polling Question #2

Mrs. X comes to you for follow-up of her weight management. She started semaglutide for weight loss 1 year ago and initially her weight went down from 190lbs to 150lbs in the first six months, but she has not lost any weight since then. She is on maximum dose of injectable semaglutide 2.4mg weekly. Her current BMI is 26. She has no other chronic medical conditions. She is asking you if she can come off semaglutide since "it's no longer working".

What do you do?

Polling Question #2

She is asking you if she can come off semaglutide since “it’s no longer working”. What do you do?

a) Continue semaglutide

b) Slowly wean off semaglutide

c) Stop semaglutide now

Polling Question #2

She is asking you if she can come off semaglutide since “it’s no longer working”. What do you do?

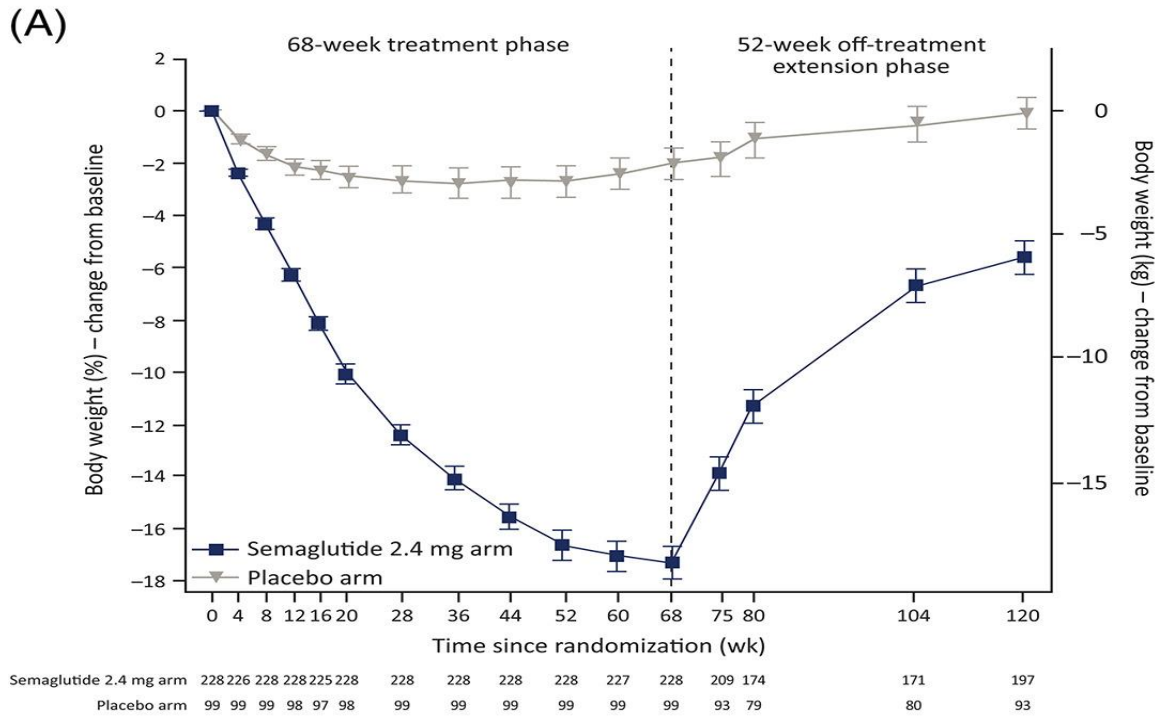
a) **Continue semaglutide**

b) Slowly wean off semaglutide

c) Stop semaglutide now

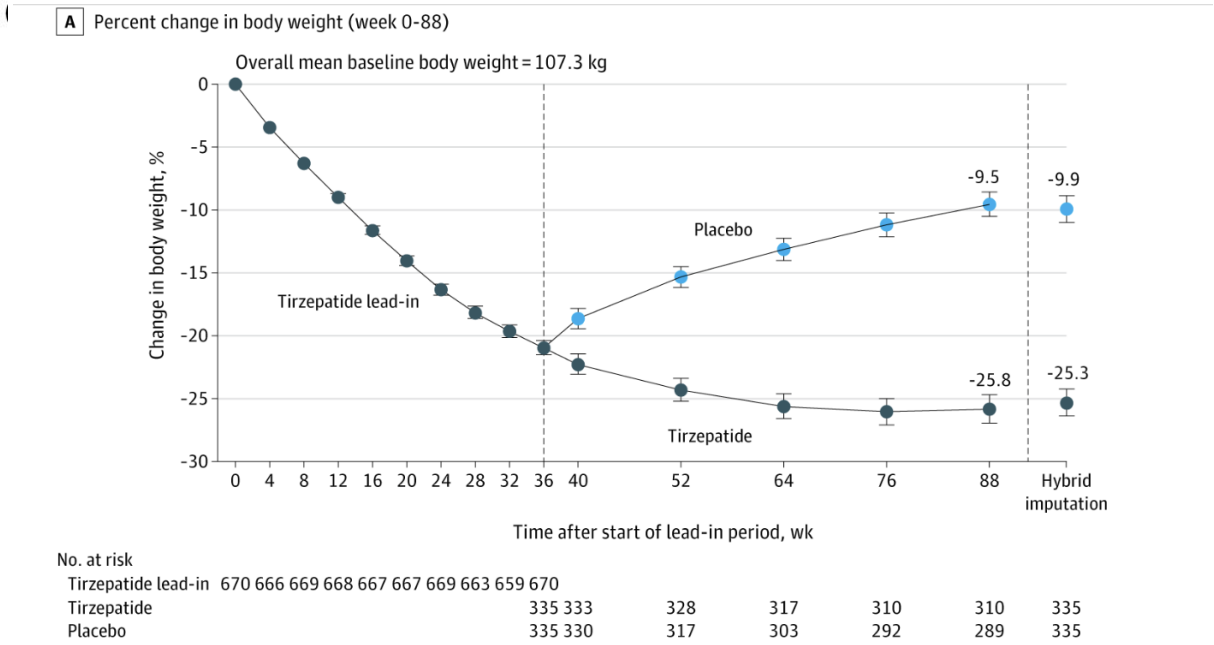
Data from treatment drugs

Semaglutide



Wilding JPH, et al. regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes Obes Metab. 2022.

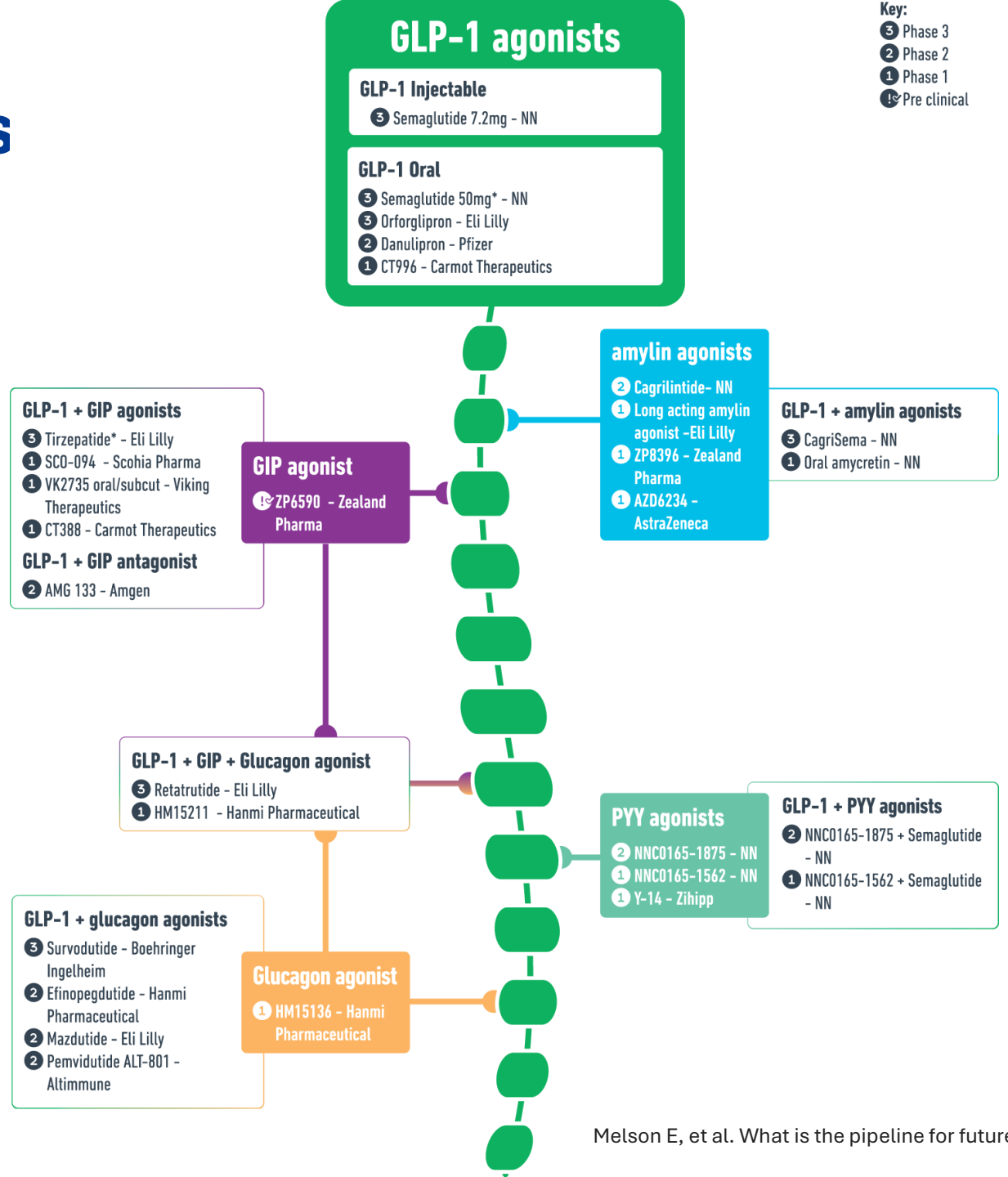
Tirzepatide



Aronne LJ, et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. *JAMA.* 2024;331(1):38–48. doi:10.1001/jama.2023.24945

Pipeline

Newer drugs in the pipeline



Melson E, et al. What is the pipeline for future medications for obesity? Int J Obes (Lond). 2024

MOC Reflective Statement

- Obesity is a **chronic**, relapsing, **serious** but **treatable medical condition** with strong genetic predisposition that has been under-treated and wrongly attributed to personal lifestyle choices alone for too long (and still is).
- We need to change the way medicine is practiced by empowering primary care providers to treat obesity
- Treat obesity early using a **person-centered, complication-based approach** rather than BMI alone.
- New-generation therapies (injectable and oral) now produce **double-digit weight loss** with meaningful improvements in cardiovascular, metabolic, liver, sleep apnea, and heart failure outcomes.
- Many Nutrient-stimulated Hormonal therapies (NuSH) in development

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