



# Medications for Obesity

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## Objectives

- Compare the pharmacotherapy options for weight management
- Examine clinical factors to consider when initiating and titrating weight management therapy
- Discuss barriers to access of weight management pharmacotherapy

## Abbreviations

- AACE – American Association of Clinical Endocrinology
- ABCD – adiposity-based chronic disease
- ORCD – obesity-related complications and disease
- BMI – body mass index
- T2DM – type 2 diabetes mellitus
- OSA – obstructive sleep apnea
- MACE – major adverse cardiovascular event
- ASCVD – atherosclerotic cardiovascular disease
- HTN – hypertension
- MASH – metabolic dysfunction-associated steatohepatitis
- PCOS – polycystic ovary syndrome
- FDA – Food & Drug Administration
- MOAIs – monoamine oxidase inhibitors

## Abbreviations

- CNS – central nervous system
- REMS – risk evaluation and mitigation strategy
- OTC – over the counter
- Rx – prescription
- GLP-1 – glucagon-like peptide-1
- GIP – gastric inhibitory polypeptide
- MEN2 – multiple endocrine neoplasia syndrome type 2
- CKD – chronic kidney disease
- HF – heart failure
- TBWL – total body weight loss
- PMH – past medical history
- BID – twice daily
- SE – side effect

# Obesity Classifications

- New (2025) AACE Consensus Statement
  - Recommends Adiposity-Based Chronic Disease (ABCD) as a diagnostic term for obesity
  - Outlines classifications by stages and presence of Obesity-Related Complications and Diseases (ORCD)

ABCD Stage	Description
1 (pre-clinical obesity)	No known obesity-related cardiometabolic, biomechanical, or other psychological disease
2	$\geq 1$ mild/moderate ORCD
3	At least one severe ORCD

# Pharmacotherapy Review

# Patient Eligibility for Pharmacotherapy

Discuss referral for bariatric surgery for patients with  $BMI \geq 35 \text{ kg/m}^2$  or  $BMI \geq 30 \text{ kg/m}^2$  with cardiometabolic disease with or without previous use of pharmacotherapy

*Historical requirement:* Inadequate response to lifestyle interventions

$BMI \geq 30 \text{ kg/m}^2$  **or**  $BMI \geq 27 \text{ kg/m}^2$  with  $\geq 1$  weight-related complication (diabetes, prediabetes, hypertension, dyslipidemia, etc.)

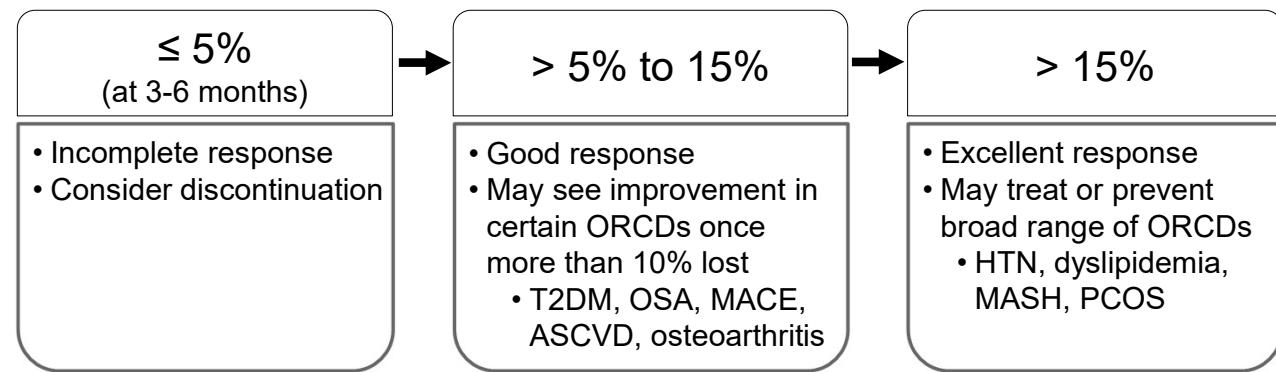
Assessment of readiness to change



Not currently pregnant (contraindication for all medications)

## Goals of Pharmacotherapy

- Achieve sufficient weight loss needed for clinical improvement



# FDA Approved Agents

① Tirzepatide	}	Second-generation medications
② Semaglutide		
③ Liraglutide	}	
④ Phentermine		
⑤ Phentermine-Topiramate		
⑥ Naltrexone-Bupropion		
⑦ Orlistat		

## Phentermine

- Sympathomimetic; reduces appetite and increases metabolism
- Schedule IV controlled substance
- Contraindications
  - History of cardiovascular disease
  - Hyperthyroidism
  - Glaucoma
  - Agitated states
  - History of drug abuse
  - Use of MAOIs within 14 days
  - Breastfeeding

## Phentermine

- Adverse effects
  - Cardiovascular – increased blood pressure and heart rate
  - CNS – anxiety, insomnia, irritability, delirium, psychosis
- Dosing
  - Dosing can vary; typically, 37.5 mg in 1 or 2 divided doses
    - Take on an empty stomach (30 minutes before or 1 hour after eating) for best absorption
  - Lomaira® → 8 mg three times daily 30 minutes before meals

## Phentermine

- Approved for “short-term” weight loss but used off-label beyond 3 months
  - State laws may restrict to short-term use or require meeting certain weight loss thresholds
  - Long-term safety and effectiveness?

## Phentermine-Topiramate (Qsymia®)

- Addition of topiramate – decrease in cravings, increase in appetite suppression, and enhancement of satiety
- Schedule IV controlled substance with REMS program
  - Known teratogenic
- Contraindications
  - Hyperthyroidism
  - Glaucoma
  - Use of MAOIs within 14 days
- Caution
  - History of kidney stones

## Phentermine-Topiramate (Qsymia®)

- Adverse effects
  - Insomnia
  - Increased blood pressure
    - Clinical trials showed blood pressure decline
  - Increased heart rate
    - Clinically insignificant increase in clinical trials
  - Cognitive impairment, constipation, dry mouth, palpitations

## **Phentermine-Topiramate (Qsymia®)**

- Dosing
  - Once daily in the morning
  - Complex titration schedule
    - Evaluate safety and efficacy at each dose
  - Taper upon discontinuation to limit risk of seizures
    - 1 capsule every other day for 1 week then stop
- Clinical pearls
  - Lower doses of phentermine – less cardiovascular effects?
  - Savings options for cash paying patients
    - Both brand-name and generic options available

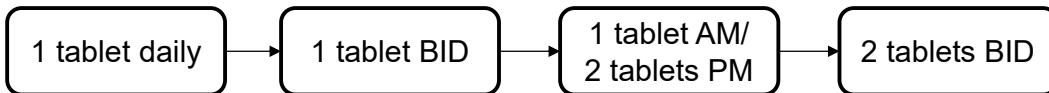
## **Bupropion-Naltrexone (Contrave®)**

- Regulate food intake and the mesolimbic reward pathways
- Contraindications
  - Chronic opioid therapy or need for short-term opioids
  - Uncontrolled hypertension
  - History or risk of seizures
  - Bulimia or anorexia nervosa
  - Abrupt discontinuation of drugs or alcohol
  - Use of MAOIs within 14 days or linezolid or IV methylene blue
- Adverse effects
  - Nausea, vomiting, constipation, headache, dizziness, increased blood pressure, changes in mood

## Bupropion-Naltrexone (Contrave®)

- Dosing

- Oral tablets contain 8 mg naltrexone / 90 mg bupropion
- Increased on a weekly basis pending tolerability



- Clinical pearls

- Savings options for cash paying patients
- Tolerability, particularly to the naltrexone component, can limit use
- Review drug interactions

## Orlistat

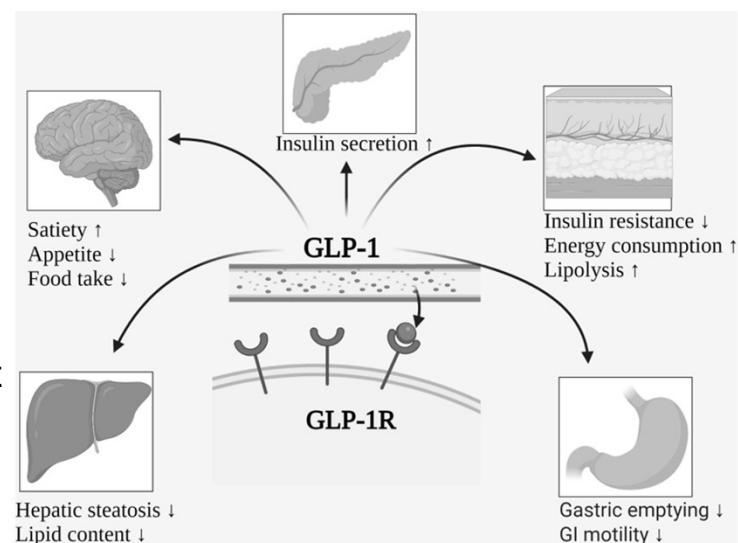
- Inhibits gastric and pancreatic lipases to decrease dietary fat absorption
- Contraindications
  - Chronic malabsorption syndrome
  - Cholestasis
- Adverse effects
  - Abdominal pain, flatulence, oily stools, fecal urgency/incontinence
  - Vitamin deficiencies - administer multivitamin daily (2 hours apart from orlistat)

## Orlistat

- Dosing
  - Take with fat-containing meals
    - Alli® (OTC) → 60 mg three times daily
    - Xenical® (Rx) → 120 mg three times daily
- Not routinely recommended
  - 2022 American Gastroenterological Association Guidelines recommend against use given limited weight loss benefit with significant gastrointestinal side effects

## Hormone Receptor Modulators

- Semaglutide (Wegovy®)
  - GLP-1 Receptor Agonist
- Liraglutide (Saxenda®)
  - GLP-1 Receptor Agonist
- Tirzepatide (Zepbound®)
  - GLP-1/GIP Receptor Agonist
  - GIP agonism has synergistic effects with GLP-1 agonism and has anti-nausea effect



Wang J-Y, Wang Q-W, Yang X-Y, Yang W, Li D-R, Jin J-Y, Zhang H-C and Zhang X-F (2023) GLP-1 receptor agonists for the treatment of obesity: Role as a promising approach. *Front. Endocrinol.* 14:1085799. doi: 10.3389/fendo.2023.1085799

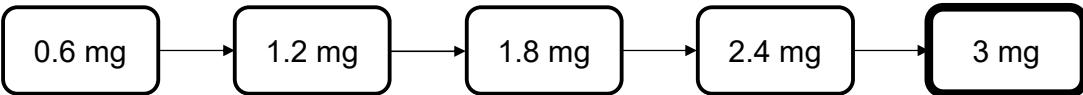
## Hormone Receptor Modulators

- Contraindications
  - Personal or family history of medullary thyroid carcinoma or MEN2
    - MEN2 includes collection of medullary thyroid carcinoma (nearly all patients), pheochromocytoma (~50%), and parathyroid disease (20-30%)
- Cautions
  - History of gastroparesis
  - History of pancreatitis
    - Consider cause of pancreatitis and if risk factor(s) have been eliminated

## Hormone Receptor Modulators

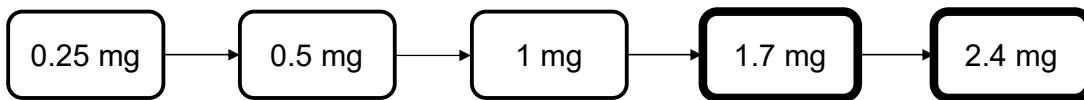
- Adverse effects
  - Nausea, vomiting, diarrhea
    - Mitigate by eating smaller, more frequent meals and avoiding high fat, overly sweet foods
  - Muscle and bone loss
    - Secondary to rapid weight reduction but not out-of-proportion
  - Constipation
    - Mitigate by increasing fiber and water intake
  - Hypoglycemia
    - Low risk as insulin secretion is stimulated through a glucose-dependent manner

## Liraglutide (Saxenda®)

- Once daily subcutaneous injection increased weekly as tolerated
  - Recommended maintenance dose is 3 mg

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graph LR; A[0.6 mg] --> B[1.2 mg]; B --> C[1.8 mg]; C --> D[2.4 mg]; D --> E[3 mg]
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- Each box contains 3 (9 mL) or 5 (15 mL) multi-use self-injectable pens that dial to any dose in the titration schedule
  - Must prescribe pen needles
- Only GLP-1 for obesity with no lean muscle mass loss seen in a research study

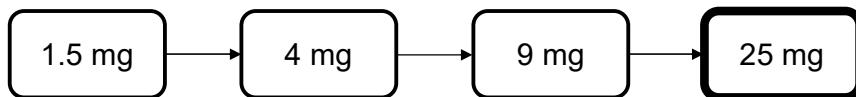
## Semaglutide (Wegovy®)

- Once weekly subcutaneous injection increased every 4 weeks as tolerated
  - Recommended maintenance dose is 2.4 mg, but 1.7 mg can also be considered a maintenance dose

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graph LR; A[0.25 mg] --> B[0.5 mg]; B --> C[1 mg]; C --> D[1.7 mg]; D --> E[2.4 mg]
```
- Each box contains 4 single-dose autoinjectors (28-day supply)

## Semaglutide (Wegovy®)

- Once daily oral tablet (approved 12/22/2025) increased every 30 days as tolerated
  - Recommended maintenance dose is 25 mg



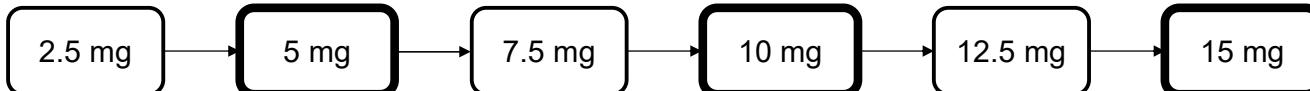
- Administration is very important for efficacy
  - Take with sip of water (up to 4 ounces) on an empty stomach and wait at least 30 minutes before eating, drinking, or taking other medications

## Semaglutide (Wegovy®)

- Additional indications
  - *Injectable only* – Noncirrhotic MASH in adults with moderate to advanced liver fibrosis (stages F2 to F3)
    - No specific BMI criteria in the clinical trial, but data for BMI < 25 kg/m<sup>2</sup> is limited
  - *Injectable and oral* – Risk reduction of major adverse cardiovascular events in adults with established cardiovascular disease and either obesity or overweight

## Tirzepatide (Zepbound®)

- Once weekly subcutaneous injection increased every 4 weeks as tolerated
  - Recommended maintenance doses are 5, 10, and 15 mg
  - Consider maintaining at a dose if achieving sufficient weight loss



- Each box contains 4 single-dose autoinjectors (28-day supply)

## Tirzepatide (Zepbound®)

- Additional indications
  - Treatment of moderate-to-severe obstructive sleep apnea in adults with obesity
    - Apnea-Hypopnea Index of  $\geq 15$
    - Maintenance dose of 10 or 15 mg

## Hormone Modulators – Clinical Pearls

- Counsel patients appropriately on purpose of these agents
  - To be used alongside changes in lifestyle
- Considered long-term therapy and not a quick fix
- Ensure adequate nutrition to prevent metabolic slowing and nutritional deficiencies
  - Low threshold to refer to a dietitian
- Ensure adequate resistance training and protein intake to prevent excess muscle and bone loss

## Hormone Modulators – Clinical Pearls

- Stay on top of hydration
  - GLP-1 hormone can reduce thirst drive
- Ask about pregnancy plans or use of contraception
  - Consider effects on hormonal contraception
  - Recommended to stop therapy 2 months prior to trying to conceive
- Consider administering before bedtime with at least 3 to 4 hours before and after meals

## Off-Label Prescribing

- Consideration for prescribing of bupropion, topiramate, and/or naltrexone as individual medications
  - Can mimic dosing of the combination agents or customize dosing based on symptom control and to limit side effects
- Cost saving option for patients without coverage
- Single agent considerations:
  - Naltrexone is only available in 50 mg tablets so difficult to mimic Contrave® dosing
  - Topiramate can cause fatigue; dose in the evening
  - If using bupropion XL, dose in the morning



## Medications for Obesity

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# Selection of Pharmacotherapy

## Selection of Pharmacotherapy

- Choose an agent based on:

Contraindications

Comorbidities

Symptom Targets

Goals of Therapy

Coverage & Cost



ABCD Stage	Description	Initial Pharmacotherapy
1	No known obesity-related cardiometabolic, biomechanical, or other psychological disease	Consider 1 <sup>st</sup> gen (unless co-morbidities guide selection)
2	≥ 1 mild/moderate ORCD	Consider 2 <sup>nd</sup> gen (unless co-morbidities guide selection)
3	At least one severe ORCD	

## ② Comorbidities / ③ Symptom Targets

Agent	Comorbidities	Symptom Targets
<b>Hormone Modulators</b>	insulin resistance (T2DM, pre-T2DM, PCOS, perimenopause), HF, cardiovascular disease, CKD, OSA (tirzepatide), MASH (injectable semaglutide), MACE (semaglutide)	appetite suppression
<b>Bupropion</b>	depression, low energy, current or prior nicotine use, emotional eating	appetite suppression, increase resting metabolic rate
<b>Naltrexone</b>	alcohol misuse	
<b>Phentermine</b>	inattention	appetite suppression, increase resting metabolic rate
<b>Topiramate</b>	migraines, insomnia, binge-eating	decrease soda intake

## ④ Goals of Therapy

- Consider patient wish for lifestyle guidance vs. medication-assisted therapy
- Preference for oral vs. injectable medication
- Choose a financially sustainable treatment
- Set a realistic weight loss goal

## 4 Goals of Therapy

Agent	Trial	Patient Population	Dose	Time Frame	%TBWL*
Tirzepatide	SURMOUNT-1		15 mg	72 weeks	22.5%
Semaglutide	STEP 1		2.4 mg	68 weeks	16.9%
Phentermine-topiramate	CONQUER	Overweight or obese + lifestyle changes	15/92 mg	56 weeks	9.8%
Liraglutide	SCALE		3.0 mg	56 weeks	8.0%
Naltrexone-bupropion	COR-I		32/360 mg	56 weeks	6.1%
Phentermine	Meta-analyses	Varied	Varied	Varied	5.5-7.7%
Orlistat	XENDOS	Obese + lifestyle changes	360 mg	4 years	5.8 kg

\*TBWL = total body weight loss

## 5 Coverage and Cost

- Medicaid
  - Coverage for *obesity* varies based on state
    - As of 10/1/25, 22 states reported coverage for obesity medications under fee-for-service Medicaid
  - Coverage of Wegovy® or Zepbound® for non-weight management indications is usually based on trial criteria
- Medicare
  - Not covered when used for *obesity*
  - Some plans cover Wegovy® or Zepbound® for their other indications usually based on trial criteria (ASCVD and OSA)
  - Wegovy® is on the list of negotiated drugs for 2027

## 5 Coverage and Cost

- Commercial insurance coverage varies
  - Coverage has become increasingly limited for hormone receptor modulators given cost to health plan
  - Typical prior authorization criteria:
    - BMI  $\geq 30$  or  $\geq 27$  with weight-related comorbidities
    - 3 to 6-month trial of lifestyle modifications
    - No concurrent FDA-approved weight loss agents
    - Continued lifestyle modifications with use of agent

## 5 Coverage and Cost

- Off-label generic agents (bupropion, naltrexone, phentermine, and topiramate) are relatively inexpensive
  - $\sim \$10-30$ /month without insurance
- Contrave<sup>®</sup> and Qsymia<sup>®</sup> are available through their respective manufacturers for  $\sim \$100$ /month
  - Phentermine-topiramate is available at local pharmacies for  $\sim \$40-80$ /month

## 5 Coverage and Cost

\*Pricing as of 1/9/26

Agent	Type	Cost per Month	Source	Notes
Tirzepatide	Vial	\$299 (2.5 mg) \$399 (5 mg) \$449 (7.5, 10, 12.5, 15 mg)	LillyDirect	<ul style="list-style-type: none"> <li>7.5 mg dose and above must be filled every 45 days for reduced cost</li> </ul>
Tirzepatide	Pen	~\$499 (all strengths)	LillyDirect or Local Pharmacy	<ul style="list-style-type: none"> <li>At local pharmacy, must use copay card and cannot have government sponsored plan</li> </ul>
Semaglutide	Pen	\$349 (all strengths)	NovoCare or Local Pharmacy	<ul style="list-style-type: none"> <li>New patients eligible for \$199/month for first 2 months</li> <li>At local pharmacy, cannot have government sponsored plan</li> </ul>
Semaglutide	Tablet	\$149 (1.5, 4 mg) \$299 (9, 25 mg)	NovoCare or Local Pharmacy	<ul style="list-style-type: none"> <li>At local pharmacy, cannot have government sponsored plan</li> </ul>
Liraglutide	Pen	\$200-700 on GoodRx® (depending on dose)	Local Pharmacy	<ul style="list-style-type: none"> <li>Cost will vary depending on pharmacy</li> <li>Supply may be limited as generic is only produced by one manufacturer</li> </ul>

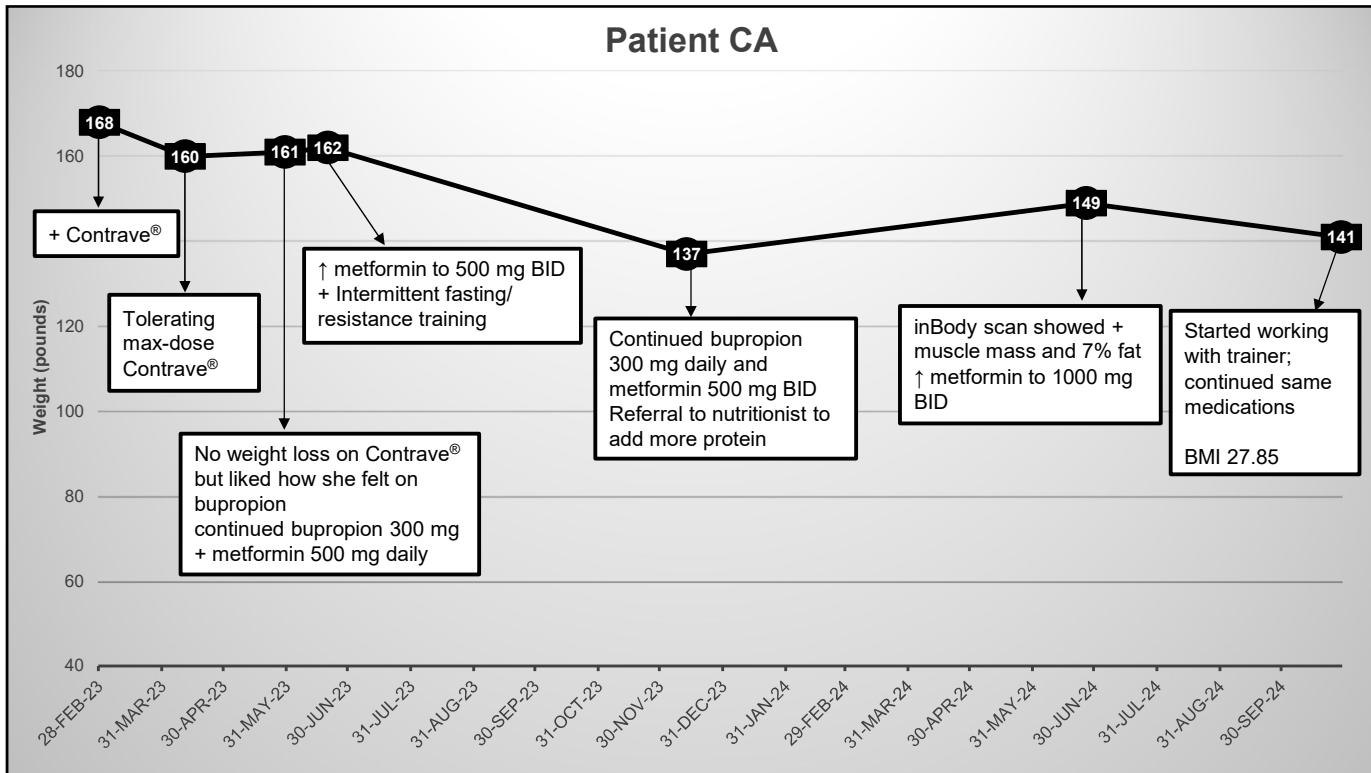
## Hormone Receptor Modulator Compounding

- FDA resolved shortages of semaglutide and tirzepatide in spring 2025
  - Compounded agents are in violation of the FDA unless they have made changes to the medication (additives, dose, etc.)
  - The compounded agents are not FDA approved for safety, efficacy, or quality
- Concerns with the compounded versions include improper storage, fraudulent drugs, dosing errors, adverse effects

## Patient Cases

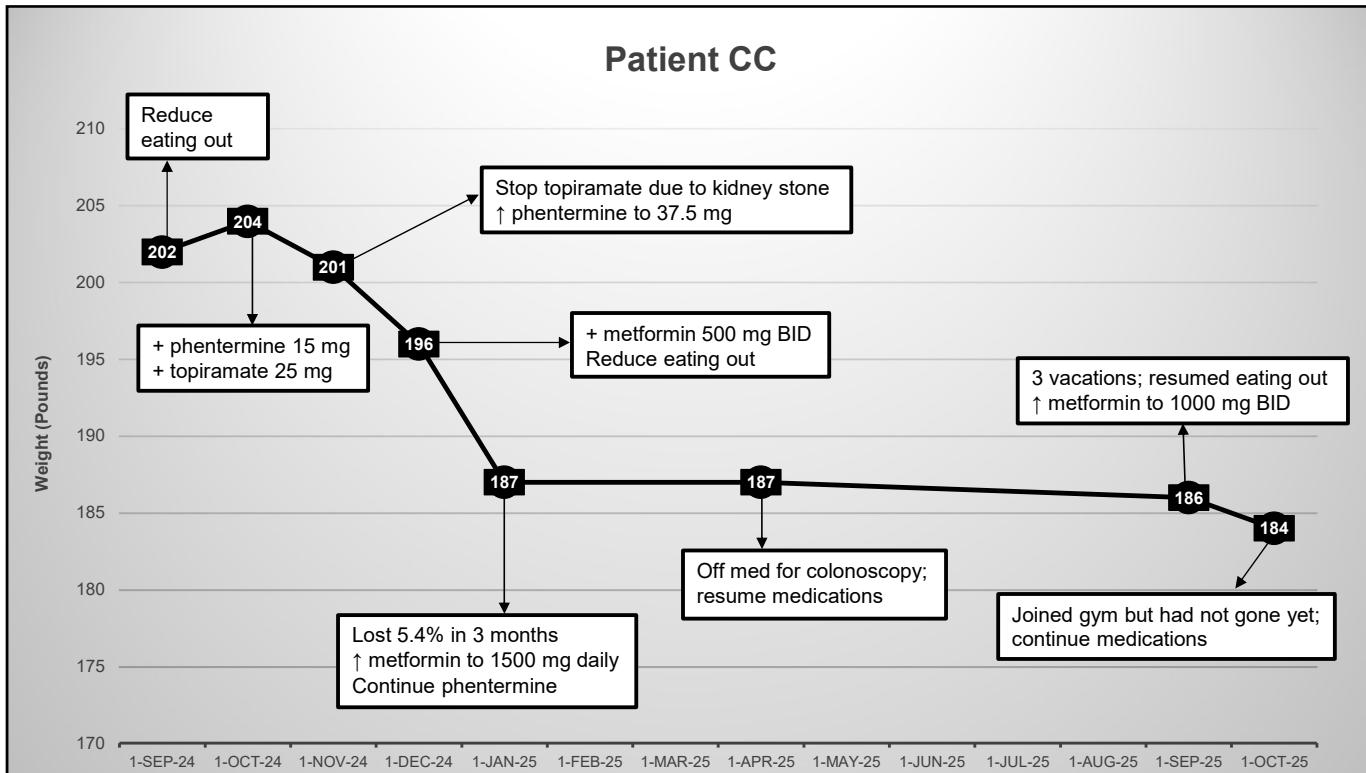
### Patient CA – 53-yo female

- PMH: remote history of breast cancer, dyslipidemia
- Initial weight: 168 lb, BMI 31 kg/m<sup>2</sup>
- Working with nutritionist and playing pickle ball 2-4x/week
- 24-hour recall
  - B: coffee, egg +/- toast
  - L: salad + grilled shrimp
  - D: some meat, vegetable, rice
  - Snack: avoids mostly
  - Bev: water only



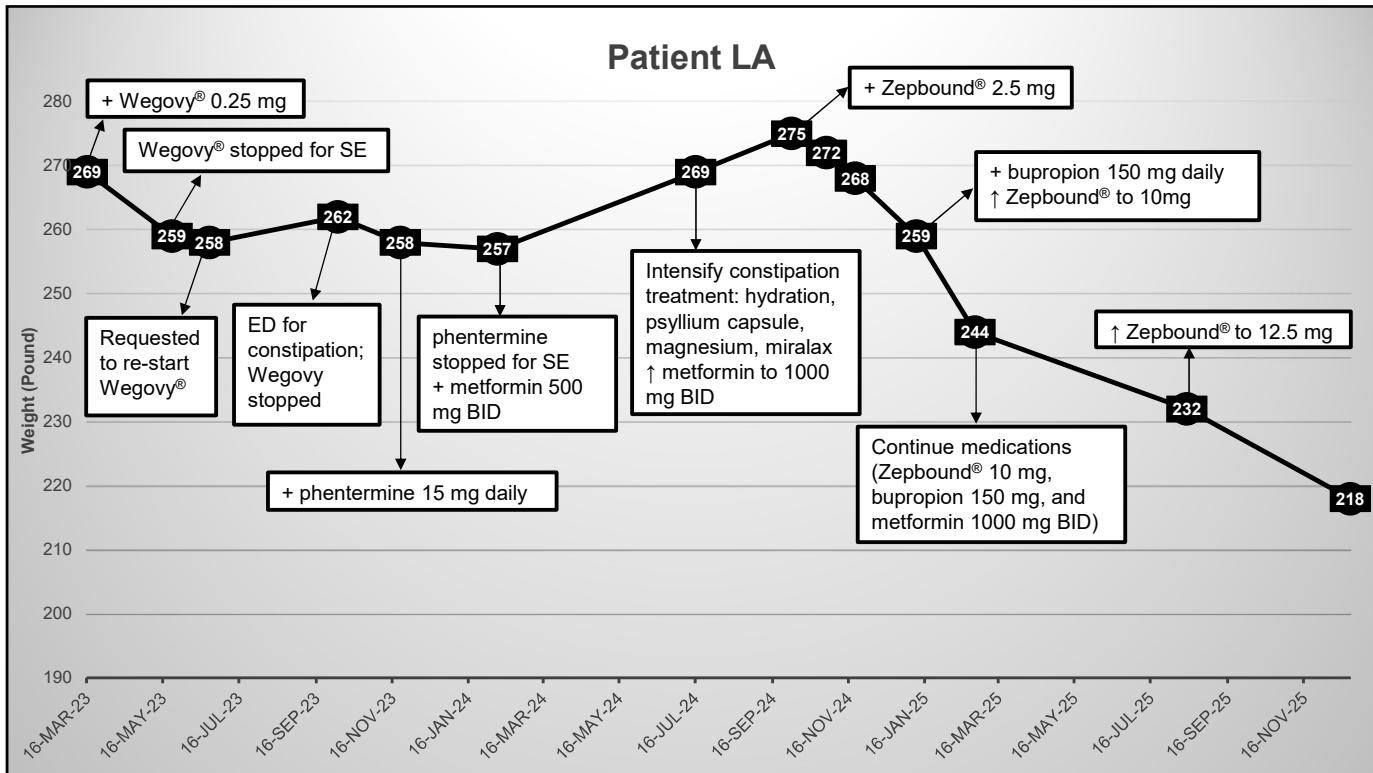
## Patient CC – 57-yo female

- PMH: Prediabetes, hyperlipidemia, chronic low back pain, hypothyroidism
- Initial weight: 202 lb, BMI 32.6 kg/m<sup>2</sup>
- Low confidence in engaging with lifestyle changes; eating out 80% of meals
- 24-hour recall
  - B: teddy grams, bagel, toast with butter
  - L: eating out (Wendy's, fast food)
  - D: eating out
  - Snack: not a lot
  - Bev: 32-oz water, diet coke



## Patient LA – 60-yo female

- PMH: OSA on CPAP, prediabetes, endometrial cancer s/p hysterectomy, lumbar radiculopathy
- Initial weight: 269 lb, BMI 38.6 kg/m<sup>2</sup>
- She read about “weight loss medications” and sister is on Ozempic; wanted to start on medications



## Pharmacotherapy Monitoring

## Follow-up Visits

- Discuss symptom control
  - Appetite suppression, hunger, cravings
- Celebrate scale and non-scale victories
- Review any side effects and ways to mitigate
- Set goals for exercise and nutrition
  - Consider referral to dietician for specific caloric intake or macronutrient goals
  - Review step counts or minutes spent strength training or participating in aerobic exercise

## Follow-up Visits

- Optimize management of comorbid conditions that can make weight loss more difficult
  - Mood disorders, diabetes, OSA, etc.
- Reduce or eliminate weight positive medications as able
  - Insulin, steroids, contraceptives, beta-blockers, etc.
- Monitor co-morbid conditions for potential changes in pharmacotherapy/management with weight loss
  - Reduction in BP meds? Or DM meds?
  - Need to check TSH in patients with hypothyroidism on treatment?

## Duration of Therapy

- Ensure the patient is responding appropriately to therapy
  - If they have not achieved > 5% weight loss after 3 months of the highest tolerated dose, discontinue the agent
- Most clinical trials had patients on the agents for more than 1 year
  - Use of these agents is not a quick-fix and must consider the long-term nature of the medications
  - Obesity is a chronic disease and suggests need for ongoing treatment to maintain weight loss
- Weight regain can be seen after discontinuation of the agents
  - Ensure exercise and nutrition are not forgotten!

## Novel Pharmacotherapies in Pipeline

GLP-1 Agonist	<ul style="list-style-type: none"> <li>• <b>Orforglipron</b> (small molecule oral GLP-1A)</li> </ul>
GLP-1/GIP Dual Agonist	<ul style="list-style-type: none"> <li>• Several investigational injectable formulations</li> <li>• Pfizer 07976016 (oral small molecule)</li> </ul>
GLP-1/Glucagon Dual Agonist	<ul style="list-style-type: none"> <li>• Weekly injections           <ul style="list-style-type: none"> <li>• <b>Survodutide</b>, pemvidutide, mazdutide, efinopegdutide</li> </ul> </li> </ul>
GLP-1 Agonist/ Amylin Analog	<ul style="list-style-type: none"> <li>• <b>Cagrilintide/semaglutide</b> (weekly injection)</li> <li>• Amycretin (oral and injectable)</li> <li>• Petrelintide (long-acting amylin analog)</li> </ul>

GLP-1/GIP/Glucagon Tri-Agonist	<ul style="list-style-type: none"> <li>• <b>Retatrutide</b> - phase 2 trial with 24.2% weight reduction at 48 weeks</li> </ul>
Muscle-Acting Drugs	<ul style="list-style-type: none"> <li>• Activin antagonists – activin is a negative regulator of muscle mass           <ul style="list-style-type: none"> <li>• Bimagrumab, garetsmab</li> </ul> </li> <li>• Myostatin inhibitors – myostatin induces muscle wasting           <ul style="list-style-type: none"> <li>• Trevogrumab</li> </ul> </li> <li>• Anabolic agents           <ul style="list-style-type: none"> <li>• Enobosarm – non-steroidal androgen receptor modulator</li> </ul> </li> </ul>

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