Clinical Applications and Safety Concerns of GLP-1 Agents

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Disclosures

- The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Learning Objectives

At the end of this session, learners should be able to:

- Recall the GLP-1 receptor agonist class, including its mechanism of action, therapeutic indications, and pharmacokinetic properties that influence clinical application
- Describe safety considerations, such as drug–drug interactions, FDA warnings, and strategies to minimize risk in prescribing
- Outline evidence for diverse clinical applications, by reviewing key clinical trials and discussing potential benefits and risks for indications beyond diabetes and weight management

Abbreviation Key

ACEi: angiotensin-converting enzyme inhibitor

ARB: angiotensin receptor blocker

AUC: area under the curve

BID: twice daily

BMI: body max index

CKD: chronic kidney disease

Cmax: maximum concentration

CNS: central nervous system

CPAP: continuous positive airway pressure

CV: cardiovascular

CVS: cardiovascular system

CYP: cytochrome p450 enzyme

DDI: drug-drug interactions

DPP-4: dipeptidyl peptidase-4 inhibitor

ER: extended release

FDA: Food and Drug Administration

GFR: glomerular filtration rate

GIT: gastrointestinal tract

GLP-1 RA: glycogen like peptide 1 receptor agonist

GLP-1: glycogen like peptide 1

HIV: human immunodeficiency virus

IgG: immunoglobulin G

IR: immediate release

MACE: major adverse cardiovascular event

MASH: metabolic dysfunction-associated steatohepatitis

NG:

OSA: obstructive sleep apnea

PAP: positive airway pressure

PO: by mouth

SI/B: suicidal ideation and behavior

Subq: subcutaneous

T2D: type 2 diabetes

Tmax: time to max concentration

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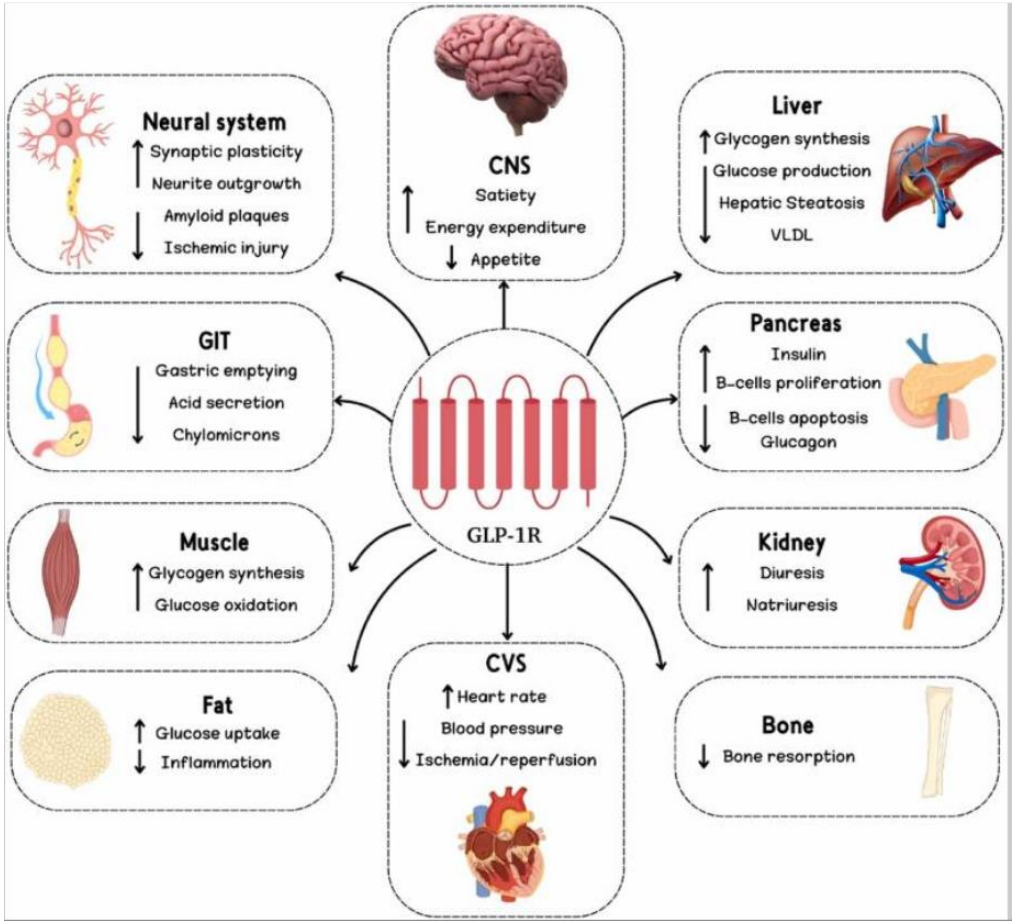
Glucagon Like Peptide-1 Hormone[1]

Produced in enteroendocrine cells of the distal small intestine and colon

Rapidly secreted post-meal and quickly degraded by DPP-4

GLP-1 Receptors widely expressed in pancreatic islets, kidney, lung, heart, and nervous system



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GLP-1 Receptor Agonist

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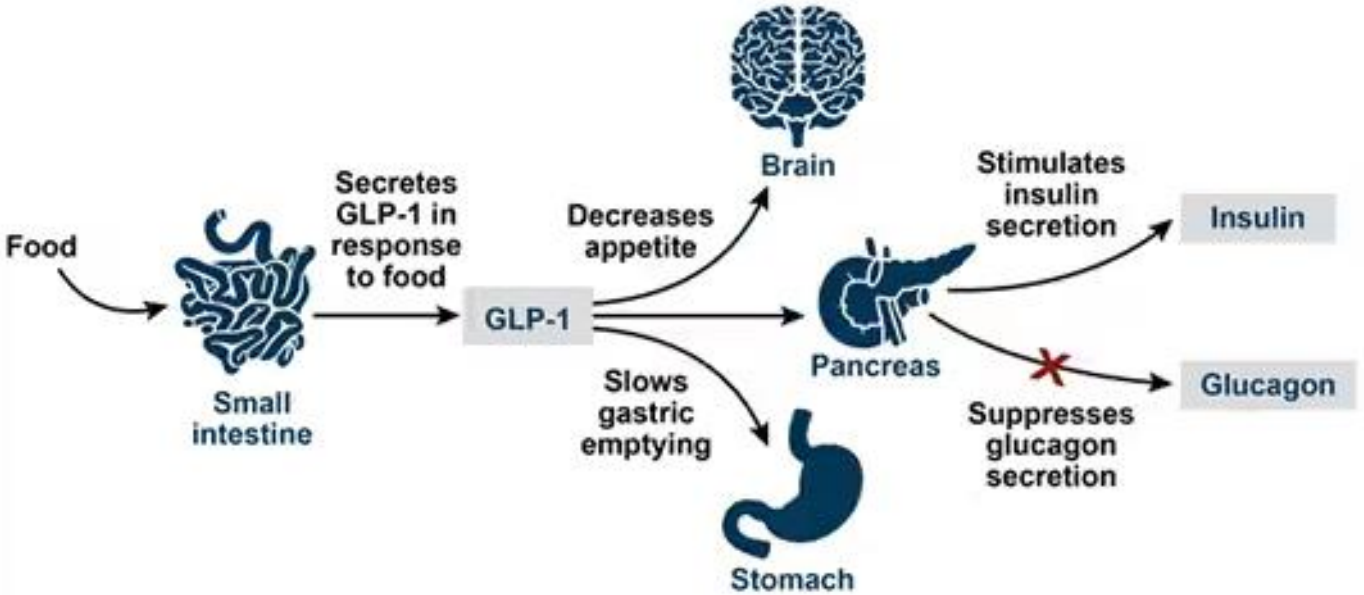
Approved Agents[2-7]

Generic Name	Brand Name(s)	FDA Approval Year(s)	Indication	Rout(s)	Frequency(s)
Tirzepatide	Mounjaro™ Zepbound™	2022 2023	T2D Weight Loss	Subq Subq	Weekly Weekly
Semaglutide	Ozempic™ Rybelsus™ Wegovy™	2017 2019 2021, 2025	T2D T2D Weight Loss	Subq PO Subq, PO	Weekly Daily Weekly, Daily
Lixisenatide	Adlyxin™	2016	T2D	Subq	Daily
Dulaglutide	Trulicity™	2014	T2D	Subq	Weekly
Liraglutide	Victoza™ Saxenda™	2010 2014	T2D Weight Loss	Subq Subq	Daily Daily
Exenatide	Byetta™ Bydureon™	2005 2017	T2D T2D	Subq Subq	BID Weekly

GLP-1 RAs
Mechanism of Action



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Pharmacokinetic Variability[9-11]

Peptide characteristics	• Large molecular weight • High polarity
DPP-4 resistance	• Alanine substitution at N-terminal position
Long vs. short acting agents	• Incorporate fatty acid conjugation using a linker or an IgG fragment crystallizable region

Pharmacokinetic Variability[9-11]

	Exenatide	Liraglutide	Dulaglutide	Semaglutide	Tirzepatide
Bioavailability	IR: rapid ER: gradual	~ 55%	47-65%	Subq: 89% Oral: 0.8%	~ 80%
Tmax	IR: ~2 h ER: weeks	~ 12 h	~ 48 h	Subq: 36-60 h	8-72 h
Half-life	~ 2.4 h	~ 13 h	~ 5 d	~ 7 d	~ 5 d
Volume of distribution	~ 28.3 L	11-24.7 L	17-19L	~ 12.5 L	~ 10.3 L
Clearance	9.1 L/h	~ 0.05 L/h	~ 0.1 L/h	~ 0.05 L/h	~ 0.061 L/h
Metabolism	Renal filtration + proteolysis	DPP-4 + neutral endopeptidase	General protein catabolism	Proteolysis +fatty acid oxidation	Peptide hydrolysis + β-oxidation

Assessment Question #1

Which of the following pharmacokinetic properties helps explain why some GLP-1 RAs are long-acting?

A. Rapid renal clearance
B. High lipophilicity
C. Fatty acid conjugation allowing albumin binding
D. Lack of DPP-4 resistance

Safety Consideration[12,13]

Category	Details
Common Adverse Effects	Nausea, vomiting, abdominal pain, diarrhea, dyspepsia, dizziness • Dose related
Contraindications	Type 1 diabetes, history of Medullary Thyroid Carcinoma, history of pancreatitis, severe gastrointestinal disease, pregnancy, breastfeeding
Warnings and Precautions	Acute pancreatitis, acute gallbladder disease, hypoglycemia, diabetic retinopathy complications
Black Box Warnings	Medullary Thyroid Cancer (Thyroid C-cell Tumors), Multiple Endocrine Neoplasia Syndrome Type 2
Perioperative Risks	Concerns about pulmonary aspiration in patients taking GLP-1 receptor agonists who undergo procedural sedation with or without general anesthesia • Discontinuation of short- acting GLP-1 RAs one day • Discontinuation of long-acting formulations at least 1 week before surgical procedures
Pharmacokinetic DDIs	Oral contraceptives, narrow therapeutic index drugs
Monitoring	Eye exam, renal function, mental health for mood disorders

Post-marketing Surveillance[14]

FDA warnings based on post-marketing surveillance data highlight several notable adverse events associated with GLP-1 RAs

- Hypersensitivity reactions
- Acute kidney injury related to volume depletion
- Severe gastrointestinal adverse reactions
- Acute gallbladder disease
- Alopecia
- Serious psychiatric adverse events, including reports of suicidal behavior or self-injury

FDA Requests Removal of Suicide Warning on GLP-1 RAs

Meta-analysis of 91 placebo-controlled trials (107,910 patients) found no signal linking GLP-1 RAs to SI/B[15]

A retrospective cohort study of over 2 million users and multiple observational analyses also showed no association

The review concluded that “the totality of these studies does not support a causal relationship between the use of GLP-1 RAs and the occurrence of SI/B”[16]

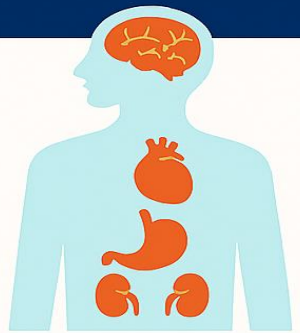
Assessment Question #2

Which adverse effect is responsible for the FDA boxed warning across all GLP-1 receptor agonists?

A. Acute pancreatitis
B. Medullary thyroid carcinoma
C. Severe hypoglycemia
D. Acute kidney injury

Pharmacokinetic DDIs Mediated by Mechanisms of Action GLP-1 RAs

RA Administration



Receptor activation in GLP-1 receptor-expressing organs

Physiological Changes

- Delayed gastric emptying
- Reduced motility
- Reduced fat mass
- Increased GFR and renal plasma flow

Pharmacokinetic Changes

- Slower absorption rate
- Decreased volume of distribution
- Modulation of CYP gene expression
- Faster renal clearance

Change in AUC and T_{max}

Image AI-generated by Daniela Miteva Kamceva, 2025, Microsoft Copilot

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GLP-1 Drug-Drug Interactions

Oral Contraceptives[9,17]

Reduced efficacy during initiation of tirzepatide or exenatide

- Reduced Cmax and AUC
- Recommendation: Backup non-oral contraceptive options for 4 weeks after initiation or dose increase of tirzepatide or exenatide

Levothyroxine[9,18]

Increased response with semaglutide

- Increased AUC
- Recommendations: Monitor for increased response when used with semaglutide[12]

Warfarin[9,19,20]

Not clinically significant DDIs

- Postmarketing: Data for exenatide include reports of elevated INR levels associated with bleeding
- Recommendation: Monitor INR closely after initiation of exenatide

New FDA Indications 2024

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New FDA Indications since 2024

CV Risk Reduction
Obstructive Sleep Apnea
Diabetes associated CKD
Metabolic dysfunction-associated steatohepatitis

Cardiovascular Risk Reduction SELECT – Trial[3,21]

Semaglutide (Wegovy™) has received FDA approval for reducing the risk of cardiovascular death, hearth attack, and stroke in adults with established cardiovascular disease and either obesity or overweight

March 2024

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Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563

Study design	Multicenter, double-blind, randomized, placebo-controlled, event-driven superiority trial
Intervention	1:1 ratio without stratification, to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo

Inclusion criteria	**Exclusion criteria**
• BMI ≥ 27 kg/m^2 • Established CV disease : • prior myocardial infarction • prior stroke • symptomatic peripheral arterial disease	• History of type 1 or type 2 diabetes • HbA1c ≥ 6.5 %

Primary outcome	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
Results	**20% relative risk reduction of Major Adverse Cardiovascular Events** • A primary cardiovascular end-point event occurred in 6.5% in the semaglutide group and in 8.0% in the placebo group • Hazard ratio=0.80 • P<0.001

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Mechanism Behind CV Risk Reduction[21]

Better glycemic control → lowers cardiometabolic risk

Weight loss → reduces atherosclerosis & hypertension risk

Improved lipids → decreases atherogenic burden

Anti-inflammatory effects → less vascular inflammation & oxidative stress

Endothelial stabilization → improved vascular tone & function

Obstructive Sleep Apnea
SURMOUNT –OSA Trial[2,22]

Tirzepatide (Zepbound™) FDA approved to treat moderate to severe OSA in adults with obesity

December 2024

ADVOCATE HEALTH

Malhotra A, Bednarik J, Chakladar S, et al. Tirzepatide for the treatment of obstructive sleep apnea: Rationale, design, and sample baseline characteristics of the SURMOUNT -OSA phase 3 trial. *Contemp Clin Trials*. 2024;141:107516. doi:10.1016/j.cct.2024.107516

Study design	Multicenter, randomized, parallel-arm, double-blind, placebo-controlled phase 3 study	
Randomization	Trial 1 • No PAP+ tirzepatide 10-15mg weekly • No PAP + placebo	Trial 2 • PAP + tirzepatide 10-15 mg weekly • PAP + placebo
Inclusion criteria	• Body mass index ≥30 kg/m^2 • Apnea-hypopnea index ≥15 events/hour	**Exclusion criteria** • CPAP • History of type 1 or 2 diabetes mellitus • Use of supplemental oxygen
Primary outcome	Change in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) from baseline	
Results	Trial 1- mean change in AHI at week 52 • **−25.3 events per hour with tirzepatide** • −5.3 events per hour with placebo • estimated treatment difference of −20.0 events per hour (P<0.001)	Trial2 –mean change in AHI at week 52 • **−29.3 events per hour with tirzepatide** • −5.5 events per hour with placebo • estimated treatment difference of −23.8 events per hour (P<0.001)

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How GLP-1 Receptor Agonists Contribute to OSA Improvement[22]

Weight Loss → Reduces upper-airway fat and mechanical load

Anti-Inflammatory Effects → Lowers systemic inflammation (e.g., hs-CRP)

Glycemic Control → Enhances insulin sensitivity and glucose regulation

Renal Benefits
FLOW – Trial[3,23]

Semaglutide (Ozempic™) approved to reduce the risk of sustained eGFR decline, end-stage kidney disease, and cardiovascular death in adults with T2D and CKD

January 2025

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Perkovic V, Tuttle KR, Rossing P, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *N Engl J Med*. 2024;391(2):109-121. doi:10.1056/NEJMoa2403347

Study design	International, double-blind, randomized, placebo-controlled trial
Intervention	1:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 1 mg or placebo

Inclusion criteria	**Exclusion criteria**
• T2DM with A1c ≤ 10% • Age ≥ 18 • eGFR 25-75 mL/min/1.73m^2 with albuminuria • On max tolerated ACEI/ARB	• Congenital or hereditary kidney diseases • Current (or within 90 days) chronic or intermittent hemodialysis or peritoneal dialysis

Primary outcome	Composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m^2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes.
Results	24% relative risk reduction of composite of kidney failure, sustained ≥50% decline in eGFR, or death from kidney/CV causes • 18.7% vs 23.2% over median 3.4-year f/u • HR 0.76 (95% CI 0.66-0.88), p< 0.0003

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Renal Benefits[23]

GLP-1 receptor agonists may directly benefit the kidneys by reducing:

- Inflammation
- Oxidative stress
- Fibrosis

Kidney and immune cells express the GLP-1 receptor

- Activation of these receptors decreases pro-inflammatory and pro-fibrotic signaling

MASH
ESSENCE – Trial[3,24]

Semaglutide (Wegovy™) had received FDA approval to treat metabolic-associated steatohepatitis in adults with moderate-to-advanced fibrosis

August 2025

ADVOCATE HEALTH

Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. *N Engl J Med*. 2025;392(21):2089-2099. doi:10.1056/NEJMoa2413258

Study design	Ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled trial
Intervention	2:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo in addition to standard care for MASH and related coexisting illnesses

Inclusion criteria	**Exclusion criteria**
• BMI ≥ 25 kg/m2 • Biopsy-confirmed MASH NAS ≥ 4 • Fibrosis stage F2 or F3 • Evidence of metabolic dysfunction	• Liver transplantation • HIV infection • Chronic liver disease other than NAFLD • Hepatic encephalopathy

Primary outcome	Resolution of steatohepatitis with no worsening of liver fibrosis after 72 weeks
Results	28.7% difference in resolution of MASH without worsening fibrosis • Resolution occur in 62.9% in semaglutide group vs 34.3% resolution rate in placebo • 95% CI 21.1-36.2 • P < 0.001

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Theoretical Mechanism[24,25]

Reduce liver fat accumulation by reducing fatty acid production via AMPK pathway

Anti-inflammatory effects by suppressing pro-inflammatory cytokines and reducing immune cell infiltration

Anti-fibrotic action through downregulation of fibrogenic gene expression

Assessment Question #3

According to the FLOW- Trial data, semaglutide were associated with which outcomes in patients with type 2 diabetes and chronic kidney disease (CKD)?

A. Reduced risk of liver fibrosis progression
B. Slower eGFR decline and reduced CV and all-cause mortality
C. Reversal of diabetic retinopathy
D. Increased hemoglobin levels

Expanded & Emerging Clinical Applications

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Neurodegenerative Diseases

GLP-1 Receptor Agonists and Alzheimer's Disease

- Growing evidence suggests that GLP-1 RAs may help reduce neuroinflammation, oxidative stress, and neuronal injury

Key Clinical Trials

- **EVOKE & EVOKE+ Trials[26]**
  - Investigating oral semaglutide with dose escalation:
    - 3 mg (weeks 0-4)
    - 7 mg (weeks 4-7)
    - 14 mg (weeks 8-156)
  - Planned 52-week extension phase of the trials discontinued
    - No significant cognitive benefits despite some biomarker improvements
- **ELAD Trial[27]**
  - Evaluating liraglutide 1.8 mg daily over 12 months
    - 50% less cortical brain volume loss compared with those in the control group

Neurodegenerative Diseases

GLP-1 RA and Parkinson's disease

- Potential to enhance autophagy, protect against mitochondrial stress, boost dopamine production, reduce neuronal loss and terminal denervation

Key Clinical Trials

- **Exenatide-PD3**[28]
  - Evaluating 2 mg exenatide weekly for 96 week
    - No evidence to support exenatide as a disease modifying treatment for patients with Parkinson's disease

- **The Lixi Park Trial**[29]
  - Lixisenatide 20 µg/day
    - Lixisenatide modestly reduced motor disability progression in patients with early Parkinson's disease

Substance Use Disorder[30-32]

- Suggests that GLP-1 agonists may reduce cravings in people with alcohol or opioid addiction

	Design	Objective	Intervention	Findings
Hendershot *et al.*, 2025	Phase 2, double-blind, randomized, parallel-arm trial	To evaluate the effects of once-weekly subcutaneous semaglutide on alcohol consumption and craving in adults with alcohol use disorder	Semaglutide (0.25 mg/week for 4 weeks, 0.5 mg/week for 4 weeks, and 1.0 mg for 1 week)	Significantly reduced drinks per drinking day (P = .04) and weekly alcohol craving (P = .01).Also predicting greater reductions in heavy drinking over time relative to placebo (P = .04)
Qeadan *et al.*, 2025	Retrospective cohort study	To assess the association between GLP-1 RA prescriptions and the risk of opioid overdose or alcohol intoxication among patients with OUD or AUD	Study analyzed de-identified electronic health record data from the Oracle Cerner Real-World Data	Patients with GLP-1 RA prescriptions had lower opioid overdose rates versus those without, with a 95% CI of 0.43–0.63
Wang *et al.*, 2024	Retrospective cohort study	To evaluate whether semaglutide is associated with lower rates of opioid overdose among patients with type 2 diabetes and opioid use disorder	Study analyzed electronic health records through TriNetX Analytics Platform	Semaglutide was associated with a significantly lower risk of opioid overdose during a 1-year follow-up compared with other antidiabetic medications, including other GLP-1RAs. HR range: 0.32-0.58

Cancer Risk Reduction[33]

Observational data shows that GLP-1 therapies might reduce obesity-related cancers

- Colon, rectum, gastric, and postmenopausal breast cancers

Key Clinical Study

- Effects of semaglutide on the antitumor immunity in a 4T1 mouse breast cancer model
  - Semaglutide slowed tumor growth progression in mice
  - Increase in immune response in lab models-increase in dendritic cells, reduce regulatory T-Cell response

Assessment Question #4

Which potential mechanism explains why GLP 1 receptor agonists are being studied for Alzheimer's disease?

A. Block neurotransmitter release in the hippocampus, reducing synaptic activity

B. Reduce neuroinflammation, oxidative stress, and neuronal injury, offering possible neuroprotective benefits

C. Enhance gastric emptying, increasing nutrient delivery to the brain

D. Selectively inhibit amyloid beta production through direct enzymatic action

Summary

1. GLP-1 receptor agonists provide significant clinical benefits across diabetes, obesity, and cardiometabolic conditions
2. Overall, key safety considerations center on gastrointestinal effects, potential gallbladder complications, renal risks, and the rare but noteworthy warning for thyroid C-cell tumors
3. With expanding indications and growing evidence, GLP 1 agents continue to reshape modern management of metabolic and cardiovascular disease, and emerging data suggest benefits that extend beyond these areas highlighting the need for continued research

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Questions?

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