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	≥ 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 ≥ 35 kg/m² or BMI ≥ 30 kg/m² with cardiometabolic disease with or without previous use of pharmacotherapy

- *Historical requirement:* Inadequate response to lifestyle interventions
- BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with ≥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

≤ 5% (at 3-6 months)	> 5% to 15%	> 15%

• Incomplete response
• Consider discontinuation
	• Good response
	• May see improvement in certain ORCDs once more than 10% lost
	  • T2DM, OSA, MACE, ASCVD, osteoarthritis
		• Excellent response
		• May treat or prevent broad range of ORCDs
		  • HTN, dyslipidemia, MASH, PCOS

FDA Approved Agents

1. Tirzepatide
2. Semaglutide

Second-generation medications

3. Liraglutide
4. Phentermine
5. Phentermine-Topiramate
6. Naltrexone-Bupropion
7. Orlistat

First-generation medications

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®)

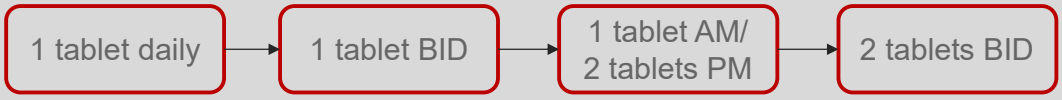
- Dosing
  - Once daily in the morning
  - Complex titration schedule
    - Evaluate safety and efficacy at each dose
  - Taper upon discontinuation to limit risk of seizures
    - 1 capsule every other day for 1 week then stop
- Clinical pearls
  - Lower doses of phentermine – less cardiovascular effects?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

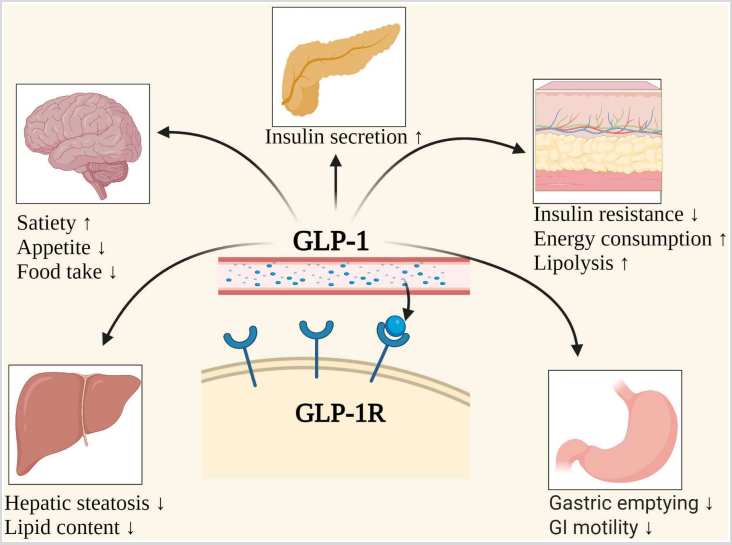
- Inhibits gastric and pancreatic lipases to decrease dietary fat absorption
- Contraindications
  - Chronic malabsorption syndrome
  - Cholestasis
- Adverse effects
  - Abdominal pain, flatulence, oily stools, fecal urgency/incontinence
  - Vitamin deficiencies - administer multivitamin daily (2 hours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

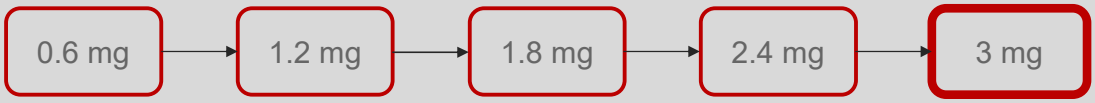
- Contraindications
  - Personal or family history of medullary thyroid carcinoma or MEN2
    - MEN2 includes collection of medullary thyroid carcinoma (nearly all patients), pheochromocytoma (~50%), and parathyroid disease (20-30%)
- Cautions
  - History of gastroparesis
  - History of pancreatitis
    - 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®)

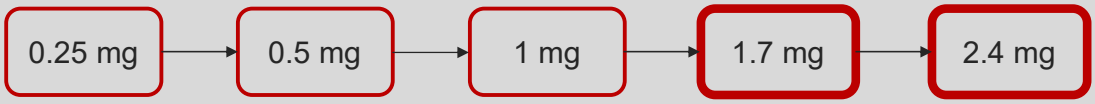
- Once daily subcutaneous injection increased weekly as tolerated
  - Recommended maintenance dose is 3 mg



- 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®)

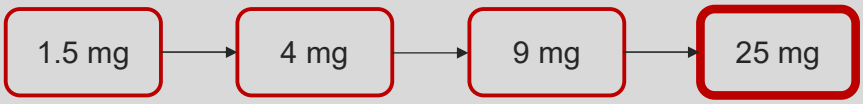
- Once weekly subcutaneous injection increased every 4 weeks as tolerated
  - Recommended maintenance dose is 2.4 mg, but 1.7 mg can also be considered a maintenance dose



- 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



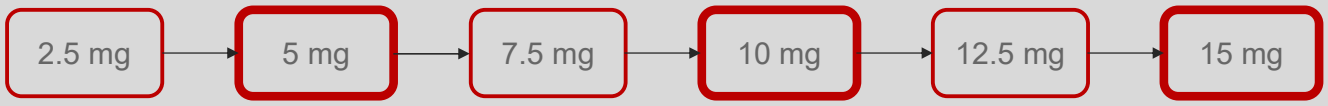
- Administration is very important for efficacy
  - Take with sip of water (up to 4 ounces) on an empty stomach and wait at least 30 minutes before eating, drinking, or taking other medications

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^2 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 ≥ 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 dietician
- 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:

1. Contraindications
2. Comorbidities
3. Symptom Targets
4. Goals of Therapy
5. Coverage & Cost

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

❷ Comorbidities / ❸ Symptom Targets

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

❹ 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	Overweight or obese + lifestyle changes	15 mg	72 weeks	22.5%
Semaglutide	STEP 1		2.4 mg	68 weeks	16.9%
Phentermine-topiramate	CONQUER		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 ≥ 30 or ≥ 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
  - ~$10-30/month without insurance
- Contrave® and Qsymia® are available through their respective manufacturers for ~$100/month
  - Phentermine-topiramate is available at local pharmacies for ~$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	• 7.5 mg dose and above must be filled every 45 days for reduced cost
Tirzepatide	Pen	~$499 (all strengths)	LillyDirect or Local Pharmacy	• At local pharmacy, must use copay card and cannot have government sponsored plan
Semaglutide	Pen	$349 (all strengths)	NovoCare or Local Pharmacy	• New patients eligible for $199/month for first 2 months • At local pharmacy, cannot have government sponsored plan
Semaglutide	Tablet	$149 (1.5, 4 mg) $299 (9, 25 mg)	NovoCare or Local Pharmacy	• At local pharmacy, cannot have government sponsored plan
Liraglutide	Pen	$200-700 on GoodRx® (depending on dose)	Local Pharmacy	• Cost will vary depending on pharmacy • Supply may be limited as generic is only produced by one manufacturer

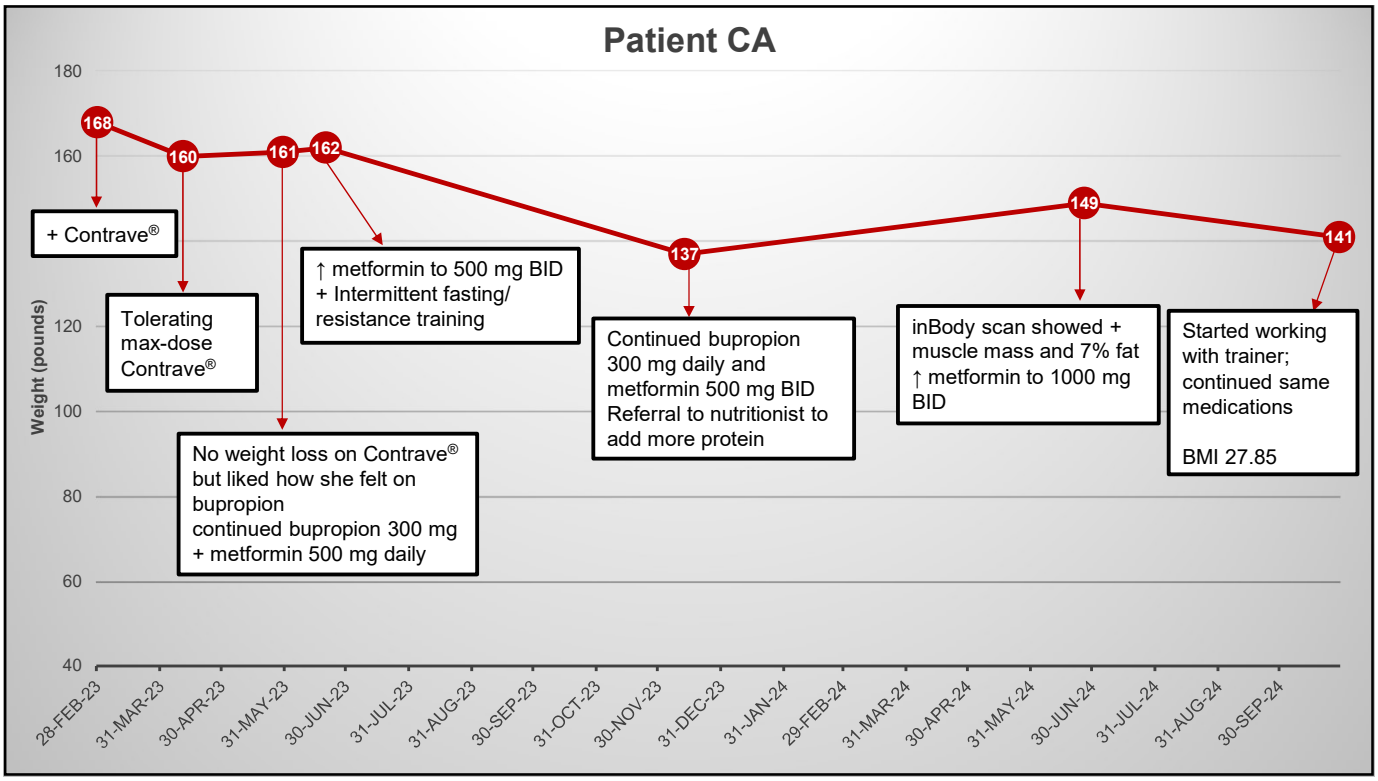
Hormone Receptor Modulator Compounding

- 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

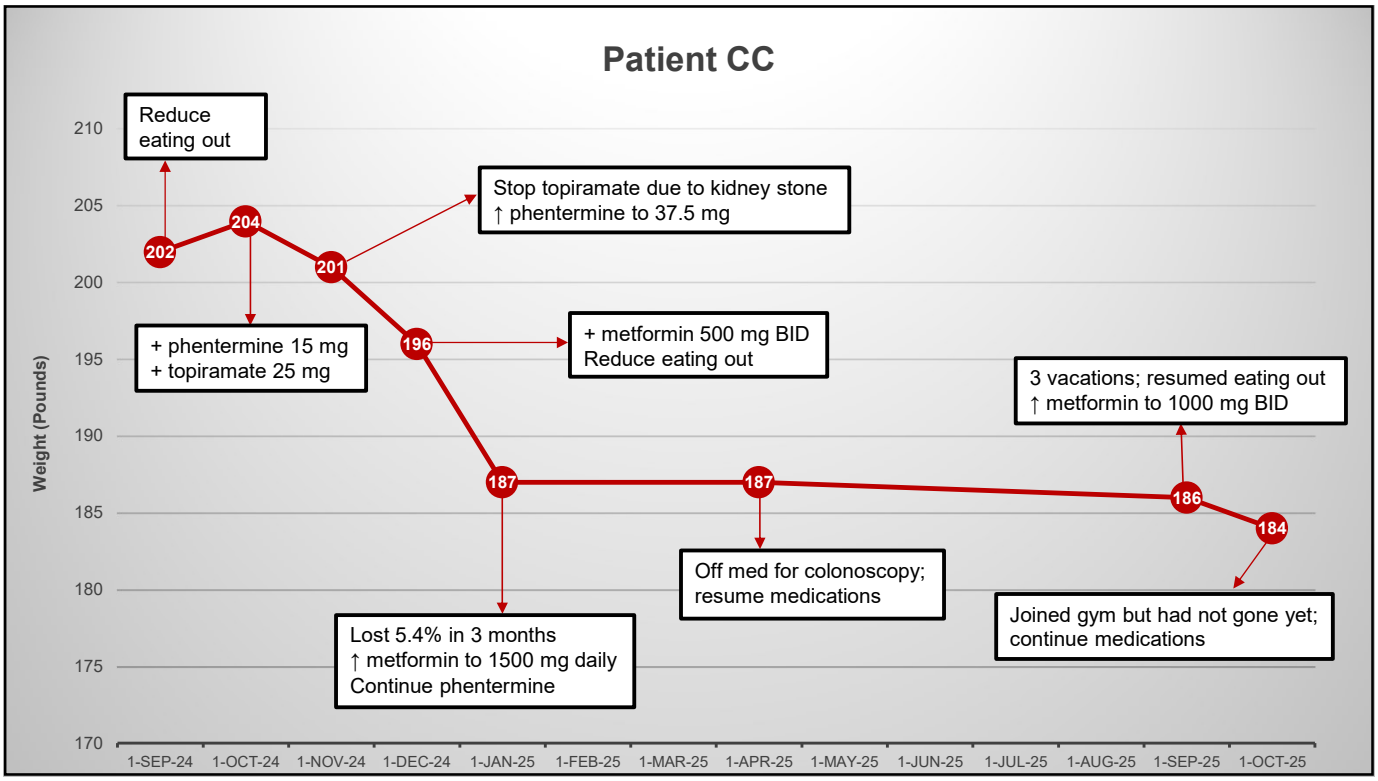
Patient CA – 53-yo female

- PMH: remote history of breast cancer, dyslipidemia
- Initial weight: 168 lb, BMI 31 kg/m^2
- 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



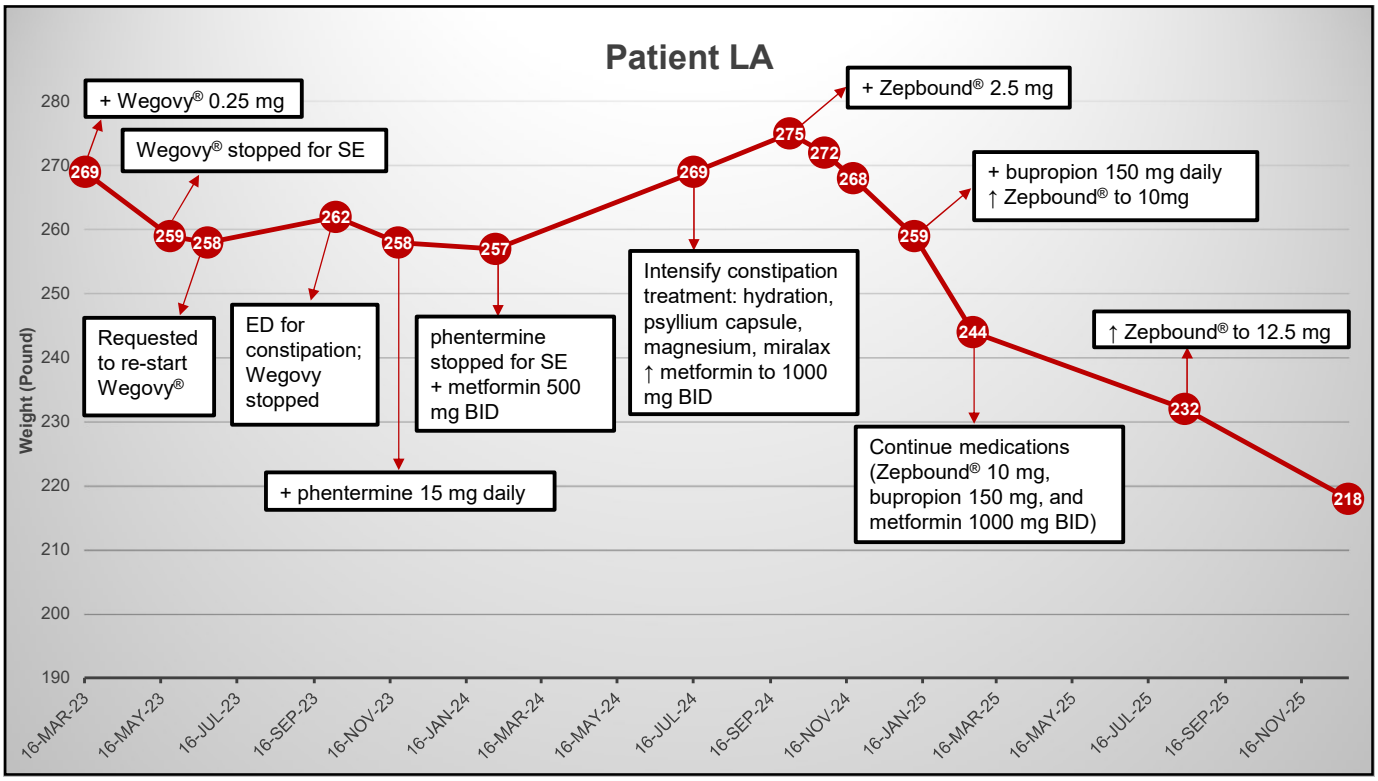
Patient CC – 57-yo female

- PMH: Prediabetes, hyperlipidemia, chronic low back pain, hypothyroidism
- Initial weight: 202 lb, BMI 32.6 kg/m^2
- 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^2
- 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	• **Orforglipron** (small molecule oral GLP-1A)
GLP-1/GIP Dual Agonist	• Several investigational injectable formulations • Pfizer 07976016 (oral small molecule)
GLP-1/Glucagon Dual Agonist	• Weekly injections • **Survodutide,** pemvidutide, mazdutide, efinopegdutide
GLP-1 Agonist/ Amylin Analog	• **Cagrilintide/semaglutide** (weekly injection) • Amycretin (oral and injectable) • Petrelintide (long-acting amylin analog)

GLP-1/GIP/Glucagon Tri-Agonist	• **Retatrutide** - phase 2 trial with 24.2% weight reduction at 48 weeks

Muscle-Acting Drugs	• Activin antagonists – activin is a negative regulator of muscle mass
	  • Bimagrumab, garetosmab
	• Myostatin inhibitors – myostatin induces muscle wasting
	  • Trevogrumab
	• Anabolic agents
	  • Enobosarm – non-steroidal androgen receptor modulator

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