Comprehensive Review of Obesity Medications Including Incretin-Based Therapies

Robert F. Kushner, MD
Professor, Emeritus
Departments of Medicine and Medical Education
Northwestern University Feinberg School of Medicine
Chicago, IL
rkushner@northwestern.edu
www.drrobertkushner.com

CONTINUING EDUCATION COMPANY

1

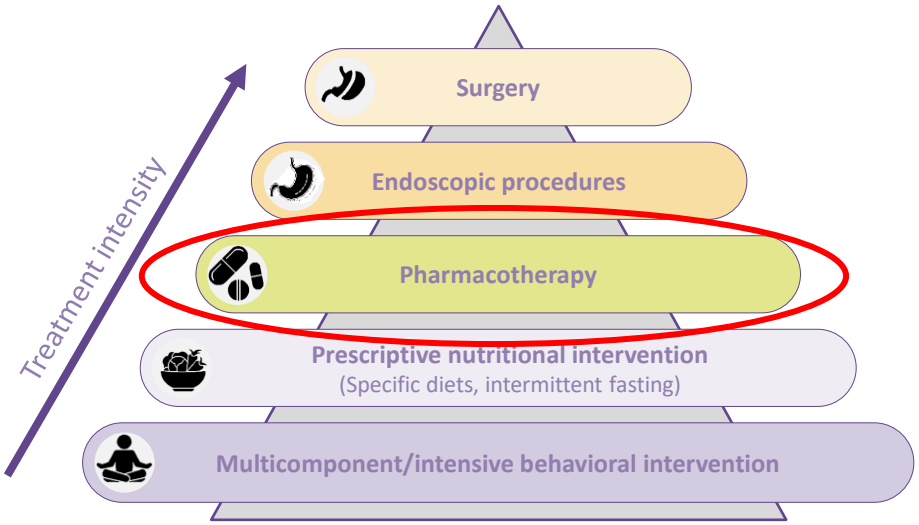
Disclosure

Advisory Board: AbbVie; Antag; AstraZeneca; Boehringer Ingelheim; Currax; Eli Lilly; Novo Nordisk; Structure; Viking Therapeutics; Weight Watcher

CONTINUING EDUCATION COMPANY

2

Obesity Treatment Pyramid



Northwestern Medicine® Feinberg School of Medicine

1. Tucker S et al. *Curr Obes Rep*. 2021;10(3):396-408. 2. Eisenberg D et al. *Obes Surg*. 2023;33(1):3-14.

3

What Is the Primary Purpose of Adjunctive Medications Used in the Treatment of Obesity?

The primary purpose of obesity medications is to -

- Impact the appetite dysregulation of the disease,
- Support adherence to lifestyle interventions by helping patients adhere to a lower calorie diet and changing their relationship with food, and
- Facilitate weight loss and improvements in health

Indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management

BMI of ≥30 or ≥27 with a weight-related complication or comorbidity*

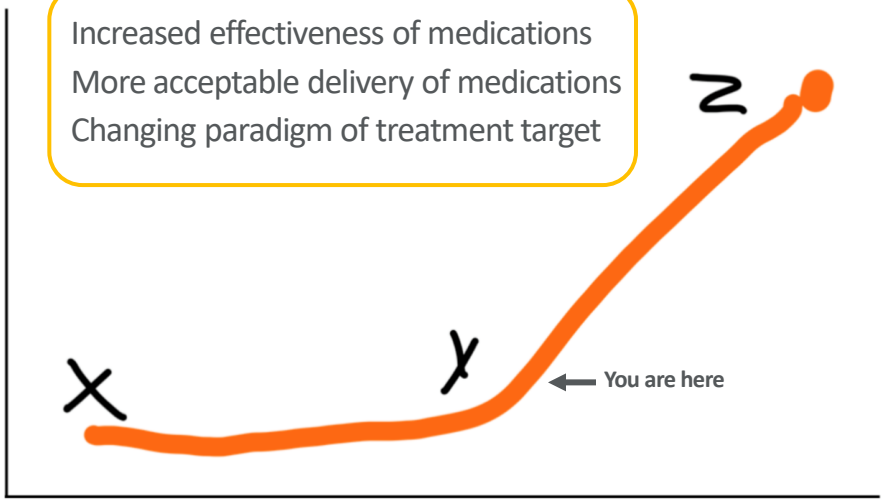
Northwestern Medicine® Feinberg School of Medicine

*BMI is no longer a criteria for Qsymia, Wegovy, and Zepbound

4

Inflection Point in Obesity Pharmacology

Increased effectiveness of medications
More acceptable delivery of medications
Changing paradigm of treatment target



Northwestern Medicine
Feinberg School of Medicine

5

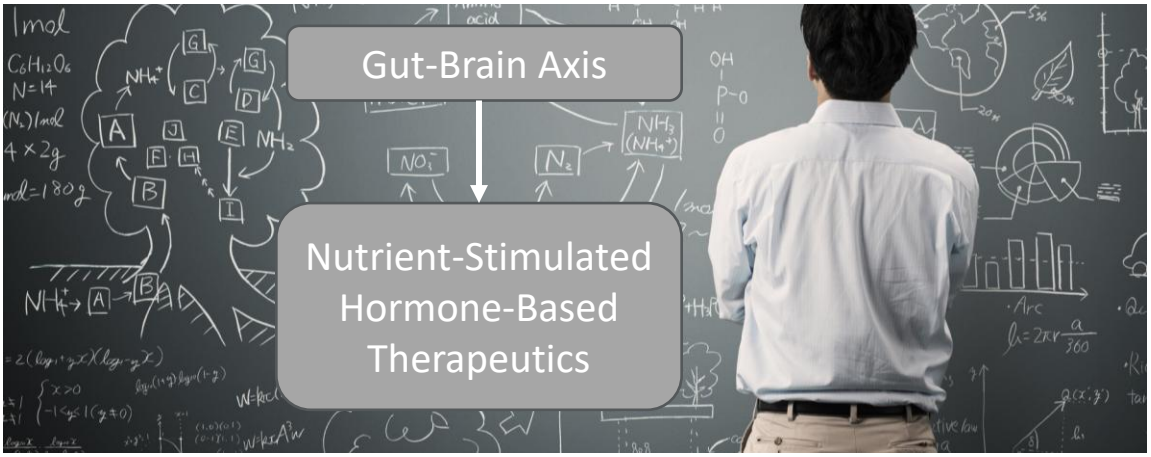
11 Key Points to Know About Obesity Medications

1. Paradigm Shift: Gut-brain axis
2. Primary action is through appetite regulation (except orlistat)
3. Efficacy
4. Heterogeneity of Treatment Effect (HTE)
5. Look for Early Response
6. Note Withdrawal Response
7. Benefits of Continued Use
8. Improved Metabolic Risk Factors
9. GLP-1 has Pleotropic Effects
10. Side Effects
11. Dose Escalation

Northwestern Medicine
Feinberg School of Medicine

6

1. A Paradigm Shift

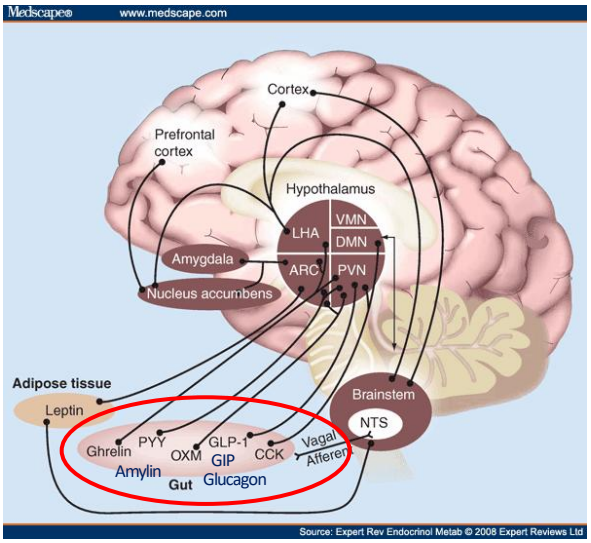


Northwestern Medicine
Feinberg School of Medicine

7

The Gut-Brain Axis

Nutrient-Stimulated Hormones



GUT

PYY= peptide YY

GLP-1 = Glucagon-like peptide 1

GIP = glucose dependent insulinotropic polypeptide

OXM=Oxyntomodulin

CCK=Cholecystokinin

BRAIN

LHA = lateral hypothalamic area

ARC = arcuate nucleus

VMN = ventromedial hypothalamus

DMN = dorsomedial hypothalamic nucleus

PVN = paraventricular nucleus

NTS = nucleus tractus solitarius

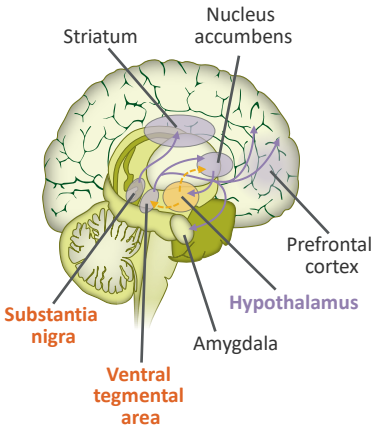
Northwestern Medicine
Feinberg School of Medicine

8

Integrated CNS Pathways Play a Key Role in Regulating Eating Behavior, Appetite, Cravings, and Body Weight

Homeostatic System
Hunger / Satiety

- Primarily driven by the arcuate nucleus of the **hypothalamus**
- Detection and integration of energy state information
  - Leptin, insulin
- Lateral hypothalamus projects to the VTA and receives input from the nucleus accumbens



Hedonic or Reward System

- Dopaminergic pathways from the **VTA or substantia nigra** to regions such as:
  - Striatum (movement, reward salience)
  - Nucleus accumbens (reward, addiction)
  - Prefrontal cortex (decision making, executive function)
  - Amygdala (memory, emotion)

CNS, central nervous system; VTA, ventral tegmental area.

Billes SK, et al. *Pharmacol Res*. 2014;84:1-11.

Northwestern Medicine® Feinberg School of Medicine

9

2. Appetite Regulation - Components of Appetite

Hunger
Drive to consume

Satiety
End state of satisfaction
(between-meal inhibition)

Fullness
Physical feeling experienced in the gut

Wanting
Motivation to consume a specific food (craving)

Satiation
Negative feedback, leading to meal termination (within-meal inhibition)

Liking (hedonic)
Sensory pleasure elicited by contact with food

Prospective food consumption
How much an individual feels they would like to eat

Northwestern Medicine® Feinberg School of Medicine

Blundell *et al. Obes Rev* 2010;11:251–270; van Can *et al. Int J Obes* 2014;38:784–93

10

FDA Approved Medications for Obesity Management: 2026

Agents	Mechanism of Action	Effect	Approval Date
Phentermine [Adipex-P, Lomaira, Fastin, Ionamin]	▪ Modified amphetamine	Appetite regulation	1959
Orlistat [Xenical, Alli]	▪ Blocks the GI lipase enzymes that absorbs fat	Reduces fat absorption	1999
Phentermine/topiramate ER [Qsymia]	▪ Modified amphetamine ▪ Augments GABA, and inhibits AMPA/kainite excitatory glutamate receptors (approved for epilepsy and migraine prophylaxis)	Appetite regulation	2012
Naltrexone/bupropion SR [Contrave]	▪ Opioid receptor blocker ▪ Increases dopamine/noradrenaline in the brain (approved for depression and smoking cessation)	Appetite regulation	2014
Liraglutide [Saxenda]	▪ Mimics action of GLP-1 gut hormone (peptide)	Appetite regulation	2014
Setmelanotide [Imcivree]	▪ Activates a specific neuro pathway (MC4R) in the brain (indication: obesity due to rare monogenetic forms of obesity)	Appetite regulation	2020
Semaglutide [Wegovy]	▪ Mimics action of GLP-1 gut hormone (peptide)	Appetite regulation	2021, 2025 (oral)
Tirzepatide [Zepbound]	▪ Mimics action of GLP-1/GIP gut hormones (peptide)	Appetite regulation	2023
Orforglipron [Foundayo]	▪ Mimics action of GLP-1 gut hormones (small molecule)	Appetite regulation	2026 (oral)

Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; October 2025. Contrave [package insert]. Brentwood, TN: Currax Pharmaceuticals LLC; May 2024. Xenical [package insert]. Montgomery, AL: H2-Pharma, LLC; November 2022. Qsymia [package insert]. Campbell, CA: VIVUS, Inc.; January 2025. Wegovy [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; December 2025. Phentermine [package insert]. Rahway, NJ: Sunrise Pharmaceutical, Inc.; April 2017. Imcivree [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; March 2025. Zepbound [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2025; Foundayo [package insert]. Indianapolis, IN: Eli Lilly and Company; March 2026

Northwestern Medicine® Feinberg School of Medicine

11

FDA Approved Medications for Obesity Management: 2026

Agents	Mechanism of Action	Effect	Approval Date
Phentermine [Adipex-P, Lomaira, Fastin, Ionamin]	▪ Modified amphetamine	Appetite regulation	1959
Orlistat [Xenical, Alli]	▪ Blocks the GI lipase enzymes that absorbs fat	Reduces fat absorption	1999
Phentermine/topiramate ER [Qsymia]	▪ Modified amphetamine ▪ Augments GABA, and inhibits AMPA/kainite excitatory glutamate receptors (approved for epilepsy and migraine prophylaxis)	Appetite regulation	2012
Naltrexone/bupropion SR [Contrave]	▪ Opioid receptor blocker ▪ Increases dopamine/noradrenaline in the brain (approved for depression and smoking cessation)	Appetite regulation	2014
Liraglutide [Saxenda]	▪ Mimics action of GLP-1 gut hormone (peptide)	Appetite regulation	2014
Setmelanotide [Imcivree]	▪ Activates a specific neuro pathway (MC4R) in the brain (indication: obesity due to rare monogenetic forms of obesity)	Appetite regulation	2020
Semaglutide [Wegovy]	▪ Mimics action of GLP-1 gut hormone (peptide)	Appetite regulation	2021, 2025 (oral)
Tirzepatide [Zepbound]	▪ Mimics action of GLP-1/GIP gut hormones (peptide)	Appetite regulation	2023
Orforglipron [Foundayo]	▪ Mimics action of GLP-1 gut hormones (small molecule)	Appetite regulation	2026 (oral)

Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; October 2025. Contrave [package insert]. Brentwood, TN: Currax Pharmaceuticals LLC; May 2024. Xenical [package insert]. Montgomery, AL: H2-Pharma, LLC; November 2022. Qsymia [package insert]. Campbell, CA: VIVUS, Inc.; January 2025. Wegovy [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; December 2025. Phentermine [package insert]. Rahway, NJ: Sunrise Pharmaceutical, Inc.; April 2017. Imcivree [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; March 2025. Zepbound [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2025; Foundayo [package insert]. Indianapolis, IN: Eli Lilly and Company; March 2026

Northwestern Medicine® Feinberg School of Medicine

12

FDA Approved Medications for Obesity Management: 2026

Agents	Mechanism of Action	Effect	Approval Date
Phentermine [Adipex-P, Lomaira, Fastin, Ionamin]	▪ Modified amphetamine	Appetite regulation	1959
Orlistat [Xenical, Alli]	▪ Blocks the GI lipase enzymes that absorbs fat	Reduces fat absorption	1999
Phentermine/topiramate ER [Qsymia]	▪ Modified amphetamine ▪ Augments GABA, and inhibits AMPA/kainite excitatory glutamate receptors (approved for epilepsy and migraine prophylaxis)	Appetite regulation	2012
Naltrexone/bupropion SR [Contrave]	▪ Opioid receptor blocker ▪ Increases dopamine/noradrenaline in the brain (approved for depression and smoking cessation)	Appetite regulation	2014
Liraglutide [Saxenda]	▪ Mimics action of GLP-1 gut hormone (peptide)	Appetite regulation	2014
Setmelanotide [Imcivree]	▪ Activates a specific neuro pathway (MC4R) in the brain (indication: obesity due to rare monogenetic forms of obesity)	Appetite regulation	2020
Semaglutide [Wegovy]	▪ Mimics action of GLP-1 gut hormone (peptide)	Appetite regulation	2021, 2025 (oral)
Tirzepatide [Zepbound]	▪ Mimics action of GLP-1/GIP gut hormones (peptide)	Appetite regulation	2023
Orforglipron [Foundayo]	▪ Mimics action of GLP-1 gut hormones (small molecule)	Appetite regulation	2026 (oral)

Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; October 2025. Contrave [package insert]. Brentwood, TN: Currax Pharmaceuticals LLC; May 2024. Xenical [package insert]. Montgomery, AL: H2-Pharma, LLC; November 2022. Qsymia [package insert]. Campbell, CA: VIVUS, Inc.; January 2025. Wegovy [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; December 2025. Phentermine [package insert]. Rahway, NJ: Sunrise Pharmaceutical, Inc.; April 2017. Imcivree [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; March 2025. Zepbound [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2025; Foundayo [package insert]. Indianapolis, IN: Eli Lilly and Company; March 2026

Northwestern Medicine® Feinberg School of Medicine

13

FDA Approved Medications for Obesity Management: 2026

Agents	Mechanism of Action	Effect	Approval Date
Phentermine [Adipex-P, Lomaira, Fastin, Ionamin]	▪ Modified amphetamine	Appetite regulation	1959
Orlistat [Xenical, Alli]	▪ Blocks the GI lipase enzymes that absorbs fat	Reduces fat absorption	1999
Phentermine/topiramate ER [Qsymia]	▪ Modified amphetamine ▪ Augments GABA, and inhibits AMPA/kainite excitatory glutamate receptors (approved for epilepsy and migraine prophylaxis)	Appetite regulation	2012
Naltrexone/bupropion SR [Contrave]	▪ Opioid receptor blocker ▪ Increases dopamine/noradrenaline in the brain (approved for depression and smoking cessation)	Appetite regulation	2014
Liraglutide [Saxenda]	▪ Mimics action of GLP-1 gut hormone (peptide)	Appetite regulation	2014
Setmelanotide [Imcivree]	▪ Activates a specific neuro pathway (MC4R) in the brain (indication: obesity due to rare monogenetic forms of obesity)	Appetite regulation	2020
Semaglutide [Wegovy]	▪ Mimics action of GLP-1 gut hormone (peptide)	Appetite regulation	2021, 2025 (oral)
Tirzepatide [Zepbound]	▪ Mimics action of GLP-1/GIP gut hormones (peptide)	Appetite regulation	2023
Orforglipron [Foundayo]	▪ Mimics action of GLP-1 gut hormones (small molecule)	Appetite regulation	2026 (oral)

Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; October 2025. Contrave [package insert]. Brentwood, TN: Currax Pharmaceuticals LLC; May 2024. Xenical [package insert]. Montgomery, AL: H2-Pharma, LLC; November 2022. Qsymia [package insert]. Campbell, CA: VIVUS, Inc.; January 2025. Wegovy [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; December 2025. Phentermine [package insert]. Rahway, NJ: Sunrise Pharmaceutical, Inc.; April 2017. Imcivree [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; March 2025. Zepbound [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2025; Foundayo [package insert]. Indianapolis, IN: Eli Lilly and Company; March 2026

Northwestern Medicine® Feinberg School of Medicine

14

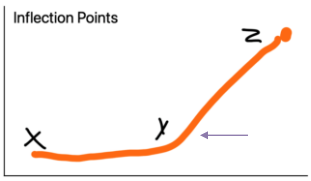
FDA Approved Medications for Obesity Management: 2026

Agents	Mechanism of Action	Effect	Approval Date
Phentermine [Adipex-P, Lomaira, Fastin, Ionamin]	▪ Modified amphetamine	Appetite regulation	1959
Orlistat [Xenical, Alli]	▪ Blocks the GI lipase enzymes that absorbs fat	Reduces fat absorption	1999
Phentermine/topiramate ER [Qsymia]	▪ Modified amphetamine ▪ Augments GABA, and inhibits AMPA/kainite excitatory glutamate receptors (approved for epilepsy and migraine prophylaxis)	Appetite regulation	2012
Naltrexone/bupropion SR [Contrave]	▪ Opioid receptor blocker ▪ Increases dopamine/noradrenaline in the brain (approved for depression and smoking cessation)	Appetite regulation	2014
Liraglutide [Saxenda]	▪ Mimics action of GLP-1 gut hormone (peptide)	Appetite regulation	2014
Setmelanotide [Imcivree]	▪ Activates a specific neuro pathway (MC4R) in the brain (indication: obesity due to rare monogenetic forms of obesity)	Appetite regulation	2020
Semaglutide [Wegovy]	▪ Mimics action of GLP-1 gut hormone (peptide)	Appetite regulation	2021, 2025 (oral)
Tirzepatide [Zepbound]	▪ Mimics action of GLP-1/GIP gut hormones (peptide)	Appetite regulation	2023
Orforglipron [Foundayo]	▪ Mimics action of GLP-1 gut hormones (small molecule)	Appetite regulation	2026 (oral)

Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; October 2025. Contrave [package insert]. Brentwood, TN: Currax Pharmaceuticals LLC; May 2024. Xenical [package insert]. Montgomery, AL: H2-Pharma, LLC; November 2022. Qsymia [package insert]. Campbell, CA: VIVUS, Inc.; January 2025. Wegovy [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; December 2025. Phentermine [package insert]. Rahway, NJ: Sunrise Pharmaceutical, Inc.; April 2017. Imcivree [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; March 2025. Zepbound [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2025; Foundayo [package insert]. Indianapolis, IN: Eli Lilly and Company; March 2026

Northwestern Medicine® Feinberg School of Medicine

15



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

N Engl J Med 2021;384:989-1002

Injected Drug Delivers Up to 20% Weight Loss in Trial

U.S. News & WORLD REPORT

'A Game Changer': Drug Brings Weight Loss in Patients With Obesity

In a clinical trial, participants taking semaglutide lost 15 percent of their body weight, on average.

The New York Times

Diabetes medication almost twice as effective as other anti-obesity drugs, researchers say

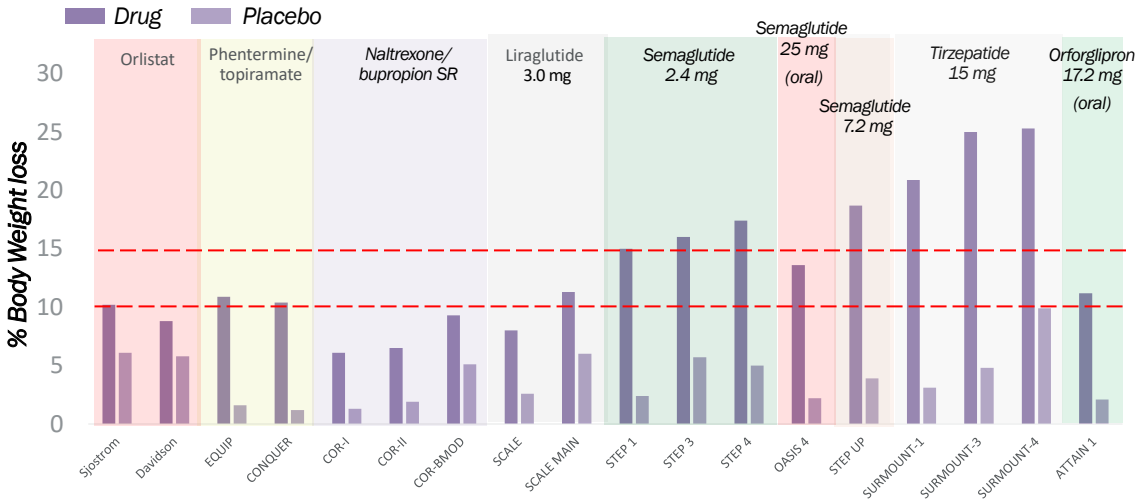
A study from Northwestern Medicine found that, at a higher dosage, the diabetes medication semaglutide is more effective than FDA-approved weight-loss drugs currently on the market.

By Mari Devereaux | Feb 10, 2021, 8:00pm CST

CHICAGO SUN-TIMES

16

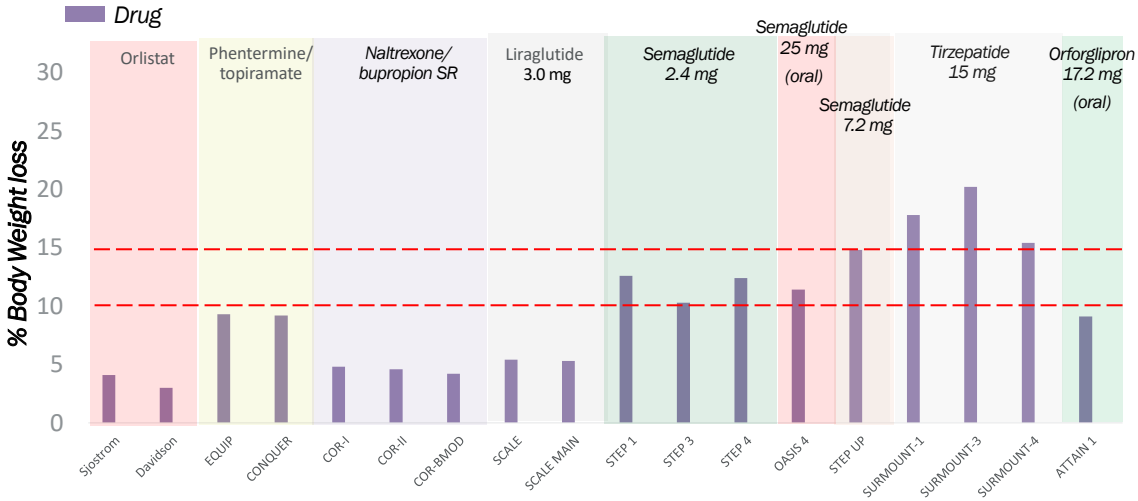
3. Efficacy. Percent Weight Loss (Drug vs Placebo) in Non-Diabetes Trials



Sjöstrom L, et al. Lancet. 1998;352(9123):167-172; Davidson MH, et al. JAMA. 1999;281(3):235-242; Allison DB, et al. Obesity (Silver Spring). 2012;20(2):330-342; Gadde KM, et al. Lancet. 2011;377(9774):1341-1352; Greenway FL, et al. Lancet. 2010;376(9741):595-605; Apovian CM, et al. Obesity (Silver Spring). 2013;21(5):935-943; Wadden TA, et al. Obesity (Silver Spring). 2011;19(1):110-120; Pi-Sunyer X, et al. N Engl J Med. 2015;373:11-22; Wadden TA, et al. Int J Obes (Lond). 2013;37(11):1443-1451; Wilding JPH, et al. N Engl J Med. 2021;384(11):989-1002; Wadden TA, et al. JAMA. 2021;325(14):140–1413; Rubino D, et al. JAMA. 2021;325(14):1414-1425; Jastreboff AM, et al. N Engl J Med. 2022;387(3):205-216; Wadden TA, et al. Nat Med. 2023;29(11):2909-2918: Aronne LJ, et al. JAMA 2024;33:38-48. Wharton S, et al. N Engl J Med. 2025;393(11):1077-1087.

17

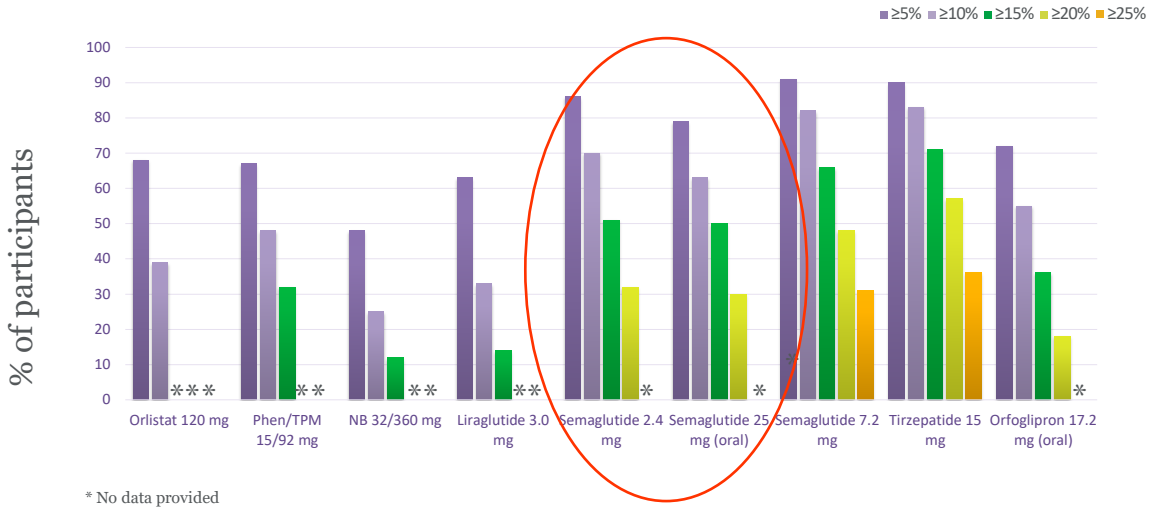
3. Efficacy. Percent Weight Loss (Placebo Subtracted) in Non-Diabetes Trials



Sjöstrom L, et al. Lancet. 1998;352(9123):167-172; Davidson MH, et al. JAMA. 1999;281(3):235-242; Allison DB, et al. Obesity (Silver Spring). 2012;20(2):330-342; Gadde KM, et al. Lancet. 2011;377(9774):1341-1352; Greenway FL, et al. Lancet. 2010;376(9741):595-605; Apovian CM, et al. Obesity (Silver Spring). 2013;21(5):935-943; Wadden TA, et al. Obesity (Silver Spring). 2011;19(1):110-120; Pi-Sunyer X, et al. N Engl J Med. 2015;373:11-22; Wadden TA, et al. Int J Obes (Lond). 2013;37(11):1443-1451; Wilding JPH, et al. N Engl J Med. 2021;384(11):989-1002; Wadden TA, et al. JAMA. 2021;325(14):140–1413; Rubino D, et al. JAMA. 2021;325(14):1414-1425; Jastreboff AM, et al. N Engl J Med. 2022;387(3):205-216; Wadden TA, et al. Nat Med. 2023;29(11):2909-2918: Aronne LJ, et al. JAMA 2024;33:38-48. Wharton S, et al. N Engl J Med. 2025;393(11):1077-1087.

18

Categorical Weight Loss



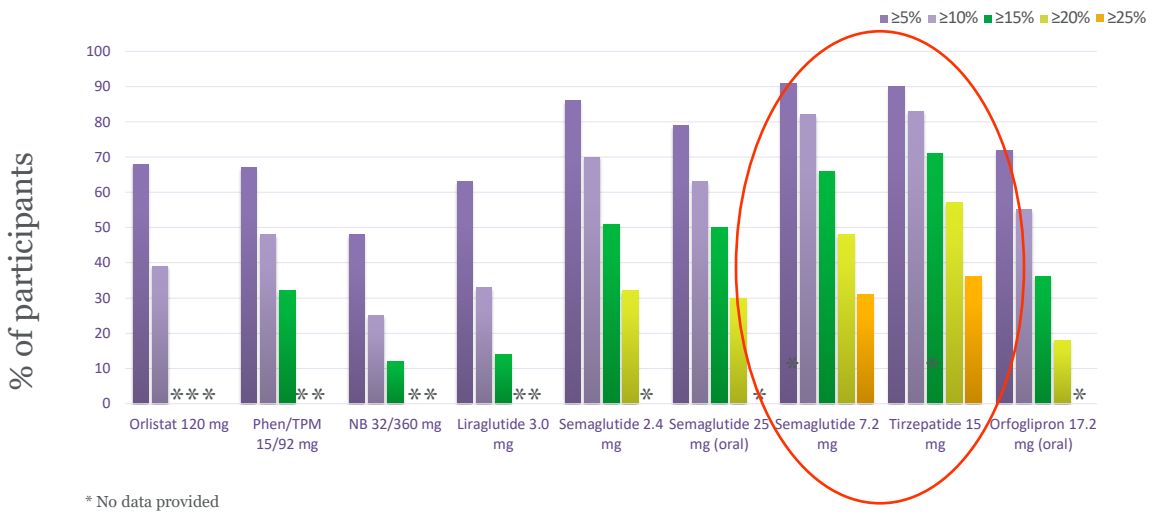
* No data provided

Northwestern Medicine® Feinberg School of Medicine

Gudzune KA, Kushner RF. JAMA. 2024;332(7):571-584.
Wharton S, et al. N Engl J Med. 2025;393:1077-1087.
Wharton S, et al. N Engl J Med 2025;393:1796-1806

19

Categorical Weight Loss



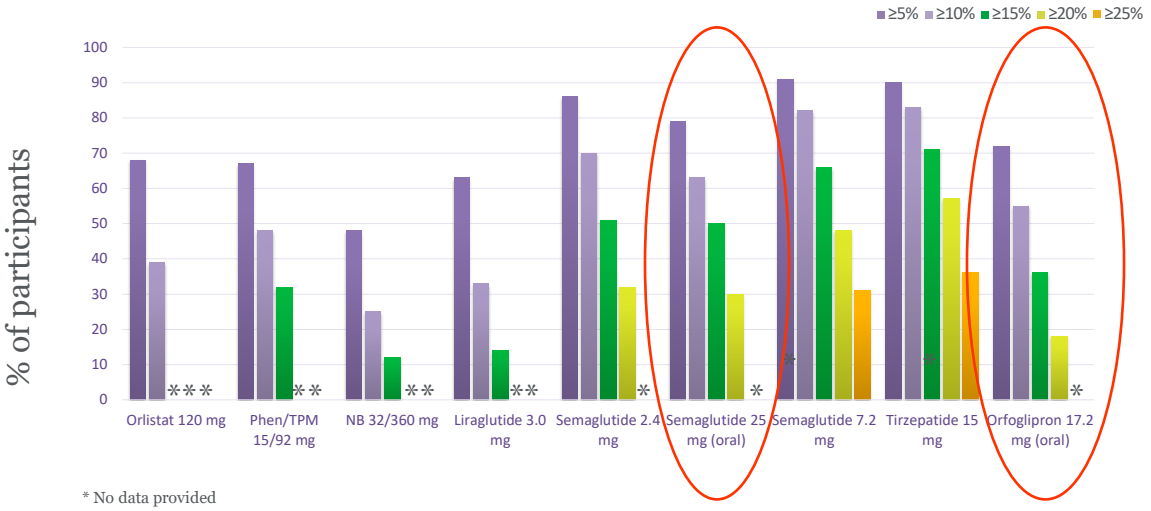
* No data provided

Northwestern Medicine® Feinberg School of Medicine

Gudzune KA, Kushner RF. JAMA. 2024;332(7):571-584.
Wharton S, et al. N Engl J Med. 2025;393:1077-1087.
Wharton S, et al. N Engl J Med 2025;393:1796-1806

20

Categorical Weight Loss



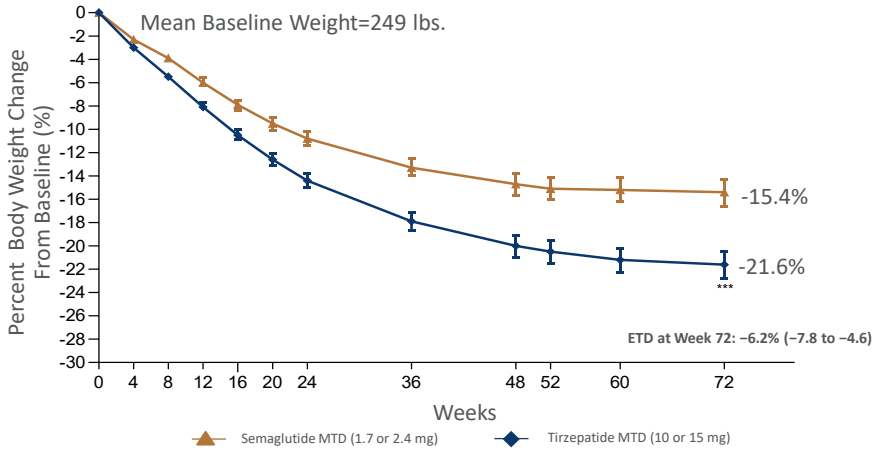
* No data provided

Northwestern Medicine® Feinberg School of Medicine

Gudzune KA, Kushner RF. JAMA. 2024;332(7):571-584.
Wharton S, et al. N Engl J Med. 2025;393:1077-1087.
Wharten S, et al. N Engl J Med 2025;393:1796-1806

21

SURMOUNT 5: Semaglutide Versus Tirzepatide
Percentage Change in Body Weight from Baseline to 72 Weeks

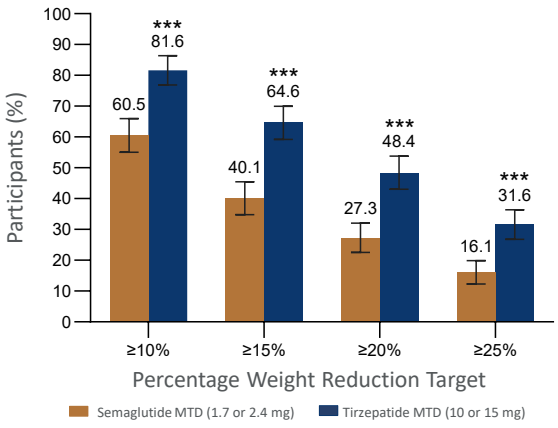


- ***p<.001 vs. semaglutide.
- CI=Confidence Interval; EAS=Efficacy Analysis Set; ETD=Estimated Treatment Difference; LSM=Least Squares Mean; MMRM=Mixed-Model for Repeated Measures; MTD=Maximum Tolerated Dose.
- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Northwestern Medicine® Feinberg School of Medicine

22

SURMOUNT 5: Semaglutide Versus Tirzepatide
Categorical Weight Loss



How much lifestyle counseling is necessary to achieve effective weight loss?

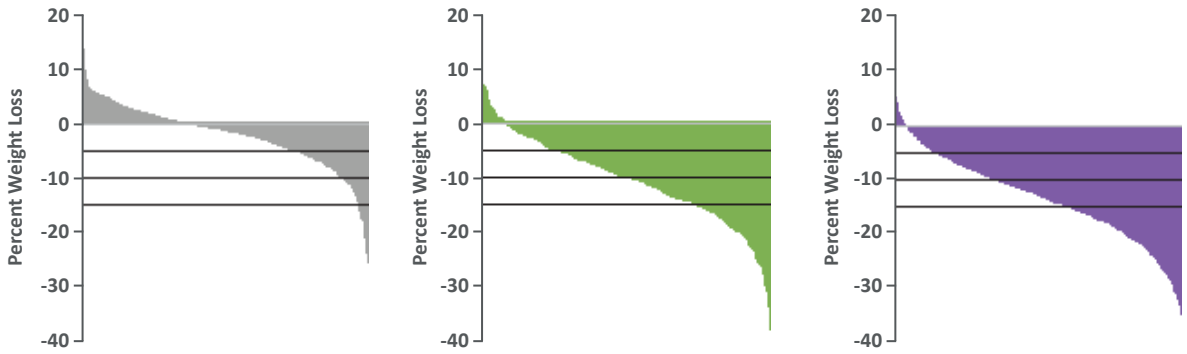
- Participants met with a dietitian, or equivalent, monthly during dose escalation and every 3 months thereafter (9 visits).
- Dietary counseling consisted of advice on healthy food choices and focus on calorie restriction using a hypocaloric diet with approximately 20% of energy from protein, and an energy deficit of approximately 500 kcal/day.
- To encourage adherence, participants were recommended to complete a 3-day diet and exercise log prior to each counseling visit.
- At Visit 2 and all subsequent visits, participants were advised to increase their physical activity to at least 150 minutes per week.

M Northwestern Medicine®
Feinberg School of Medicine

Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

23

4. Heterogeneity of Treatment Effect



Each vertical bar represents a single subject experience in subjects completing 56 weeks on study drug

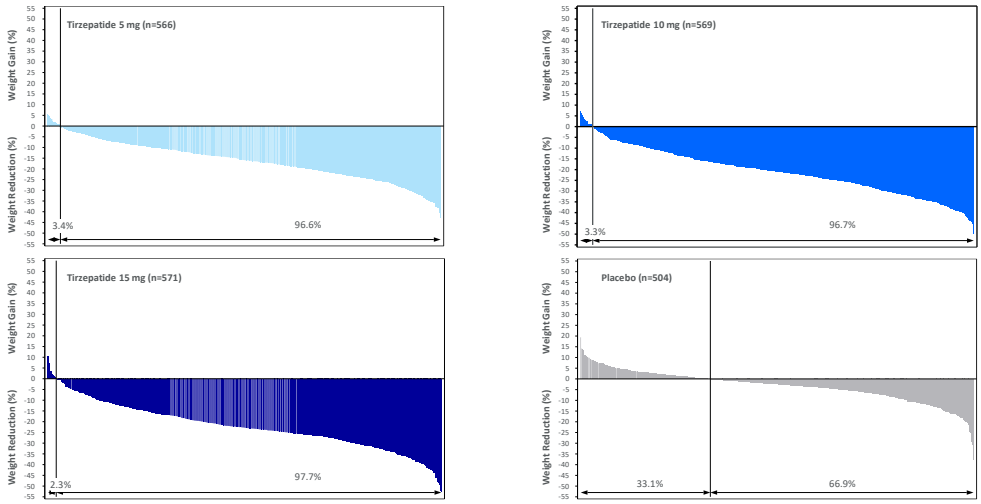
M Northwestern Medicine®
Feinberg School of Medicine

McCullough PA, Chow DT, Day WW. Weight Loss With Phentermine and Topiramate Extended-Release in Obese and Overweight Subjects Over 1 Year. Presented at the 28th National Conference of the American Association of Nurse Practitioners. June 19-23, 2013.

24

#4 Heterogeneity of Treatment: Tirzepatide Waterfall Plots

Body weight reduction was observed in 96.6%, 96.7% and 97.7% participants of tirzepatide 5 mg, 10 mg, and 15 mg groups respectively, compared to 66.9% of participants in the placebo group

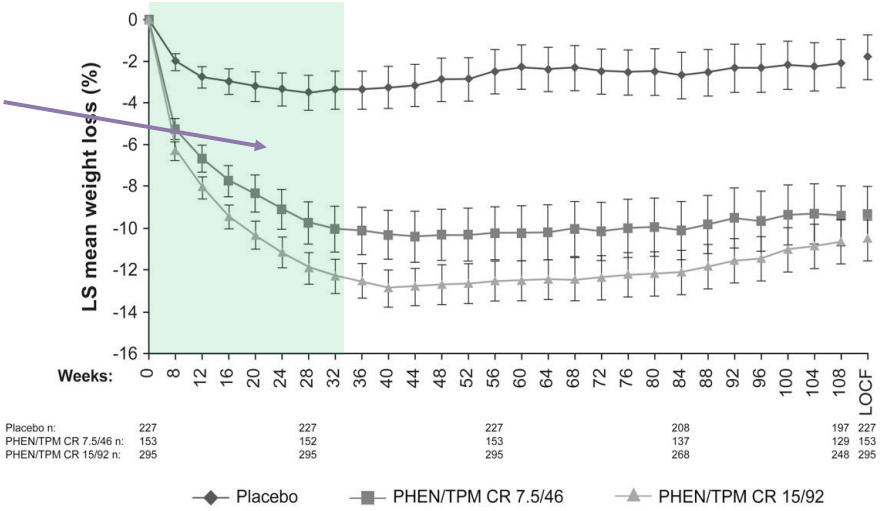


Jastreboff AM, et al. *New Engl. J. Med.* 2022;387(3):205-216.

25

5. Look for Early Response

Note active weight loss period



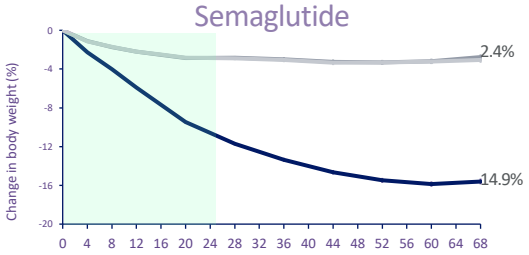
Northwestern Medicine
Feinberg School of Medicine

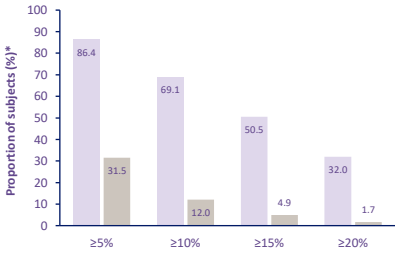
Garvey WT, et al. *Am J Clin Nutr*. 2012;95:297-308.

26

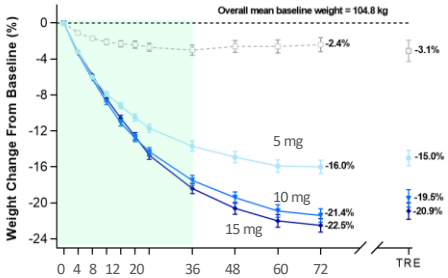
STEP 1 and SURMOUNT 1

Semaglutide

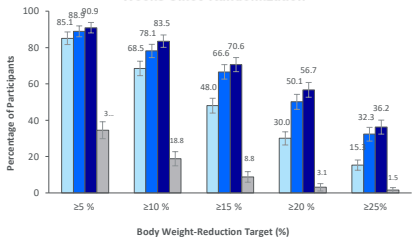




Tirzepatide



TRE – treatment-regimen estimand



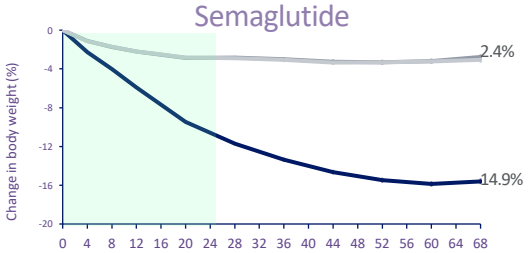
Northwestern Medicine® Feinberg School of Medicine

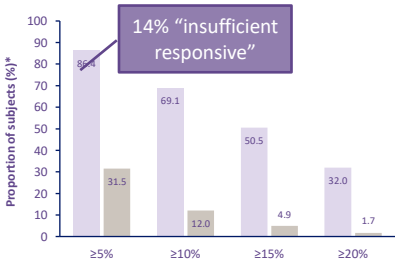
Wilding JPH, et al. N Engl J Med 2021;384:989-100; Jastreboff AM, et al N Engl J Med 2022;387:205-216

27

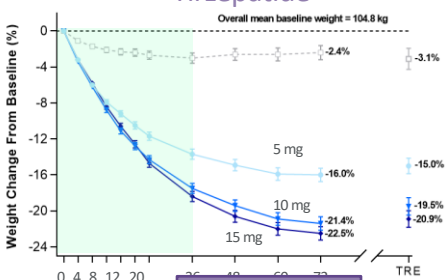
STEP 1 and SURMOUNT 1

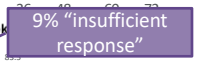
Semaglutide



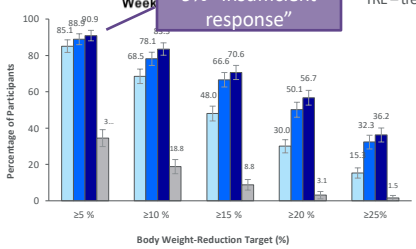


Tirzepatide





TRE – treatment-regimen estimand

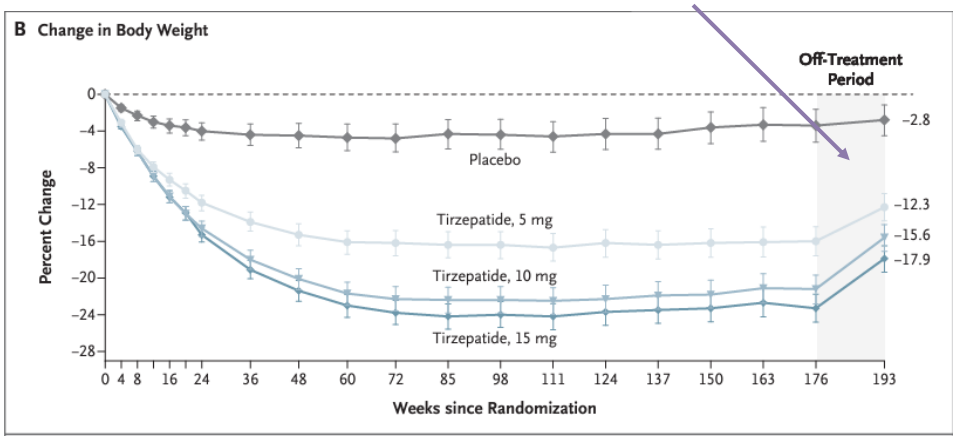


Northwestern Medicine® Feinberg School of Medicine

Wilding JPH, et al. N Engl J Med 2021;384:989-100; Jastreboff AM, et al N Engl J Med 2022;387:205-216

28

6. Note Withdrawal Response 3-Year Study of Tirzepatide



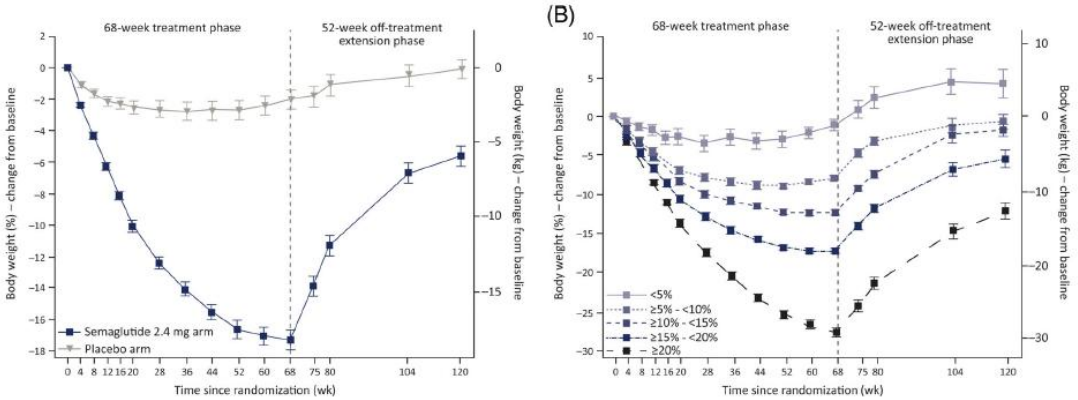
1032 patients with prediabetes and a BMI of ≥ 30 kg/m² or ≥ 27 kg/m² and comorbidities

Northwestern Medicine® Feinberg School of Medicine

Jastreboff AM et al. N Engl J Med 2024

29

The STEP 1 Trial Extension of Semaglutide 2.4 mg



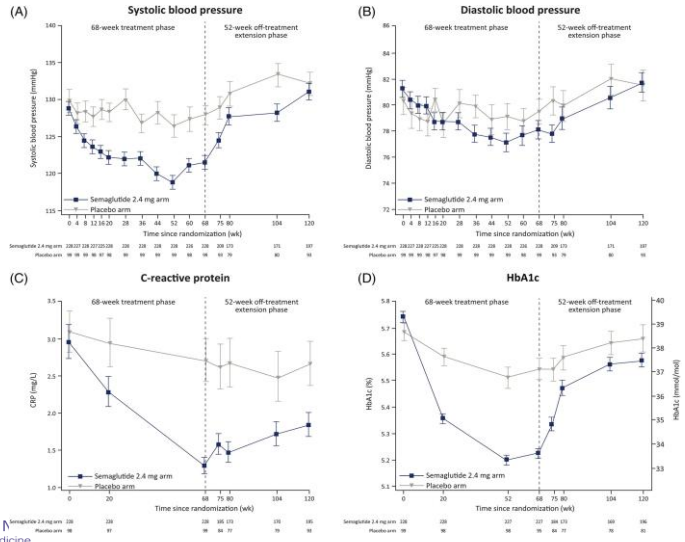
N=327 subject

Northwestern Medicine® Feinberg School of Medicine

Wilding JPH et al. Diab Obes Metab 2022:1-12

30

The STEP 1 Trial Extension of Semaglutide 2.4 mg

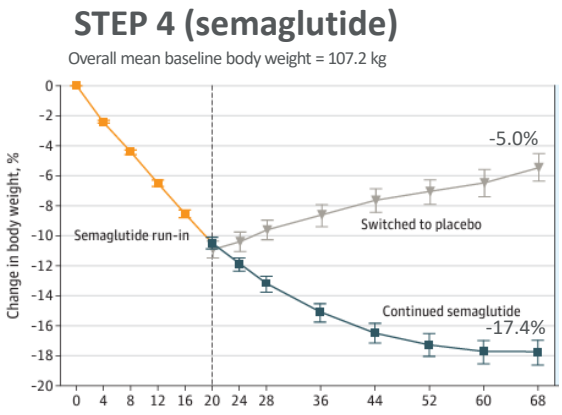


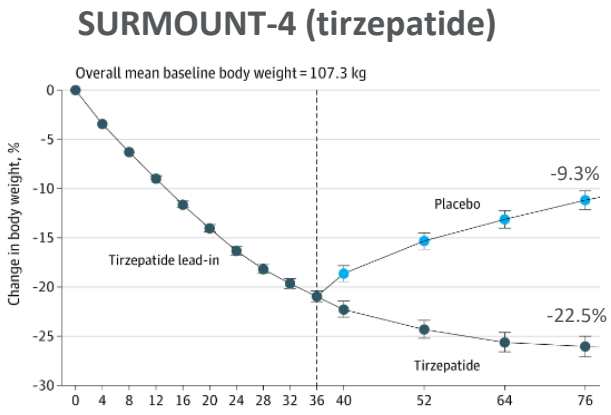
Northwestern Medicine Feinberg School of Medicine

Wilding JPH et al. Diab Obes Metab 2022:1-12

31

What Happens When You "Blindly" Stop the Medication?



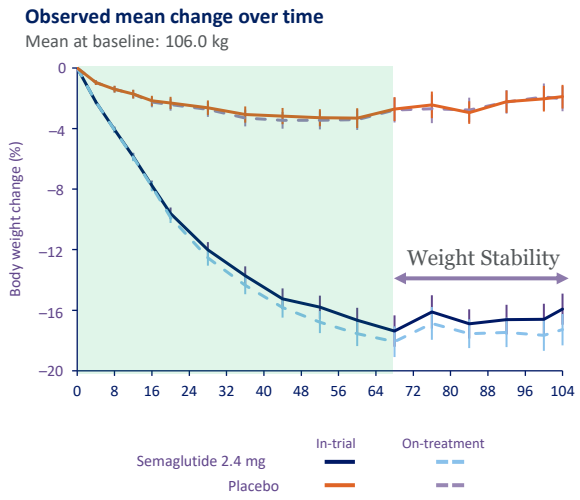


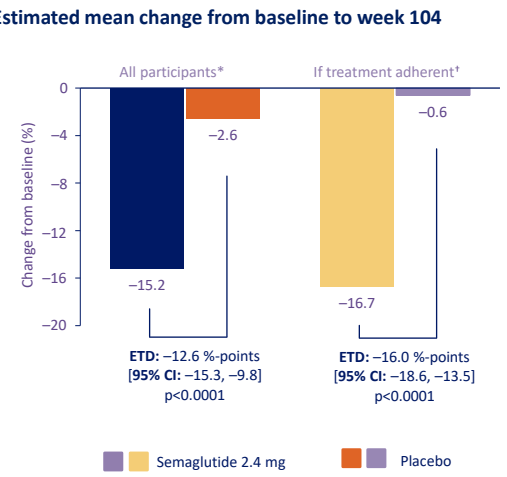
Northwestern Medicine Feinberg School of Medicine

Rubino D et al. JAMA 2021 Apr 13;325(14):1414-1425; Aronne LJ et al. JAMA 2023 (online)

32

7. Benefit of Continued Use: STEP 5 Semaglutide Trial



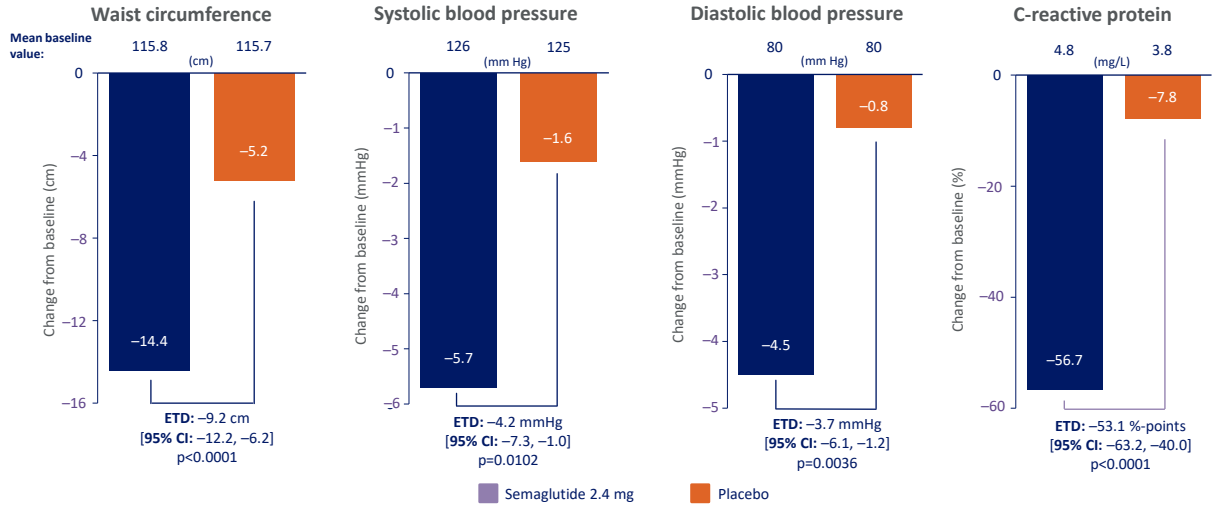


M Northwestern Medicine®
Feinberg School of Medicine

Garvey WT et al. Nature Medicine 2022;28:2083-2091

33

8. Improved Cardiovascular Risk Factors *STEP 5 Semaglutide Trial*

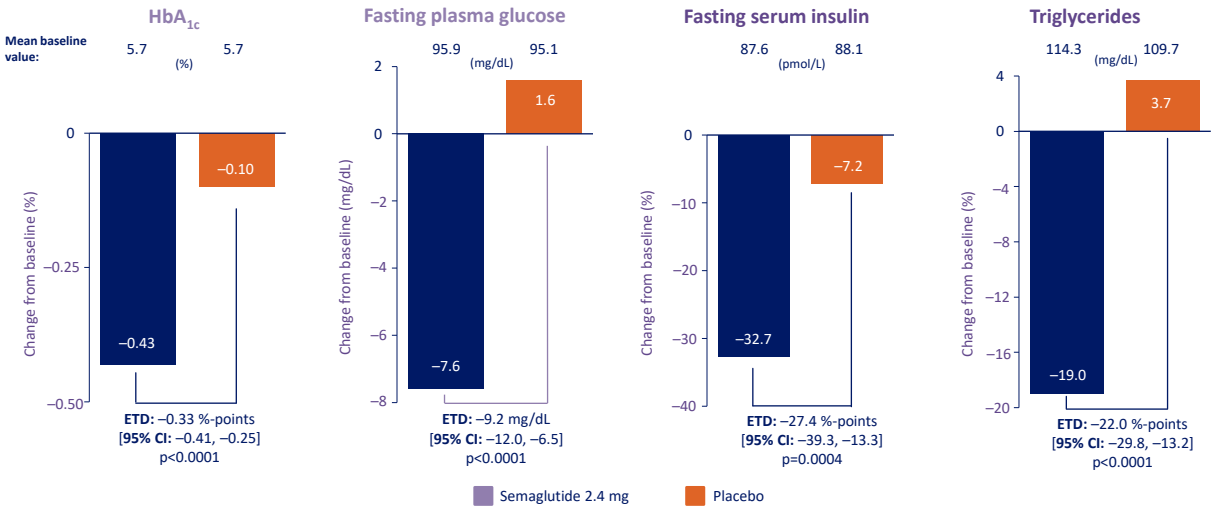


Garvey WT, et al. *Nat Med*. 2022;28(10):2083-2091.

M Northwestern Medicine®
Feinberg School of Medicine

34

8. Improved Metabolic Risk Factors
STEP 5 Semaglutide Trial



Garvey WT, et al. *Nat Med*. 2022;28(10):2083-2091.

Northwestern Medicine
Feinberg School of Medicine

35

Efficacy: Comparison of Effect on Cardiometabolic Risk Factors Across Drugs
A Qualitative Comparison

	Orlistat	Phentermine/ topiramate ER	Naltrexone/ bupropion SR	Liraglutide 3.0 mg	Semaglutide 2.4 mg	Tirzepatide 15 mg	Orforglipron 17.2 mg
BP	↓	↓	↑	↓	↓↓	↓↓	↓
HR	↓	↑	↑	↑	↑	↑	↑
WC	↓	↓	↓	↓	↓↓	↓↓	↓
LDL	↓↓	↓	↓	↓	↓	↓	↓
HDL	↑	↑	↑	↑	↑	↑	↑
TG	↓↓	↓↓	↓↓	↓↓	↓↓↓	↓↓↓	↓↓
A1C	↓	↓	↓	↓↓	↓↓↓	↓↓↓	↓

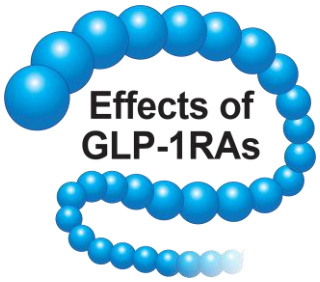
BP = blood pressure; HDL = high-density lipoprotein; HR = heart rate; LDL = low-density lipoprotein; TG = triglycerides; WC = waste circumference.
Adipex-P (phentermine) prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/088023s037lbl.pdf; Xenical (orlistat) prescribing information. http://www.gene.com/download/pdf/xenical_prescribing.pdf; Qsymia (phentermine/topiramate ER) prescribing information. https://qsymia.com/pdf/prescribing-information.pdf; Contrave (naltrexone SR/bupropion SR) prescribing information. http://www.contrave.com/pdf/contrave_pi.pdf; Saxenda (liraglutide 3.0 mg) prescribing information. http://novo-pi.pnittest.com/saxenda.pdf.

Northwestern Medicine
Feinberg School of Medicine

36

9. GLP-1 Has Pleotropic Effects

Weight Loss



Pleiotropic Effects

Northwestern Medicine
Feinberg School of Medicine

37

Pleiotropic Effects of Nutrient-Stimulated Hormone-Based Therapeutic Medications

Pancreas
- ↑ β-cell function
- ↑ Glucose-dependent insulin secretion
- ↑ Insulin biosynthesis
- ↓ Postprandial glucagon secretion
- ↓ β-cell apoptosis

GI tract
- ↓ Gastric emptying
- ↓ GI motility

Liver
- ↑ Hepatic insulin sensitivity
- ↓ De novo lipogenesis
- ↓ VLDL-TG production/secretion

Brain
- ↓ Body weight
- ↑ Satiety
- ↓ Appetite
- ↓ Energy intake
- ↓ Food cravings
- ↑ Eating control

Cardiovascular
- ↑ Fatty acid metabolism
- ↓ Inflammation
- ↓ Systolic blood pressure
- ↓ CV risk

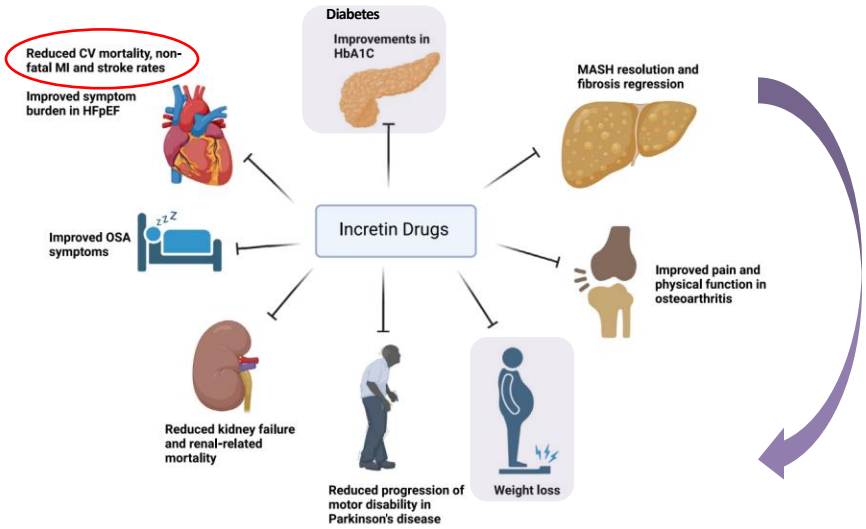
Kidney
- ↓ Albuminuria
- ↑ Natriuresis
- ↓ Inflammation
- ↓ Oxidative stress

Daniels S, et al. Trends in endocrinology and metabolism, 2025-04, Vol.36 (4), p.301-315

Northwestern Medicine
Feinberg School of Medicine

38

GLP-1 and GIP/GLP-1 (Incretin) Medications Have Diverse Beneficial Effects on Multiple Obesity-Related Complications



CV-Cardiovascular; MI-myocardial infarction; HFpEF-heart failure with preserved ejection fraction; OSA-obstructive sleep apnea; MASH-metabolic dysfunction-associated steatohepatitis

Northwestern Medicine Feinberg School of Medicine

Elangovan H, et al, Hepatology Intern 2025;19:337-348

39

Rationale for SELECT

Individuals with overweight or obesity and high cardiovascular risk, but without established diabetes, are candidates for heart disease secondary prevention.

Mediation by Weight Loss + **Mediation by semaglutide** = **Cardiovascular Event Reduction**

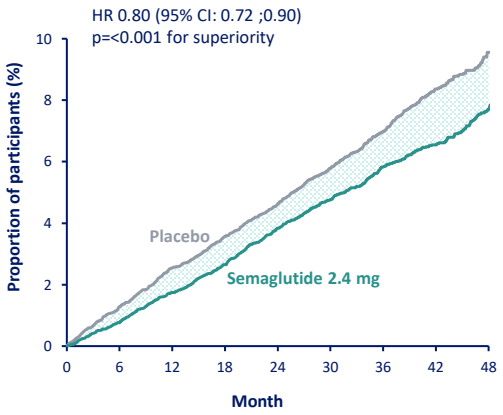
SELECT was not a weight loss study. It was a heart disease prevention study.

Northwestern Medicine Feinberg School of Medicine

Ryan DH, et al. Am Heart J 2020;229:61-69.

40

SELECT: Semaglutide 2.4 mg CVOT



20% reduction in MACE*

Semaglutide 2.4 mg significantly reduced MACE* incidence

versus placebo† over a period of up to 5 years[1]

All three components (CV death, non-fatal MI and non-fatal stroke) contributed to this MACE reduction[1]

The effect of semaglutide 2.4 mg on MACE* appeared to be **consistent across different patient subgroups**

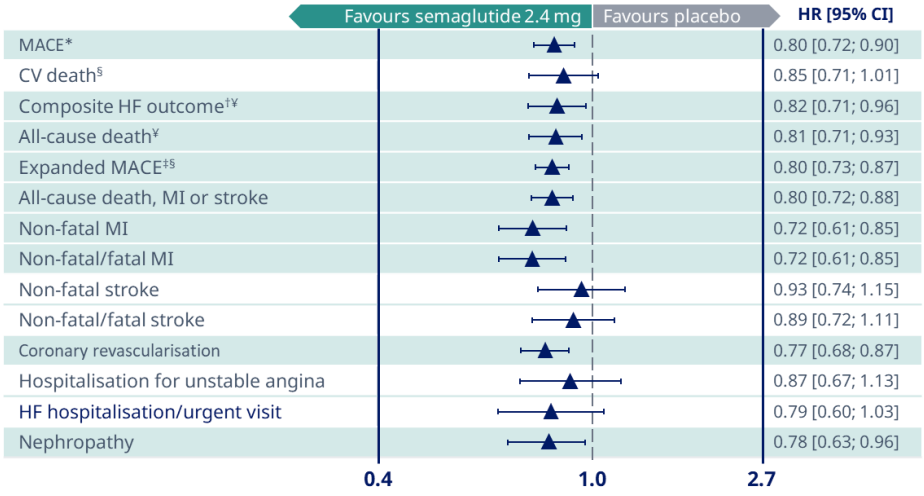
MACE, major adverse cardiovascular events; MI, myocardial infarction

Lincoff AM, et al. *N Engl J Med*. 2023. doi:10.1056/NEJMoa2307563

Northwestern Medicine® Feinberg School of Medicine

41

SELECT: Semaglutide 2.4 mg Showed Consistent Beneficial Effects Across All Measured CV Outcomes



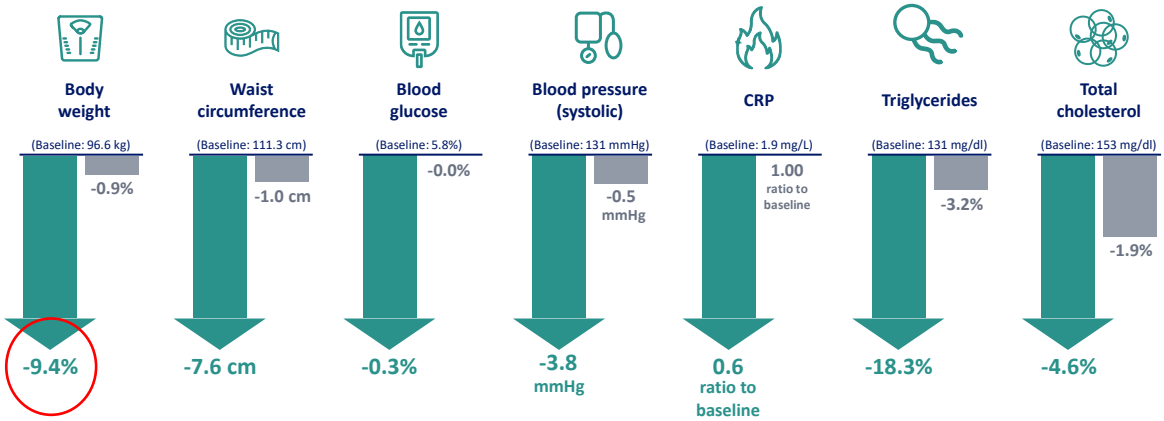
Lincoff AM, et al. *N Engl J Med*. 2023. doi:10.1056/NEJMoa2307563

Northwestern Medicine® Feinberg School of Medicine

42

SELECT – Changes in Cardiometabolic Parameters

Change from baseline to Week 104 in semaglutide 2.4 mg and placebo groups[1]

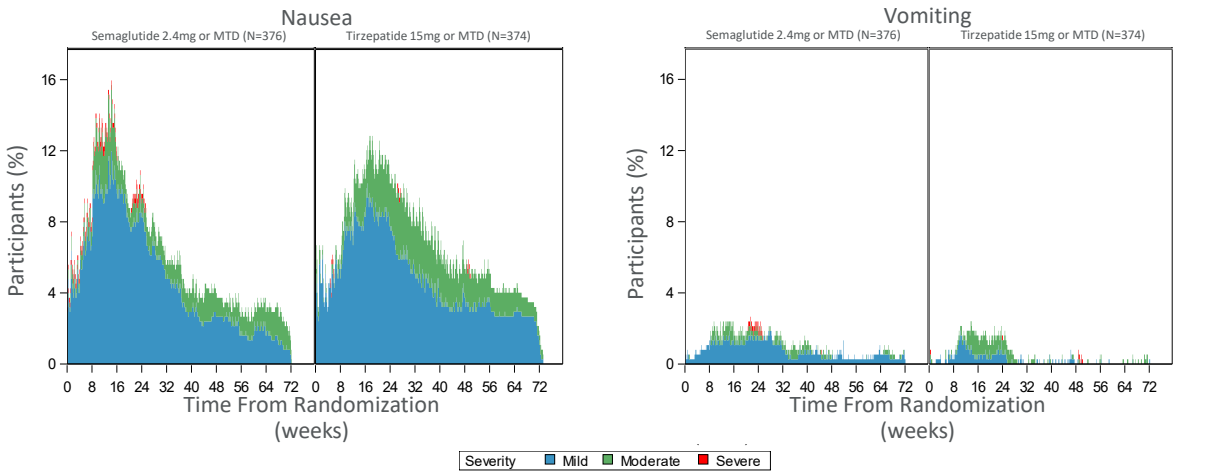


Northwestern Medicine® Feinberg School of Medicine

[1]Lincoff AM, et. N Engl J Med 2023;389:2221-2232

43

10. Common Adverse Events with Semaglutide 2.4 mg and Tirzepatide 15 mg
Prevalence of Nausea and Vomiting: SURMOUNT 5 Trial

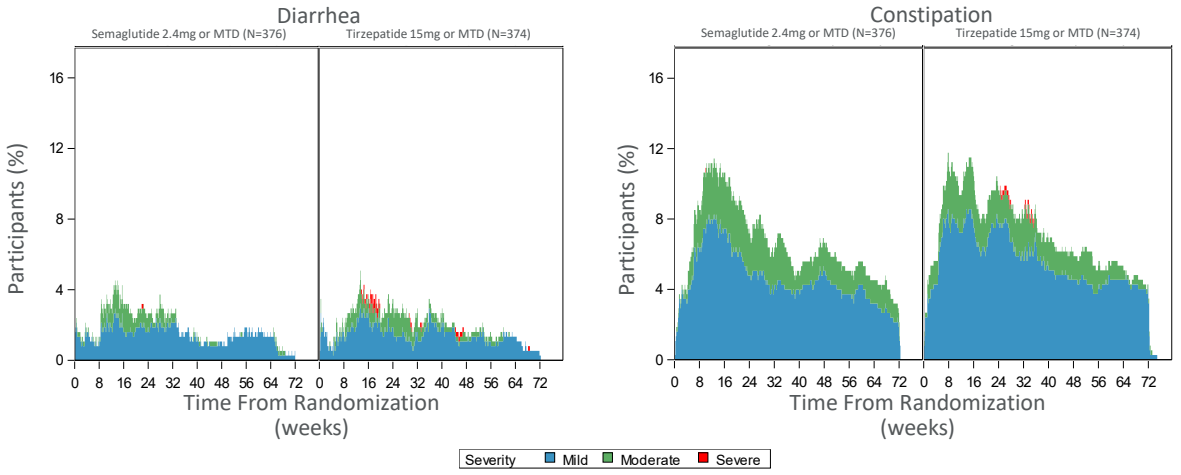


- Prevalence of nausea and vomiting. Proportions are based on number of participants at risk. Prevalence refers to the proportion of participants who have an event during a time interval.
- mITT=Modified Intent-to-Treat. MTD=Maximum Tolerated Dose; SEMA=Semaglutide; TZP=Tirzepatide.
- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 (Ahead of print).

Northwestern Medicine® Feinberg School of Medicine

44

10. Common Adverse Events with Semaglutide 2.4 mg and Tirzepatide 15 mg
Prevalence of Diarrhea and Constipation: SURMOUNT 5 Trial

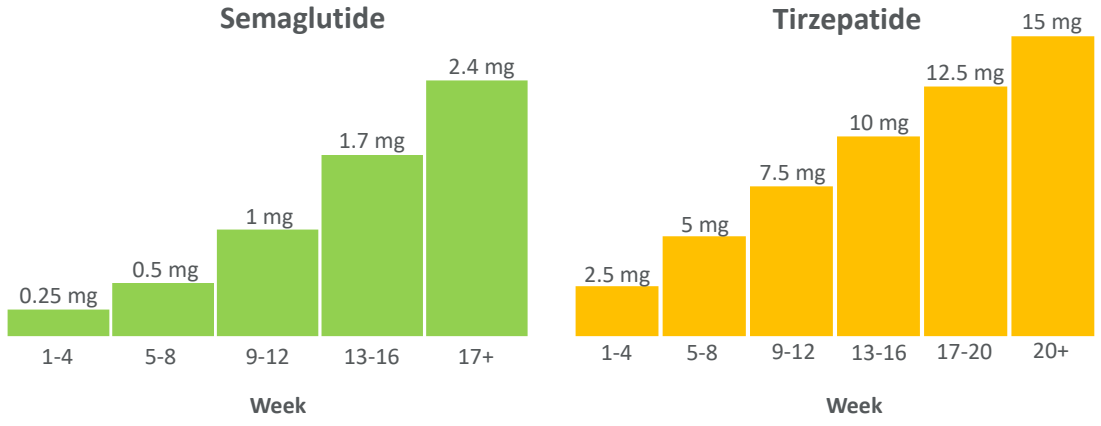


- Prevalence of nausea and vomiting. Proportions are based on number of participants at risk. Prevalence refers to the proportion of participants who have an event during a time interval.
- mITT=Modified Intent-to-Treat. MTD=Maximum Tolerated Dose; SEMA=Semaglutide; TZP=Tirzepatide.
- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 (Ahead of print).

Northwestern Medicine® Feinberg School of Medicine

45

11. Dose Escalation for Injectable Agents

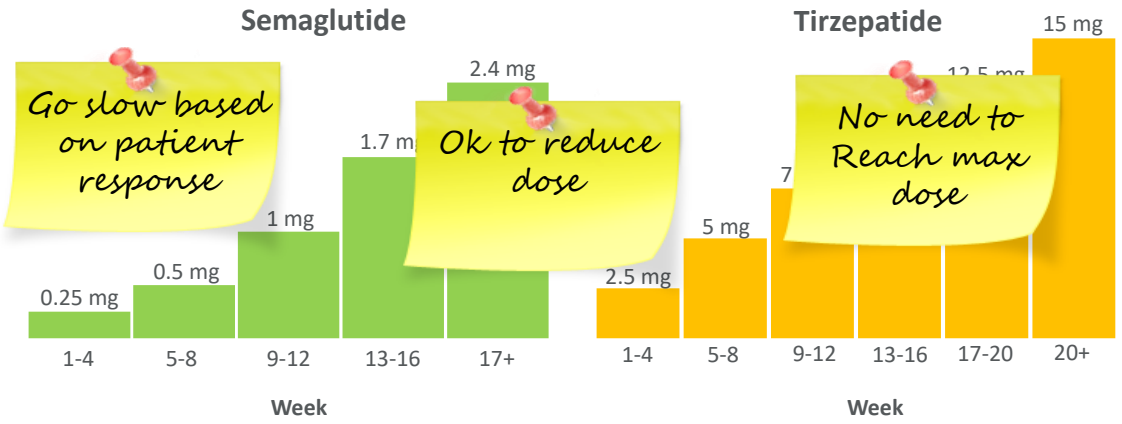


Northwestern Medicine® Feinberg School of Medicine

FDA Prescribing Information.

46

11. Dose Escalation

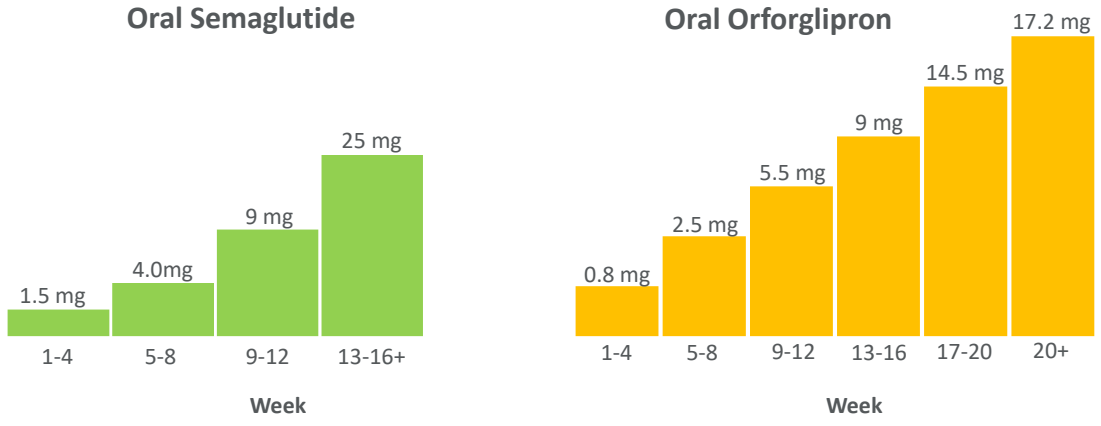


Northwestern Medicine® Feinberg School of Medicine

FDA Prescribing Information.

47

11. Dose Escalation for Oral Agents



Northwestern Medicine® Feinberg School of Medicine

FDA Prescribing Information.

48

Anticipatory Counseling for GLP-1 Medications

GI side effects are typically mild-moderate and temporary in nature
HCPs should titrate doses up to help mitigate adverse events.

- ✓ Eat slowly
- ✓ Smaller portions
- ✓ Do not skip meals
- ✓ Stop eating when feeling full
- ✓ Keep hydrated
- ✓ Plan meals and snacks in advance
- ✓ Reduce greasy and fatty foods
- ✓ Refrain from lying down after a meal

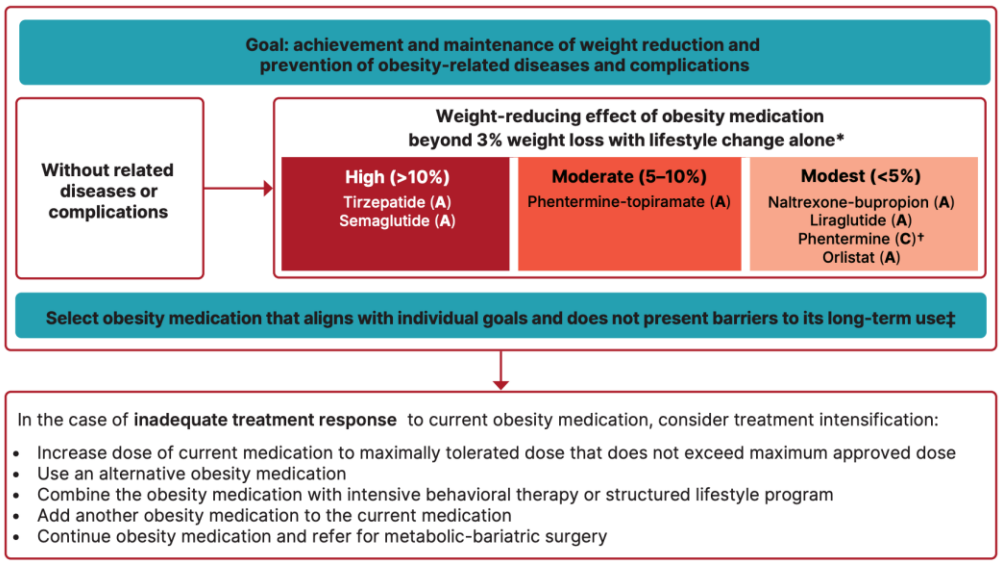
Other Considerations

- Slow dose escalation
- Reduce dose if indicated
- Treat nausea, vomiting and constipation with medication if needed

FDA Prescribing Information; Wharton S, et al. *Postgrad Med.* 2022; Gorgojo-Martinez JJ, et al. *J Clin Med.* 2023.

49

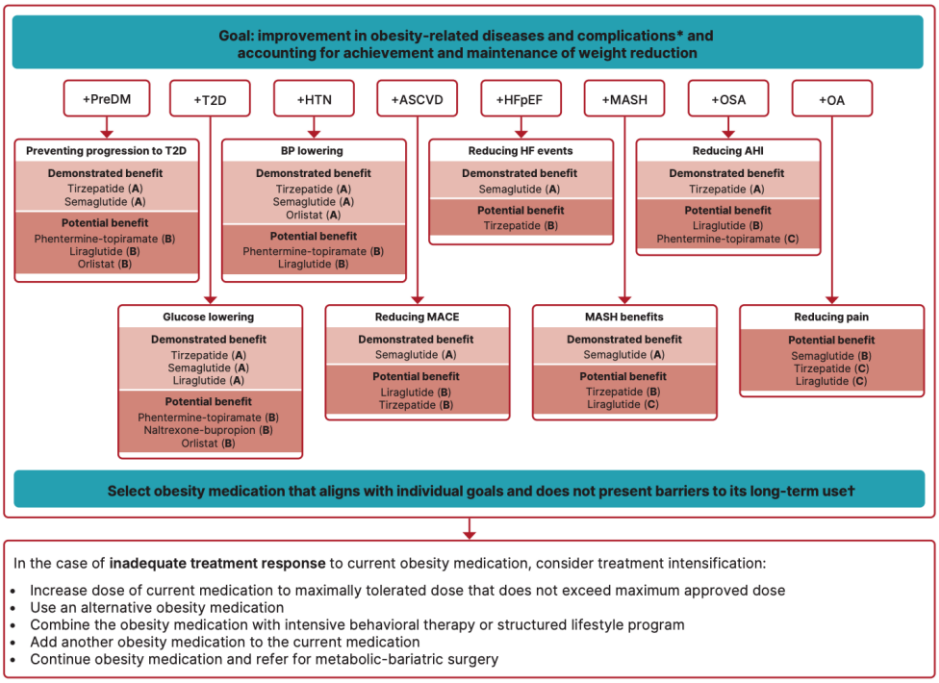
ADA Standards of Care in Overweight and Obesity: Treatment Algorithms



1. American Diabetes Association Professional Practice Committee for Obesity. *DOCM CARE.* 2026; doci250008. Reprinted with permission from the American Diabetes Association, Inc. Copyright 2026.

50

ADA Standards of Care in Overweight and Obesity: Treatment Algorithms



In the case of **inadequate treatment response** to current obesity medication, consider treatment intensification:

- Increase dose of current medication to maximally tolerated dose that does not exceed maximum approved dose
- Use an alternative obesity medication
- Combine the obesity medication with intensive behavioral therapy or structured lifestyle program
- Add another obesity medication to the current medication
- Continue obesity medication and refer for metabolic-bariatric surgery

1. American Diabetes Association Professional Practice Committee for Obesity. *DOCM CARE.* 2026; doci250008. Reprinted with permission from the American Diabetes Association, Inc. Copyright 2026.

51

Approved and Emerging Obesity Pharmacological Therapies: Nutrient-Stimulated Hormone-Based Therapeutics

Mechanism	Drug	Phase 3 Program	Route	Development Stage	Weight Loss	Weeks
GLP-1 RA 2.4 mg GLP-1 RA 7.2 mg	Semaglutide	STEP STEP UP	SC SC	Approved '21 Approved '26	15.2% 18.7%	104 72
GLP-1/GIP RA	Tirzepatide	SURMOUNT	SC	Approved '23	20.9%	72
GLP-1 RA	Semaglutide (SNAC)	OASIS	Oral	Approved '25	13.6%	68
GLP-1 small molecule RA	Orforglipron	ATTAIN	Oral	Approved '26	11.2%	72
GLP-1 RA + Amylin RA	CagriSema*	REDEFINE	SC	Phase 3	20.4%	68
GLP-1/Glucagon RA	Survodutide Mazdutide Pemvidutide	SYNCHRONIZE GLORY MOMENTUM	SC SC SC	Phase 3 Phase 3 Phase 2	16.6% 15.4% 15.6%	76 48 48
GLP-1/GIP/Glucagon RA	Retatrutide	TRIUMPH	SC	Phase 3	29.9%	104
GLP-1 RA + GIPR antagonist	MariTide	MARITIME	SC Monthly	Phase 2	16.2%	52
GLP-1 small molecule RA	Aleniglipron	ACCESS	Oral	Phase 2	12.1%	36
Amylin RA	Eloralintide	ENLIGHTEN	SC	Phase 2	17.5%	48

* Submitted to FDA for approval

Kushner RF, et al. JAMA 2024;332;571-584; Kushner RF, et al. JAMA 2025;334(17):1551-1552

52

Practical Take Aways

- Pharmacotherapy is an evidence-based, effective treatment for obesity. It addresses the underlying biological appetite dysregulation of the disease
- By knowing the expected weight loss trajectories and side effects, we can better monitor our patients for effectiveness, responsiveness, and tolerability
- Medications will likely be needed to be used long-term. When the medication is stopped suddenly, the appetite dysregulation returns followed by weight recurrence
- Hormonal treatment of obesity (e.g., GLP-1, GIP, amylin, glucagon) represents a new paradigm in obesity therapeutics

Northwestern Medicine®
Feinberg School of Medicine