Hot Topics in Medicine: Updates in the Treatment of Overweight and Obesity

July 2, 2025

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Learning Objectives

- Recognize weight bias and develop approaches for addressing obesity and overweight with patients
- Discuss lifestyle intervention recommendations for patients with overweight and obesity.
- Discuss medical treatment options for obesity and overweight

Outline

Prevalence of Obesity

Diagnosing Overweight and Obesity

- Treatment of Obesity
 - Oral medications
 - ▶ Injectables: GLP1 and dual GLP1/GIP agonists the data
- Clinical Approach to Overweight and Obesity
 - Weight Bias
 - Obtaining a history
 - Setting Expectations
 - Monitoring for complications

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2011





*Sample size <50, the relative standard error (dividing the standard error by the prevalence) \geq 30%, or no data in a specific year.

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2015





*Sample size <50, the relative standard error (dividing the standard error by the prevalence) \geq 30%, or no data in a specific year.

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2019





*Sample size <50, the relative standard error (dividing the standard error by the prevalence) \geq 30%, or no data in a specific year.

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2023



*Sample size <50, the relative standard error (dividing the standard error by the prevalence) \geq 30%, or no data in a specific year.



If current trends continue, in 2030:

- MORE than HALF of the global population, will be living with either overweight or obesity
 - ▶ 1 in 4 people (nearly 2 billion) will have obesity.
- Lower income countries are disproportionately affected by Obesity
- Childhood obesity rates are rising more rapidly than in adults
 - Rates are predicted to **double** among boys to 208 million (100% increase)
 - Rates are predicted to more than double among girls to 175 million (125% increase)
- Global economic impact of overweight and obesity will reach \$4.32 trillion annually by 2035 ~3% of global GDP

The World Obesity Atlas https://data.worldobesity.org

Diagnosing overweight and obesity

- Most common:
 - ▶ $BMI = Mass (kg) / Height (m)^2$
- Children and teens age <18</p>
 - ► Overweight BMI ≥85th percentile
 - ► Obesity BMI ≥95th percentile

BMI	Classification	
18.5 – 24.9	Normal weight	
25.0 – 29.9	Overweight	
≥30.0	Obese	
30.0 – 34.9	Class I Obesity	
35.0 – 39.9	Class II Obesity	
≥ 40.0	Class III Obesity	

BMI is not a perfect screening tool

Most common:

- ▶ BMI = Mass (kg) / Height (m)²
- Affected by ethnicity

Other measures:

- Waist:Hip Ratio (WHR)
- ► Waist Circumference (WC)
- WC correlates with intraabdominal visceral fat on CT better than WHR
- WC is associated with all-cause and CV mortality independent of BMI

BMI	Classification	Asians
18.5 – 24.9	Normal weight	18.5 – 22.9
25.0 – 29.9	Overweight	23.0 - 26.9
≥30.0	Obese	≥27.0
30.0 - 34.9	Class I Obesity	27.0 - 29.9
35.0 – 39.9	Class II Obesity	30.0-34.9
≥ 40.0	Class III Obesity	≥35.0

(WHO 2004)

Ross et al. Nat Rev Endo. Volume 16 | March 2020 | 177

Diagnosing overweight and obesity

Most common:

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- Affected by ethnicity

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≥ 40.0	Class III Obesity	≥35.0

(WHO 2004)

<u>Medical Therapy Indicated:</u> BMI ≥27 with a weight-related comorbidity BMI ≥30

Weight-related medical conditions

- Diabetes
- Dyslipidemia
- CVD (HTN, HF, CAD, AFib)
- Stroke/VTE
- GI (MASLD/MASH, GERD, gallbladder disease)
- MSK (Osteoarthritis, Gout)
- Reproductive (PCOS)
- Respiratory (OSA/OHS, Asthma)
- Cancer
- Depression?

e.g. people with obesity or overweight are 2-4 times more likely to develop Endometrial Cancer and twice as likely to develop kidney, liver, gastric cancers (CDC)

WHI data indicate that $\geq 5\%$ intentional weight loss was associated with reduced cancer risk

Luo et al. JNCI Cancer Spectr. 2019 Dec; 3(4): pkz054.



NATIONAL CANCER INSTITUTE

cancer.gov/obesity-fact-sheet apted from Centers for Disease Control & Prevention

Outline

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How much weight loss is needed?

Clinically relevant weight loss: ~5-10%

- Based on large-scale lifestyle intervention studies
 5-7% weight loss led to improvements in metabolic parameters such as BP, lipids, glucose levels.
 - Diabetes Prevention Program (DPP)
 - Finnish Diabetes Prevention Study

6 medications are FDA-approved for long-term use for weight loss

Medicatior	1	Dosage form	Approximate Weight loss above placebo
Orlistat (Alli OTC)		PO TID	3%
Phentermin (Qsymia)	e/Topiramate	PO Daily	9%
Naltrexone (Contrave)	/Bupropion	PO BID	4%
Liraglutide (Saxenda)		INJ Daily	6%
Semaglutic (Wegovy)	le	INJ Weekly	12-13%
Tirzepatide (Zepbounc		INJ Weekly	18%

Orlistat (Alli)

- Lipase inhibitor reduced
 intestinal fat absorption
- RCT, N = 238; mean BMI 37
- Mean weight loss x 52 wks
 - Placebo: -5.4%
 - Orlistat: -8.5%
 - 1/3 of patients had \geq 5%
- A/E: GI (8% d/c)
- Vitamin supplementation (ADE) recommended



Finer et al. Int Journal of Obesity vol 24, 306–313 (2000)

Naltrexone/Bupropion (Contrave)

- Appetite suppression, reduced cravings
- RCT N = 800; mean BMI 36-7
- Mean weight loss x 56 wks
 - Placebo: -5.1%
 - Contrave: -6.1-6.4%
 - Contrave + IBT: -9.3%
- A/E: GI, HA, dizziness, fatigue - 46% d/c (24% due to A/E)
- CI: seizures, eating d/o, opioids

*IBT = intensive behavioral therapy



Wadden et al. Obesity. 2011 (1):110-20 Greenway et al. Lancet 376, 9741, 21–27 2010, p595-605 Apovian et al. Obesity. 2013 (5):935-43 Halpern et al. Expert Opinion on Drug Safety 16;1, 2017

Phentermine/ Topiramate (Qsymia)

- Appetite suppression
- RCT: N =2500; mean BMI 42
- Mean weight loss x 56 wks (+Extension up to 2 years)
 - Placebo: -1.6% (-1.8%)
 - Dose 7.5/46 mg: -5.2% (-9.3%)
 - Dose 15/92 mg: -10.9% (-10.5%)
- A/E: dry mouth, dizziness, constipation, insomnia, brain fog paresthesia (2% d/c)
- Monitor K, Cr, HCO3, bHCG
- CI: CAD, Pregnancy, hyperthyroid, glaucoma



Garvey et al. Amer J of Clin Nut 95;2. 2012, 297-308

6 medications are FDA-approved for long-term use for weight loss

Medication	Dosage form	Approximate Weight loss above placebo
Orlistat (Alli OTC)	POTID	3%
Naltrexone/Bupropion (Contrave)	PO Daily	4%
Phentermine/Topiramate (Qsymia)	PO BID	9%
Liraglutide (GLP1) (Saxenda)	INJ Daily	6%
Semaglutide (GLP1) (Wegovy)	INJ Weekly	12-13%
Tirzepatide (GLP1+GIP) (Zepbound)	INJ Weekly	18%

GLP1 mechanisms of action

- Endogenous T_{1/2} 1-2 min
- Clinical applications focused on extending half-life
- Initially developed as a drug for T2DM
- Pts noted to have significant weight loss





Intro to the GLP1/Dual Agonist Trials:

STEP

SURPASS

SELECT

SUSTAIN First published in 2017; **semaglutide** at lower doses 0.5 and 1.0 mg/week **reduces A1c 1.6 –1.8%** in patients <u>with T2DM.</u> (Ozempic) -> Weight also down 10-14 lbs

First published in 2021; **semaglutide** at the higher dose of 2.4 mg/week reduces **WEIGHT** in patients *with Obesity without* T2DM. (Wegovy)

First published in 2021; **tirzepatide reduces A1c 1.9 – 2.1%** in patients <u>*with* T2DM</u>. (Mounjaro)

SURMOUNT First published in 2022; tirzepa with Obesity without T2DM.

First published in 2022; **tirzepatide** reduces **WEIGHT** in patients *with Obesity without* **T2DM**. (Zepbound)

Published in 2024: **semaglutide** reduces risk of MACE in patients with Obesity **without T2DM**

STEP1: Semaglutide for weight loss (Wegovy)





- Double-blind RCT, N = 1961
- ► BMI ≥ 30 or ≥27 with ≥ 1 weight-related condition, NO DM
- Intervention
 - Lifestyle intervention: Q4 week counseling on 500 kcal deficit, 150 min per week activity
 - +Semaglutide 2.4 mg weekly
 - OR +Placebo
- T = 68 weeks followed by 7-week washout
- Primary outcomes: weight, 5% weight loss

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

STEP 1: Demographic and Clinical Characteristics of the Participants at Baseline

STEP



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

STEP 1: Effect of Semaglutide, as Compared with Placebo on Body Weight.



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

- Mean weight loss with semaglutide:
- 14.9% (230 →195 lbs)
- Mean weight loss with placebo:
 2.4% (230# →224#)

STEP

86% of participants on
semaglutide had at least 5%
weight loss (clinically significant)
vs 31.5% with placebo

Adverse effects:

- Primarily GI
- 7% of patients discontinued drug (vs 3% in placebo)

STEP 1 Extension: 2 year follow up off semaglutide x 12 months



N = 327; mean age 48-50; 66%
 Women, 75% white, BMI 38

STEP

- Mean wt loss at 12 mo: 17% on semaglutide vs 2% placebo
- After 1 year OFF therapy mean weight loss 6% (vs 0% placebo):
 - 2/3 of the weight regained at 1 year – what happens with longer follow up?
- Other cardiometabolic improvements also returning to baseline (e.g. A1c, BP)

Wilding et al. Diabetes Obesity Metabolism, Volume: 24, Issue: 8, Pages: 1553-1564. 2022

STEP 5 = 2 year continuation of semaglutide 2.4 mg weekly





- N = 304 , mean age 47, ~75% women, 90% White, BMI 38.5
- Primary end points weight loss, and 5% weight loss.
- Semaglutide group average15% weight loss (vs 2.6% placebo)
- 77% achieved 5% weight loss

Garvey et al. Nat Med 28, 2083–2091 (2022).

*Important to set expectations about continued need for medical therapy

SURMOUNT – Tirzepatide for weight loss



≥5% Weight Reduction at 72 Weeks



- Phase 3 double-blind RCT, N = 2539
- Mean age 45y, 67% women, 70% White, Mean BMI 38
- Intervention x 72 weeks;
 - +Lifestyle counseling re: -500kcal diet and 150 min/week activity +

SURMOUNT

- ▶ Tirzepatide 5, 10, 15 mg weekly
- ► Or Placebo
- Primary outcomes: weight, 5% weight loss
- Adverse effects: Primarily GI (4-7% discontinued)

Jastreboff et al. N Engl J Med 2022; 387:205-216

SURMOUNT-4: Stopping treatment with tirzepatide leads to weight regain

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



- Phase 3 RCT
- 36-week open label runin (N = 783)

SURMOUNT

- 52 week double-blind, placebo-controlled period (N = 670 randomized)
- Max tolerated dose of tirzepatide (10 or 15 mg weekly)

ORIGINAL ARTICLE

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Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

Authors: A. Michael Lincoff, M.D. , Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., SELECT Trial Investigators^{*} Author Info & Affiliations

Published November 11, 2023 | N Engl J Med 2023;389:2221-2232 | DOI: 10.1056/NEJMoa2307563

VOL. 389 NO. 24

ORIGINAL ARTICLE

Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

Authors: Mikhail N. Kosiborod, M.D., Mark C. Petrie, M.D., Barry A. Borlaug, M.D., Javed Butler, M.D., Melanie J. Davies, M.D., G. Kees Hovingh, M.D., Dalane W. Kitzman, M.D., +25, for the STEP-HFpEF DM Trial Committees and Investigators^{*} Author Info & Affiliations

Published April 6, 2024 ORIGINAL ARTICLE

f in 🖂

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

f X in ⊠

Authors: Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D.
, Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D.
, Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators Author Info & Affiliations

Published May 24, 2024 | N Engl J Med 2024;391:109-121 | DOI: 10.1056/NEJMoa2403347 | VOL. 391 NO. 2

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

Authors: A. Michael Lincoff M D 💷 Kirstine Brown-Frandsen M.D. Helen M. Colhoun, M.D. John Deanfield, M.D., Scott SELECT Trial Investigat FDA-APPROVED INDICATIONS FOR SEMAGLUTIDE Published November VOL. 389 NO. 24 2017- Ozempic approved for treatment of T2DM 2021 – Wegovy approved for treatment of Obesity/Overweight 2022 – Wegovy approved for treatment of Obesity/Overweight in children \geq 12 years old 2024 – Wegovy approved for secondary prevention of CV death and myocardial infarction, stroke in patients with Overweight/Obesity in 🖂 e in 2025 – Ozempic Approved to reduce risk of CKD progression in patients with T2DM with CKD , Peter Rossing, M.D., D.M.Sc. ወ Authors: Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D. 回 , Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D. ወ , Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators* Author Info & Affiliations Published May 24, 2024 | N Engl J Med 2024;391:109-121 | DOI: 10.1056/NEJMoa2403347 | VOL. 391 NO. 2

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ORIGINAL ARTICLE

f in ⊠

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

Authors: Rohit Loomba, M.D. , Mark L. Hartman, M.D., Eric J. Lawitz, M.D., Raj Vuppalanchi, M.D., Jérôme Boursier, M.D., Ph.D., Elisabetta Bugianesi, M.D., Ph.D., Masato Yoneda, M.D., Ph.D., , for the SYNERGY-NASH Investigators^{*} Author Info & Affiliations

Published June 8, 2024

ORIGINAL ARTICLE

f in 🖾

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

Authors: Atul Malhotra, M.D., Ronald R. Grunstein, M.D., Ph.D., Ingo Fietze, M.D., Terri E. Weaver, Ph.D., Susan Redline, M.D., M.P.H., Ali Azarbarzin, Ph.D., Scott A. Sands, Ph.D., +5, for the SURMOUNT-OSA Investigators^{*} Author Info & Affiliations

Published June 21, 2024 | DOI: 10.1056/NEJMoa2404881



Coming soon:

- Oral GLP1 agonists Semaglutide, Orforglipron and others
 - >90% of patients have \geq 5% weight loss
 - Average weight loss up to ~15%
- Dual agonists with other incretin hormones
- Triple agonists (e.g. Retatrutide GLP1, GIP, glucagon)
 - ▶ >90% of patients have \geq 5% weight loss
 - ► Average weight loss up to ~25%

FDA accepts filing application for oral semaglutide 25 mg, which if approved, would be the first oral GLP-1 treatment for obesity

NEWS PROVIDED BY NOVO NORDISK INC. → May 02, 2025, 14:27 ET

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Addressing Weight Bias and An Approach to Discussing Weight

Weight bias = Implicit or explicit negative attitude towards someone because of their weight

Weight bias

- Exists among healthcare professionals
- Impacts patient outcomes
- Create a supportive/welcoming environment:
 - Appropriately sized chairs in the waiting room and clinic without arms
 - Scale in a private or semi-private location
 - Appropriate-sized equipment such as blood pressure cuffs
- Discussing weight during the visit:
 - Ask permission
 - Avoid attributing all health issues to a person's weight
 - Less emphasis on weight and greater emphasis on beneficial effects of healthy lifestyle (diet, sleep, mental health and physical activity)

Obtaining a Weight History

- Was weight a concern for you as a child?
 - ► Early onset (< 5-10 yo)+ hyerphagia → consider genetic testing</p>
- ▶ When did you feel like weight first became a concern?
- What has been your usual adult weight?
- What is your highest adult weight?
- What approaches have you tried and what has/hasn't worked?
- Were there any life events or medications/medical problems that led to weight gain/loss?
- Establish <u>health-related</u> goals



Initiating GLP1a and dual agonist therapy



- Contraindications to use (boxed warning)
 - Personal or family history of Medullary Thyroid Cancer
 - ▶ 1 to 2 % of thyroid cancers in the United States
 - ▶ 75% sporadic, 25% associated with MEN2
 - Multiple endocrine neoplasia syndrome type 2 (MEN 2).
 - ▶ Rare: 1:30,000, Autosomal Dominant
 - Relative contraindication: Pancreatitis
 - Gallstone-related pancreatitis is a concern with rapid weight loss.
- ▶ Titration start low, go slow
 - Weekly for liraglutide and monthly for semaglutide/tirzepatide
 - ► No side effects
 - No excess/rapid weight loss

Injectables: Setting Expectations

- Real-world discontinuation rates are high (>40-60%)
 - Side effects
 - Cost/Coverage
- Side effects are common (>80-90%)
- In clinical trials, weight loss is initially rapid but plateaus at 6-12 months
- Long-term therapy (similar to treatment of other metabolic disease)
 - Discontinuation leads to weight regain
- Medications are an adjunct to aid success with lifestyle change (it's still hard work!)

Follow up and Monitoring: Lifestyle intervention is key to long-term success

- Physical activity for weight loss: 150-300 min per week
- Monitor for Sarcopenia / Osteopenia
 - Optimize protein intake* (lean dairy/meat, plant-based proteins)
 - ▶ 1-1.5g/kg IBW for weight loss in addition
 - Resistance exercises lift weights/use resistance bands to build muscle
 - ▶ 15-20 minutes 2x per week
- Monitor for Excess weight loss, nutrition deficiency
 - -1-2 lbs per week is recommended pace
 - Dietician referral to set macronutrient goals
- Optimize sleep
- Adjust medications for other conditions:
 - ▶ HTN, Diabetes, Thyroid disease or other weight-based medications

* if your pt has CKD – consult with their nephrologist

3 final thoughts...

1. Medical therapy is approaching the efficacy of metabolic and bariatric surgery



*With insurance (Lexicomp accessed 6/30/25) **Out-of-pocket from the manufacturer \$500/mo) ***OTC = \$36/mo

Collazo-Clavell Mayo Clin Proc. n June 2019;94(6):933-935

2. These medications are less expensive in other countries

List prices of drugs used for weight loss in the U.S. and peer nations

	 Ozempic (semaglutide, injection) 	Rybelsus (semalglutide, tablets)	Wegovy (semaglutide, injection)	Mounjaro (tirzepatide, injection)
U.S.	\$936	\$936	\$1,349	\$1,023
• Japan	\$169	\$69	-	\$319
Canada	\$147	\$158	-	-
+ Switzerland	\$144	\$147	-	-
Germany	\$103	-	\$328	-
Netherlands	\$103	\$203	\$296	\$444
	\$96	\$103	-	-
👯 United Kingdom	\$93		-	-
🌄 Australia	\$87	-	-	-
France	\$83	-	-	-

Note: List prices in \$USD based on web searches as of August 15, 2023. Prices are for one-month supply of Ozempic 1mg, Rybelus 7mg, Wegovy 2.4mg, and Mounjaro 15mg. Some drugs are not available in all countries and prices were unable to be found in other countries. Some drugs are approved for diabetes and prescribed off-label for weight loss.

Source: KFF analysis • Get the data • PNG



Kaiser Family Foundation Aug 2023

3. Obesity is a condition of disrupted fat metabolism - weight is homeostatically regulated



- Energy expenditure in food-restricted mice (diet) decreased
- Energy expenditure in the semaglutide-treated group remained at baseline levels.
 - ► →Semaglutide maintains metabolic activity (i.e. prevents compensatory downregulation of energy expenditure) despite weight loss

Incretin-based therapies, like bariatric surgery, modify the weight (fat mass) set point.

People on Drugs Like Ozempic Say Their 'Food Noise' Has Disappeared For some, it's a startling side effect.

🛱 Share full article 🔗 🗍 🖵 1.4K



By Dani Blum



"It is hard to explain what life is like on this medication to people who don't have trouble controlling their weight. I'm not hungry all the time. I'm not thinking about food incessantly. I'm not obsessing about what I wish I could eat and what I can't. My mental health, and even my temperament, improved so much that my whole family rejoiced."

Aaron E. Carroll (@aaronecarroll) is the chief health officer for and a distinguished professor of pediatrics at Indiana University.

https://www.nytimes.com/2023/06/21/well/eat/ozempic-food-noise.html https://www.nytimes.com/2023/09/09/opinion/weight-loss-antidepressants-stigma.html

Take home points:

- Obesity is a metabolic disease based on biology, not willpower (calories in = calories out is NOT what the current data supports!).
- Clinically Important weight loss: 5% -10%
- Incretin-based therapies (e.g. GLP1a/GIP) represent a new era of metabolic disease treatment and are approaching the efficacy of bariatric surgery
- Long-term therapy is important
 - Analogous to other chronic disease therapy
 - Discontinuation leads to weight regain in most patients
- Lifestyle interventions (including but not limited to diet, activity and sleep) are still the foundation of weight maintenance

Thank you!