GLP-1 Receptor Agonists: Evidence, Efficacy, and Evolving Roles

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Shaveta Gupta, MD

LOUISIANA DEPARTMENT OF HEALTH

Objectives

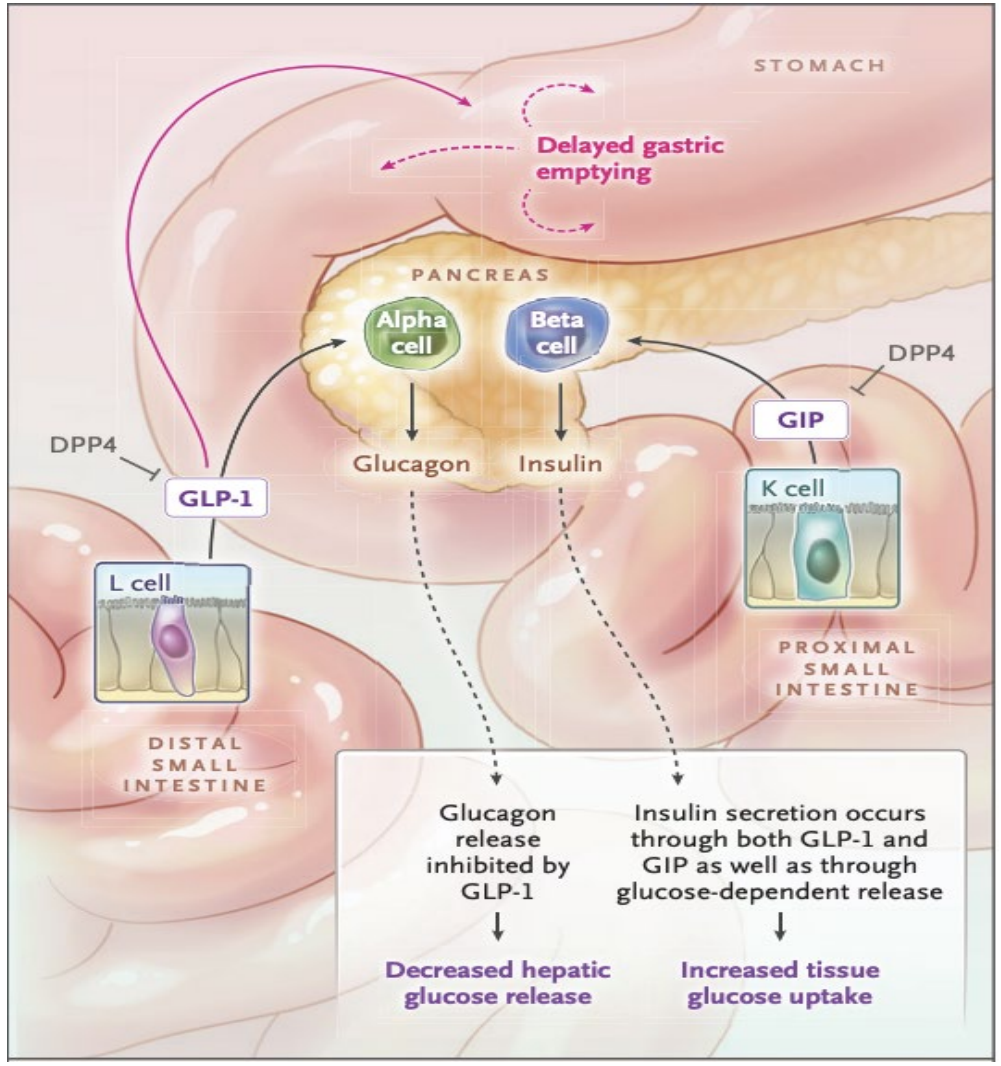
- **Summarize the indications for GLP-1 and dual GIP/GLP-1 receptor agonists**
- **Guide evidence-based agent selection across metabolic indications**
- **Discuss new and evolving therapies/indications**

Why it Matters?

- From glucose-lowering agents to a multi-organ therapeutic class
- Indications now include
  - Diabetes,
  - Obesity,
  - Cardiovascular risk reduction,
  - Chronic kidney disease,
  - Obstructive sleep apnea, and
  - Metabolic dysfunction–associated steatohepatitis

Drucker, Nature Medicine 32,47-57 (2026)

Mechanism of action



- Promote glucose-mediated insulin release
- Slows gastric emptying,
- Inhibition of glucagon secretion,
- Beneficial changes in the intestinal microbiome, and
- Direct effects on hypothalamic nuclei to enhance satiety
- Stimulate beta-cell prosurvival and proliferation mechanisms to maintain islet cell mass

GLP-1 Receptor Agonists DOI: 10.1056/NEJMra2500106
Incretin hormones and type 2 diabetes. Diabetologia 2023;66:1780-1795

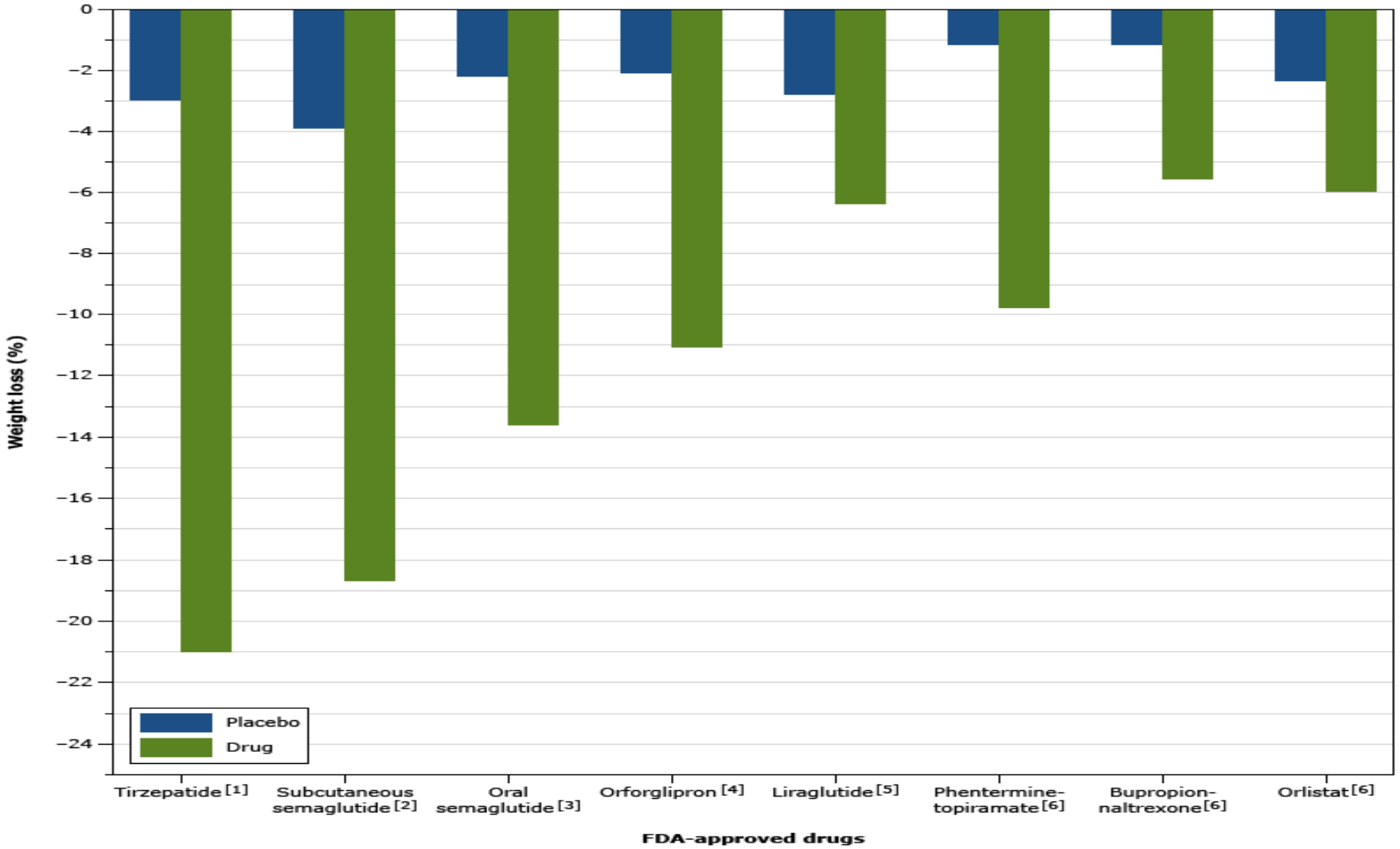
Glycemic efficacy in type 2 diabetes

Tirzepatide and subcutaneous semaglutide have the greatest glucose lowering efficacy.

Agent	Glycemic Efficacy (A1c lowering %)
Dulaglutide	-1 to -1.5
Semaglutide subs	-1.5 to 2
Semaglutide oral	-0.7 to -2
Tirzepatide	-2 to -2.5

Cardoso et al., Journal of Clinical Investigation, 2026
Yao et al., BMJ, 2024

Efficacy for Weight loss



Uptodate- obesity in adults: drug therapy

- Greatest benefit
  - -Young
  - -Female
  - -higher baseline BMI
  - -without diabetes, and
  - -longer duration of treatment
- Weight regain occurs if GLP-1-based therapy is discontinued

Wong HJ et al Diabetes Care. 2025 Feb 1;48(2):292-300. doi: 10.2337/dc24-1678. PMID: 39841962

West S et al BMJ. 2026 Jan 7;392:e085304. doi: 10.1136/bmj-2025-085304. PMID: 41500720; PMCID: PMC12776922..

- Subcutaneous semaglutide 7.2 mg has been approved by the US Food and Drug Administration (FDA) for the treatment of obesity in those who require additional weight reduction after tolerating the 2.4 mg dose for at least four weeks (Up to 3% additional reduction)

Wharton S et al Lancet Diabetes Endocrinol. 2025;13(11):949. Epub 2025 Sep 14.

Cardiovascular outcomes

- GLP-1RAs have shown to reduce MACE including cardiovascular death, MI, and stroke by 14%
- Both the oral as well as injectable semaglutide -> benefit.
- Also, cardioprotective in patients with obesity but without diabetes
- Tirzepatide - patients with obesity and heart failure with preserved ejection fraction -> reduced CV death or worsening heart failure

Lee et al Diabetes Care 2025
McGuire et al SOUL NEJM 2025
Lincoff et al SELECT NEJM 2023
Packer M et al *N Engl J Med* 2025;392:427-437

Cardiovascular outcomes

- Interruption or discontinuation of glucagon-like peptide 1 (GLP-1)-based therapy is common and may result not only in weight regain but also in loss of the cardioprotective effects of treatment.
- This was seen in people who discontinued treatment within 1.5 years or had a treatment interruption of ≥1.5 years.

BMJ Med. 2026;5(1):e002150. Epub 2026 Mar 18

Renal outcomes

- Ozempic - FDA approved for reducing the risk of kidney disease in persons with type 2 diabetes
  - Slows progression of CKD
  - Reduces albuminuria
  - Lowers both cardiovascular and all-cause mortality
  - Injectable form
  - The benefit occurs irrespective of concomitant SGLT-2 inhibitor use therefore combination therapy is recommended.

Perkovic et al NEJM 2024; 391(2):109. Epub 2024 May 24

Mann JFE et al Nature medicine 2024.

OSA

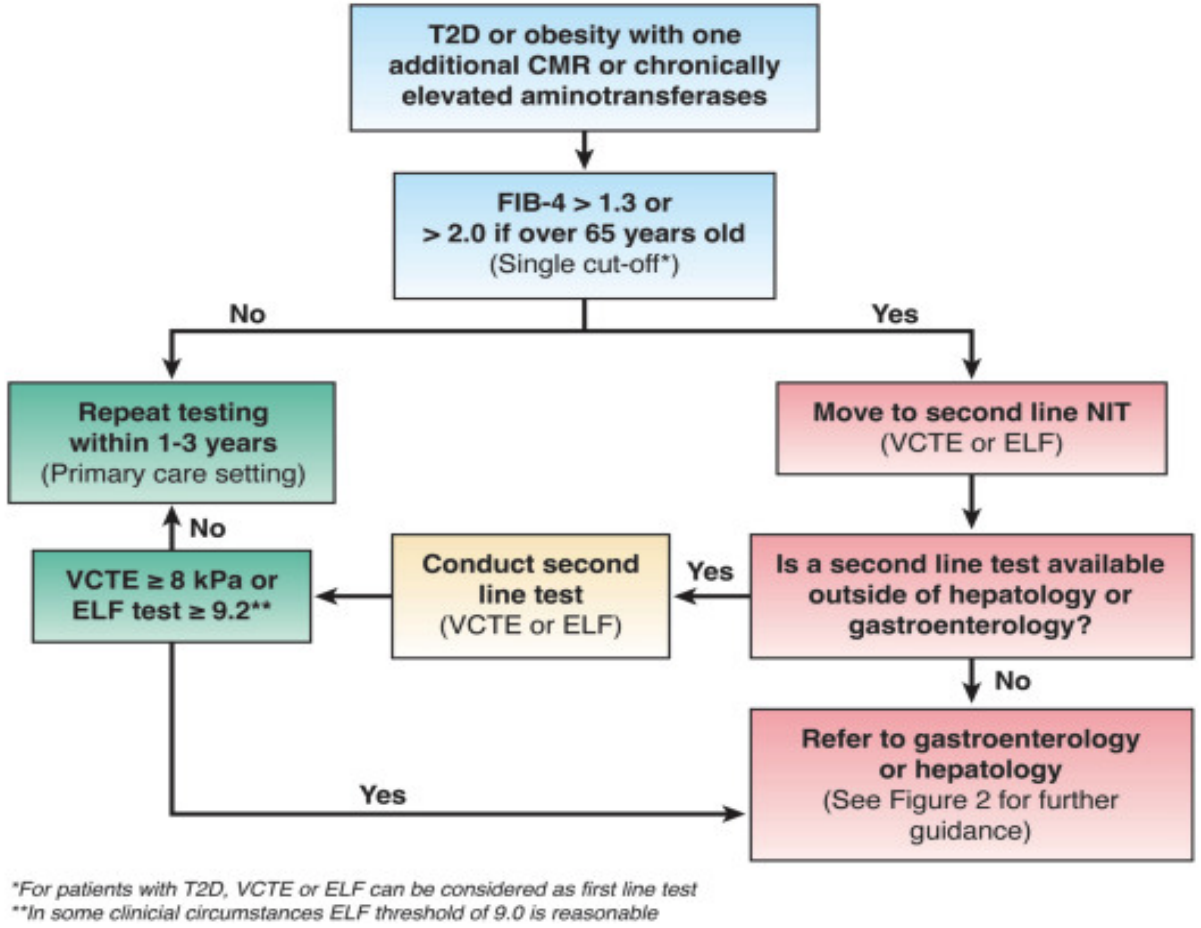
- Moderate to severe obstructive sleep apnea (AHI > 15) and obesity
- Tirzepatide – First FDA approved drug therapy

Malhotra A et al NEJM 2024

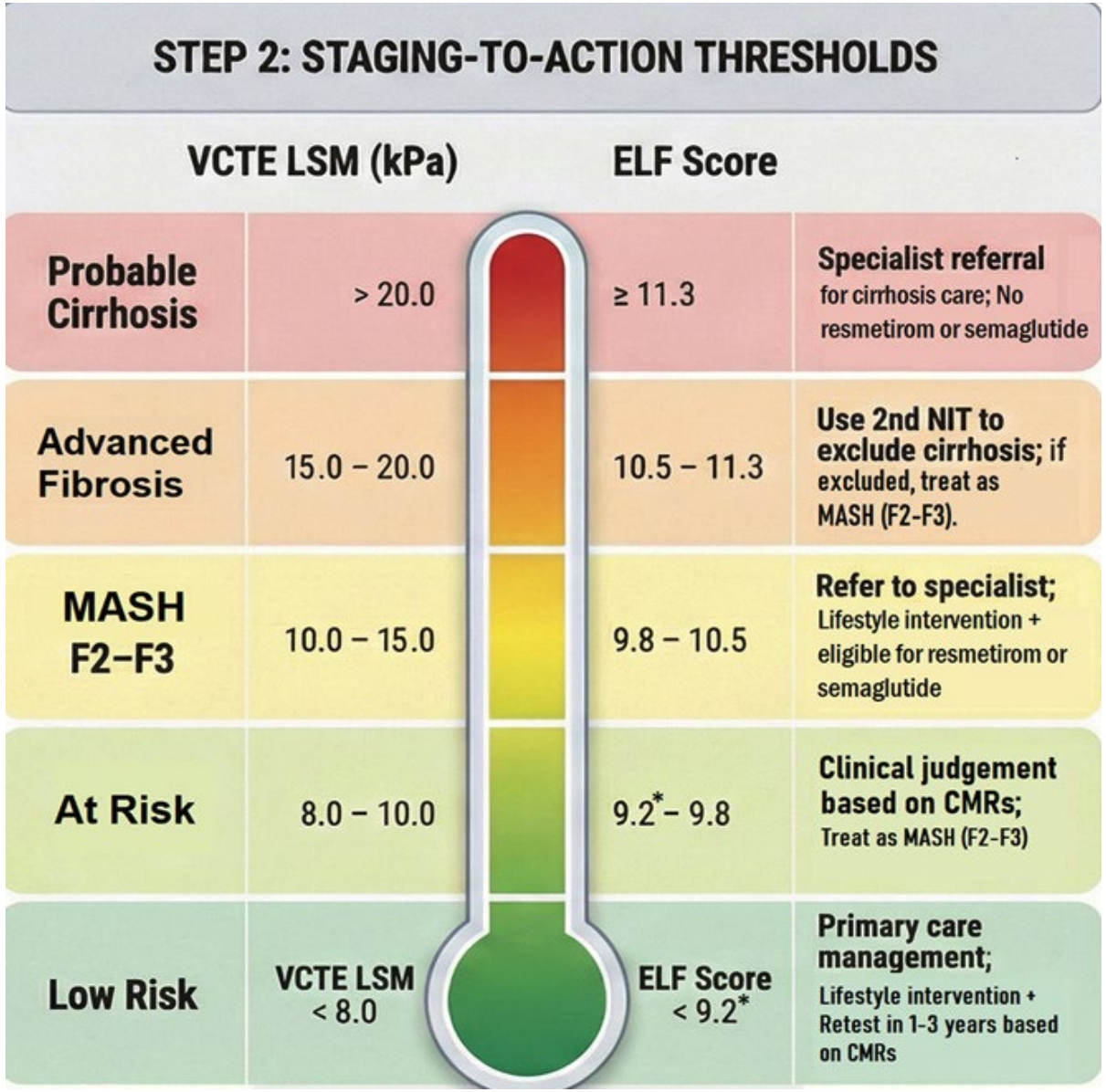
Metabolic dysfunction-associated steatohepatitis

- **MASLD** = metabolic dysfunction-associated steatotic liver disease (hepatic steatosis + a cardiometabolic risk factor).
- **MASH** = the inflammatory, progressive form (steatohepatitis).
- **Fibrosis** - drives prognosis: F2-F3 stage identifies patients at risk of progression to cirrhosis and liver-related complications.

Metabolic dysfunction-associated steatohepatitis



Younossi Z et al Clinical Gastro and Hep,2026;24,2333-2347



Younossi Z et al Clinical Gastro and Hep,2026;24,2333-2347

Metabolic dysfunction-associated steatohepatitis

- Semaglutide – FDA approved for Noncirrhotic MASH in adults with moderate-to-advanced liver fibrosis (stages F2 to F3)
- Tirzepatide also has significant benefit.
- Not approved by FDA at present.
- Not indicated for cirrhosis

Sanyal et al ESSENSE NEJM 2025
Loomba et al SYNERGY- NASH NEJM 2024

Oral Agents

- Oral Semaglutide
- - Take Fasting, at least 30 mins before breakfast or other oral medications, with no more than 4 oz of plain water.
- Dose Titration
- Day 1 through day 30: 1.5 mg once daily.
- Day 31 through day 60: 4 mg once daily.
- Day 61 through day 90: 9 mg once daily.
- Day 91 and thereafter (maintenance dosage): 25 mg once daily.

Wharton et al OASIS 4 NEJM 2025

Oral Semaglutide

- Prefer
  - Needle aversion and local skin reactions
  - No cold chain needed
  - Comparable weight efficacy
  - Cardiovascular risk reduction present
- NOT preferred
  - Absorption and bioavailability dependent on administration
  - Strict administration requirements
  - Daily dosing

Plotkin et al Diabetes, Obesity & Metabolism 2026

Orforglipron

- Oral glucagon-like peptide-1 (GLP-1) receptor agonist
- Approved by FDA for obesity
- Simpler administration requirements compared with oral semaglutide
- Dose modification needed for those on CYP3A4 inhibitors or inducers.

Wharton S et al N Engl J Med. 2025;393(18):1796. Epub 2025 Sep 16.

Retatrutide

- A third-generation, triple GLP-1–GIP–glucagon receptor agonist
- Excellent glycemic efficacy in T2D in phase 2 randomized trial

Rosenstock J et al. Lancet 2023;402:529-544

Evolving indications

- T2DM and peripheral artery disease with intermittent claudication -> Semaglutide improved the treadmill walking distance
- Glucose lowering with GLP-1RAs was associated with a statistically significant reduction in all-cause dementia.

Seminer A et al Neurol. 2025;82(5):450
Bonaca et al Lancet 2025;405(10489):1580.Epub 2025 Mar 29.