

# Pharmacotherapy for Obesity: GLP-1s and Beyond

Dr. Nisha Kuruvadi, DO, DABOM, DABLM



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Dr. Nisha Kuruvadi, DO,  
DipABOM, DipABLM

- Triple Board-Certified Physician
  1. Internal Medicine
  2. Obesity Medicine
  3. Lifestyle Medicine
- Diplomate of the American Board of Obesity Medicine
- Dipomate of the American Board of Lifestyle Medicine
- Chair of the Media & Communications Committee for the Obesity Medicine Association (OMA)
- Secretary of the Culinary Medicine Lifestyle Medicine Member Interest Group
- Articles Featured in Times of San Diego, Sharp Health News, SoMeDocs, Healio, Physicians Weekly, Kevin MD

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## Disclosures

Nothing to disclose.

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### Learning Objectives

1. Evaluate the indications and eligibility criteria for FDA-approved anti-obesity medications based on BMI, comorbidities, and clinical context.
2. Compare mechanisms of action, expected weight loss outcomes, and key adverse effects among commonly used anti-obesity medications.
3. Apply evidence-based strategies to select and initiate appropriate pharmacotherapy for obesity while integrating lifestyle interventions and monitoring treatment response.

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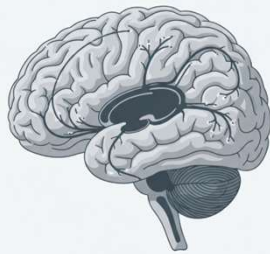
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### Obesity as a Chronic Disease

Chronic, relapsing, multifactorial disease

- Biologic drivers of weight regain: ↓ leptin, + ghrelin, adaptive thermogenesis
- Central pathways: hypothalamic appetite regulation, reward circuitry (dopamine)
- Environmental + genetic interplay: high heritability (~40–70%)

Clinical implication: requires long-term, multimodal therapy (lifestyle + pharmacotherapy ± procedures)



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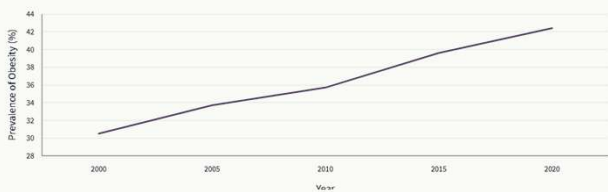
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### Prevalence of Obesity in the US



The prevalence of obesity in the US has steadily increased over the past two decades, highlighting the need for comprehensive public health interventions

\*Centers for Disease Control and Prevention (CDC)

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### Health Risks of Obesity

<p> <b>Cardiovascular/Heart Diseases</b> Heart disease, high blood pressure, high cholesterol, stroke</p>	<p> <b>Nonalcoholic Fatty Liver Disease</b> Cirrhosis</p>
<p> <b>Type 2 Diabetes</b> Excess body fat can lead to insulin resistance and an increased likelihood of developing type 2 diabetes</p>	<p> <b>Cancer</b> Colon, Breast, Uterine, Cervix, Esophagus, Kidney, Prostate, Pancreas</p>
<p> <b>Respiratory/Lung Disorders</b> Obstructive sleep apnea, Hypoventilation syndrome</p>	<p> <b>Gynecologic Conditions</b> Abnormal menses, Infertility, Polycystic Ovarian Syndrome (PCOS)</p>
<p> <b>Musculoskeletal Issues</b> Osteoarthritis, Joint pain, Decreased mobility</p>	<p> <b>Stroke, Cataracts, Dementia, Depression</b></p>

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### Addressing Weight Bias and Misconceptions

- **Obesity is a Complex, Chronic Condition**  
Involves genetics, environment, hormones, and behavior.
- **"Eat Less, Move More" is an Oversimplification**  
Weight loss is multifaceted and often requires medical intervention.
- **Stigma Around Weight Loss Medications**  
Medications are seen as "the easy way out" but are an important tool in managing obesity.
- **Challenging Weight Bias**  
Obesity deserves compassionate, non-judgmental care.

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### Challenging Unrealistic Expectations

- **Unrealistic 'Before & After' Imagery**  
Often depict extreme transformations with unrealistic body ideals
- **The "No Gimmicks" Myth**  
Suggesting weight loss should rely on willpower alone ignores obesity's complexity
- **Medications Are Not a Gimmick**  
Medications are a legitimate tool in treatment





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### How Much Weight Loss is Needed to Decrease Complications?

- **5-10% of Total Body Weight Makes a Big Difference**  
Even modest weight loss can improve blood pressure, cholesterol, and blood sugars.
- **Weight Loss Targets for Specific Conditions:**
  - Diabetes, High blood pressure, High Cholesterol: 5-10%
  - Sleep Apnea, Fatty Liver Disease: ~10%
- **Good News:** Any amount of weight loss can lead to health benefits!

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### The Obesity Set Point



Based on genetic factors, your body weight stays within a certain range, or set point. In order to maintain balance, the brain adjusts the body's hunger and metabolism to stay within this "set-point" weight range.

**Starvation** ← **Your Weight** → **Overfed**

Hunger ↑      ↓ Hunger

Metabolism ↓      ↑ Metabolism

Set-Point

The set-point sets the amount of body fat that the brain believes is necessary to sustain and maintain using energy, metabolism, and hunger.

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### FDA-Approved Weight Loss Medications

 **Criteria for Use:**

- BMI ≥27 with a co-morbid condition (e.g., diabetes, hypertension, high cholesterol, sleep apnea).
- BMI ≥30 without co-morbidities.

 **How They Help:**

- **Boost Weight Loss Results:** Medications amplify the effects of lifestyle changes.
- **Improve Long-Term Success:** Help patients stick to healthy habits more consistently and lower the obesity set point.
- **Support Overall Health:** Address both weight loss and associated medical conditions.

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### How Long Do We Use Medications?



**Weight loss medications are long-term treatments.**

- These medications are used for long-term maintenance of weight loss.
- Stopping often leads to weight regain.



**Evaluating Effectiveness:**

- Assess response after 3 months.
- Need a 5% weight loss by 3 months of use to continue the medication.
- If not achieved, consider other medications

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**Patient Case:**


**Patient Profile:**  
Age: 42 years old female

BMI: 32

Prediabetes, A1c: 5.9%

**History:**  
Lifestyle changes attempted for 1 year without success.

**Clinical Question:**  
Should weight loss medication be started?



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### Phentermine

**How it works:** Lowers appetite, helps you feel full

**Dosage:** Once daily (15 mg or 37.5 mg) or Smaller 8 mg dose up to 3x/day

**Why it's used:**  
Low cost  
Trusted for decades  
Doesn't appear to cause addiction


**Side effects:**

- ↑ BP, ↑ Heart rate, Jittery/nervous feeling
- Trouble sleeping
- Constipation, Dry mouth

**Not for:**

- Uncontrolled BP, Heart disease
- Glaucoma
- Hyperthyroidism
- Pulmonary hypertension
- Certain meds (MAO inhibitors)
- Past substance abuse
- Pregnant/breastfeeding

**Things to keep in mind:**  
Controlled medication  
Approved only for short-term use (3 months)



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### Phentermine/Topiramate ER (Qsymia)

**How it works:** Combines phentermine + topiramate for stronger appetite control

**Dosage:** Slowly increased up to max 15 mg/92 mg once daily

**Why it's used:**

- One of the most effective oral options (lose about 10% of body weight over a year)
- FDA-approved for patients ≥12 years

**Side effects:**

- ↑ BP, ↑ Heart rate
- Kidney stones
- Numbness/tingling
- Anxiety/Depression, Insomnia
- Dry mouth, altered taste
- Constipation

**Not for:**

- Glaucoma
- Hyperthyroidism
- Certain meds (MAO inhibitors)
- Pregnancy or breastfeeding (requires reliable birth control)

**Things to keep in mind:**

- Controlled medication
- Must taper off slowly to avoid seizures

**Alternative Off-Label Cost-Saving Option:**

- If brand-name Qsymia is expensive, generic phentermine + topiramate can be used.
- Start half of phentermine 37.5 mg in the morning and topiramate 25 mg at night.
- Gradually increase doses as needed based on tolerance and weight loss goals.

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### Naltrexone/Bupropion ER (Contrave)

**How it works:** Combines two medications:

1. Bupropion (an antidepressant that also affects dopamine and norepinephrine) — helps reduce appetite and increase energy use
2. Naltrexone (used for alcohol and opioid dependence) — blocks brain signals that drive cravings

**Dosage:** Slowly increased over 4 weeks to 2 tablets twice a day

**Side effects:**

- Nausea, vomiting, diarrhea, constipation
- Headache, dizziness, trouble sleeping

**Not for:**


- Seizure history
- Eating disorders
- Opioid use
- Uncontrolled BP
- Pregnancy or breastfeeding

**Why it's used:**

- Non-controlled medication
- Helpful for cravings (food & alcohol)
- Lose about 5% of body weight over a year

**Things to keep in mind:** Can be costly

Specialty Pharmacy (Ridgeway Mail Order Pharmacy) - \$99/month



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### Orlistat

**How it works:** Blocks fat absorption in the gut (lipase inhibitor)

**Dosage:** Taken 3x/day with meals. Works best with a low-fat diet

**Why it's used:**

- Not a controlled medication
- Safe for long-term use
- Approved for teens ≥ 12 years

**Side effects:**

- Cramps, gas, oily spotting, loose stools
- ↓ Absorption of fat-soluble vitamins (A, D, E, K)
- Rare: kidney and liver injury

**Not for:**

- Malabsorption conditions
- Vitamin D deficiency
- Pregnancy

**Things to keep in mind:**

- GI side effects limit use
- Rarely prescribed or taken due to side effects

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## Semaglutide (Wegovy / Ozempic)

**How it works:** GLP-1 receptor agonist → increases fullness, lowers appetite

- Wegovy = for weight loss
- Ozempic = for diabetes

**Dosage:** Weekly injection, Slowly increased:  
0.25 mg → 0.5 → 1 → 1.7 → 2.4 mg

**Why it's used:**

- Very effective (lose about 10–15% of body weight over about a year)
- Helps lower blood sugars (benefit for diabetes)
- Approved for teens ≥ 12 years

**Side effects:**

- Nausea, vomiting, diarrhea, constipation, abdominal pain, bloating, indigestion
- Headache, dizziness, fatigue
- Rare: pancreatitis, gallbladder problems

**Not for:**

- Personal/family history of medullary thyroid cancer, MEN 2A/2B
- History of pancreatitis
- Gastroparesis
- Pregnancy or breastfeeding

**Things to keep in mind:**

- High cost, limited insurance coverage
- GI side effects common

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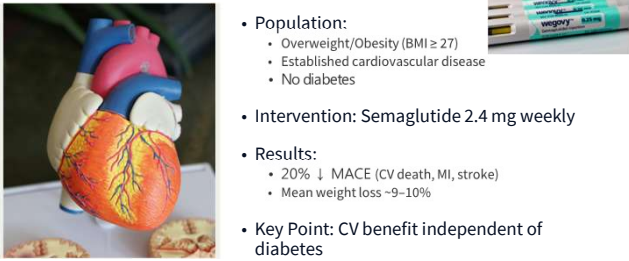
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## Semaglutide (Wegovy) - SELECT Trial



- **Population:**
  - Overweight/Obesity (BMI ≥ 27)
  - Established cardiovascular disease
  - No diabetes
- **Intervention:** Semaglutide 2.4 mg weekly
- **Results:**
  - 20% ↓ MACE (CV death, MI, stroke)
  - Mean weight loss ~9–10%
- **Key Point:** CV benefit independent of diabetes

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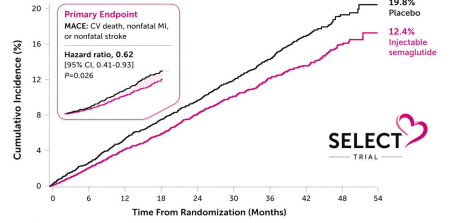
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## SELECT Clinical Implications



**Primary Endpoint**  
MACE: CV death, nonfatal MI, or nonfatal stroke  
Hazard ratio, 0.62  
[95% CI, 0.41–0.93]  
P<0.006

19.8% Placebo  
12.4% injectable semaglutide

**SELECT TRIAL**

No. at Risk	0	6	12	18	24	30	36	42	48	54
Injectable semaglutide	8,803	8,561	8,427	8,254	7,229	5,777	4,126	1,734	71	
Placebo	8,801	8,487	8,326	8,164	7,101	5,660	4,015	1,672	59	

MACE, major adverse cardiovascular events; CV, cardiovascular; MI, myocardial infarction.  
Linosoff AM, et al. *N Engl J Med*. 2023;389:2221-2232.

- First CV outcomes trial in obesity without diabetes
- Expands indication for GLP-1 use
- Supports obesity as a treatable CV risk factor

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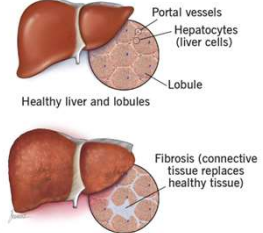
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### Wegovy (Semaglutide) - Liver Fibrosis Indication



**Healthy liver and lobules**

- Portal vessels
- Hepatocytes (liver cells)
- Lobule

**Fibrosis (connective tissue replaces healthy tissue)**

- **FDA-Approved Use**
  - Adults with **non-cirrhotic MASH** dysfunction-associated steatohepatitis
  - **Moderate-to-advanced fibrosis (F2-F3)**
  - **Adjunct to lifestyle therapy** (diet + exercise)
- **Key Trial Data (ESSENCE, Phase 3)**
  - + MASH resolution without fibrosis worsening vs placebo
  - Significant improvement in liver fibrosis after ~72 weeks

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### Oral Semaglutide (Wegovy) Tablet




**1.5 mg**  
once daily  
**DAYS 1-30**

START HERE




**4 mg**  
once daily  
**DAYS 31-60**

WORK YOUR WAY UP



**9 mg**  
once daily  
**DAYS 61-90**



**25 mg**  
once daily  
**DAYS 91 and onward**

STAY

Cash pay: \$149 for 1.5 mg & 4 mg      \$299 for 9 mg and 25 mg

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### Oral Semaglutide (Wegovy Tablet) vs. Injectable Semaglutide (Wegovy)

	Oral Semaglutide (Wegovy Tablet)	Injectable Semaglutide (Wegovy)
Route	Oral tablet, once daily	Subcutaneous injection, weekly
FDA Approval for Obesity	2026	Since 2021
Weight Loss Efficacy	~16-17% at 64 weeks	~15-17% at 68 weeks
Dosing Requirements	Empty stomach, with a small sip of water only, wait 30 min before eating	Flexible timing
Side Effects (GI)	Nausea, vomiting, constipation	Nausea, vomiting, constipation
Ideal Patient	Needle-averse adults with obesity/overweight	Adults with obesity/overweight

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### Tirzepatide (Zepbound/Mounjaro)

**How it works:** Dual GIP + GLP-1 receptor agonist → reduces appetite, increases fullness

- Zepbound = for weight loss
- Mounjaro = for diabetes

**Dosage:** Weekly injection, Slowly increased:  
2.5 mg → 5 → 7.5 → 10 → 12.5 → 15 mg

**Why it's used:**

- Very effective (lose about 15-20% of body weight over a little more than a year)
- Helps lower blood sugars (benefit for diabetes)
- Pediatric use under study

**Side effects:**

- Nausea, vomiting, diarrhea, constipation, abdominal pain, bloating, indigestion
- Headache, dizziness, fatigue
- Rare: pancreatitis, gallbladder problems

**Not for:**

- Personal/family history of medullary thyroid cancer, MEN 2A/2B
- History of pancreatitis
- Gastroparesis
- Pregnancy or breastfeeding

**Things to keep in mind:**

- High cost, limited insurance coverage
- GI side effects common

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### Tirzepatide (Zepbound) - SURMOUNT Trial



- Population: Obesity or overweight (BMI ≥30 or ≥27 + comorbidity)
- Results (SURMOUNT-1):
  - ~15-21% weight loss
  - Dose-dependent effect
- Up to ~50% of patients achieved ≥ 20% weight loss
- Key Point: Most effective pharmacotherapy to date

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### Tirzepatide (Zepbound) - SURMOUNT - OSA



**SURMOUNT-OSA**  
Tirzepatide in Obstructive Sleep Apnea

- ✓ Significant reduction in apnea-hypopnea index (AHI)
- ✓ Many patients achieved improvement or resolution of OSA

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## Liraglutide (Saxenda / Victoza)

**How it works:** GLP-1 receptor agonist → slows stomach emptying, decreases hunger

- Saxenda = for weight loss
- Victoza = for diabetes

**Dosage:** Daily subcutaneous injection. Slowly increased weekly:  
0.6 mg → 1.2 → 1.8 → 2.4 → 3 mg daily

**Why it's used:**

- Daily dosing allows slower, gradual titration → can reduce nausea and other gastrointestinal side effects compared with weekly injections.
- Helps lower blood sugars (benefit for diabetes)
- Approved for teens ≥ 12 years

**Side effects:**

- Nausea, vomiting, diarrhea, constipation, abdominal pain, bloating, indigestion
- Headache, dizziness, fatigue
- Rare: pancreatitis, gallbladder problems

**Not for:**

- Personal/family history of medullary thyroid cancer, MEN 2A/2B
- History of pancreatitis
- Gastroparesis
- Pregnancy or breastfeeding

**Things to keep in mind:**

- Daily injection may be a barrier
- High cost

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## GLP-1 Medications: Addressing Media Concerns



**Vision Concerns (NAION):**

- Rare condition causing sudden vision loss
- Studies show very few cases in patients on semaglutide
- Absolute risk remains extremely low
- Obesity itself increases risk for diabetic eye problems, which GLP-1s can help reduce



**Thyroid Cancer:**

- Early rodent studies suggested potential risk, but human data does not show increased thyroid cancer
- Avoid in patients with a personal/family history of medullary thyroid cancer or MEN 2

**Key Takeaways:**

- Extensive human studies show low rates of serious adverse effects
- Help reduce obesity-related complications: high blood pressure, diabetes, heart disease
- Discuss individual risks with your healthcare provider

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## Lisdexamfetamine (Vyvanse)

**FDA-approved for Binge Eating Disorder**


- Reduces frequency and intensity of binge episodes
- Helps to regain control over eating behaviors

**How it works**

- Acts on the brain to reduce binge eating urges and control appetite

**Dosage**

- Slowly increased up to 60 mg once daily in the morning



**VYVANSE**  
Controlled Substance Status

**Side effects:**

- Appetite suppression/weight loss (intended, but may be excessive)
- Nervous system: anxiety, irritability, insomnia, jitteriness
- Digestive: nausea, vomiting, diarrhea, constipation, abdominal discomfort
- Other: dry mouth, dizziness, increased heart rate

**Not for:**

- History of stimulant abuse
- Anyone who has used MAO inhibitors in the last 14 days

**Things to keep in mind**

- Controlled medication → risk of abuse
- Cost can be high
- Monitor heart rate, blood pressure, and mood

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### Setmelanotide (Imcivree)

**Use:** FDA-approved for rare **genetic** forms of obesity caused by defects in the MC4R pathway

- Helps regulate appetite and energy balance

**How it works:** MC4R agonist → signals the brain to reduce hunger and promote satiety

**Dosage:**

- Daily subcutaneous injection, usually in the morning
- Start at 1 mg, gradually increase as tolerated
- Approved for children 6 years and older, dose adjusted by weight

**Side effects:**

- Skin darkening
- Injection site reactions
- Nausea, vomiting, headache, depression
- Increased heart rate or blood pressure

**Not for:**

- Pregnancy or breastfeeding
- Known hypersensitivity

**Things to keep in mind:**

- Only for specific genetic obesity
- Expensive; requires genetic testing and specialty pharmacy approval.
- [www.UncoveringRareObesity.com](http://www.UncoveringRareObesity.com)

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### Setting Realistic Expectations

**Average Weight Loss**

Expect an average weight loss of 1-2 pounds per week through a combination of diet and exercise.

**Individual Factors**

Weight loss results can vary significantly based on factors like age, gender, metabolism, starting weight, and adherence to the program.

**Plateaus and Setbacks**

It's normal to experience weight loss plateaus or setbacks. Persistence and adjusting your approach can help you overcome these challenges.

**Long-Term Sustainability**

Sustainable weight loss requires lifestyle changes, not just quick fixes. Focus on developing healthy habits that you can maintain over time.

**Realistic Goal Setting**

Set achievable, incremental goals rather than aiming for unrealistic or rapid weight loss. This will help you stay motivated and engaged.

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### Tailoring Medication Selection

Medical History Evaluation

Body Mass Index (BMI) Assessment

Comorbidity Identification

Medication Interaction Check

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**Patient Case**

Patient Profile:  
52 year old Male  
BMI 32

PMH: Uncontrolled hypertension

Symptoms: Snores at night, experiences fatigue

Clinical Questions:  
Best medication option to start?  
Which medication to avoid?



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**Lifestyle and Medication Integration**

Lifestyle Changes	Weight Loss Medications	Integrated Approach	Personalized Treatment Plan
Important to incorporate healthy lifestyle changes such as a balanced diet, regular exercise, and behavioral changes to support long-term weight loss.	Weight loss medications can be used along with lifestyle changes to enhance the effectiveness of the weight loss efforts.	Synergistic benefits of combining weight loss medications with lifestyle changes.  This integrated approach can lead to greater and more sustainable weight loss outcomes.	Develop a personalized treatment plan that takes into account a person's unique needs, preferences, and medical history to optimize the integration of lifestyle changes and weight loss medications.

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**Emerging Medications: The Future of Obesity Treatment**

- **Retatrutide (in research, not FDA-approved):** Triple agonist (GIP, GLP-1, Glucagon receptors)
  - Early studies show significant weight loss beyond current GLP-1/GIP agents (tirzepatide)
  - Still in clinical trials, not yet available
- **Other areas of research:**
  - Orforglipron (oral GLP-1)
  - Cagrilintide (amylin analog, often combined with GLP-1)
  - Goal: more effective, safer, and longer-lasting options for patients
- The future of obesity medicine is **rapidly evolving**, with many promising therapies on the horizon.



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**Thank You**

Dr. Nisha Kuruvadi, DO, DABOM, DABLM

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