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Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Medicating the Patient with Obesity

Donna Ryan, MD
Professor Emerita
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Disclosures

- Advisor or Consultant: Novo Nordisk, Pfizer, Real Appeal, Epitomee, Gila Therapeutics, Xeno Bioscience, Calibrate, Naturally Slim Wondr Health, Lilly Advisory, YSOPIA, Altimmune, IFA Celtic, Ro, Scientific Intake, Amgen, Zealand
- Speakers Bureau: Novo Nordisk
- Ownership Interest: Gila Therapeutics, Xeno Bioscience, Epitomee, Calibrate, Roman and Scientific Intake
- Research: SELECT Steering Committee (Novo Nordisk)

Objectives:

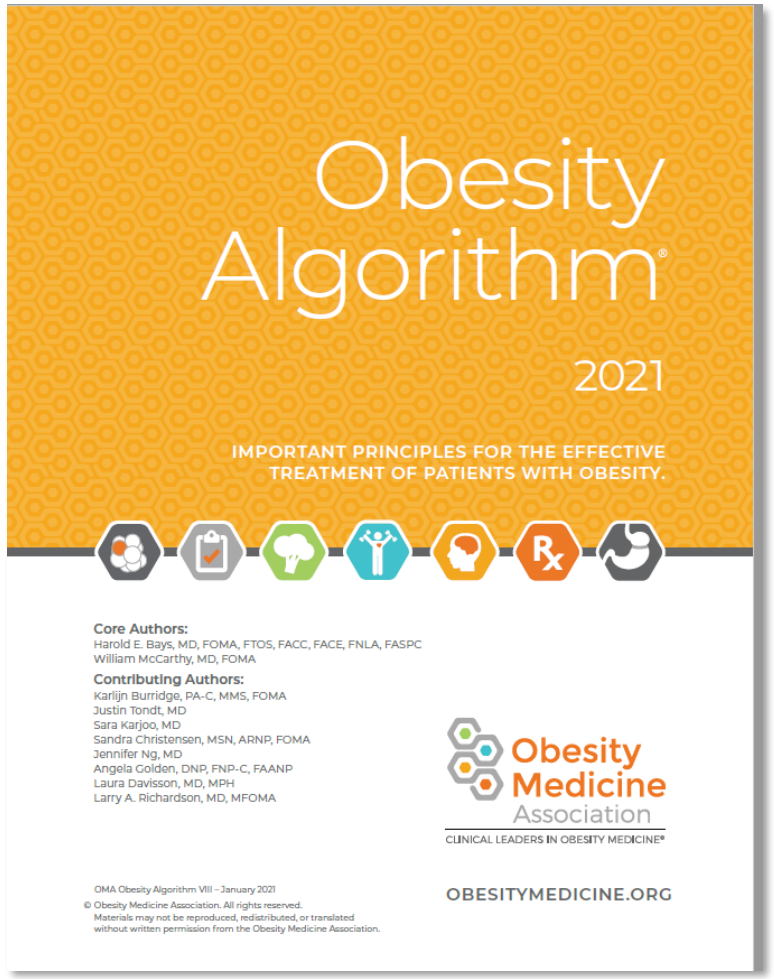
At the completion of the presentation, attendees will be able to

Describe the rationale and principles for using medications in patients with obesity both to avoid further gain and to promote and sustain weight loss

Identify commonly used medications that promote weight gain and alternatives that are weight neutral or promote weight loss

Describe medications approved for chronic weight loss or used off-label to promote weight loss

Good resources and key references



https://obesitymedicine.org/obesity-algorithm/


THE JOURNAL OF FAMILY PRACTICE

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Drs. Saunders, Igel, and Shukla reported no potential conflict of interest relevant to this article.

Dr. Aronne reported that he is a consultant/advisor to Eisai, Gelesis, GI Dynamics, Jamieson Labs, JOMA Health, Novo Nordisk A/S, Pfizer Inc, and VIVUS; a shareholder of Gelesis, Jamieson Labs, Myos Corp, and Zafgen; and a member of the board of directors of Gelesis, and Myos Corp. Dr. Aronne also reported receiving research funding from Aspire Bariatrics and Eisai.

Drug-induced weight gain: Rethinking our choices

Weight gain secondary to medications is a potentially modifiable risk. Here's how to optimize drug choices for patients with several common conditions.

PRACTICE RECOMMENDATIONS

› *Choose weight-loss-promoting medications, such as metformin, sodium-glucose co-transporter 2 inhibitors, and glucagon-like peptide-1 agonists, and weight-neutral medications, such as DPP-4 inhibitors, as first- and second-line agents for patients with type 2 diabetes who are overweight or obese.* (A)

› *Prescribe angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers as first- and second-line antihypertensive therapy for patients who are overweight or obese.* (A)

› *Select antidepressants that promote weight loss, such as bupropion, or weight-neutral agents, such as fluoxetine and sertraline, for patients who are overweight or obese and require treatment for depression.* (B)

Strength of recommendation (SOR)
(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Medications can have an unpredictable and variable effect on weight. Some drugs trigger weight gain in one patient while inducing weight loss in another. Others may lead to weight loss initially but cause weight gain when taken long term.[1] Often, a drug's effect on a patient's weight depends on his or her medical history and lifestyle, including factors like insulin resistance, diet, and exercise level.

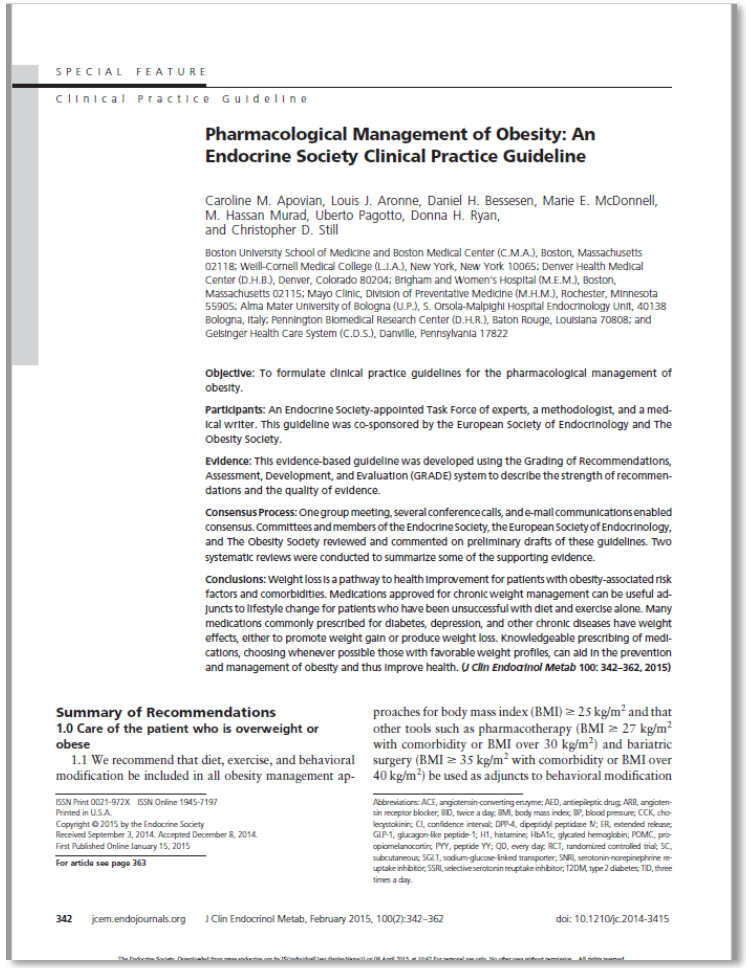
To make matters worse, clinical studies of drug-related effects on weight can be misleading. Because researchers often report a mean weight change—an average of those who had little or no change in weight when taking the drug and individuals who may have gained a significant amount of weight—a drug's potential to cause weight gain may be underestimated. Few studies include an analysis of the range—eg, how many participants gained or lost various percentages of body weight. What's more, pharmacology studies typically follow participants for a few months to a few years, whereas weight changes can be cumulative when a medication is taken for many years.

The nation's continually growing obesity epidemic makes it crucial for physicians to consider the weight effects of medications being prescribed and to balance the benefits of treatment with the potential for weight gain. Until recently, the medical literature offered little guidance.

In 2015, the Endocrine Society published clinical practice guidelines for pharmacologic management of obesity, including data on medications that cause weight gain and suggesting alternatives that are weight-neutral or promote weight loss.[2]

In the pages that follow, we present case studies, tables, and a review of the latest evidence to highlight optimal drug treatment for patients who are overweight or obese, and are also being treated for diabetes, hypertension, and depression. You'll find a brief discussion of weight management strategies related to other drugs and conditions in the sidebar on page 786.[2-5]

J Fam Pract 2016 Nov;65(11):780-788.


SPECIAL FEATURE
Clinical Practice Guideline

Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

Caroline M. Apovian, Louis J. Aronne, Daniel H. Bessesen, Marie E. McDonnell, M. Hassan Murad, Uberto Pagotto, Donna H. Ryan, and Christopher D. Still

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Objective: To formulate clinical practice guidelines for the pharmacological management of obesity.

Participants: An Endocrine Society-appointed Task Force of experts, a methodologist, and a medical writer. This guideline was co-sponsored by the European Society of Endocrinology and The Obesity Society.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, the European Society of Endocrinology, and The Obesity Society reviewed and commented on preliminary drafts of these guidelines. Two systematic reviews were conducted to summarize some of the supporting evidence.

Conclusions: Weight loss is a pathway to health improvement for patients with obesity-associated risk factors and comorbidities. Medications approved for chronic weight management can be useful adjuncts to lifestyle change for patients who have been unsuccessful with diet and exercise alone. Many medications commonly prescribed for diabetes, depression, and other chronic diseases have weight effects, either to promote weight gain or produce weight loss. Knowledgeable prescribing of medications, choosing whenever possible those with favorable weight profiles, can aid in the prevention and management of obesity and thus improve health. *J Clin Endocrinol Metab* 100: 342–362, 2015)

Summary of Recommendations

1.0 Care of the patient who is overweight or obese

1.1 We recommend that diet, exercise, and behavioral modification be included in all obesity management approaches for body mass index (BMI) ≥ 25 kg/m^2 and that other tools such as pharmacotherapy (BMI ≥ 27 kg/m^2 with comorbidity or BMI over 30 kg/m^2) and bariatric surgery (BMI ≥ 35 kg/m^2 with comorbidity or BMI over 40 kg/m^2) be used as adjuncts to behavioral modification

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For article see page 363

Abbreviations: ACE, angiotensin-converting enzyme; AED, antiepileptic drug; ARB, angiotensin receptor blocker; BID, twice a day; BMI, body mass index; BP, blood pressure; CCK, cholecystokinin; CI, confidence interval; DPP-4, dipeptidyl peptidase IV; ER, extended release; GLP-1, glucagon-like peptide-1; HT, histamine; HbA1c, glycated hemoglobin; POMC, proopiomelanocortin; PYY, peptide YY; QD, every day; RCT, randomized controlled trial; SC, subcutaneous; SGLT, sodium-glucose-linked transporter; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; T2DM, type 2 diabetes; TID, three times a day.

The J Clini Endo & Metabolism 100.2 (2015): 342-362.

Pharmacologic Treatment of Overweight and Obesity in Adults

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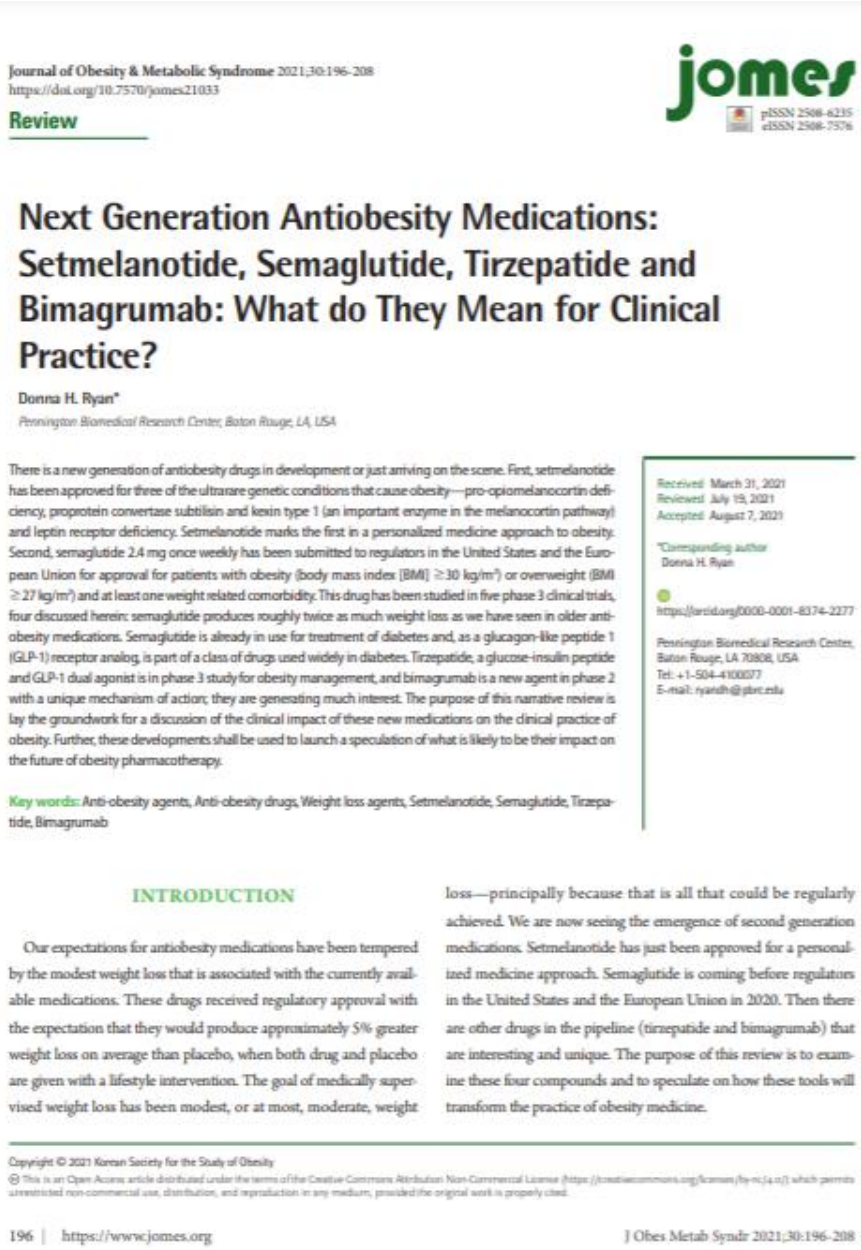
Updated: August 2, 2021

https://www.endotext.org/chapter/pharmacologic-treatment-of-overweight-and-obesity-in-adults/#toc-semaglutide-2-4/

Good resources



Journal of Obesity & Metabolic Syndrome 2021;30:196-208
https://doi.org/10.7570/jomes21033

Review

jomes
pISSN 2508-6235
eISSN 2508-7576

Next Generation Antiobesity Medications: Setmelanotide, Semaglutide, Tirzepatide and Bimagrumab: What do They Mean for Clinical Practice?

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There is a new generation of antiobesity drugs in development or just arriving on the scene. First, setmelanotide has been approved for three of the ultrarare genetic conditions that cause obesity—pro-opiomelanocortin deficiency, proprotein convertase subtilisin and kexin type 1 (an important enzyme in the melanocortin pathway) and leptin receptor deficiency. Setmelanotide marks the first in a personalized medicine approach to obesity. Second, semaglutide 2.4 mg once weekly has been submitted to regulators in the United States and the European Union for approval for patients with obesity (body mass index [BMI] ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) and at least one weight related comorbidity. This drug has been studied in five phase 3 clinical trials, four discussed herein: semaglutide produces roughly twice as much weight loss as we have seen in older antiobesity medications. Semaglutide is already in use for treatment of diabetes and, as a glucagon-like peptide 1 (GLP-1) receptor analog, is part of a class of drugs used widely in diabetes. Tirzepatide, a glucose-insulin peptide and GLP-1 dual agonist is in phase 3 study for obesity management, and bimagrumab is a new agent in phase 2 with a unique mechanism of action; they are generating much interest. The purpose of this narrative review is lay the groundwork for a discussion of the clinical impact of these new medications on the clinical practice of obesity. Further, these developments shall be used to launch a speculation of what is likely to be their impact on the future of obesity pharmacotherapy.

Key words: Anti-obesity agents, Anti-obesity drugs, Weight loss agents, Setmelanotide, Semaglutide, Tirzepatide, Bimagrumab

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INTRODUCTION

Our expectations for antiobesity medications have been tempered by the modest weight loss that is associated with the currently available medications. These drugs received regulatory approval with the expectation that they would produce approximately 5% greater weight loss on average than placebo, when both drug and placebo are given with a lifestyle intervention. The goal of medically supervised weight loss has been modest, or at most, moderate, weight loss—principally because that is all that could be regularly achieved. We are now seeing the emergence of second generation medications. Setmelanotide has just been approved for a personalized medicine approach. Semaglutide is coming before regulators in the United States and the European Union in 2020. Then there are other drugs in the pipeline (tirzepatide and bimagrumab) that are interesting and unique. The purpose of this review is to examine these four compounds and to speculate on how these tools will transform the practice of obesity medicine.

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Rationale and Principles for Medicating the Patient with Obesity

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Indication for Medication in Weight Management
(from the label of all FDA-approved medications)

- As an adjunct to diet and physical activity for chronic weight management in adults with initial
- BMI >30 kg/m^2 or
- BMI >27kg/m^2 with one or more obesity associated comorbidities

Guidelines and professional societies add that patients should have been unsuccessful at lifestyle efforts to lose weight or maintain weight loss.

Jensen MD, et al. 2013 AHA/ACC/TOS guideline… Circulation. 2014;129(25 SUPPL. 1):102-138.
Garvey WT, et al. AACE /ACE Guidelines. Endocrine 2016;22 Suppl 3:1-203.
Apovian CM, et al. Endocrine guideline. J Clin Endocrinol Metab. 2015;100(2):342-362.

Principles in Prescribing Antiobesity Medications

- Medications work through biology to help patients lose more weight than they would with lifestyle efforts alone.
- Medications improve health through weight loss and, sometimes, through additional benefits on obesity comorbidities. Choose with this in mind.
- There is heterogeneity in treatment response for any type of obesity intervention, including medication.
- As with other chronic diseases, continued therapy is needed to sustain weight loss. Lifelong treatment is needed.

https://www.endotext.org/chapter/pharmacologic-treatment-of-obesity/

Best Practices in Prescribing a Medication with an Indication for Chronic Weight Management

- Know the contraindication and side effect profiles of AOMs.
- Know the dual benefits of the medications you prescribe.
- Engage patients in the prescribing decision.
- It’s not just about prescribing. Comprehensive care requires a team approach.
- Combinations of AOMs are an emerging trend.

https://www.endotext.org/chapter/pharmacologic-treatment-of-obesity/

Best Practices in Avoiding Medication Induced Weight Gain

- Some medications for diabetes, mental health issues and other conditions can promote weight gain
- Know the medications that commonly drive weight gain and for patients with obesity seek alternatives that are weight neutral or associated with weight loss.
- When a weight-gain producing medication is unavoidable, consider adding a medication known to produce weight loss to limit weight gain effects.

What does a holistic approach look like for weight-management interventions?

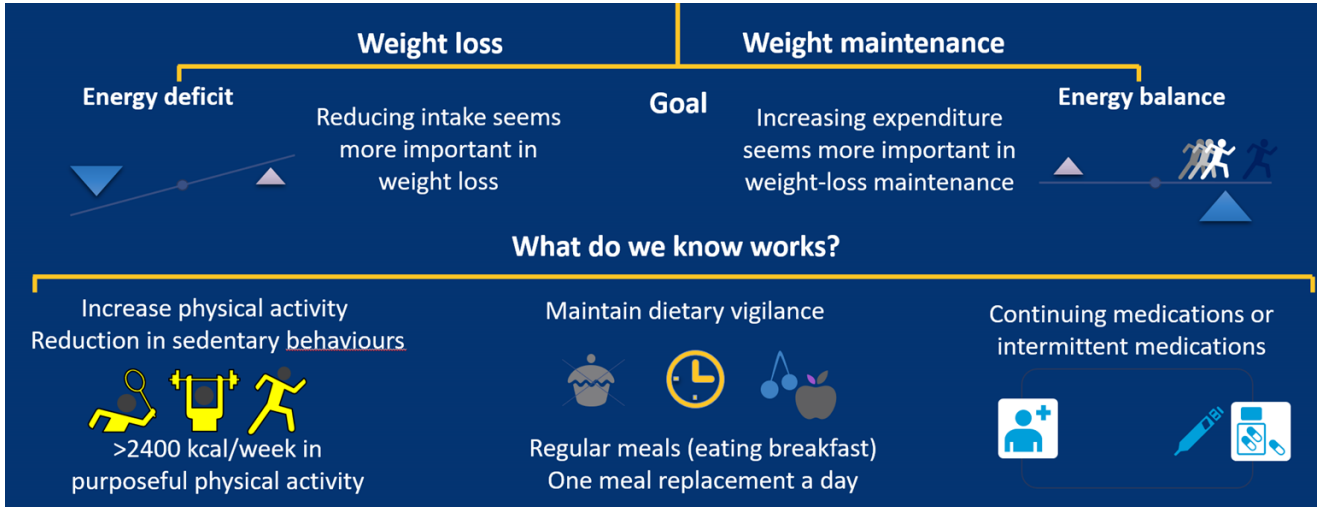
Avoiding hypoglycemia

Managing depression and mental health

Stress management

Avoiding medication-induced gain

Good sleep hygiene



Financial management skills

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Avoiding and Remediating Medication Induced Weight Gain

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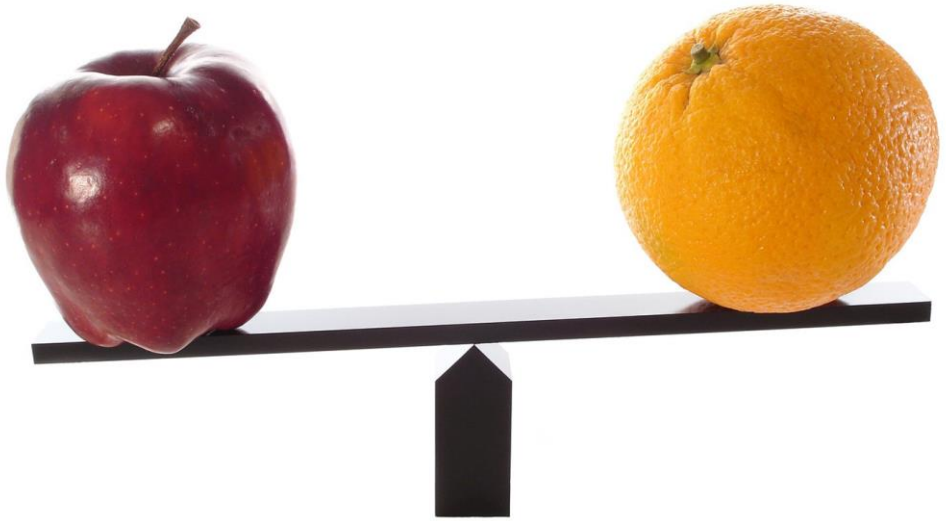
Understanding the evidence about medication induced weight gain…

- Evidence of medication-associated weight effects is derived from studies where weight was *not* the primary endpoint, and where comparisons were not head-to-head.
- There is variability in susceptibility to weight gain with medications. Reports of average weight loss may underestimate the effect in susceptible individuals.



Strategy for Identifying and Managing Medication Induced Weight Gain

- Take a history that includes medication use.
- Know medications that drive weight gain in susceptible individuals
- Use alternative medications that are weight neutral or associated with weight loss, if possible.
- Counsel patients about the possibility of weight gain.
- Consider adding a medication known to produce weight loss, when weight gain inducing medications are unavoidable.

Medications that Promote Weight Gain

In SOME patients…

- Antidepressants
- Antipsychotics
- Mood stabilizers
- Antidiabetic medications
- Glucocorticoid
- Anti-seizure medications
- Migraine medications
- Chemotherapies
- HIV therapies
- Pain and Neuropathy medications
- Organ transplant medications

Medication Induced Weight Gain and Alternative Approaches for Diabetes Medications

Weight Gain	Weight Neutral	Weight Loss
Insulin	Alpha-glucosidase inhibitors	GLP-1 Receptor Agonists
Meglitinides	Bromocriptine	Metformin
Sulfonylureas	Colesevelam	Pramlintide
Thiazolidinediones	DPP-4 inhibitors	SGLT2 inhibitors

Medication Induced Weight Gain and Alternative Approaches for Cardiovascular Medications

Weight Gain	Weight Neutral

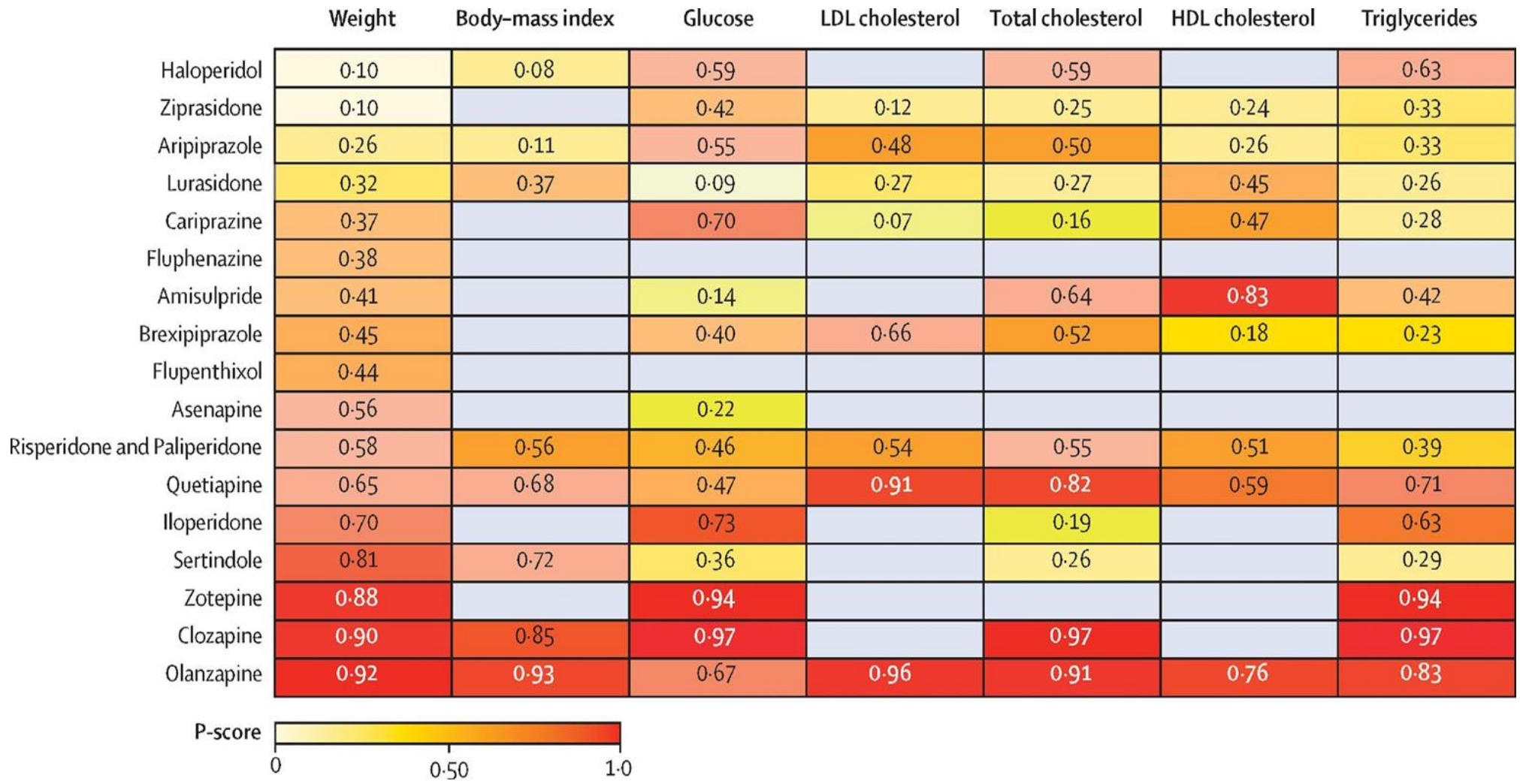
• Beta adrenergic blockers –
  • propranolol
  • atenolol
  • metoprolol
 	
• Calcium channel blockers – older agents (nifedipine, amlodipine) promote water gain
	• Beta adrenergic blockers -carvedilol, nebivolol more likely to be weight neutral
	
	• Ace Inhibitors
	
	• Angiotensin Receptor Blockers
	
	• Thiazides

Antidepressants and Effects on Weight

	Gain	Neutral	Loss
Tricyclic antidepressants	amitryptyline doxepin imipramine nortriptyline		
SSRIs	paroxetine	fluoxetine sertraline	
MAOIs	isocarboxazid phenelzine		
SNRIs	duloxetine venlafaxine		
others	mirtazepine brexpiprazole trazodone		bupropion

Saunders KH, et al. Drug-induced weight gain: Rethinking our choices. J Fam Pract. 2016 Nov;65(11):780-788.

Heat Map: Weight and Metabolic Effects of Antipsychotics



Pillinger T, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. The Lancet Psychiatry, Volume 7, Issue 1, 64 - 77

Antipsychotics and Effects on Weight: Second Generation Antipsycotics Are More Likely to Produce Weight Gain

Most consistently cause weight gain	Neutral or variable effects on body weight
Clozapine	Amisulpride
Olanzapine	Aripiprazole
Chlorpromazine	Asenipine
Brexpiprazole	Cariprazine
Iloperidone	Haloperidol
Lithium	Loxipine
Quetiapine	Lurasidone
Risperidone	Ziprasidone
Thioridazine	Paliperidone
Zotepine (not available in US)	Perphenazine

If patients on antipsychotics experience weight gain, consider adding a medication known to produce weight loss

- **Metformin** in antipsychotic weight gain
  - Meta analysis 12 studies, 743 patients, metformin produced -3.24% weight loss and metabolic improvement.
    - de Silva et al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry (2016) 16:341
- **Liraglutide** for antipsychotic weight gain
  - Randomized trial of 103 patients on olanzapine or clozapine. Liraglutide 3 mg produced -5.3 kg and metabolic improvement.
    - Larsen JR, et al. Effect of Liraglutide Treatment on Prediabetes and Overweight or Obesity in Clozapine- or Olanzapine-Treated Patients With Schizophrenia Spectrum Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2017 Jul 1;74(7):719-728.
- **Topiramate** for antipsychotic weight gain
  - Review of meta-analysis and randomized trials showed weight loss efficacy in antipsychotic induced weight gain with topiramate 25 mg titrated up to 100-300 mg.
    - Generali JA, Cada DJ. Topiramate: antipsychotic-induced weight gain. Hosp Pharm. 2014;49(4):345-347.

Mood Stabilizers and Body Weight effects

May increase body weight	Variable or neutral effects
Gabapentin	Lamotrigine (sometimes reported to ↓ body weight)
Divalproex	Oxcarbazepine
Lithium	
Valproate	
Vigabatrin	
Cariprazine	
Carbamazepine	

Other medications associated with weight effects:

- Glucocorticoids
- Anti-seizure medications
- Migraine medications
- Cancer Chemotherapies
- HIV therapies
- Pain and Neuropathy medications
- Organ transplant medications

For more information, go to OMA Obesity Algorithm 2023

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Prescribing Medications to Help Patients Achieve and Sustain Weight Loss

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What is the goal of weight loss?

- Reduce excess abnormal body fat that is affecting health.

What is the goal of medicating for weight loss?

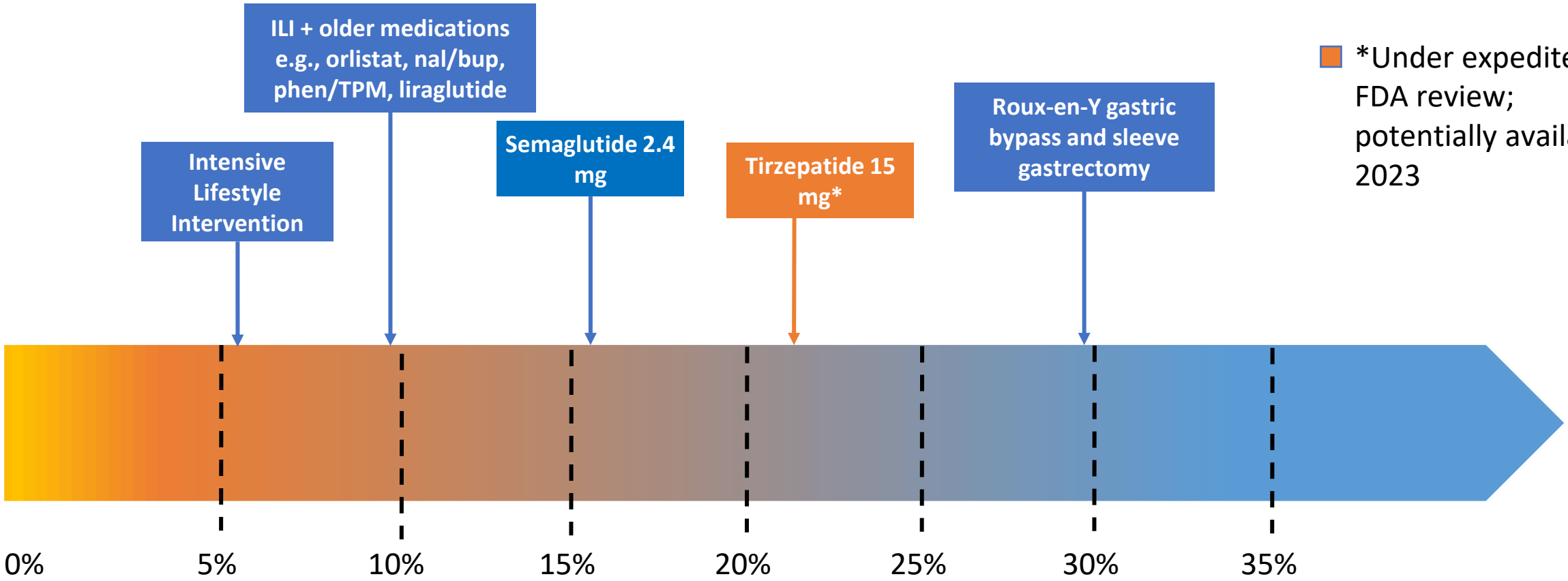
- Patients are more likely to lose more weight and thus achieve health benefits if medication are given to support lifestyle changes.

Weight Loss Benefits Begin with Modest Weight Loss, but Greater Weight Loss Produces Greater Benefits

Measures of glycemia[1]	**-3%**
Triglycerides[1]	
HDL cholesterol[1]	**-5%**
Systolic and diastolic blood pressure	
Hepatic steatosis measured by MRS[2]	
Measures of feeling and function: Symptoms of urinary stress incontinence[3] Measures of sexual function[4,5] Quality of life measures(IWQOL)[6]	
NASH Activity Score measured on biopsy[7]	**-10%**
Apnea-hypopnea index[8]	
Reduction in CV events, mortality, remission of T2DM	**-15%**

1. Wing et al. Diabetes Care 2011;34:81-1486. 2. Lazo et al. Diabetes Care 2010;33:2156–63.3. Phelan et al. Urol. 2012;187:939-44.
4. Wing et al. Diab Care 2013;36:2937-44. 5. Wing et al. Journal of Sexual Medicine 2010 ; 7:156-65.
6. Crosby, Manual for the IWQOL-LITE Measure. 7. Promrat et al. Hepatology 2010;51:121–29. 8. Foster et al. Arch Intern Med 2009;169:1619–26.

Available Treatments for Obesity



Not all agents are available in all regions; always consult local prescribing information. Direct comparisons between data cannot be made due to differences in trial designs.
*40-week study duration; **20-week study duration.

ILI, Intensive Lifestyle Intervention; nal/bup, naltrexone/bupropion; phen/TPM, phentermine/topiramate
Allison DB, et al. *Obesity*. 2012;20(2):330-342. [EQUIP]; Gadde KM , et al. *Lancet*. 2011;37:1341-1352. [CONQER]; Greenway FL, et al. *Lancet*. 2010;376:595-605. [COR-I]; Apovian CM, et al. *Obesity*. 2013;21:935-943 [COR-II];
Wadden TA, et al. *Obesity*. 2011;19(1):110-120. [COR-BMOD]; Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22. [SCALE];
Wadden TA, et al. *In J Obes*. 2013;37:1443-1451. [SCALE MAIN]; Enebo LB, et al. *Lancet*. 2021;397(10286):1736-1748. [Cag + Sema]; Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989. [STEP 1];
Wadden TA, et al. *JAMA*. 2021;325(14):1403-1413. [STEP 3]; Rubino D, et al. *JAMA*. 2021;325(14):1414-1425. [STEP 4];
Ryan D. *Lancet Diabetes Endocrinol*. 2021;9(5):252-254. [STEP]; Sjöström L, et al. *N Engl J Med*. 2007;357:741-52. [Surgery]; Frias JP, et al. *Lancet*. 2021 [SURPASS-2].

Key Strategy for using anti-obesity medications

We want to achieve health benefits mediated through weight loss.

We want our antiobesity medications to provide additional benefits independent of weight loss

LDL reduction - orlistat; glycemic improvement - GLP-1 RAs

Ask Two Questions Before Selecting the Prescription AOM

1. Are there contraindications, drug-drug interactions, or undesirable adverse effects associated with this medication that could be problematic for the patient?

2. Can this medication improve other existing symptoms or conditions?

Things to consider when choosing a medication

slide courtesy Dominica Rubino

Appropriate Patient Selection
Medical weight loss?
After surgery?
Benefits vs risks?
Reproductive age?

Economics

Comorbidities
T2DM? Depression? HTN?
HR?
Sleep apnea? Insomnia?
GI? Migraines?
CVD? Glaucoma?
Nephrolithiasis?
RI? Alcohol?

Anticipate AEs and efficacy

Recognize individual variation in response; trial and error

Manage expectations of medication effects and underlying physiology (teach the patient) and set realistic goals

Context of Patient
Support, lifestyle management, preference (injection vs oral), AE potential (comfort level)

Concomitant Medications
Antidiabetic medications?
Antidepressants? CNS drugs? Diuretics?
Sleep medications?
Migraine medications?

Older medications and how they work

Agent	Action	Approval by US FDA	Scheduled Drug
Phentermine (for short term use)	• Sympathomimetic amine; norepinephrine release and to lesser extent releases other monoamines	Approved 1959	• YES
Orlistat Does not have an appetite effect	• Pancreatic lipase inhibitor; Blocks absorption of 30%of ingested dietary fat	Approved 1999 OTC Approved 2006	• NO
Phentermine/ Topiramate ER	• Sympathomimetic • Anticonvulsant (GABA receptor modulator carbonic anhydrase inhibitor, glutamate antagonist)	Approved 2012	• YES
Naltrexone ER/ Bupropion ER	• Opioid receptor antagonist • Dopamine/norepinephrine reuptake inhibitor	Approved 2014	• NO
Liraglutide 3.0 mg	• GLP-1 receptor agonist	Approved 2014	• NO

OTC: over the counter; ER: extended release; GABA: gamma-aminobutyric acid;

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

Phentermine: FDA-Approved for Obesity Management: Short-Term Use

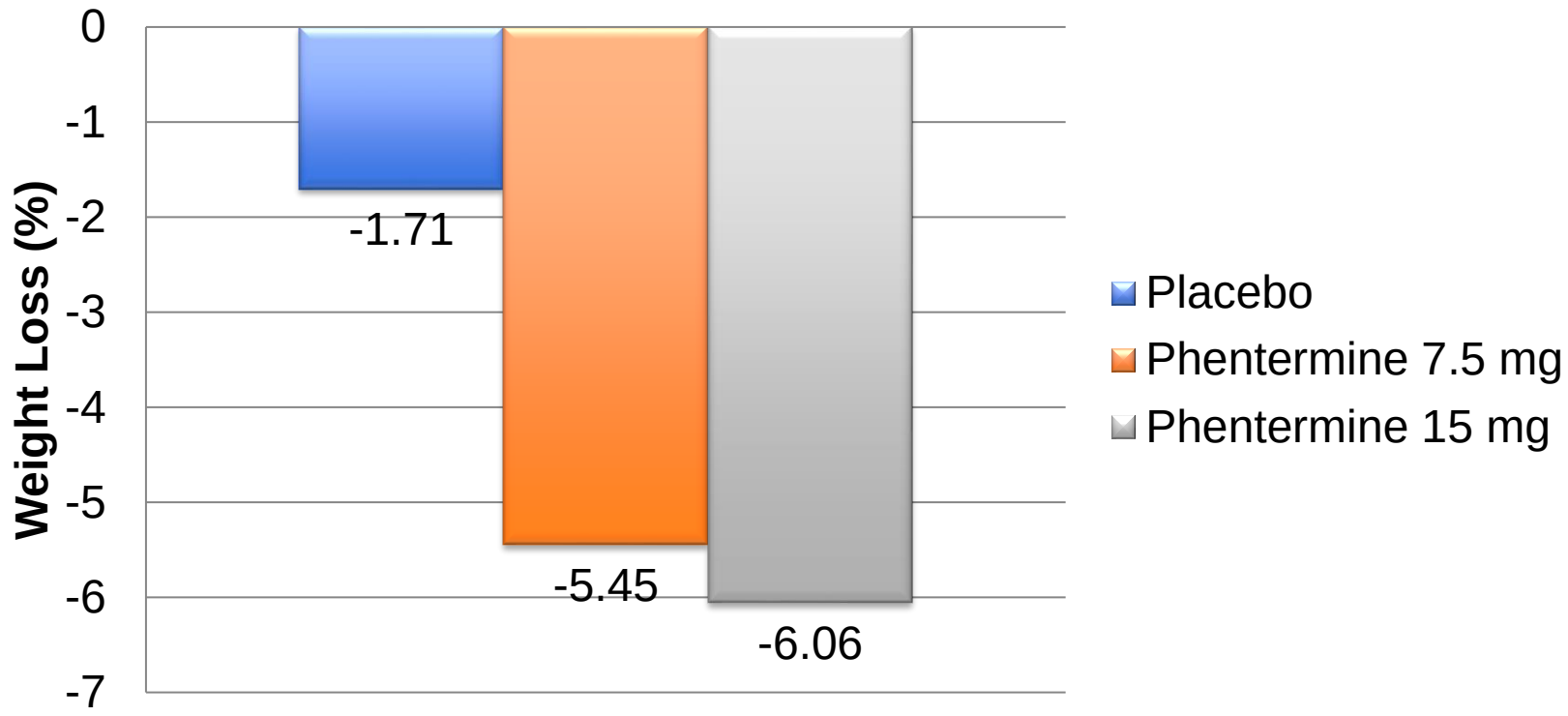
- Sympathomimetic agent; Scheduled drug (II or IV)
- Common adverse events[1]: insomnia, elevated heart rate, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastrointestinal distress, anxiety, restlessness

ENDO Pharmacotherapy Guidelines[2]: "In patients with uncontrolled hypertension or a history of heart disease, we recommend against using sympathomimetic agents phentermine and diethylpropion.

1⊗⊗⊗? (strong rec, moderately high quality evidence)

1. Yanovski SZ, Yanovski JA. *JAMA*. 2014;311:74-86
2. Apovian CM, Aronne LJ, Bessesen DH et al. Pharmacologic Management of obesity: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100(2):342–362.

Dose and Weight Loss with Phentermine: Randomized comparison of weight loss at 28 weeks with lifestyle intervention and placebo, phentermine 7.5 mg or phentermine 15 mg



Data shown are LS mean and all comparisons are statistically significant.
Treatment arms not shown are topiramate 46 mg and 92 mg and phentermine/topiramate ER 7.5/ 46 mg and 15/92 mg.

Aronne LJ, et al. *Obesity* 2013. 21, 1-9.

Orlistat 120 mg 3 times daily by prescription
Orlistat 60 mg 3 times daily OTC

- Blocks absorption of 30% ingested fat (intestinal lipase inhibitor)
- 120 mg TID with meals (Rx) or 60 mg TID (OTC)
- Available world-wide
- Generally safe; Contraindications: pregnancy, chronic malabsorption syndrome, cholestasis
- Reinforces low fat diet, has efficacy in LDL lowering
- No effect on appetite
- Must counsel patients regarding gastrointestinal side effects and steatorrhea
- Consider using with Metamucil, multivitamin at bedtime

Information from product label

Liraglutide 3.0 mg

- Liraglutide is GLP-1 receptor agonist, given by daily injection
- Not scheduled
- Tolerability issues: nausea – requires dose escalation from 0.6 mg
- Safety issues: pancreatitis risk; gall bladder disease risk; contraindicated with history of MEN II or medullary thyroid cancer.
- Has indication for diabetes at 1.8 mg dose, so has a secondary benefit on glycemia; not indicated for the treatment of type 2 diabetes, but is indicated as an adjunct to lifestyle intervention for chronic weight management in type 2 diabetes.

Information from product label

Phentermine/ Topiramate ER recommended dose 7.5 mg/46 mg

- Two common medications, at low dose
- Acts centrally to reduce food intake
- Scheduled (DEA) in US
- Titrate to 7.5 mg/46 mg
- Produces greatest weight loss, on average
- Tolerability issues: taste disturbance (carbonation),
- Safety issues: teratogenicity (topiramate), glaucoma (topiramate)
- Obtain negative pregnancy test before use and monthly in women of child-bearing potential

Information from product label

Naltrexone SR/ Bupropion SR 32/360 mg tabs

- Two common medications; reduces food intake centrally & may affect craving
- Not scheduled
- Titrate to 32 mg/360 mg
- Tolerability issues: nausea – requires dose escalation from 8 mg/90 mg
- Safety issues: opioid antagonist (naltrexone), lowers seizure threshold and can unmask mania and increase suicidality risk (bupropion)
- Has indication for smoking cessation and depression (bupropion)

Information from product label

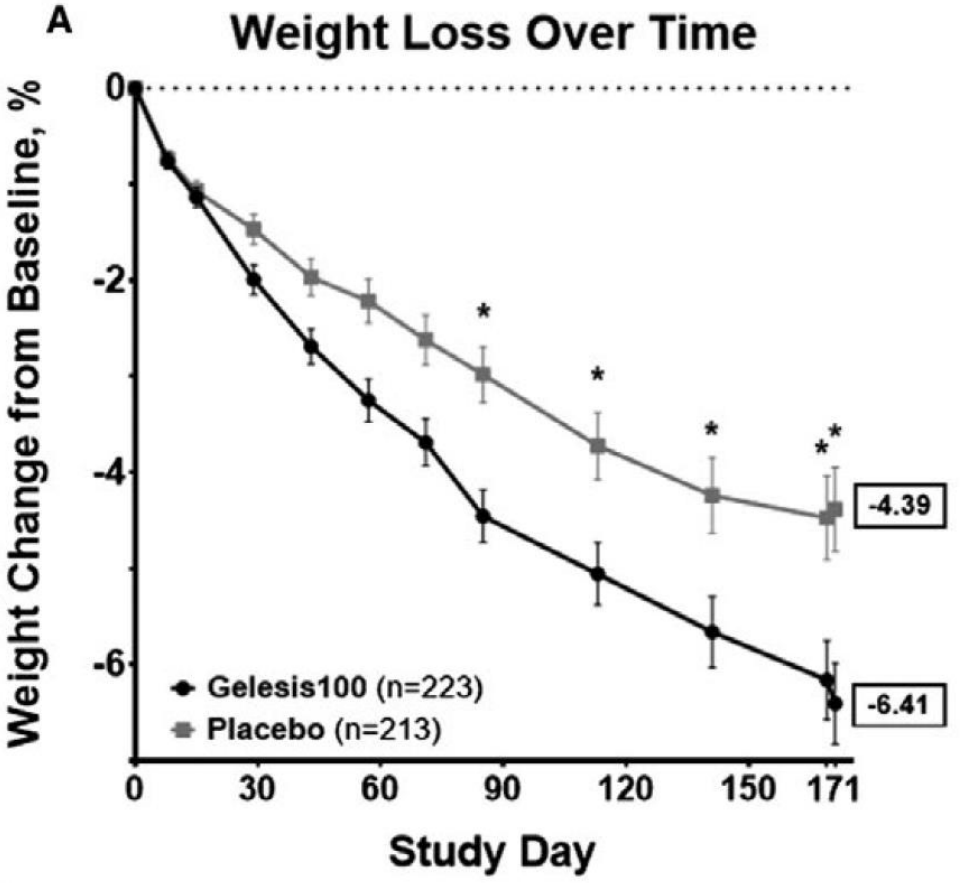
Newer Medications and How They Work

Agent	Action	Approval by US FDA	Scheduled Drug
Setmelanotide[1,2]	• Binds and activates melanocortin receptors MC4R, MC3R, and MC1R	Approved by FDA 2020	• NO
Gelesis 100[3]	• Non-absorbable hydrogel taken with water before meals; activates stretch receptors in stomach	Cleared as a device, 2020	• NO
Semaglutide 2.4 mg[4]	• GLP-1 analogue	Approved by FDA 2021	• NO

1. Clement K, et al. Nat Med 2018; 24: 551–5.
2. https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-first-treatment-weight-management-people-certain-rare-genetic-conditions
3. https://www.endotext.org/chapter/pharmacologic-treatment-of-obesity/
4. Kushner RF, et al. Obesity (Silver Spring). 2020;28(6):1050-1061.

Gelesis 100

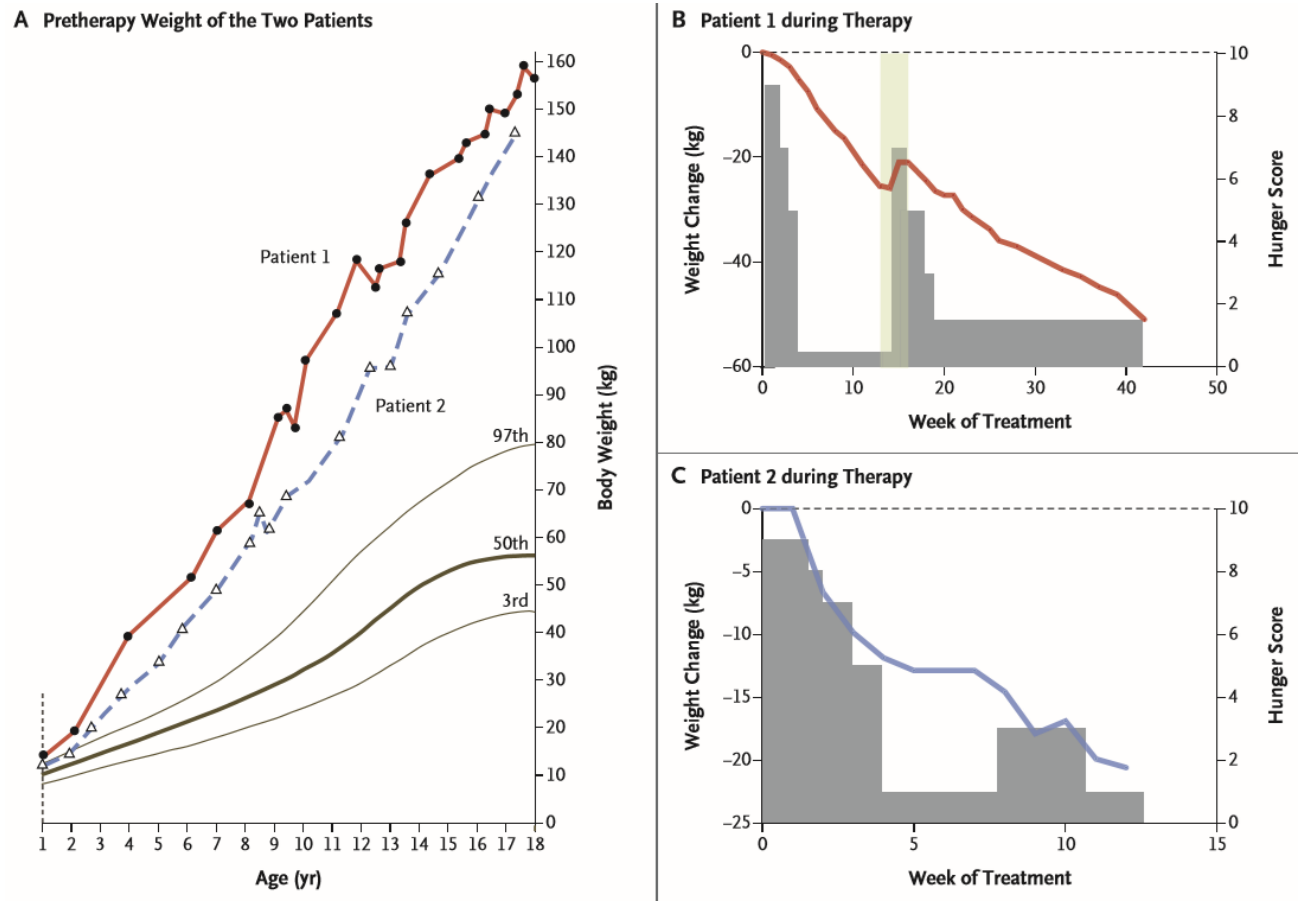
- The newest FDA-cleared device
- Currently available in some specialty offices and online through telemedicine
- Indication for adults with BMI 25-40
- Three caps taken orally with glass (500 cc) of water before meals, activates stretch receptors, reduces meal size
- Non-absorbable hydrogel
- Should not be given when there are anatomical abnormalities of the esophagus or GI transit issues
- For dosing with other medicines, consider gelesis as a food and don't dose with medicines that require an "empty stomach."



Greenway FL et al. Obesity (2019) 27, 205-216.

Precision medicine: setmelanotide (MC4 RA)

2 patients with POMC genetic defects

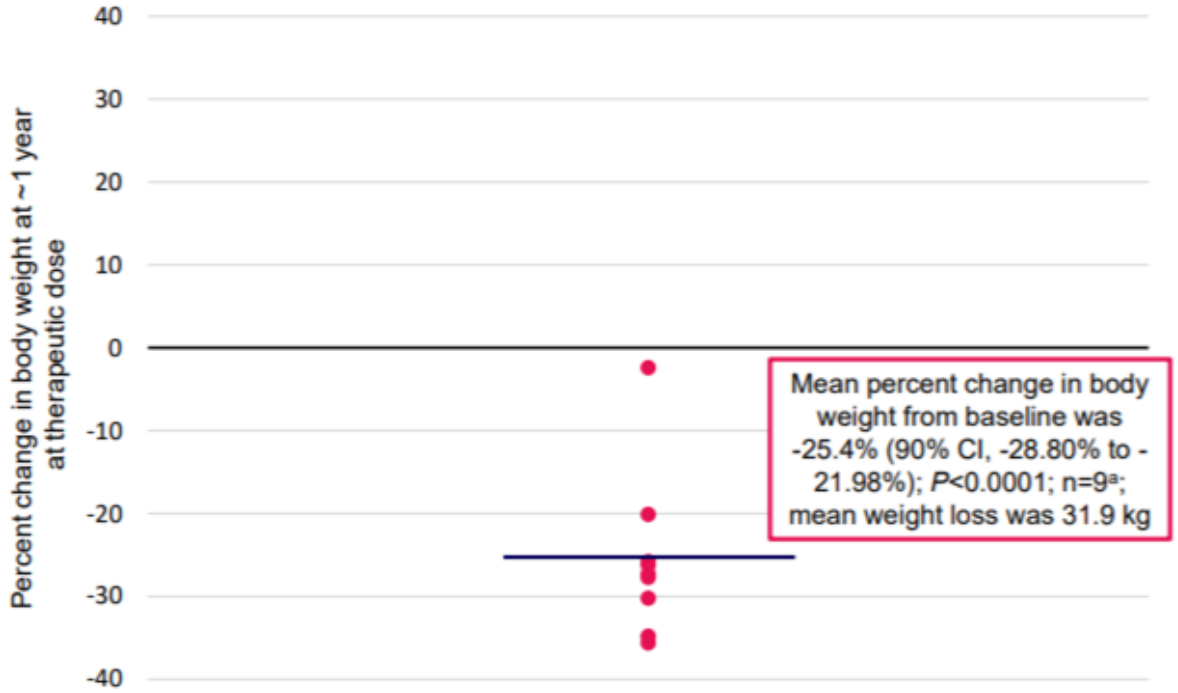


Kuhnen P, et al. *N Eng J Med*. 2016;375:240-246.

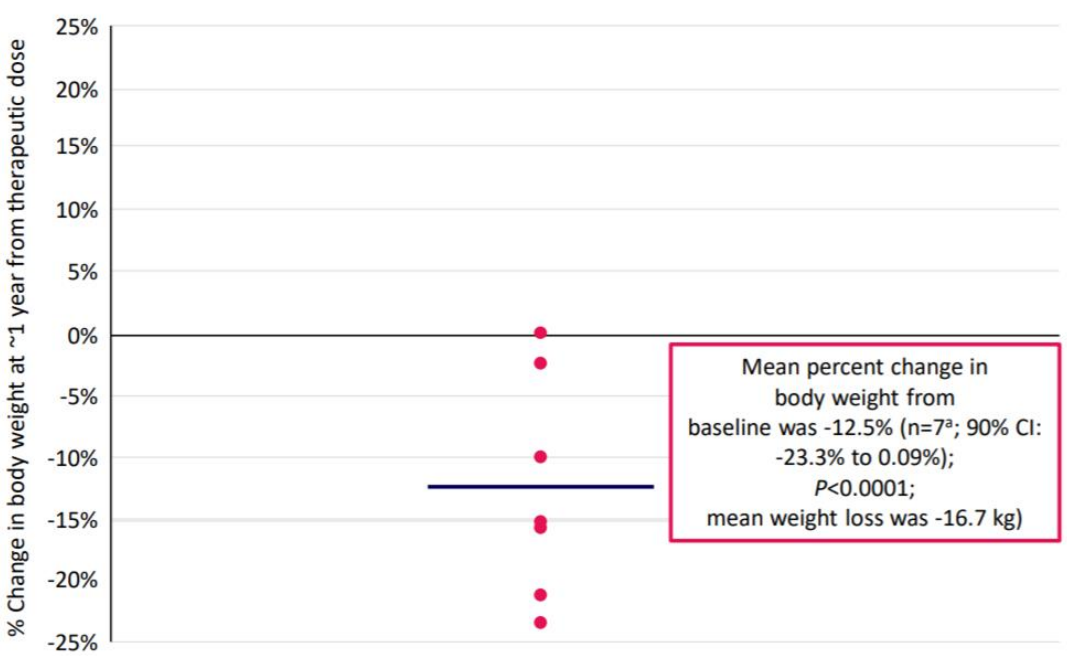
Setmelanotide in POMC and LEPR Deficiency.

In these studies, the drug was administered daily, starting at 1 mg to patients with homozygous genetic deficiency in POMC, PCSK1 and Leptin Receptor. There was maximum 32 weeks of open-label therapy for responsive patients.

SETMELANOTIDE IN POMC DEFICIENCY



SETMELANOTIDE IN LEPR DEFICIENCY



Note: Y axis scales are not identical.

Clément K, et al. Lancet Diabetes Endocrinol 2020; 8 (12): 960-970.

Setmelanotide approval

- Indication: “chronic weight management in patients six years and older with obesity due to rare genetic conditions confirmed by genetic testing:

  pro-opiomelanocortin (POMC) deficiency

  proprotein subtilisin/kexin type 1 (PCSK1) deficiency

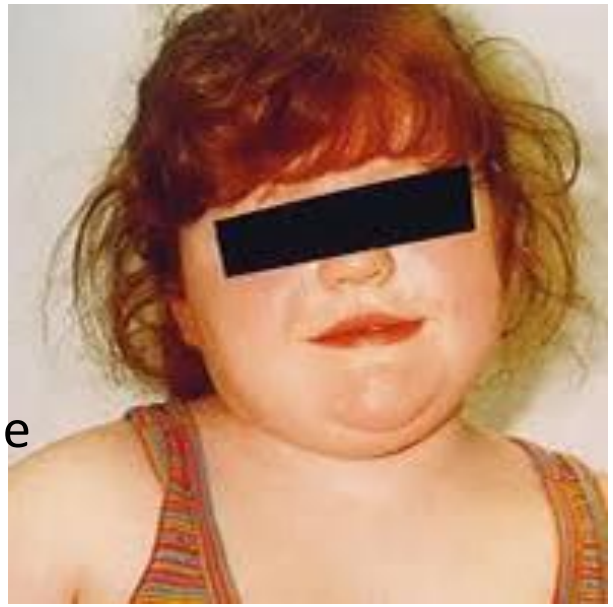
  leptin receptor (LEPR) deficiency

  Bardet Biedl syndrome

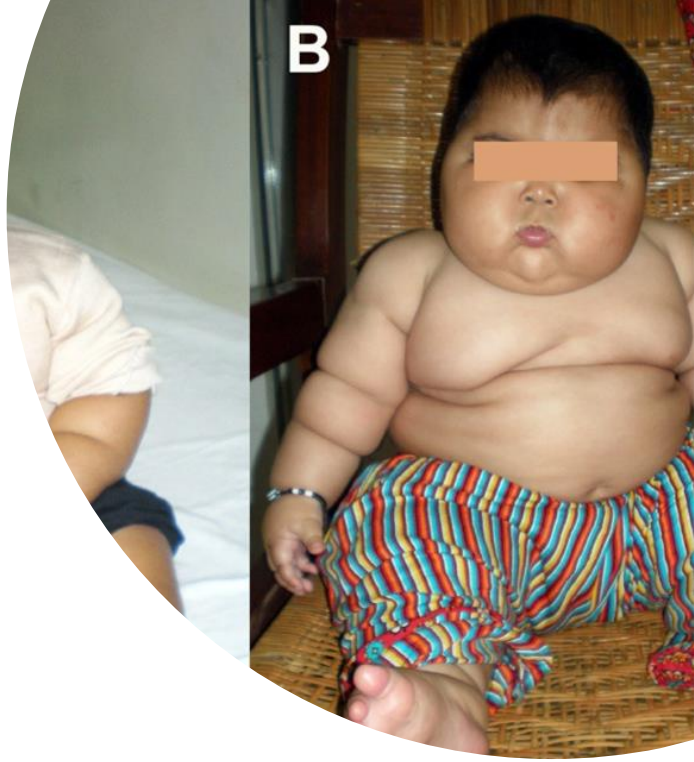
- priced at $330 per mg, making annual costs very high for this drug which requires daily subcutaneous injection and where doses begin at 1 mg. (setmelanotide price, 2021)

https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-weight-management-people-certain-rare-genetic-conditions

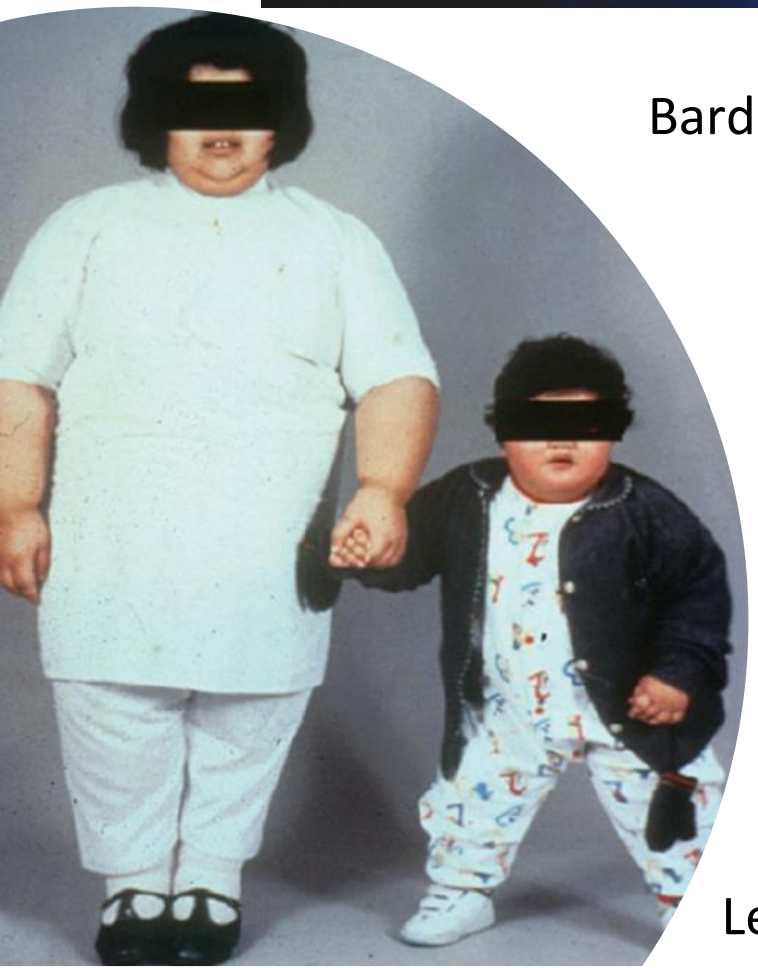
Bardet Biedl Syndrome



POMC deficiency



LEPR deficiency

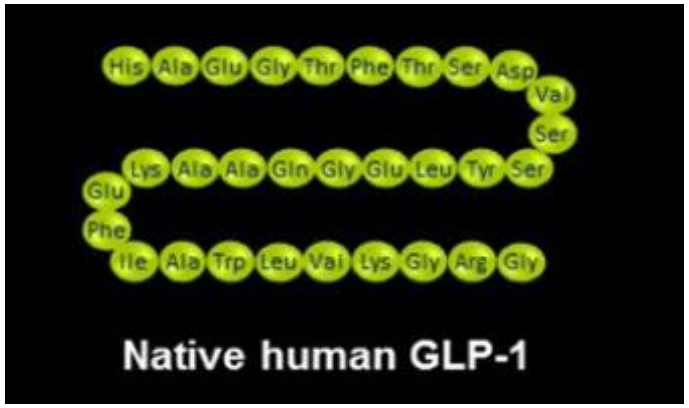


Leptin deficiency

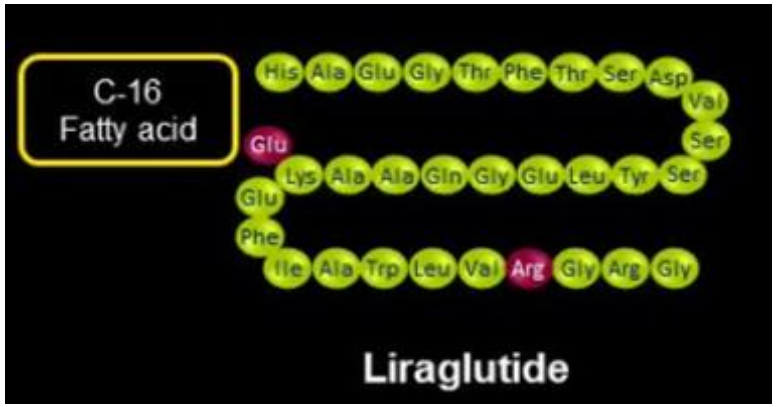
GENETIC OBESITY

ULTRA RARE
CHILDHOOD ONSET
SEVERE OBESITY
MARKED HYPERPHAGIA

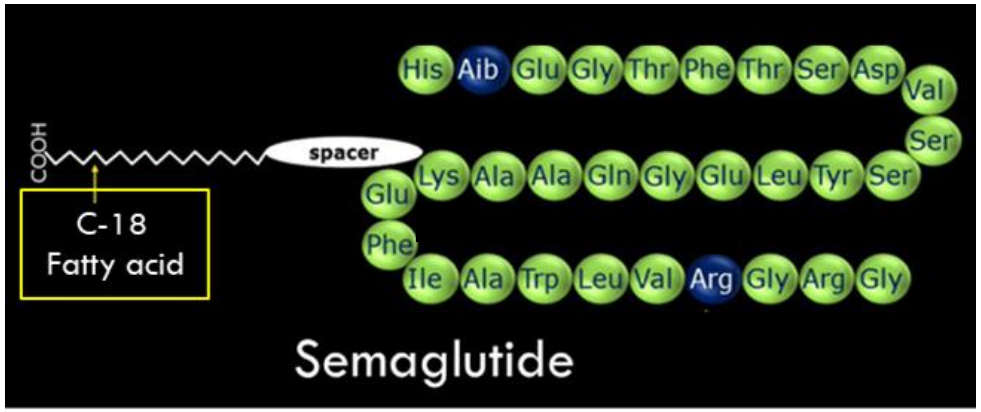
GLP 1 Physiology to pharmacology



- Half life 1-2 minutes
- Deactivated by DPP-4



- 97% homology
- Arginine replaces lysine @ 28
- Lysine at 20 is conjugated to c-16 palmitic acid via gamma glutamic acid spacer (albumen binding)
- Forms heptamers
- Reduced degradation and clearance
- Half Life 13 hours

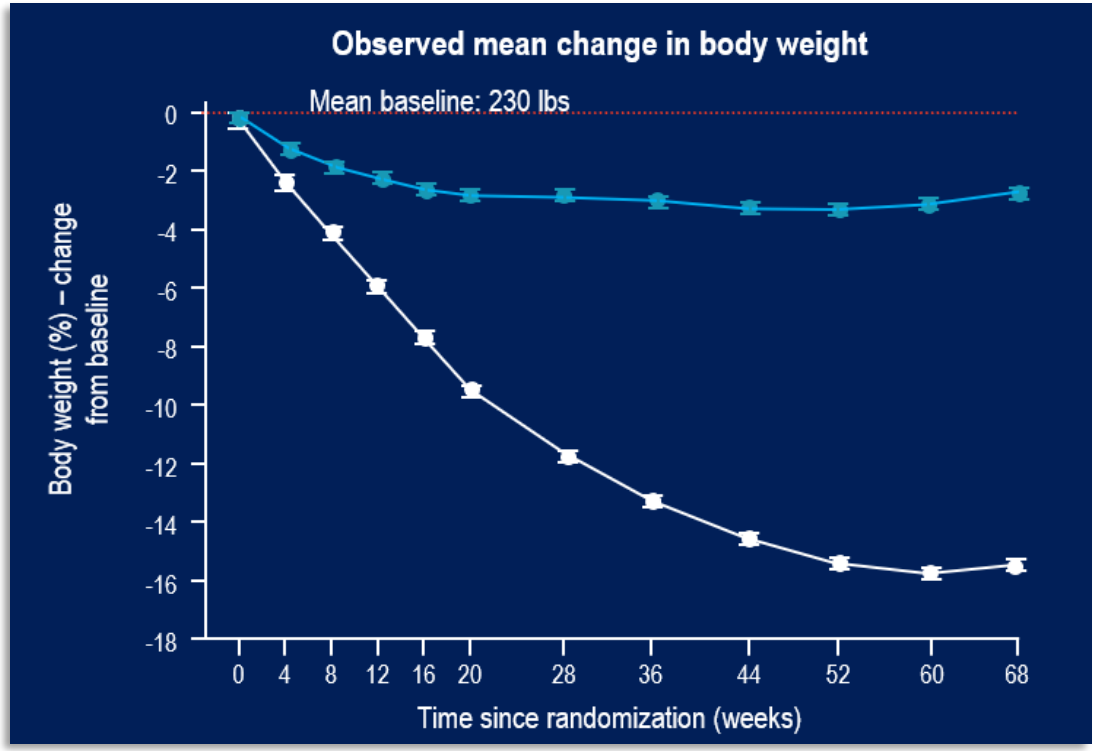


- 94% homology
- Arginine replaces lysine @ 28
- Aminoisobutyric acid replaces glycine at position 2 (resists degradation)
- C-18 fatty acid and lengthier spacer attached to Lysine (albumen binding)
- Reduced degradation and clearance
- Half Life 165 hours

Brandt SJ, et al. Journal Internal Medicine 2018. 284: 581-602.

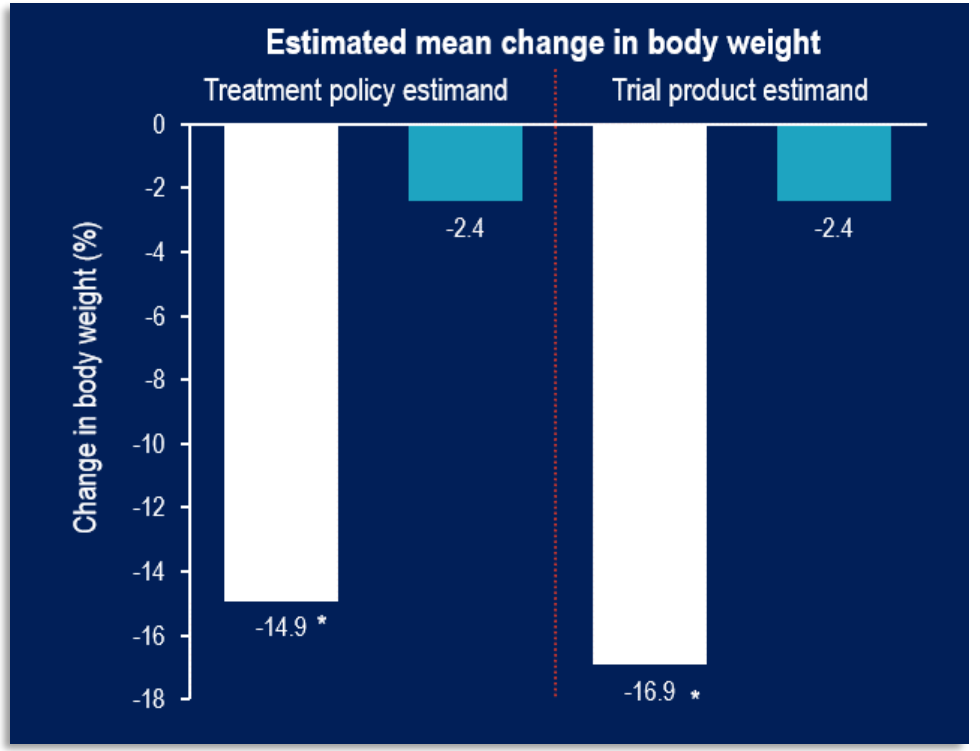
STEP 1 – Change in Body Weight

- 1961 adults with BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 and ≥1 weight-related coexisting condition who did NOT have diabetes
- Primary endpoint: % change in body weight and weight reduction of ≥ 5%



Semaglutide 2.4 mg

Placebo



*Statistically significant vs placebo.
Primary estimand = effect regardless of treatment discontinuation or rescue intervention

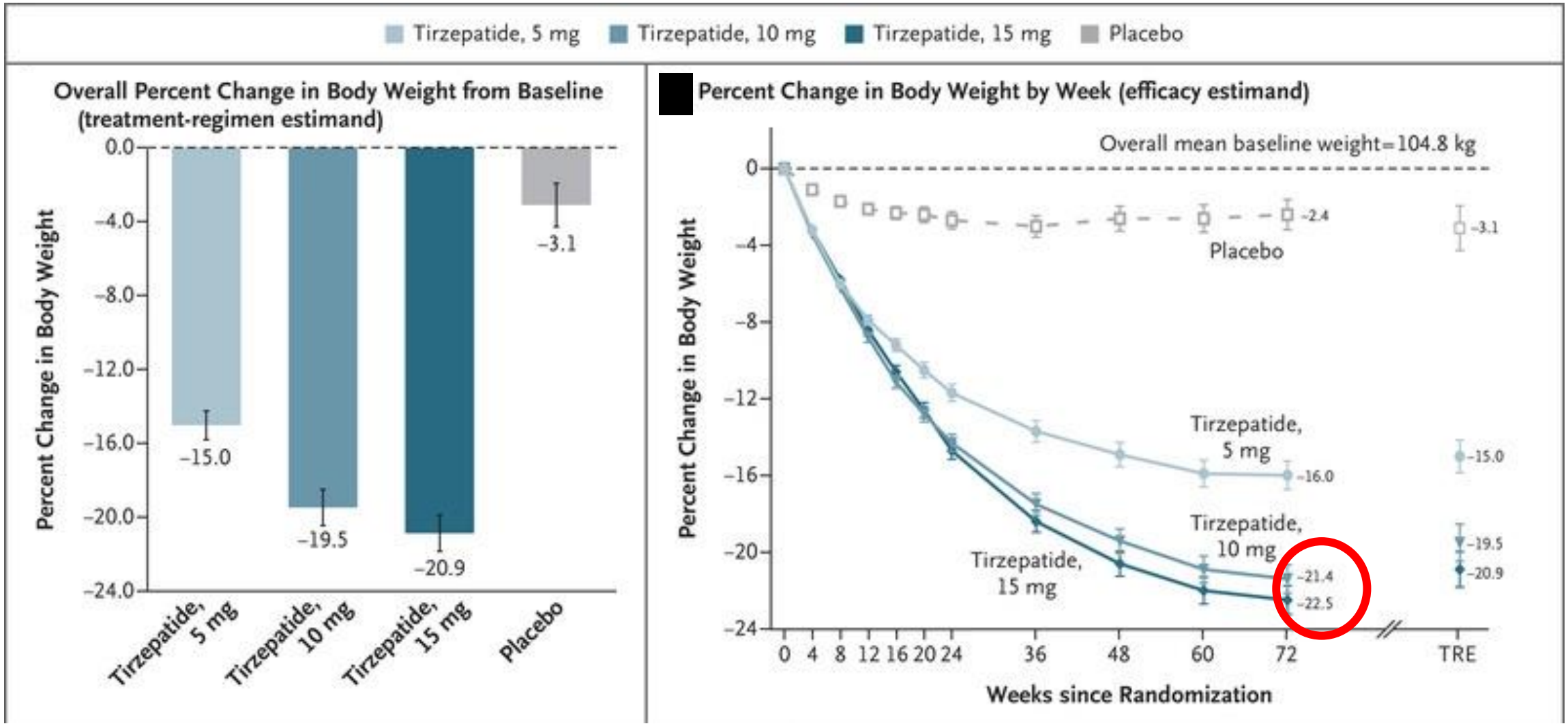
Wilding JPH, et al. N Engl J Med 2021;384:989-1002.

Semaglutide 2.4 mg

- Semaglutide is a GLP-1 receptor agonist, given by weekly injection
- Not scheduled
- Safety and tolerability profile similar to liraglutide
- Tolerability issues: nausea – requires dose escalation from 0.25 mg
- Safety issues: pancreatitis risk; gall bladder disease risk; contraindicated with history of MEN II or medullary thyroid cancer.
- Has indication for diabetes at 0.5, 1.0 and 2.0 mg dose, so has secondary benefit on glycemia; not indicated for the treatment of type 2 diabetes, but is indicated as an adjunct to lifestyle intervention for chronic weight management in type 2 diabetes.

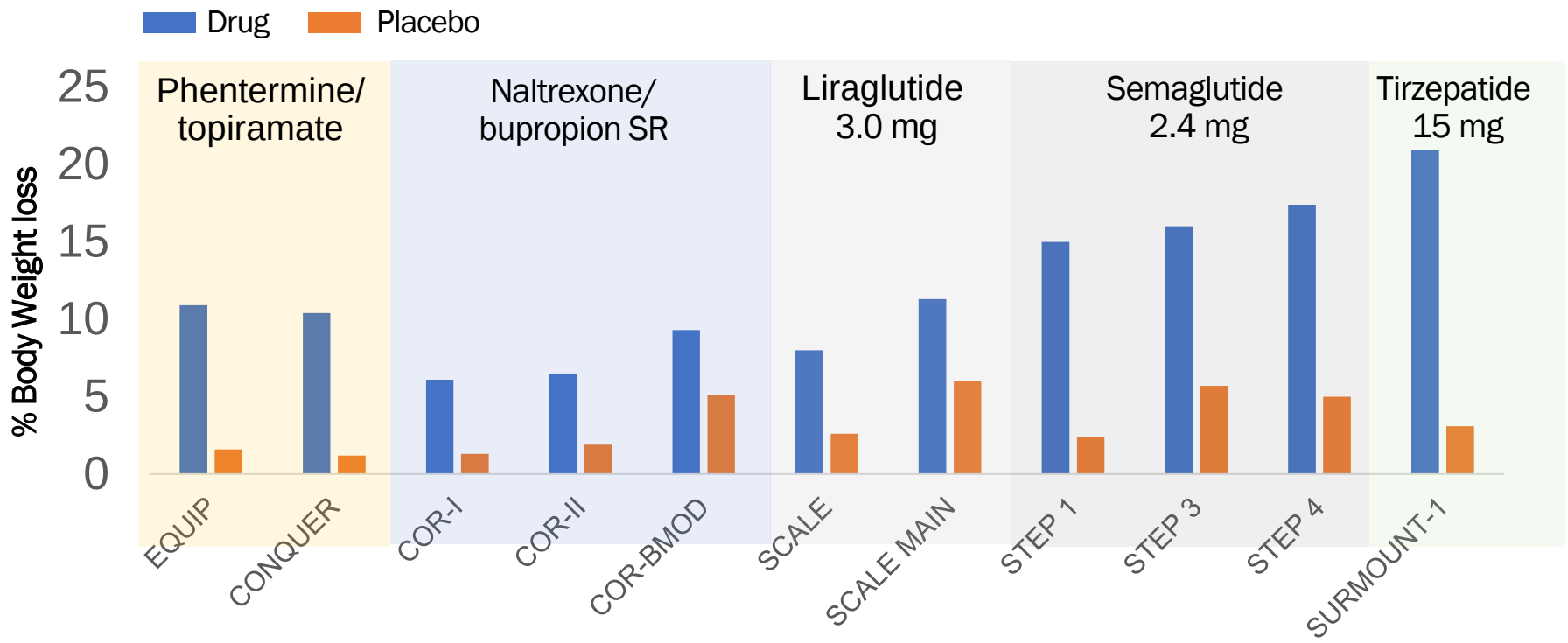
Information from product label

SURMOUNT-1 (Tirzepatide) Under review at FDA. Not yet approved for weight management



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

Percent Weight Loss (Drug vs Placebo) for Appetite Regulation Medications in Patients Without T2DM[1-11]



Note: Tirzepatide is not yet approved for anti-obesity management.

*Tirzepatide has US FDA Fast Track designation for obesity indication. Dosing based on highest dose in SURMOUNT-1 trial.

1. Allison DB et al. *Obesity (Silver Spring)*. 2012;20(2):330-342. 2. Gadde KM et al. *Lancet*. 2011;377(9774):1341-1352. 3. Greenway FL et al. *Lancet*. 2010;376(9741):595-605. 4. Apovian CM et al. *Obesity (Silver Spring)*. 2013;21(5):935-943. 5. Wadden TA et al. *Obesity (Silver Spring)*. 2011;19(1):110-120. 6. Pi-Sunyer X et al. *New Engl J Med*. 2015;373(1):11-22. 7. Wadden TA et al. *Int J Obes (Lond).* 2013;37(11):1443-1451. 8. Wilding JPH et al. *New Engl J Med*. 2021;384(11):989-1002. 9. Wadden TA et al. *JAMA.* 2021;325(14):1403-1413. 10. Rubino D et al. *JAMA.* 2021;325(14):1414-1425. 11. Jastreboff AM et al. *N Engl J Med*. 2022;387:205-216.

Agent	Common AE	Contraindication	Warnings and Precautions
Phentermine	**Insomnia** Dry mouth Agitation Constipation	**CVD, CHF, arrhythmias** **Uncontrolled hypertension** MAOI use, Hyperthyroidism Glaucoma, Pregnancy	Primary pulmonary hypertension Sympathomimetic effects Abuse potential
Orlistat	**GI complaints of steatorrhea**	**Chronic malabsorption**, **Gallbladder disease, pregnancy**	**May decrease cyclosporine exposure; Liver failure** **Multivitamin administration; Psyllium mucilloid**
Phentermine/ topiramate ER	Dry mouth Paresthesias Headache, Insomnia	Glaucoma, Hyperthyroidism MAOI use, Pregnancy	**Teratogenicity – obtain pregnancy tests** Metabolic acidosis, **Glaucoma**, suicidal behavior
Naltrexone SR/ Bupropion SR	**Nausea** GI complaints Headache Insomnia	Seizure disorder Uncontrolled hypertension **Chronic opioid use** MAOI use	**Suicidal behavior** Elevated blood pressure, pulse Glaucoma, Hepatotoxicity, Pregnancy
Liraglutide 3.0 mg	**Nausea** GI complaints	**Personal/family history of medullary thyroid carcinoma or MEN2** Pregnancy	Thyroid c-cell tumors (rodents) **Acute pancreatitis** **Gallbladder disease** Hypoglycemia**,** Renal impairment, Suicidal behavior
Semaglutide 2.4 mg	**Nausea** GI complaints	**Personal/family history of medullary thyroid carcinoma or MEN2** Pregnancy	Thyroid c-cell tumors (rodents) **Acute pancreatitis** **Gallbladder disease** Hypoglycemia**,** Renal impairment, Suicidal behavior
Gelesis	GI Side effects: abdominal distention	**Esophageal abnormalities that might effect transit.**	Counsel patients that Gelesis is like food when taking other meds

All data from product labels. Important adverse events, contraindications, warning/precautions are described; please refer to medication package inserts for complete information

Anti-Obesity Pharmacotherapy Improves CV Risk Factors

	Orlistat	Phentermine/ Topiramate ER	Naltrexone/ Bupropion ER	Liraglutide 3.0 mg	Semaglutide 2.4 mg
WC	↓	↓	↓	↓	↓
BP	↓	↓	↑	↓	↓
HR	↓	-	↑	↑	↑
LDL-C	↓	↓	↓	↓	↓
HDL-C	↑	↑	↑	↑	↑
TG	↓↓	↓↓	↓↓	↓↓	↓↓
A1C	↓	↓	↓	↓↓↓	↓↓↓

A1C = glycated hemoglobin; BP = blood pressure; HDL = high-density lipoprotein; HR = heart rate; LDL = low-density lipoprotein; TG = triglycerides; WC = waist circumference.
All data from drug labels

Cardiovascular Outcomes with Anti-Obesity Medications

Phen/TPM[1,2]

The AQCLAIM CVOT trial
Ongoing

- Global RCT, 16,000 participants
- Primary objective: evaluate effect of long-term treatment on incidence of nonfatal MI, nonfatal stroke, or CV death in overweight and obese subjects with documented CVD

Nal/Bup[1,3,4]

The Light Study
Unblinded early and prematurely terminated

- Global RCT, 8910 participants
- Primary outcome (3-point MACE) with nal/bup vs placebo (n, %):* 90 (2.0) vs 102 (2.3) [HR, 0.88; adjusted 99.7% CI, 0.57-1.34]

Liraglutide 3.0 mg[4,5]

***Post hoc* analysis**

- Pooled data from a 2-year Phase 2 dose-finding trial and 4 Phase 3a RCTs (SCALE) trials, 5908 participants
- Primary outcome (3-point MACE) with liraglutide 3.0 mg vs placebo (n, %): 8 (0.002) vs 10 (0.04) [HR, 0.42; 95% CI, 0.17-1.08]

*** After 50% of planned events.**

CI, confidence interval; CV, cardiovascular; CVD cardiovascular disease; CVOT, cardiovascular outcomes trial; HR, hazard ratio; Lira, liraglutide; MACE, major adverse cardiovascular events; MI, myocardial infarction; nal/bup, naltrexone/bupropion; phen/TPM, phentermine/topiramate; RCT, randomized controlled trial.

1. Wilding JPH and Jacob S. *Obes Rev*. 2021;22:e13112; 2. EU Clinical Trials Register. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=AQCLAIM. Accessed July 2021; 3. Nissen SE, et al. *JAMA*. 2016;315:990-1004; 4. Cataldi M, et al. *International Journal of Obesity Supplements.* 2020;10:14-26; 5. Davies M, et al. *Diabetes Obes Metab*. 2018;20:734-739.

SELECT TRIAL: SEMAGLUTIDE 2.4 MG WEEKLY CARDIOVASCULAR OUTCOME TRIAL POWERED FOR SUPERIORITY

- 17,500 participants age ≥45, BMI ≥27, with prior cardiovascular disease (myocardial infarction, stroke, symptomatic peripheral artery disease) but without established type 2 diabetes or A1c ≥6.5%[1]
- Semaglutide 0.5 mg and 1 mg reduced MACE in individual with type 2 diabetes (SUSTAIN 6)[2]
- The exclusion of patients with diabetes in SELECT avoids the argument that improved glycemic control is the mechanism by which semaglutide reduces risk

1. Ryan DH et al. Am Heart J 2020;229:61-69.
2. Marso SP, et al. N Engl J Med 2016; 375:1834-1844.

GLP-1 has pleiotropic effects

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

Secondary Analysis of Look AHEAD shows CV Morbidity and Mortality Improvement for those who lost >10%

Lancet Diabetes Endocrinol. 2016 Nov;4(11):913-921. doi: 10.1016/S2213-8587(16)30162-0. Epub 2016 Aug 30.

Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial.

Look AHEAD Research Group.

- **Primary outcome**: composite of death from cardiovascular causes, non-fatal acute myocardial infarction, non-fatal stroke, or admission to hospital for angina.
- **Secondary outcome** included the same indices plus coronary artery bypass grafting, carotid endartectomy, percutaneous coronary intervention, hospitalisation for congestive heart failure, peripheral vascular disease, or total mortality
- "…participants in the intensive lifestyle intervention group who lost at least 10% of their bodyweight had a 20% lower risk of the primary outcome (adjusted HR 0·80, 95% CI 0·65-0·99; p=0·039), and a 21% lower risk of the secondary outcome (adjusted HR 0·79, 95% CI 0·66-0·95; p=0·011)…"

Look AHEAD
Action for Health in Diabetes

LANCET DIABETES ENDOCRINOL. 2016 11: 913-

CMHC
Cardiometabolic Health Congress

www.cardiometabolichealth.org

Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Medicating the Patient with Obesity – Concluding Remarks

Donna Ryan, MD
Professor Emerita
Pennington Biomedical Research Center

Things to remember….

- There are no average patients. Mean weight loss is only a guide. There is variation in weight loss response. Some patients will respond well and others will not respond. We cannot predict response in advance, though early weight loss is a predictor of ultimate weight loss.

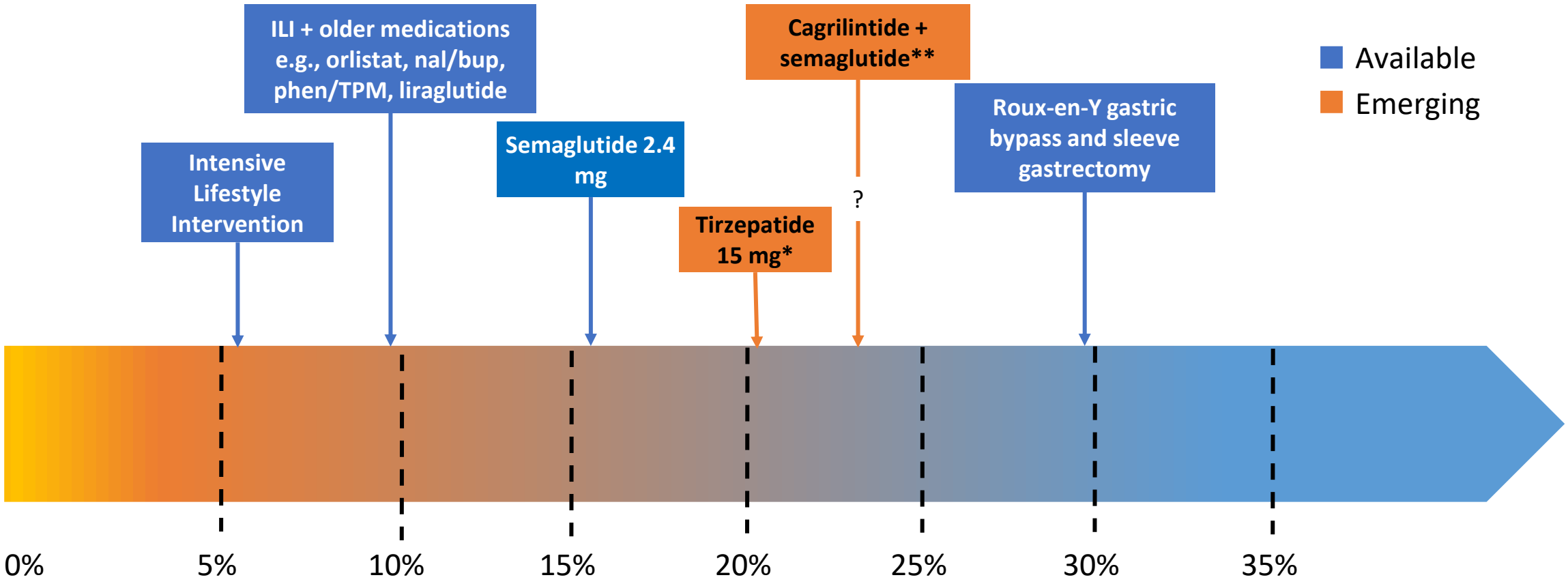
- Medications for weight management are intended to be taken for the long term, like a antihypertensives and medications for diabetes management.

In practice, obesity specialists use medications on-label and off-label

Phentermine and Diethylpropion	Phentermine Topiramate	Liraglutide 3.0	Naltrexone Bupropion	Orlistat
Semaglutide 2.4	Gelesis	SGLT 2 inhibitors	Metformin	Bupropion
Topiramate	GLP 1RAs	Zonisamide	Pramlintide	

HTTPS://WWW.ENDOTEXT.ORG/CHAPTER/PHARMACOLOGIC-TREATMENT-OF-OBESITY/

Available and Emerging Treatments for Obesity



Not all agents are available in all regions; always consult local prescribing information. Direct comparisons between data cannot be made due to differences in trial designs.

*40-week study duration; **20-week study duration.

ILI, Intensive Lifestyle Intervention; nal/bup, naltrexone/bupropion; phen/TPM, phentermine/topiramate

Allison DB, et al. *Obesity*. 2012;20(2):330-342. [EQUIP]; Gadde KM , et al. *Lancet*. 2011;37:1341-1352. [CONQER]; Greenway FL, et al. *Lancet.* 2010;376:595-605. [COR-I]; Apovian CM, et al. *Obesity.* 2013;21:935-943 [COR-II]; Wadden TA, et al. *Obesity*. 2011;19(1):110-120. [COR-BMOD]; Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22. [SCALE]; Wadden TA, et al. *In J Obes*. 2013;37:1443-1451. [SCALE MAIN]; Enebo LB, et al. *Lancet*. 2021;397(10286):1736-1748. [Cag + Sema]; Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989. [STEP 1]; Wadden TA, et al. *JAMA*. 2021;325(14):1403-1413. [STEP 3]; Rubino D, et al. *JAMA*. 2021;325(14):1414-1425. [STEP 4]; Ryan D. *Lancet Diabetes Endocrinol*. 2021;9(5):252-254. [STEP]; Sjöström L, et al. *N Engl J Med*. 2007;357:741-52. [Surgery]; Frias JP, et al. *Lancet.* 2021 [SURPASS-2].

Did we achieve our objectives?

At the completion of the presentation, attendees will be able to

Describe the rationale and principles for using medications in patients with obesity both to avoid further gain and to promote and sustain weight loss;

Identify commonly used medications that promote weight gain and alternatives that are weight neutral or promote weight loss;

Describe medications approved for chronic weight loss or used off-label to promote weight loss.

Thank you!

Donna.Ryan@pbrc.edu