WEIGHT LOSS MEDICATIONS

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Allina Health

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OBJECTIVES

Upon completion of this lecture, participants should be able to:

- Understand the prevalence and disease burdens related to obesity
- Compare and contrast medications for weight loss
- Counsel patients on the use of GLP-1 agonists for weight loss

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Diagnostic Criteria

BMI (kg/m^2)	Classification
≤18.5	Underweight
18.5 – 24.9	Normal/healthy weight
25 – 29.9	Overweight
≥30	Obesity

https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html

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Disease Impacts

- US obesity prevalence increased from 30% in 2017 to 42% in 2020
- Patients who have overweight/obesity are at increased risk of:

Hypertension	CAD/stroke	Certain types of cancer
Dyslipidemia	Body pain	Mental illness (e.g., depression, anxiety)
Type 2 diabetes	Sleep apnea	Low qualify of life

https://www.cdc.gov/healthyweight/effects/index.html

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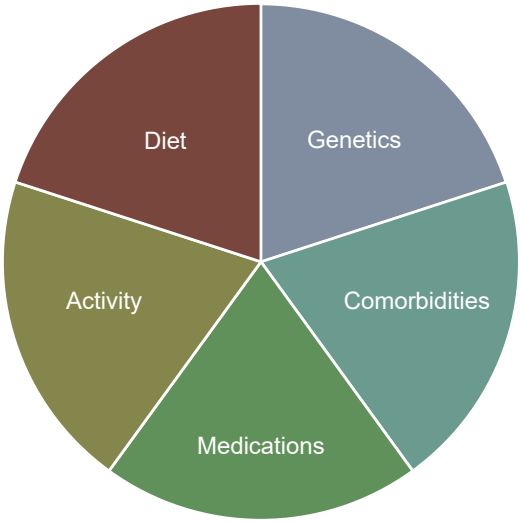
Factors Potentially Affecting Weight



Garvey, WT, et al. *Endocr Pract*. 2016;22(suppl 3):1-203.

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Weight Loss Guidelines

2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Nutrition, American Society for Parenteral and Enteral Nutrition, American Society for Preventive Cardiology, American Society of Hypertension, Association of Black Cardiologists, National Lipid Association, Preventive Cardiovascular Nurses Association, The Endocrine Society, and WomenHeart: The National Coalition for Women With Heart Disease

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY

*W. Timothy Garvey, MD, FACE[1]; Jeffrey I. Mechanick, MD, FACP, FACE, FACN, ECNU[2]; Elise M. Brett, MD, FACE, CNSC, ECNU[3]; Alan J. Garber, MD, PhD, FACE[4]; Daniel L. Hurley, MD, FACE[5]; Ania M. Jastreboff, MD, PhD[6]; Karl Nadolsky, DO[7]; Rachel Pessah-Pollack, MD[8]; Raymond Plodkowski, MD[9]; and Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines**

Gastroenterology 2022;163:1198–1225

GUIDELINES

AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity

Eduardo Grunvald,[1,*] **Raj Shah,**[2,*] **Ruben Hernaez,**[3,4,5,*] Apoorva Krishna Chandar,[6] Octavia Pickett-Blakely,[7] Levi M. Teigen,[8] Tasma Harindhanavudhi,[9] Shahnaz Sultan,[10] Siddharth Singh,[11] and Perica Davitkov,[6,12] on behalf of the AGA Clinical Guidelines Committee

2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for Metabolic and Bariatric Surgery

Dan Eisenberg, M.D.[a,*], Scott A. Shikora, M.D.[b], Edo Aarts, M.D., Ph.D.[c], Ali Aminian, M.D.[d], Luigi Angrisani, M.D.[e], Ricardo V. Cohen, M.D., Ph.D.[f], Maurizio De Luca, M.D.[g], Silvia L. Faria, Ph.D.[h], Kasey P. S. Goodpaster, Ph.D.[d], Ashraf Haddad, M.D.[i], Jacques M. Himpens, M.D., Ph.D.[j], Lilian Kow, B.M.B.S., Ph.D.[k], Marina Kurian, M.D.[l], Ken Loi, M.B.B.S., B.Sc. (Med)[m], Kamal Mahawar, M.B.B.S., M.Sc.[n], Abdelrahman Nimeri, M.D., M.B.B.Ch.[o], Mary O'Kane, M.Sc., R.D.[p], Pavlos K. Papasavas, M.D.[q], Jaime Ponce, M.D.[r], Janey S. A. Pratt, M.D.[a,s], Ann M. Rogers, M.D.[t], Kimberley E. Steele, M.D., Ph.D.[u], Michel Suter, M.D.[v,w], Shanu N. Kothari, M.D.[x]

Jensen, MD, et al. *Circulation*. 2014;129(suppl 2):S102-38.
Garvey, WT, et al. *Endocr Pract*. 2016;22(suppl 3):1-203.
Eisenberg, D, et al. *Surg Obest Relat Dis*. 2022;18(12):1345-56.
Grunvald E, et al. *Gastroenterology*. 2022;163(5):1198-1225.

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Weight Loss Goals

- Benefits seen with losing as little as 5% total body weight
- Initial goal to lose 5-10% of body weight
- Some patients may benefit from additional weight loss

Jensen, MD, et al. *Circulation*. 2014;129(25 suppl 2):S102-38.

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Comprehensive Lifestyle Intervention

LIFESTYLE THERAPY

Evidence-based lifestyle therapy for treatment of obesity should include three components

MEAL PLAN	PHYSICAL ACTIVITY	BEHAVIOR
• Reduced-calorie healthy meal plan • ~500–750 kcal daily deficit • Individualize based on personal and cultural preferences • Meal plans can include: Mediterranean, DASH, low-carb, low-fat, volumetric, high protein, vegetarian • Meal replacements • Very low-calorie diet is an option for selected patients and requires medical supervision Team member or expertise: dietitian, health educator	• Voluntary aerobic physical activity progressing to >150 minutes/week performed on 3–5 separate days per week • Resistance exercise: single-set repetitions involving major muscle groups, 2–3 times per week • Reduce sedentary behavior • Individualize program based on preferences and take into account physical limitations Team member or expertise: exercise trainer, physical activity coach, physical/occupational therapist	An interventional package that includes any number of the following: • Self-monitoring (food intake, exercise, weight) • Goal setting • Education (face-to-face meetings, group sessions, remote technologies) • Problem-solving strategies • Stimulus control • Behavioral contracting • Stress reduction • Psychologic evaluation, counseling, and treatment when needed • Cognitive restructuring • Motivational interviewing • Mobilization of social support structures Team member or expertise: health educator, behaviorist, clinical psychologist, psychiatrist

Garvey, WT, et al. *Endocr Pract*. 2016;22(suppl 3):1-203.

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Bariatric Surgery Candidates

- Patients with BMI ≥35 kg/m^2
- Consider for BMI 30-34.9 kg/m^2 with metabolic disease
- Suggested to adjust threshold to BMI 27.5 kg/m^2 in Asian patients

Eisenberg, D, et al. *Surg Obest Relat Dis*. 2022;18(12):1345-56.

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Weight Loss Medications

- Recommended after inadequate response to lifestyle interventions for patients with:
  - BMI ≥30 kg/m^2

  or
  - BMI ≥27 kg/m^2 with weight-related complications (e.g., dyslipidemia, hypertension, type 2 diabetes)

Grunvald E, et al. *Gastroenterology*. 2022;163(5):1198-1225.

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Weight Loss Medications Withdrawn from Market

- Methamphetamine (abuse/addiction)
- Fenfluramine/dexfenfluramine (cardiac valve problems, pulmonary HTN)
- Phenylpropanolamine (hemorrhagic stroke)
- Sibutramine (MI/stroke)
- Lorcaserin (cancer)

Muller TD, et al. *Nat Rev Drug Discov*. 2022;21(3):201-23.

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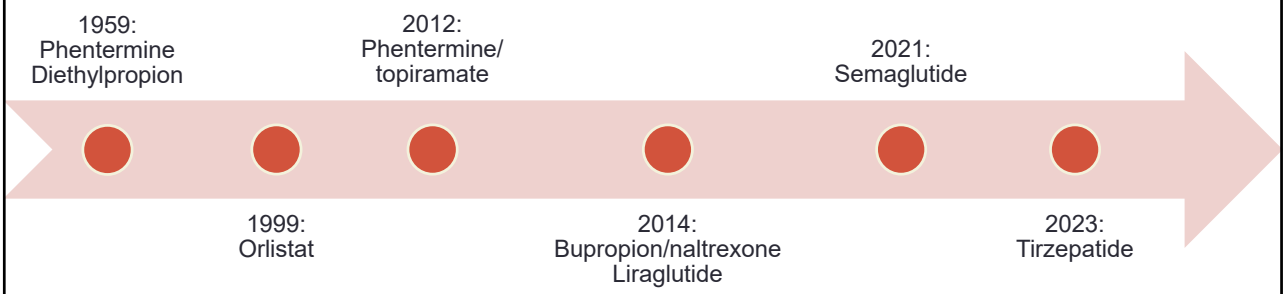
Current Weight Loss Medication Timeline



Muller TD, et al. *Nat Rev Drug Discov*. 2022;21(3):201-23.

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Oral Weight Loss Medications*

Medication	Mechanism of Action	Common Adverse Effects	Contraindications
Orlistat (Xenical®, Alli®)	GI and pancreatic lipase inhibitor (decrease lipid absorption)	Oily stools, oily spotting, fecal urgency, fecal incontinence, vitamin ADEK deficiencies	Cholestasis, malabsorption
Phentermine/topiramate (Qsymia®)	NE agonist/ GABA agonist, glutamate antagonist (suppress appetite)	Paresthesia, dry mouth, constipation, insomnia, cognitive dysfunction, anxiety, depression	Uncontrolled HTN, cardiovascular disease, arrhythmias, hyperthyroidism, glaucoma, history of drug abuse, 'agitated states'
Naltrexone/bupropion (Contrave®)	Opioid receptor antagonist / Dopamine and NE reuptake inhibitor (increase satiety, suppress appetite)	Nausea, headache, constipation, dizziness, dry mouth, vomiting	Uncontrolled HTN, seizures or high risk of seizures, anorexia/bulimia, opioid agonists

*Phentermine and diethylpropion not included (only indicated for treatment up to 12 weeks)

Garvey, WT, et al. *Endocr Pract*. 2016;22(suppl 3):1-203.

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GLP-1 Agonist Mania

Tik Tok

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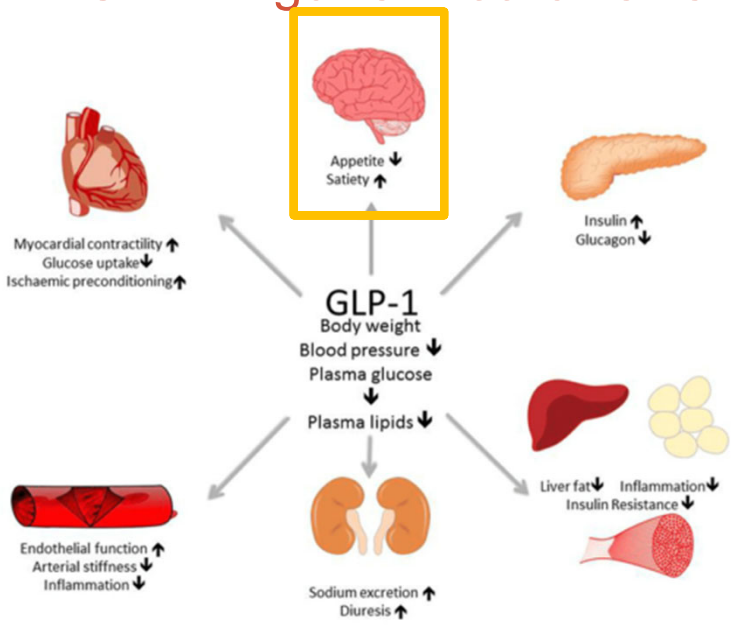
GLP-1 Agonist Mechanisms of Action



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GLP-1 Agonists for Weight Loss

- Liraglutide (Saxenda®) and semaglutide (Wegovy®)
  - Higher dosing than for diabetes treatment
- Common adverse effects:
  - Nausea, vomiting, diarrhea, constipation
- Contraindications:
  - Personal/family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2

Garvey, WT, et al. *Endocr Pract*. 2016;22(suppl 3):1-203.

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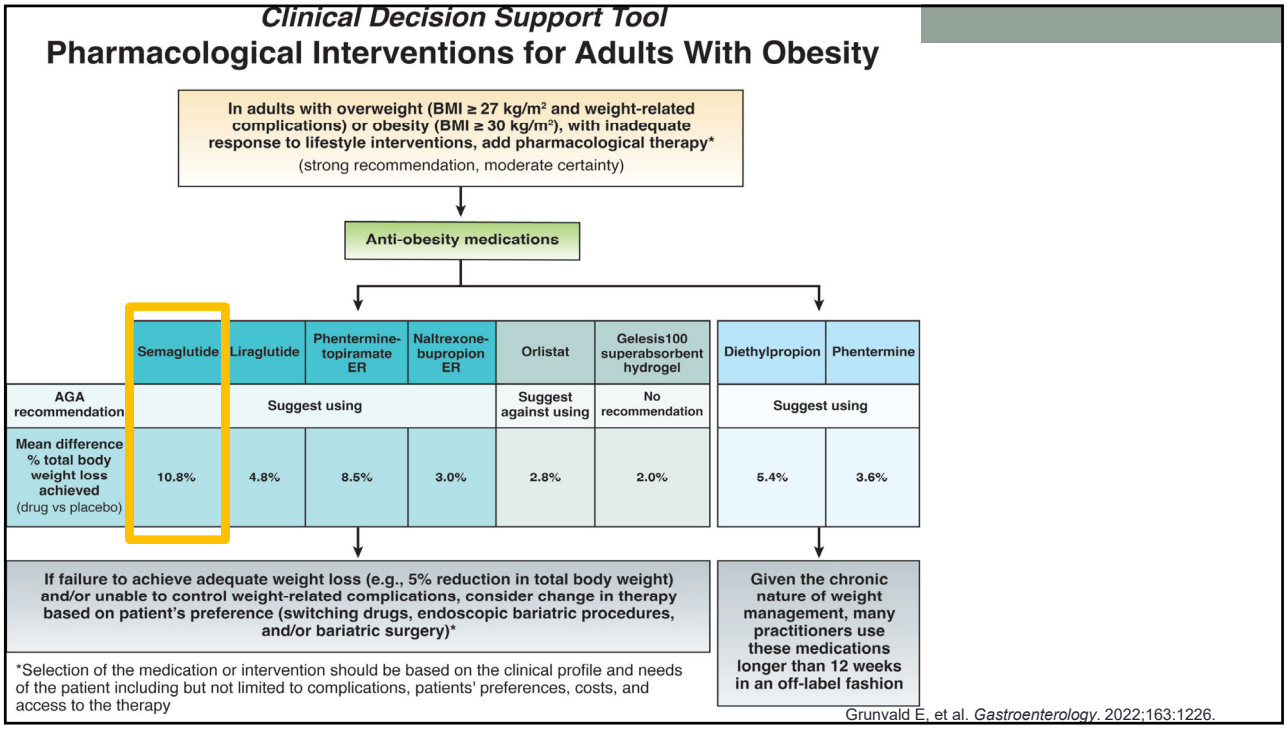

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Semaglutide Formulations

Wegovy® (semaglutide)	Ozempic® (semaglutide)	Rybelsus® (semaglutide)
FDA approved for weight loss	FDA approved for type 2 diabetes	FDA approved for type 2 diabetes
Maximum dose 2.4 mg subQ injection once weekly	Maximum dose 2 mg subQ injection once weekly	Maximum dose 14 mg by mouth once weekly
Autoinjector device (single-use)	Pen/pen needle device	Administration with <4 oz water, on empty stomach, 30 minutes before food/drinks/other medications

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STEP 1 Trial

- Randomized, double-blind controlled trial
- 1961 adults without diabetes and with BMI ≥30, or BMI ≥27 + weight-related complication
- Semaglutide titrated to 2.4 mg weekly vs placebo (both in addition to lifestyle interventions) for 68 weeks
- Co-primary outcomes:
  - Percentage change in body weight
  - Achievement of ≥5% weight loss

Wilding JPH, et al. *N Engl J Med*. 2021;382(11):989-1002.

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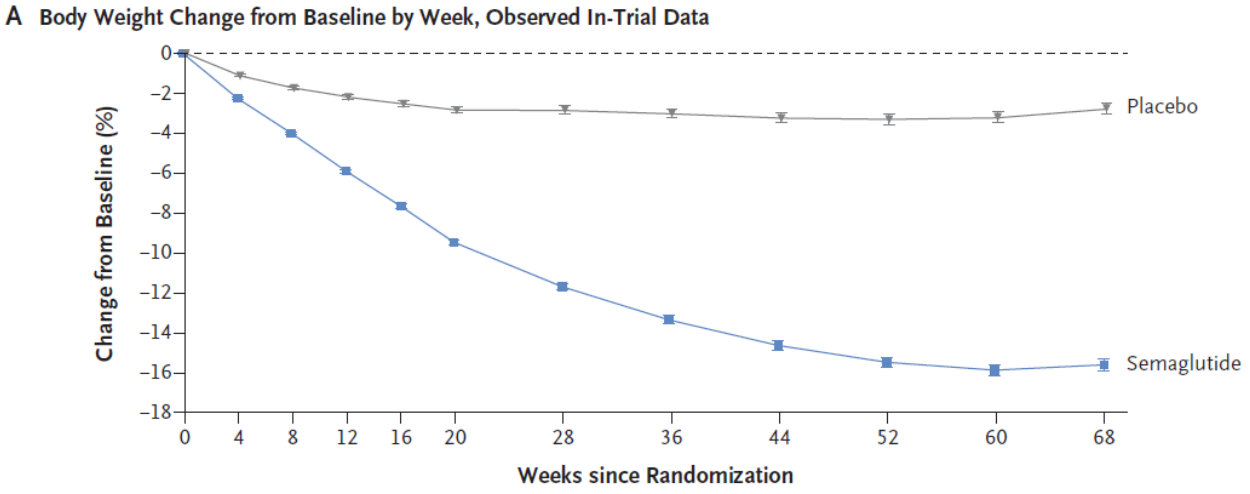
STEP 1 Results



Wilding JPH, et al. *N Engl J Med*. 2021;382(11):989-1002.

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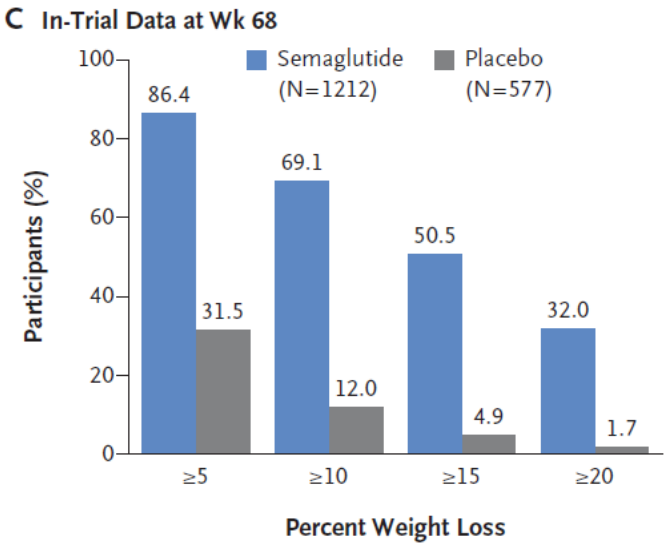
STEP 1 Results



Wilding JPH, et al. *N Engl J Med*. 2021;382(11):989-1002.

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Adverse Effects

- Nausea 44% vs 17%
- Diarrhea 32% vs 16%
- Vomiting 25% vs 7%
- Constipation 23% vs 10%
- Gallbladder disorders 2.6% vs 1.2%
- Acute Pancreatitis 0.2% vs 0%

Wilding JPH, et al. *N Engl J Med*. 2021;382(11):989-1002.

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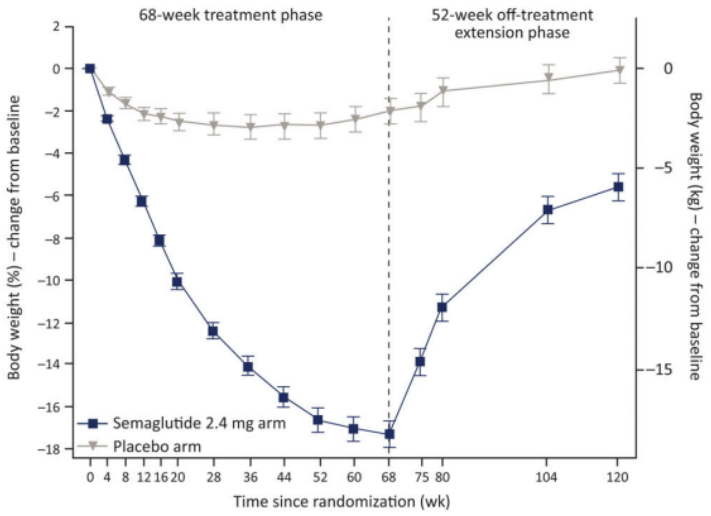
Weight Change after Discontinuation



Wilding, JPH, et al. *Diabetes Obes Metab*. 2022;24(8):1553-64.

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Wegovy® Treatment Duration Beyond 68 weeks?

- 15.2% average weight loss maintained up to 2 years (104 weeks) with extended treatment duration
- Additional data supporting use for up to 4-5 years with maintained weight loss (cardiovascular outcomes trial)

Garvey WT, et al. *Nat Med*. 2022;28(10):2083-91.
Lincoff AM, et al. *N Engl J Med*. 2023;389:2221-32.

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New Therapeutic Target: Tirzepatide

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Tirzepatide (Zepbound®)

- Combined GLP-1/GIP agonist
  - Thought to have synergistic incretin effects ('twin'cretin)
- FDA approved for weight loss 12/2023
- Previously approved for type 2 diabetes under name Mounjaro® (equivalent dosing)

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SURMOUNT-1 Trial

- Phase 3, double-blind randomized controlled trial
- 2359 adults without diabetes and with BMI ≥30, or BMI ≥27 + weight-related complication
- Tirzepatide (titrated to 5, 10 or 15 mg) subQ injection weekly or placebo (both in addition to lifestyle interventions) for 72 weeks
- Co-primary outcomes:
  - Percentage change in body weight
  - Achievement of ≥5% weight loss

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

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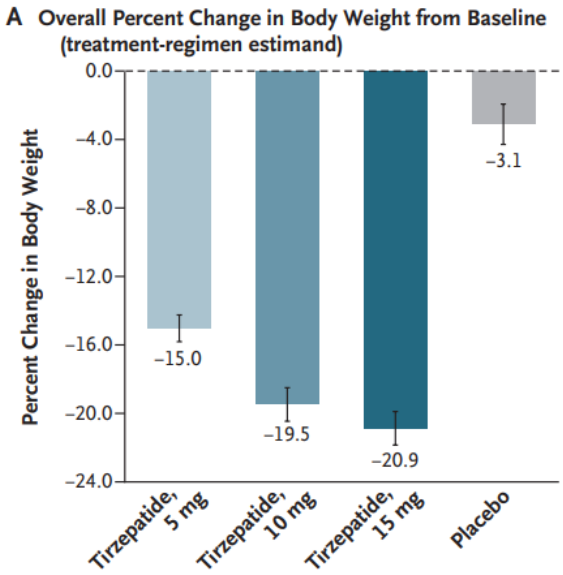
SURMOUNT-1 Results



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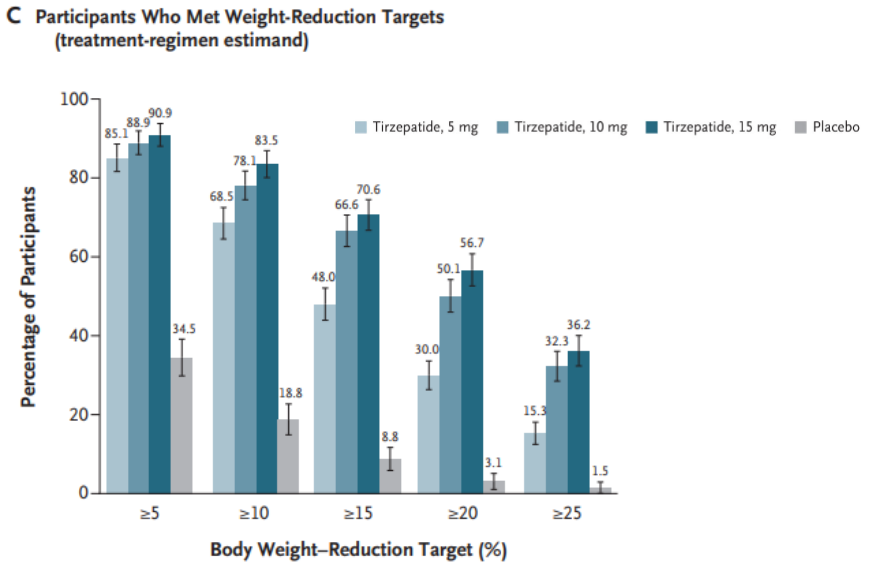
SURMOUNT-1 Results



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

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Semaglutide vs Tirzepatide

	Semaglutide (Wegovy®)	Tirzepatide (Zepbound®)
Dosing	0.25-2.4 mg subQ weekly. Titrate monthly to maximum tolerated dose	2.5-15 mg subQ weekly. Titrate monthly to at least 5 mg weekly, can consider further titration
Efficacy	~10-15% weight loss after ~1 year	~15-20% weight loss after ~1 year
Cardiovascular outcomes data	Yes	Unknown
Cost	~$1300/month	~$1100/month
Impacts on oral hormonal contraception	Clinically significant effects not seen	Yes. Recommended to use backup method for 4 weeks after initiation of tirzepatide and for 4 weeks after each dose escalation
Impacts on absorption of other medications	Noted to delay gastric emptying, monitoring effects of other medications is recommended	

Skelley, JW, et al. *J Am Pharm Assoc*. 2023;S1544-3191(23)00370-9.
Lincoff AM, et al. *N Engl J Med*. 2023;389:2221-32.

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GLP-1 Agonist Clinical Pearls

- Titrate to target dose for maximum weight loss
- GI side effects often improve over time
- Eating smaller meals and avoiding greasy/fatty foods can help minimize GI side effects
- Greatest weight loss success was seen in combination with diet and exercise

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Accessibility: Insurance Coverage/Supply

- Weight loss medication coverage varies
  - Specific criteria for use if covered
  - Medications for 'weight loss' not currently covered by Medicare
    - GLP-1 agonists covered if for diabetes
    - Wegovy® may now be covered by some plans in patients with cardiovascular disease + elevated BMI
- Copay cards available for commercially insured patients
- Mounjaro®, Ozempic® and Rybelsus® only covered for patients with diabetes
- Supply shortages

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GLP-1 Agonists and Surgery

- Can delay gastric emptying, especially with new start/dose titration
- Concerns about risk of regurgitation/aspiration during general anesthesia
- Risk increases in patients with GI side effects
- American Society of Anesthesiologists recommendations:
  - Do not take once daily GLP-1 agonists on day of surgery
  - Do not take once weekly GLP-1 agonists for 1 week prior to surgery
  - If GLP-1 agonist not held as recommended, proceed with 'full stomach' precautions

American Society of Anesthesiologists Consensus-Based Guidance on Preoperative Management of Patients (Adults and Children) on Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists | American Society of Anesthesiologists (ASA) (asahq.org)

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Other Lingering Questions

- At what point is re-titration needed after holding GLP-1 agonist?
- Optimal duration of therapy
- Long-term safety profile
- Older patients

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Summary

- Obesity prevalence in the US is increasing, which may pose significant health burdens
- Comprehensive lifestyle interventions are recommended for all patients trying to lose weight
- Semaglutide and tirzepatide are the most efficacious medications available for weight loss at this time

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Questions?

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