

Beyond Blood Sugar: The Rise of Incretin- Based Therapies

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APP Pharmacology Grand Rounds

05/06/2026

Special Thanks: Sarah Wigfield, PharmD, BCACP

Relevant Financial Relationships

- Kaitlin Mockus, faculty for this CME activity, has no relevant financial relationship(s) to disclose.

Objectives

- Compare available **incretin-based therapies (GLP-1 receptor agonists and dual GLP-1/GIP agonists)** based on FDA-approved indications, efficacy, and cardiometabolic benefits.
- Select the most appropriate incretin-based therapy for a given patient based on treatment goals, comorbidities, contraindications, and patient-specific factors.
- Develop monitoring plans and patient counseling strategies to mitigate risk of side effects.

Miracles, Myths, and Misinformation, Oh My!

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INTRODUCING

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The easiest way to start a GLP-1.



weight loss by hers



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Compounded Injectable Tirzepatide (GLP-1/GIP)
Fridays



\$200.00
Compound Semaglutide (Prescribed) | GLP-1 Weight...
Liferx md



Amazon.com: GLP-1 Patches (2Pack - 60),GLP-...

Agenda

1. Mechanism of Action

2. Indications & Place in Therapy

3. Contraindications & Precautions

4. Monitoring Parameters

5. Side Effects & Mitigation Strategies

6. Patient Counseling Points

7. Drug Interactions

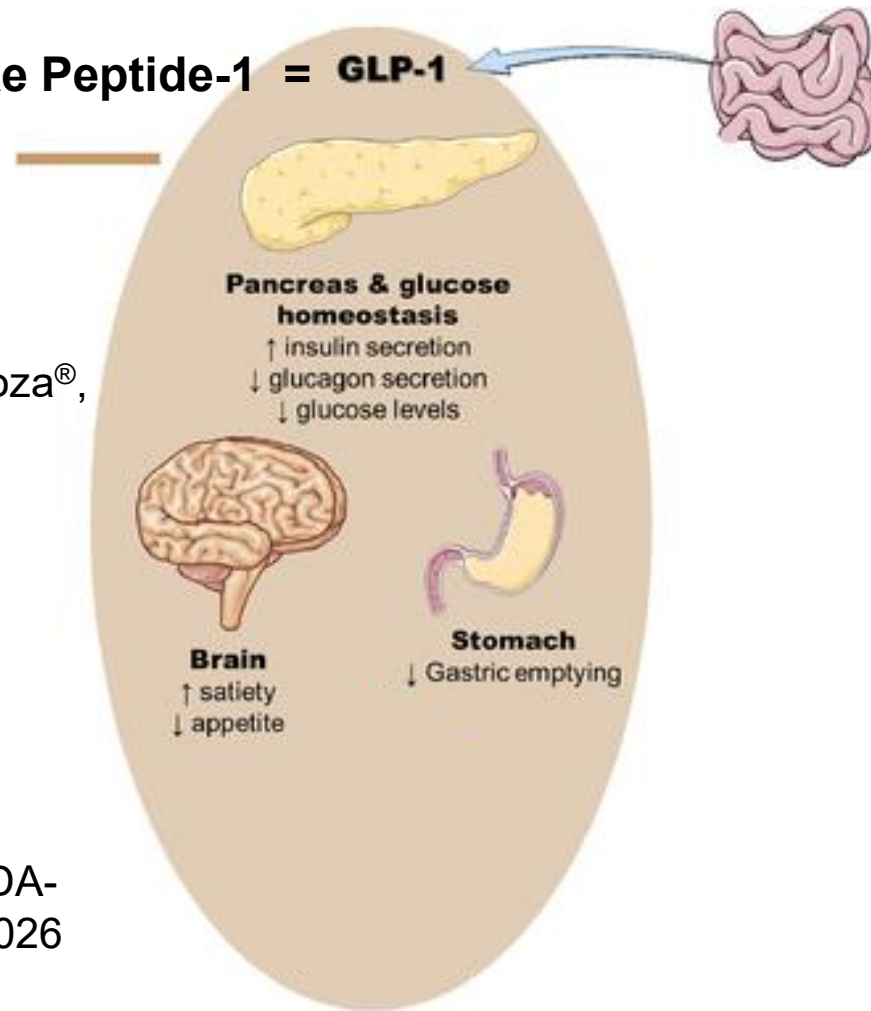
8. In the Pipeline

Incretin-Based Therapies - Mechanism of Action

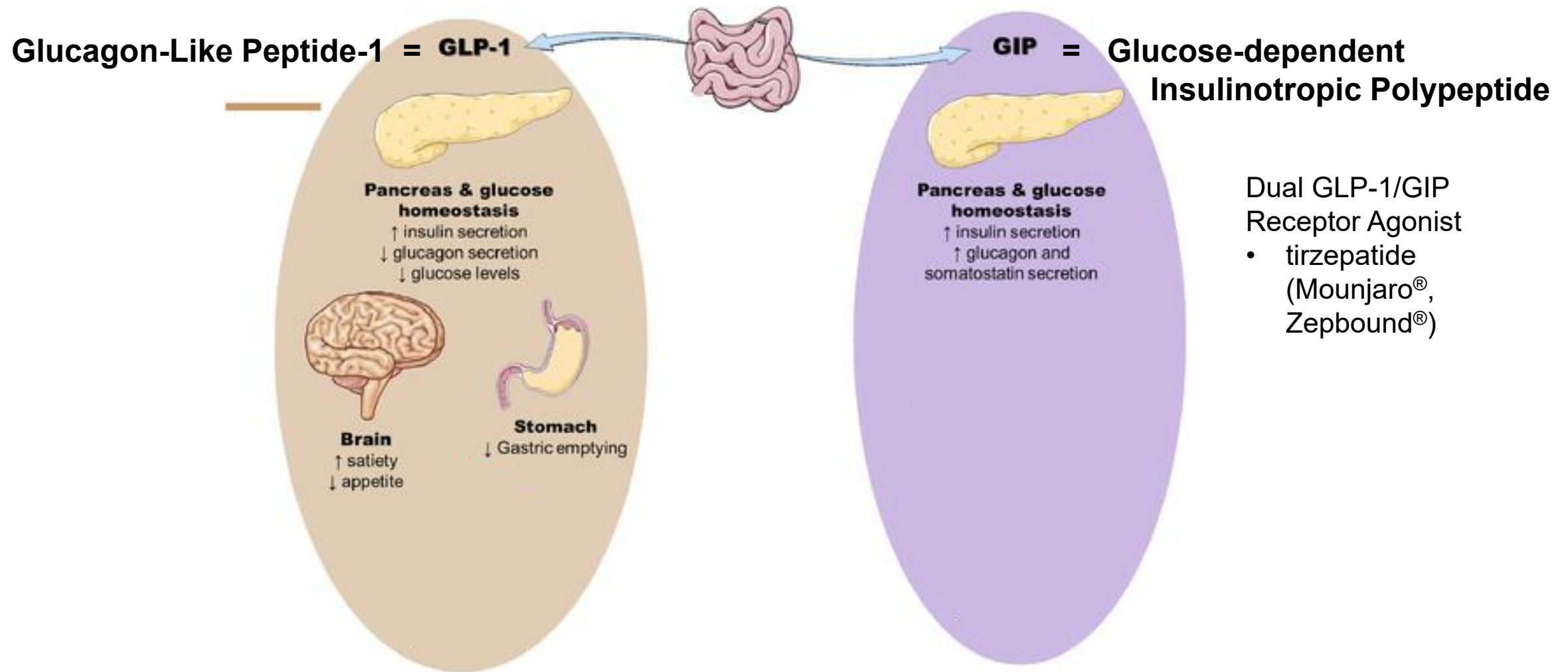
Glucagon-Like Peptide-1 = GLP-1

GLP-1 Receptor
Agonists:

- liraglutide (Victoza[®], Saxenda[®])
- dulaglutide (Trulicity[®])
- semaglutide (Ozempic[®], Rybelsus[®], Wegovy[®])
- orforglipron (Foundayo[®]) FDA-approved 4/1/2026



Incretin-Based Therapies - Mechanism of Action



Therapy Selection

Indications & Place in Therapy

FDA-Approved Indications

Specific to each agent and brand name

As adjunct to diet and exercise

- Type 2 Diabetes
- Obesity (BMI ≥ 30 kg/m²)
- Overweight (BMI ≥ 27 kg/m²) with at least 1 weight-related comorbidity (examples):
 - Pre-diabetes
 - Cardiovascular disease
 - Dyslipidemia
 - Metabolic dysfunction-associated steatohepatitis (MASH)
 - Hypertension
 - Obstructive sleep apnea (OSA)
- Cardiovascular risk reduction in patients with a history of a heart attack, stroke or symptomatic peripheral artery disease *AND* with a BMI ≥ 30 kg/m²
- Noncirrhotic MASH, with moderate-to-advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in adults
- Moderate-to-Severe OSA *AND* with a BMI ≥ 30 kg/m²

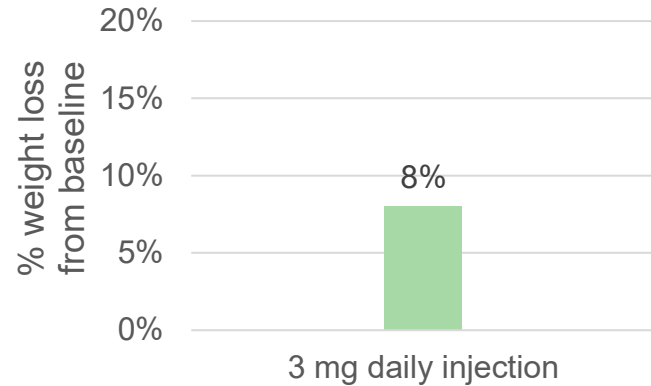
Generic Name	Brand Name	Dosing	FDA-Approved Indications				
			Type 2 Diabetes	Obesity/ Overweight	CV Risk Reduction	MASH	OSA
liraglutide	Victoza®	<ul style="list-style-type: none"> Daily injection Increase dose weekly: 0.6 mg, 1.2 mg, 1.8 mg 	✓				
	Saxenda®	<ul style="list-style-type: none"> Daily injection Increase dose weekly: 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, 3 mg 		✓			
dulaglutide	Trulicity®	<ul style="list-style-type: none"> Weekly injection Increase dose monthly: 0.75 mg, 1.5 mg, 3 mg, 4.5 mg 	✓				
semaglutide	Ozempic®	<ul style="list-style-type: none"> Weekly injection Increase dose monthly: 0.25 mg, 0.5 mg, 1 mg, 2 mg 	✓				
	Rybelsus®	<ul style="list-style-type: none"> Daily pill by mouth Increase dose monthly: 3 mg, 7 mg, 14 mg 	✓				
	Wegovy®	<ul style="list-style-type: none"> Weekly injection Increase dose monthly: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg, (Wegovy HD® 7.2 mg) 		✓	✓	✓	
		<ul style="list-style-type: none"> Daily pill by mouth Increase dose monthly: 1.5 mg, 4 mg, 9 mg, 25 mg 		✓	✓		
tirzepatide	Mounjaro®	<ul style="list-style-type: none"> Weekly injection Increase dose monthly: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg 	✓				
	Zepbound®	<ul style="list-style-type: none"> Weekly injection Increase dose monthly: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg 		✓			✓
orforglipron	Foundayo®	<ul style="list-style-type: none"> Daily pill by mouth Increase dose monthly: 0.8 mg, 2.5 mg, 5.5 mg, 9 mg, 14.5 mg, 17.2 mg 		✓			

Generic Name	Brand Name	Additional Cardiometabolic Benefits (≠ FDA-Approval)			
		↓ Cardiovascular Risk	↑ Renal Function, ↓ Albuminuria, Slow Progression of CKD	Potential Benefit in MASH & MASLD	HFpEF
liraglutide	Victoza®	In T2DM + high CV risk (LEADER 2016)	In T2DM (LEADER 2016)	(LEAN 2015)	
dulaglutide	Trulicity®	In T2DM (REWIND 2019)	In T2DM (REWIND 2019)	In T2DM (D-LIFT 2020)	
semaglutide	Ozempic®	In T2DM + high CV Risk (SUSTAIN-6 2016)	In T2DM (FLOW 2024) (<i>strongest evidence</i>)	(ESSENSE 2025)	
	Rybelsus®	In T2DM + ASCVD or CKD (SOUL 2025)			
	Wegovy® SQ	✓		✓	In Review for FDA Approved Indication (STEP-HFpEF 2023)
	Wegovy® PO	✓			
tirzepatide	Mounjaro® Zepbound®			(SYNERGY-NASH 2024)	↓ worsening HF events, ↑ health status per KCCQ score (SUMMIT 2024)

Primary Literature Summary for Weight Loss

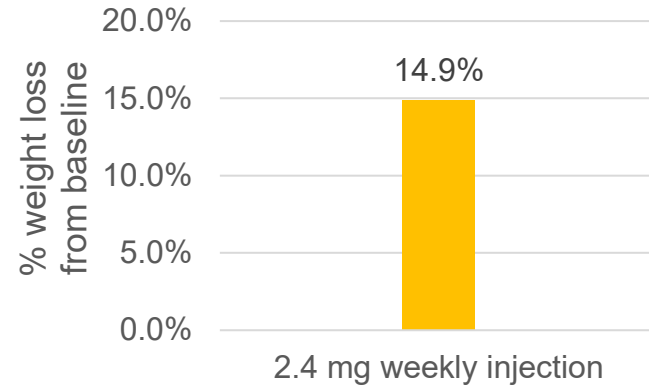
SCALE 2015

liraglutide (Saxenda®), 56 weeks



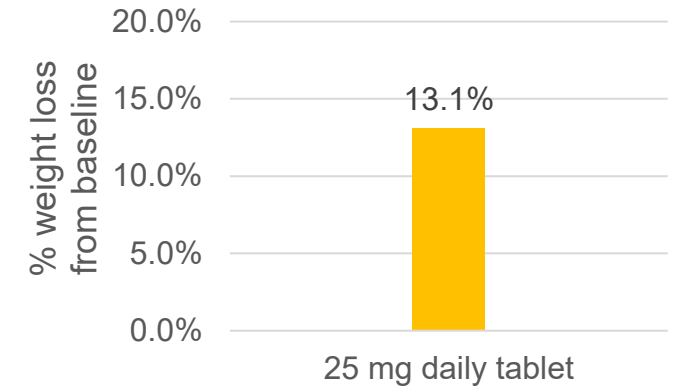
STEP 1 2021

semaglutide (Wegovy®), 68 weeks



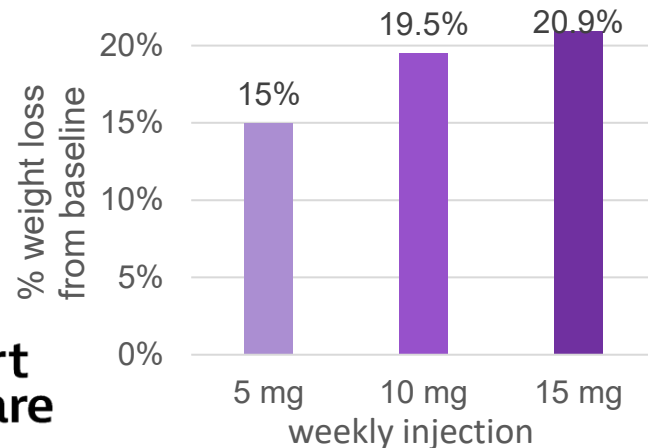
OASIS 4 2025

semaglutide (Wegovy®), 64 weeks



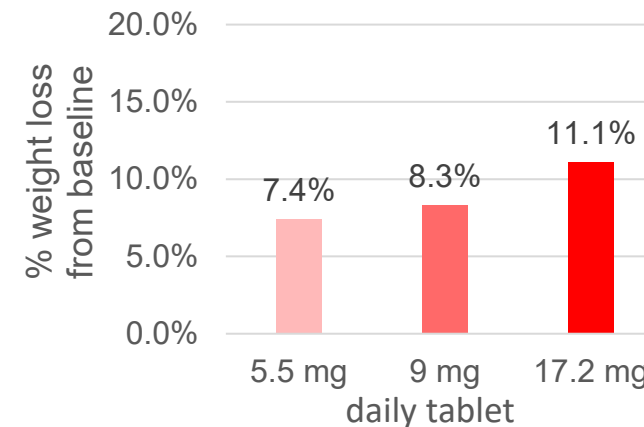
SURMOUNT-1 2022

tirzepatide (Zepbound®), 72 weeks



ATTAIN-1 2025

orforglipron (Foundayo®), 72 weeks



Oral Administration Requirements

semaglutide (Rybelsus[®], Wegovy[®])

- Take first in the morning with *no more than 4 ounces of plain water*
- Wait 30 minutes before consuming other food, beverage, or medication

orforglipron (Foundayo[®])

- Without regard to food or other medications

Summary of Therapy Selection

- FDA-approved indication
- Additional cardiometabolic benefits
- A1c lowering efficacy
- Weight loss efficacy
- Ease of administration

Contraindications

Personal or family history of medullary thyroid carcinoma

Multiple endocrine neoplasia syndrome type 2 (MEN2)

Pregnancy

Serious hypersensitivity reaction to the medication

Precautions

- Pancreatitis history or risk factors
 - Significantly elevated triglycerides (>500-1,000 mg/dL)
 - Excessive alcohol intake
- Altered kidney function
 - Limited clinical evidence
 - No dose adjustments necessary
 - Use with caution when initiation or escalating doses
- Type 1 diabetes
- Gastroparesis

Surgical Precautions

- Froedtert Guidelines
 - Weekly: hold dose within 1 week prior to procedure
 - Daily: hold day of procedure
- Or, individualized decision based on:
 - Indication (e.g. importance of maintaining glycemic control)
 - Duration of therapy (delayed gastric emptying in first 8-12 weeks of therapy)^{18,19}
 - Concomitant medications that may slow gastric emptying (e.g. opioids, PPIs)

Monitoring Parameters

A1c

Patient
tolerance

Pancreatitis
Risk

- Triglycerides
- Alcohol use
- Lipase, amylase

Renal
function

Weight

Side Effects

Common

- Decreased appetite
- Nausea
- Vomiting
- Constipation
- Diarrhea
- Belching
- Heartburn
- Injection site reactions
- Hair loss/thinning

Rare but serious

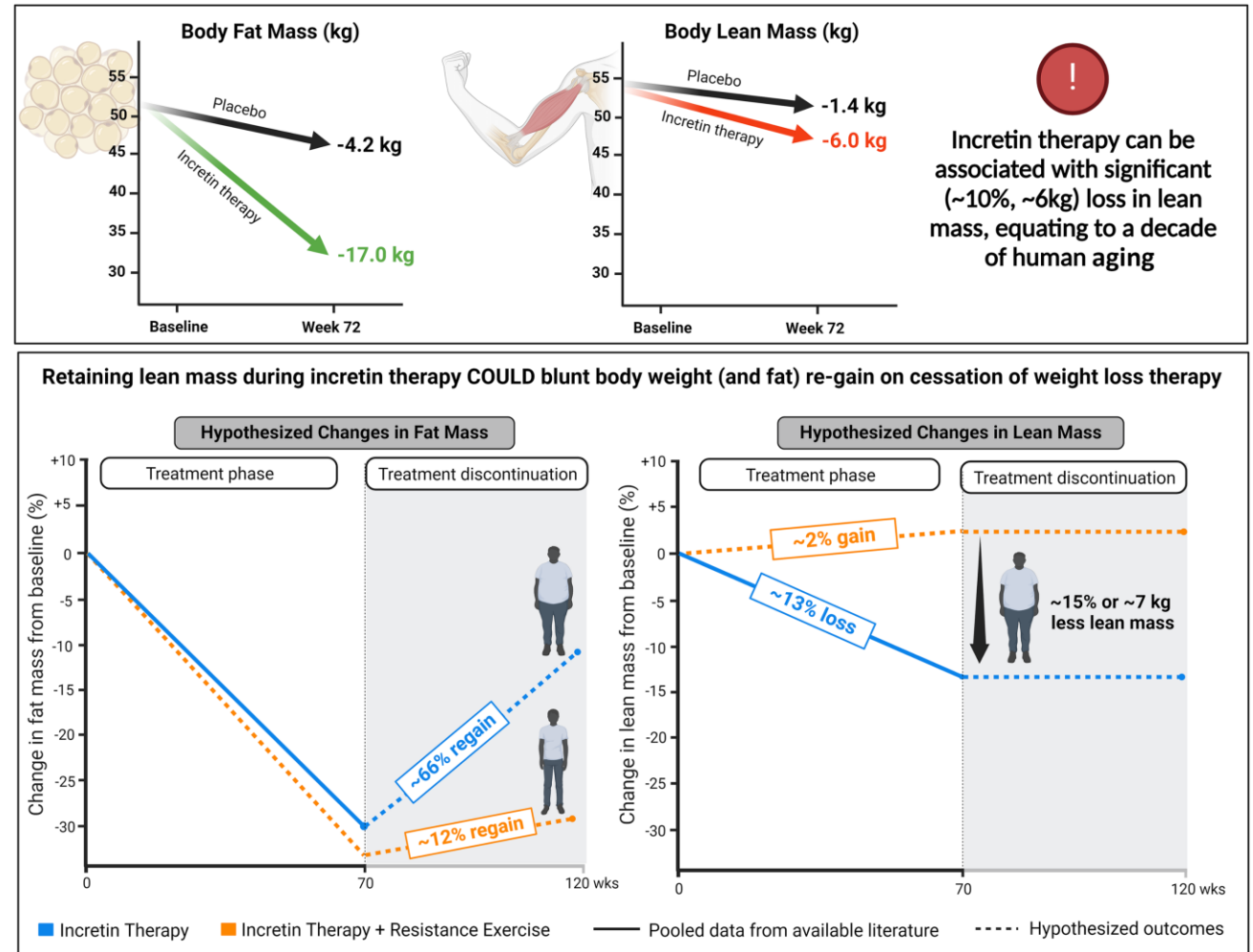
- Pancreatitis
- Ileus
- Diabetic retinopathy
- Acute kidney injury (secondary to GI losses from vomiting, diarrhea)

Tips for Mitigating Gastrointestinal Side Effects²⁰

- Lowest initial dose, slow dose titrations
- Adequate hydration
- Smaller, frequent meals
- Avoid fatty, greasy, or spicy foods
- Eat slowly
- Avoid over-eating
- Adequate fiber intake
- OTC medications

Optimizing Safe & Effective Weight Loss

- In conjunction with diet and exercise
- Calorie deficit
- Protein with every meal and snack
- Referral to nutrition and/or behavioral health
- Minimum 150 minutes of physical activity weekly
- Resistance exercise to minimize muscle mass loss²¹



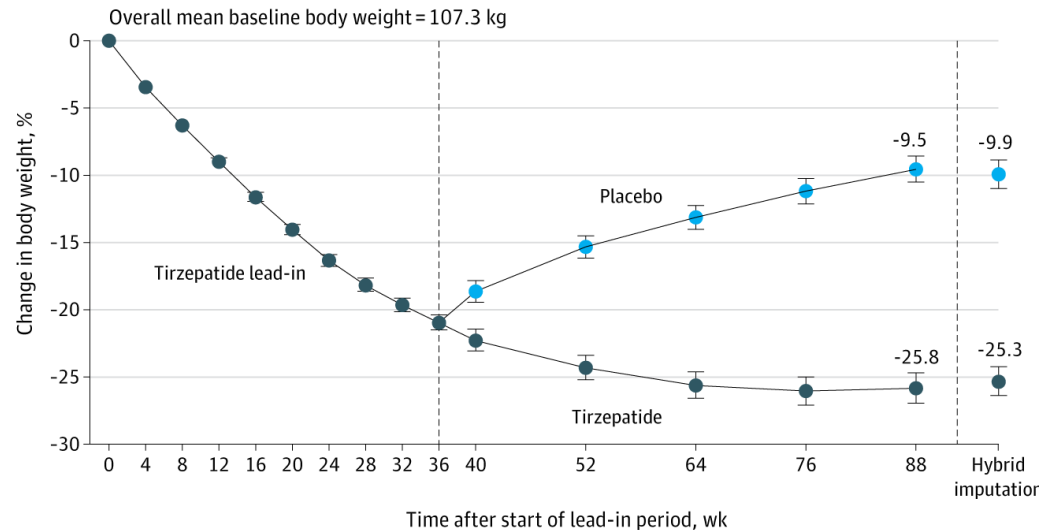
!
 Incretin therapy can be associated with significant (~10%, ~6kg) loss in lean mass, equating to a decade of human aging

Discontinuation of Therapy (Obesity & Overweight)

SURMOUNT-4 2024

- 36 week lead in: all patients on tirzepatide 10 mg or 15 mg weekly (mean 20.9% weight reduction)
- Randomized 1:1 to:
 - Continue tirzepatide → additional 5.5% weight loss
 - Switch to placebo → 14% weight regain

A Percent change in body weight (week 0-88)



No. at risk	0	4	8	12	16	20	24	28	32	36	40	52	64	76	88	Hybrid imputation
Tirzepatide lead-in	670	666	669	668	667	667	669	663	659	670						
Tirzepatide										335	333	328	317	310	310	335
Placebo												335	330	292	289	335

No set guidelines, Options include:

- Decreasing dose each month
- Extend dosing interval (e.g. weekly to every 10-14 days)
- Discontinue
 - May be most likely to cause return of appetite & cravings, but is not harmful

Continue diet/exercise to reduce weight regain

Drug Interactions

All Incretin Therapies

- Insulin & sulfonylureas → hypoglycemia risk
- Consider ~20% reduction in insulin dose if glucose is well controlled

Drug Interactions

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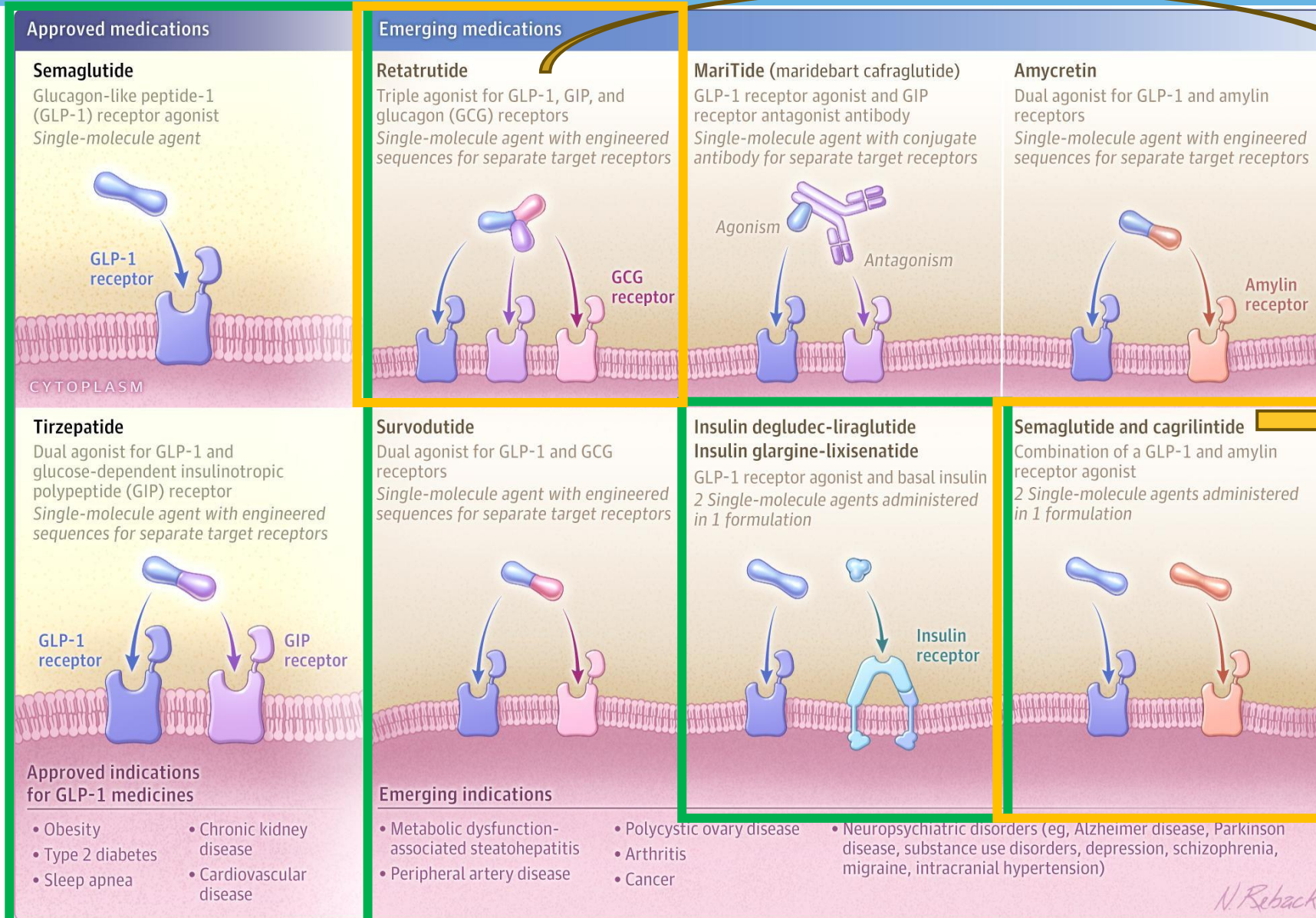
tirzepatide

- Decreases effectiveness of hormonal oral contraceptive pills (OCPs)
- Use backup contraception for first 4 weeks following initiation & dose increase of tirzepatide

Drug Interactions - orforglipron

Interacting Drug(s)	Management	Select Example(s)
Oral contraception pills	Backup contraception 30 days after initiation & dose increases	Norethindrone & ethinyl estradiol
Simvastatin	Max simvastatin dose of 20 mg daily	
Strong CYP3A4 Inducers	Avoid orforglipron (lack of efficacy)	Carbamazepine, phenytoin, phenobarbital, rifampin
Strong CYP3A4 Inhibitors	Max orforglipron dose of 9 mg daily (increased side effect risk)	Ketoconazole, itraconazole
Strong CYP3A4 Inhibitors that are also OATP1B1 Inhibitors	Avoid orforglipron	Clarithromycin, ritonavir

Incretin-Based Therapies In the Pipeline



Retatrutide weekly injection New Drug Application (NDA) anticipated to be submitted late 2026

CagriSema[®] weekly injection under FDA review with possible approval later 2026

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Questions?

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Supplementary Slides

Cost and Coverage

- Often covered for Type 2 Diabetes with prior authorization
- Variable coverage for weight loss
- Copay Card
 - Trulicity[®], Ozempic[®], Rybelsus[®], Mounjaro[®], Zepbound[®], Wegovy[®], or Foundayo[®]
- Patient Assistance Program (Type 2 Diabetes)
 - Ozempic[®], Rybelsus[®], or Victoza[®] – for uninsured patients only
 - Trulicity – if meeting certain criteria: [LillyCaresMedicalExceptionRequestForm.pdf](#)
- Cash Pay Programs by drug manufacturers
 - NovoCares Pharmacy: Ozempic[®], Wegovy[®]
 - Lilly Direct Pharmacy: Zepbound[®], Foundayo[®]
- Compounded products NOT recommended

Interruptions in Therapy

TABLE 2

Considerations for Resuming a GLP-1 Receptor Agonist After a Prolonged Lapse in Therapy

Agent	Last Dose Administered	Recommendation(s) for Resuming Therapy
Dulaglutide*	1.5 mg once weekly	<ul style="list-style-type: none">• Resume at 1.5 mg once-weekly dose.• Expect comparable tolerability to that experienced prior to dose interruption.
	3 or 4.5 mg once weekly	<ul style="list-style-type: none">• Use best judgment if ≥ 3 doses are missed.<ul style="list-style-type: none">• It is unknown whether tolerance to the GI adverse events will remain if reinitiated at the higher dose after ≥ 3 missed doses.• Decision can be informed by patient's prior GI tolerability.• In consideration of the above, clinicians may consider reinitiating at 1.5 mg once weekly.
Injectable semaglutide†	1 mg once weekly	<ul style="list-style-type: none">• If ≤ 2 doses are missed, reinitiate at 1 mg once weekly.• If 3–4 doses are missed, reinitiate at 0.5 mg weekly.• If ≥ 5 doses are missed, reinitiate at 0.25 mg once weekly.
Tirzepatide‡	≥ 5 mg once weekly	<ul style="list-style-type: none">• If ≤ 2 doses are missed, reinitiate at the same dose (provided the dose was adequately tolerated).• If ≥ 3 doses are missed, reinitiate at 5 mg once weekly.

[Open in a separate window](#)

*Based on manufacturer-provided information (20).

†Based on personal communication with C. Wong on 27 February 2023.

‡Based on supplementary material published with ref. 21.

Medication	Dose	Side Effects (Treatment versus Placebo)			
		Nausea	Vomiting	Diarrhea	Constipation
liraglutide (Saxenda®)	3 mg daily	40.2% vs. 14.7	16.3% vs. 4.1%	20.9% vs. 9.3%	20.0% vs. 8.7%
semaglutide (Wegovy®)	2.4 mg weekly injection	35.9% vs. 10.4%	21.4% vs. 3.5%	22.8% vs. 9.6%	29.8% vs. 9.3%
	25 mg daily tablet	44.2% vs. 17.4%	24.8% vs. 6.6%	31.5% vs. 15.9%	23.4% vs. 9.5%
tirzepatide (Zepbound®)	5 mg weekly injection	24.6% vs. 9.5%	8.3% vs. 1.7%	18.7% vs. 7.3%	16.8% vs. 5.8%
	10 mg weekly injection	33.3% vs. 9.5%	10.7% vs. 1.7%	21.2% vs. 7.3%	17.1% vs. 5.8%
	15 mg weekly injection	31% vs. 9.5%	12.2% vs. 1.7%	23% vs. 7.3%	11.7% vs. 5.8%
orforglipron (Foundayo®)	5.5 mg daily tablet	28.9% vs. 10.4%	13.0% vs. 3.5%	21.0% vs. 9.6%	21.7% vs. 9.3%
	9 mg daily tablet	35.9% vs. 10.4%	21.4% vs. 3.5%	22.8% vs. 9.6%	29.8% vs. 9.3%
	17.2 mg daily tablet	33.7% vs. 10.4%	24.0% vs. 5.9%	23.1% vs. 9.6%	25.4% vs. 9.3%