Promising Potentials of GLP1-RA's

Michelle Lazaro Miller, PharmD
MG Hornick, PhD

Roosevelt University, College of science, Health, and Pharmacy

Disclosures and Conflict of Interest

Michelle Lazaro Miller and MG Hornick declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings and honoraria.

Disclosure of AI Use

ChatGPT 4.0 was utilized to assist with the generation of tables, visual aids, content refinement, and reference organization throughout this presentation. July 4 2025.

Pharmacist Objectives

At the conclusion of this program, the pharmacist will be able to:

1. Discuss the clinical evidence supporting the off-label use of GLP-1 RA medications in conditions beyond diabetes and weight management
2. Describe the potential impact of GLP-1 RA's on evolving treatment strategies and their role in expanding therapeutic options across multiple medical conditions
3. List examples of how GLP-1 RA's are being studied for conditions beyond diabetes and weight management

Technician Objectives

At the conclusion of this program, the pharmacy technician will be able to:

- Identify conditions other than diabetes and weight management, for which GLP-1 receptor agonists may be used or studied
- List all current GLP1-RA's on the market
- Recognize when a patient may need to be referred to the pharmacist or physician for an adverse drug reaction

Which of the following conditions currently has the strongest evidence supporting the use of GLP-1 receptor agonists?

A. Rheumatoid arthritis
B. Asthma
C. Alcohol use disorder
D. Cardiovascular disease

Pre-Test Questions

True or False:

Liraglutide, dulaglutide, and semaglutide are FDA-approved to lower the risk of heart attack or stroke in certain adults.

Pre-Test Questions

Which condition is currently under investigation for potential benefit with GLP-1 RAs but does not have an FDA-approved indication?

A. Alcohol use disorder
B. Alzheimer's disease
C. Rheumatoid arthritis
D. All of the above

Pre-Test Questions

Promising Potentials of GLP1-RA's

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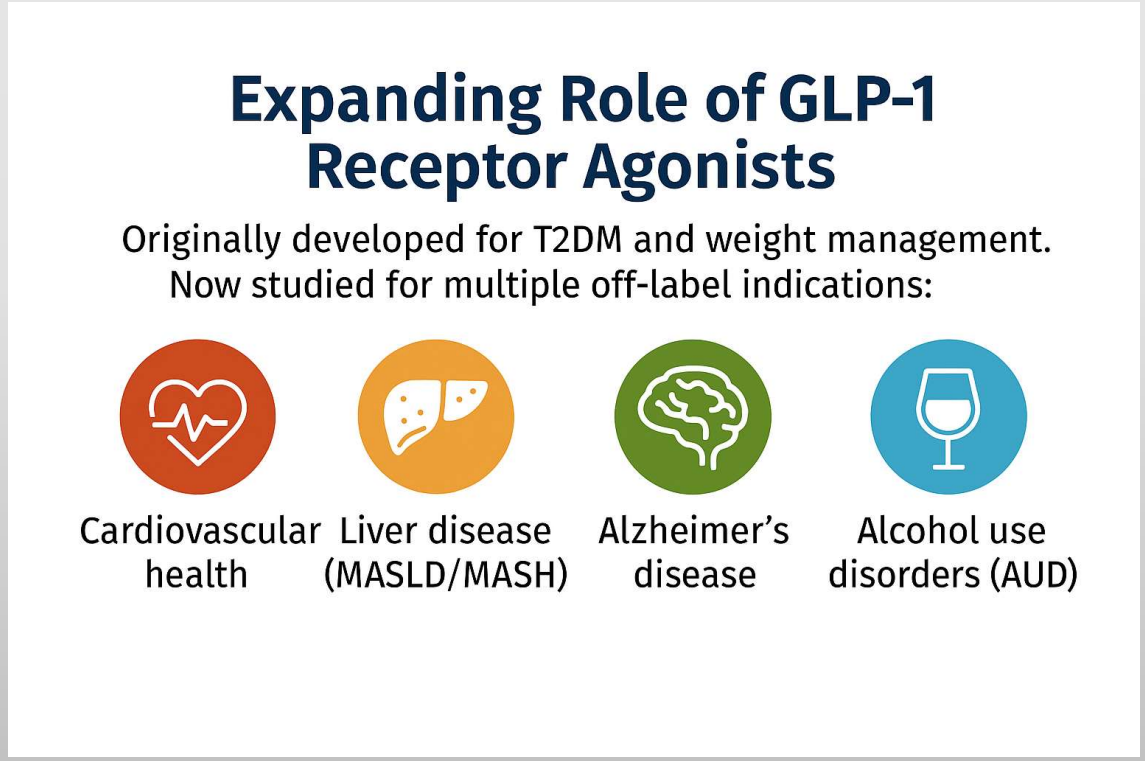
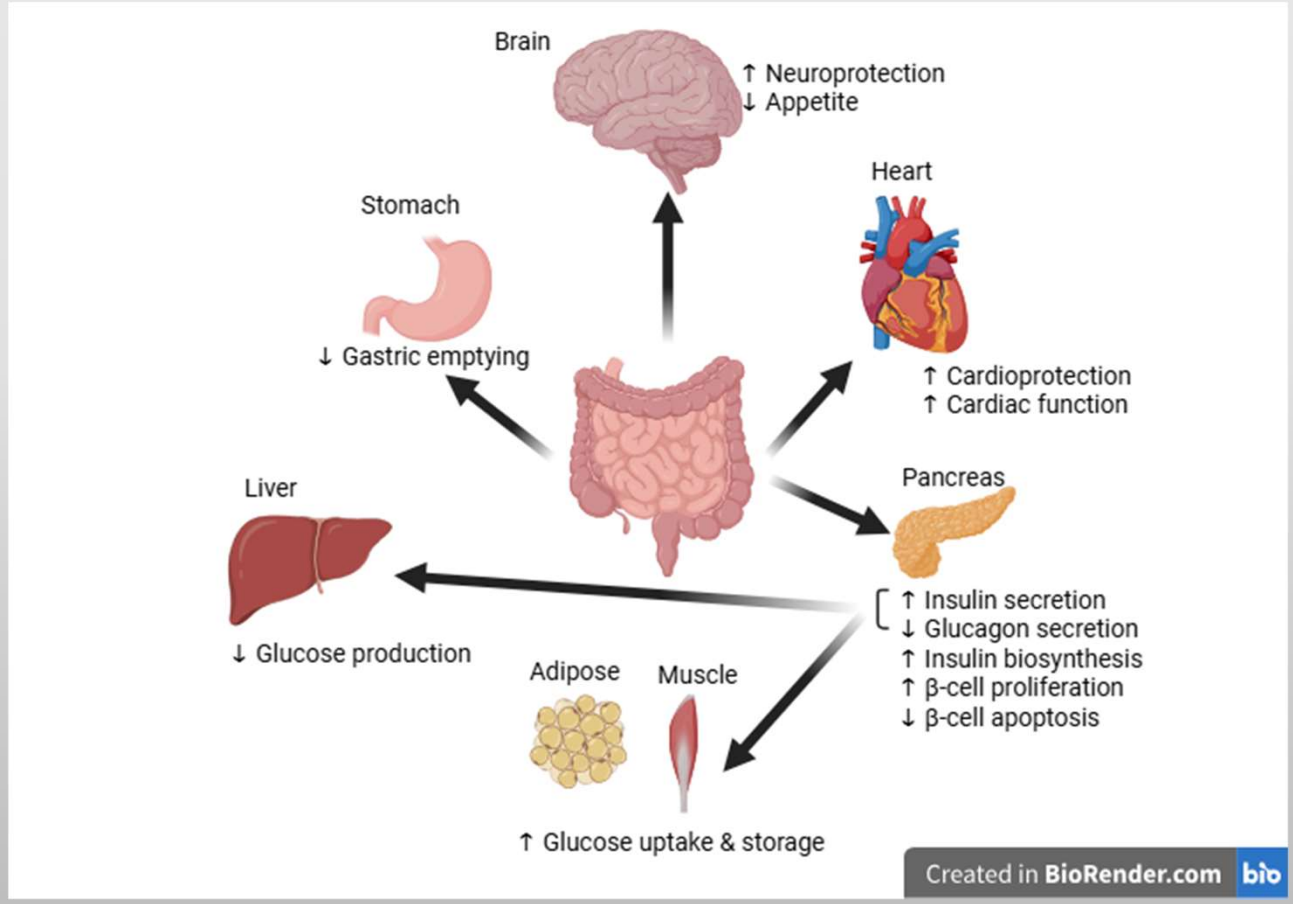
Expanding Role of GLP-1 Receptor Agonists



Overview of GLP-1 Activity



Diabetes – Perspectives in Drug Therapy.

Mechanism of Action

- Glucagon-like Peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Polypeptide (GIP) are incretin hormones inactivated by dipeptidyl peptidase-4 (DPP-4)
- GLP-1 receptor agonists stimulate insulin secretion after an oral glucose load

StatPearls. 2024. Glucagon-Like Peptide-1 Receptor Agonists..

Other effects of GLP—RA's

- Delays gastric emptying
- Inhibits glucagon production from pancreatic α cells
- Decreases pancreatic β cell apoptosis; promotes β cell proliferation
- Lowers SBP & DBP along with total cholesterol
- Improves left ventricular ejection fraction, myocardial contractility, coronary blood flow, cardiac output & endothelial function
- Increases glucose uptake in muscles and adipose tissue
- Decreases glucose production in the liver
- Increases satiety in the hypothalamus
- Improves neurovascular function, reduces inflammation, enhances neuronal survival, promotes neurogenesis & synaptic plasticity

StatPearls. 2024. Glucagon-Like Peptide-1 Receptor Agonists..

Pharmacokinetics

- Subcutaneous administration → rapid absorption & peak concentration in hours
- Oral administration → GI absorption; first pass metabolism
- Low volume of distribution, mainly remaining in bloodstream but with an affinity for pancreatic cells and other metabolic control sites
- Undergoes primary metabolism in kidneys & liver via hydrolysis (exenatide) or proteolytic cleavage in various tissues via DPP-4 and other enzymes (liraglutide, semaglutide)
- Excreted in urine as smaller, inactive fragments

StatPearls. 2024. Glucagon-Like Peptide-1 Receptor Agonists..

Adverse Effects & Contraindications

- Adverse Effects: nausea/vomiting, diarrhea/constipation, dizziness, mild tachycardia, headaches, dyspepsia, injection site reactions
- Contraindications:
  - Hypersensitivity
  - Pregnancy
  - Severe GI disorders (gastroparesis, inflammatory bowel disease)
  - Personal/family history of multiple endocrine neoplasia 2 (MEN 2A), multiple endocrine neoplasia 2B (MEN 2B), or medullary thyroid cancer
  - Pancreatitis
  - Severe renal dysfunction

Caution should be used with regard to compounded GLP-1 formulations

StatPearls. 2024. Glucagon-Like Peptide-1 Receptor Agonists..

Cardiovascular Benefits

Cardiovascular Disease

- Cardiovascular disease (CVD) is the leading cause of death in people with type 2 diabetes mellitus (T2DM)
- ADA and ACC/AHA now prioritize glucose-lowering agents with demonstrated cardiovascular benefit
- Insulin resistance, inflammation, endothelial dysfunction, and dyslipidemia contribute to atherosclerotic cardiovascular disease (ASCVD)

Front. Clin. 2023; 4:1293926: 1-6

GLP1-RA's and Cardiovascular Benefits

- Cardioprotective in that they reduce inflammation, oxidative stress, and endothelial dysfunction
- Improve lipid profiles and promote weight loss and blood pressure reduction
- Demonstrated a class-wide cardiovascular benefits, consistently reducing cardiovascular risk in patients with type 2 diabetes
- Decrease in 3-point MACE: Major Adverse Cardiovascular Events (CV death, nonfatal MI, nonfatal stroke)

Front. Clin. 2023; 4:1293926: 1-6

Liraglutide-LEADER Trial 2016

- Included 9,340 patients with T2DM and established cardiovascular disease, high CV risk or chronic kidney disease
- Liraglutide reduced MACE by 13% compared to placebo
- Significant reduction in cardiovascular death
- Improved glycemic control, contributes to weight loss and lower blood pressure, delayed progression atherosclerosis via anti-inflammatory pathways
- Additional benefits included decreased nephropathy events

*N Engl J Med.*2016: 375(4):311–22.

Semaglutide-SUSTAIN-6 Trial 2016

- Included 3297 patients with T2DM,established cardiovascular, disease or high CV risk
- Reduced MACE by 26%
- Statistically significant reduction in nonfatal stroke
- Promotes weight loss and reduction in systolic blood pressure
- No increase in heart failure hospitalization
- Potential benefit in heart failure with preserved ejection fraction (HFpEF) is under investigation

N Engl J Med (2016) 375(19):1834–44

Dulaglutide- REWIND Trial 2019

- 9,901 patients with T2DM, only 31% with prior cardiovascular disease
- Most preventive-focused trial among GLP-1 RA cardiovascular outcomes trials
- Long trial duration, 5.4 years
- Decrease the risk of MACE by 12%
- Consistent across subgroups, including patients without established ASCVD
- Promotes modest weight loss and reduction in blood pressure
- No increase in hospitalization for heart failure
- Slowed progression of albuminuria, suggests possible renal benefit

Lancet. 2019; 394(10193):121–30

Tirzepatide vs Dulaglutide SURPASS-CVOT Trial 2025

- GIP/GLP dual agonist
- Not yet FDA-approved for cardiovascular outcomes yet, Lilly plans to submit by end of 2025
- Phase 3, non-inferiority randomized controlled trial comparing tirzepatide with dulaglutide for safety and efficacy
- First GLP1 head-to-head cardiovascular outcomes study
- 4.5 years, longest and largest study of tirzepatide

Eli Lilly and Co. News Release July 31, 2025

Tirzepatide vs Dulaglutide SURPASS-CVOT Trial 2025 (cont'd)

- 13, 299 patients with T2DM, established atherosclerotic disease, HbA1c ≥7% to ≤10.5%, and body mass index ≥25
- Demonstrated a non-inferior rate of MACE including cardiovascular death, heart attack or stroke compared to dulaglutide
  - 8% lower for tirzepatide than dulaglutide
- Improved A1C, weight, renal function, and all-cause mortality

Eli Lilly and Co. News Release July 31, 2025

Cardiovascular Trial Summary

Trial	Agent	Population	Primary Outcome	Result	Notes
LEADER	Liraglutide	T2DM + high CV risk	3-point MACE	↓13% vs placebo	Reduced CV death
SUSTAIN-6	Semaglutide	T2DM + high CV risk	3-point MACE	↓26% vs placebo	Significant stroke reduction
REWIND	Dulaglutide	T2DM, 31% with prior CV events	3-point MACE	↓12% vs placebo	Effective in primary and secondary prevention
SURPASS-CVOT	Tirzepatide*	T2DM + established CV	3-point MACE + kidney outcomes, reduced overall death	↓8% vs dulaglutide	Non-inferior to dulaglutide

N Engl J Med 2016: 375(19):1834–44
Lancet. 2019; 394(10193):121–30
N Engl J Med.2016: 375(4):311–22.
Eli Lilly and Co. News Release July 31, 2025

*Not FDA approved

Obstructive Sleep Apnea and Cardiovascular Disease

- OSA is defined by a 4% desaturation hypopnea threshold
- In the US, approximately 17% of women and 34% of men have mild OSA, and 6% of women and 13% of men with moderate–severe OSA
- Obesity is a major risk factor; mechanisms likely include excess fat in upper-airway structures (ex: tongue fat) that promotes collapsibility
- OSA is an atherosclerotic cardiovascular disease risk factor
- Weight loss is disease-modifying for many patients, but sustained loss via lifestyle change alone is difficult in practice

Contemp Clin Trials. 2024

Tirzepatide-SURMOUNT-OSA Trial 2024

- Phase 3, placebo controlled, 52 week, randomized controlled trial evaluating safety and efficacy of tirzepatide for obstructive sleep apnea(OSA) and obesity
- 469 patients with moderate to severe OSA (Apnea Hypopnea Index (AHI) of ≥15 events/hour,) BMI≥30, T2DM excluded
- Two arms: patients with and without use of positive airway pressure(PAP)
- Each arm reported: 42-50% reductions in AHI and 18-20% reduction of body weight

N Engl J Med. 2024 Oct 3;391(13):1193-1205

Semaglutide-STRIDE 2025

- Phase 3b, double-blind, randomized, placebo-controlled trial
- 1363 patients with T2DM and Peripheral Artery Disease (PAD) with intermittent claudication
- Maximum walking distance from baseline was significantly greater in the semaglutide group than the placebo group

Lancet. 2025;405(10489):1580-1593

Potential Benefits for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

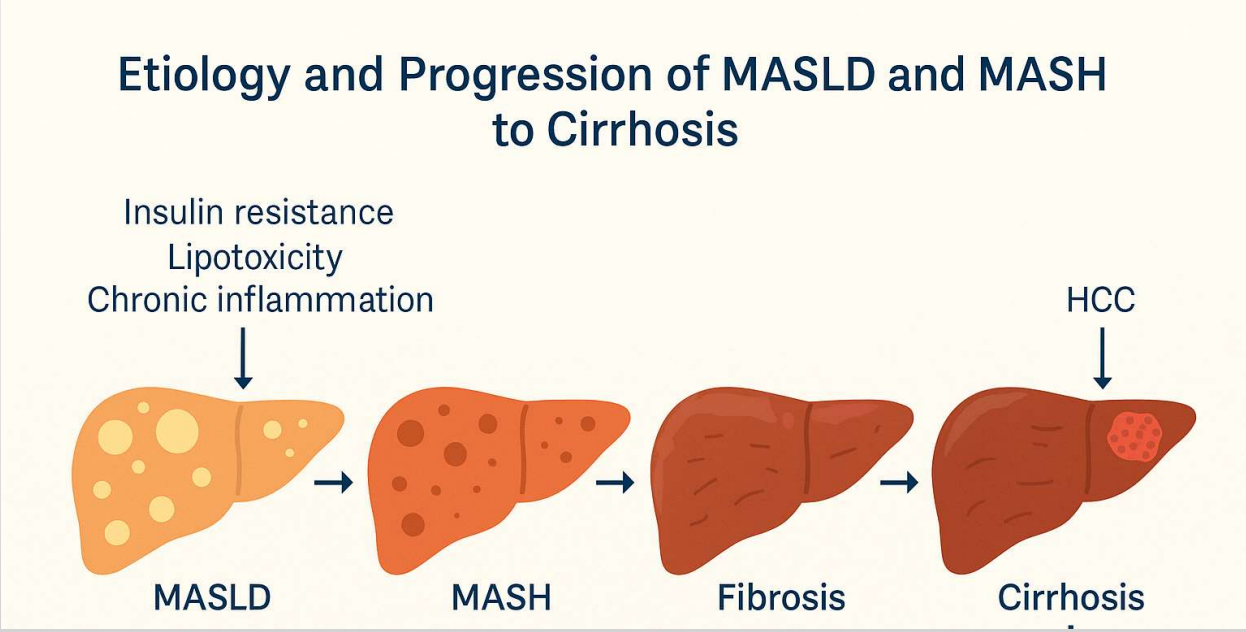
Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

- MASLD, formerly referred to as non-alcoholic fatty liver disease (NAFLD), is a reclassification of the condition
  - Defined as: Hepatic steatosis in individuals with ≥1 cardiometabolic risk factor in the absence of harmful alcohol intake
- MASLD includes steatosis linked to obesity, hypertension, T2DM, or dyslipidemia
- Affects over 30% of the global population and is a leading cause of chronic liver disease
- GLP-1 RAs are under investigation for therapeutic benefit in MASLD due to their anti-inflammatory and weight-reducing effects

Int. J. Mol. 2025;26(7):2959

MASH vs. MASLD

- MASH or metabolic-dysfunction associated steatohepatitis is a progressive form of MASLD characterized by inflammation and further liver damage
- The stage at which steatosis transitions into active disease with risk for fibrosis and cirrhosis
- Up to 1/3 of patients with MASLD progress to MASH



Int. J. Mol. 2025;26(7):2959

Relationship Between MASLD/MASH and Type 2 Diabetes Mellitus

- 65% of T2DM patients have MASLD
  - 14% have advanced fibrosis, and 6% have cirrhosis
  - GLP-1 RAs improve insulin sensitivity and hepatic outcomes-potential dual-benefit therapy
- Hyperglycemia and insulin resistance drive hepatic inflammation and fibrogenesis
- MASLD risk in patients should be monitored with uncontrolled T2DM

Int. J. Mol. 2025;26(7):2959

Semaglutide in MASH-Phase 3 ESSENCE Trial Findings 2025

- Randomized, double-blind, placebo-controlled study
- 72-week interim analysis of 1197 patients with biopsy-confirmed MASH and fibrosis stages 2-3
- MASH resolution: 62.9% (semaglutide) vs. 34.3% (placebo)
- Fibrosis improvement (≥1 stage): 36.8% vs. 22.4%
- Weight loss: decrease of 10.5% vs. 2.0%

N Engl J Med. 2025;392(21):2089-2099.

Semaglutide in MASH-Phase 3 ESSENCE Trial Findings 2025

- Semaglutide (Wegovy 2.4mg) was FDA approved August 15th, 2025, under accelerated approval based on improvement of MASH and fibrosis
- Ongoing approval for this indication depends on confirmation and clear demonstration of clinical benefit in a follow-up trial

US Food and Drug Administration

Tirzepatide in MASH – SYNERGY-NASH Trial Findings 2024

- Tirzepatide is a dual GIP/GLP-1 agonist approved for T2DM and obesity
- SYNERGY-NASH trial: 52-week biopsy-confirmed MASH
- MASH resolution: 44% (5 mg), 56% (10 mg), 62% (15 mg) vs. 10% (placebo)
- Fibrosis improvement (≥1 stage): 51–55% vs. 30% (placebo)
- No worsening of fibrosis or steatohepatitis with tirzepatide
- Safety in cirrhosis not yet assessed, future studies needed

N Engl J Med. 2024;391(4):299-310

Comparison of Semaglutide vs Tirzepatide in MASH

Agent	Trial Name	Trial Phase	MASH Resolution	Fibrosis Improvement (≥1 stage)	Weight Loss	Evidence in Cirrhosis	Outcomes Summary
Semaglutide (Wegovy)	ESSENCE	Phase 3	62.9%	36.8%	−10.5%	Limited	Significant histologic benefit, FDA approved
Tirzepatide	SYNERGY-NASH	Phase 2b	44–62% (dose-dependent)	51–55%	Up to 15%	Limited	Greater metabolic impact; promising fibrosis reversal

N Engl J Med. 2025;392(21):2089-2099.
N Engl J Med. 2024;391(4):299-310.

Potential Benefits for Alzheimer's Disease (AD)

GLP1-RA's and Alzheimer's Benefits

- T2DM is an independent risk factor for cognitive decline and AD
- GLP-1 receptors are expressed in the brain, particularly in regions associated with memory and learning
- Limited pharmacologic options to prevent progression of mild cognitive impairment and AD

J Alzheimers Dis Rep. 2025;9:25424823251342182

GLP1-RA MOA in Alzheimer's Disease

- Neuroprotective pathways:
  - Decreases neuroinflammation and oxidative stress
  - Increases synaptic plasticity and neurogenesis
- Preclinical studies show reduced amyloid-beta plaques and tau phosphorylation
- Improves cerebrovascular function
  - Insulin signaling in the brain
  - Mitochondrial health

J Alzheimers Dis Rep. 2025;9:25424823251342182

Dulaglutide and Cognitive Outcomes – REWIND Trial 2020

- Exploratory analysis
- 8,828 with cognitive testing (Montreal Cognitive Assessment and Digit Symbol Substitution Test) at baseline and follow-up
- 14% decreased risk of cognitive impairment after baseline score adjustment

Lancet Neurol. 2020;19(7):582-590.

Meta-Analysis 2024

- Objective: To evaluate the efficacy of GLP-1 RAs on cognitive outcomes in Alzheimer's and mild cognitive impairment
- Included studies: 10 randomized controlled trials (RCTs) with 823 patients

JAMA Neurol. 2025;82(5):450-460.

Meta-Analysis Highlights

- GLP-1 RAs showed statistically significant improvement in:
    - Mini-Mental State Examination
    - Alzheimer's Disease Assessment Scale-Cognitive Subscale
- Best outcomes were observed in early AD and mild cognitive impairment subgroups
- Semaglutide and liraglutide most studied and both demonstrated consistent benefit

JAMA Neurol. 2025;82(5):450-460.

Oral Semaglutide and Alzheimer's Disease – EVOKE and EVOKE+ Trials, 2021

- 1840 patients with early-stage symptomatic AD
  - EVOKE+ allowed pts with evidence of small vessel pathology
- On-going phase 3, randomized, double-blind, placebo controlled, parallel group, 104-weeks with a 52-week sub-study
  - Sub-study will be examining cerebrospinal fluid biomarkers
- Completion of main phase study 2025, 52-week extension expected in October 2026

Alzheimers Res Ther. 2025;17(1):14

GLP1-RA's and Alzheimer's Disease Summary

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Study	Agent	Population	Design	Primary Outcome	Status
REWIND Cognitive Substudy	Dulaglutide	T2DM patients, no dementia	Exploratory in CVOT (Phase 3)	Cognitive composite decline	14% ↓ risk (adjusted), trend toward protection
Meta-Analysis (2024)	Multiple GLP-1RAs	Alzheimer's disease & Mild Cognitive Impairment (RCTs pooled)	Systematic review + meta-analysis	Global cognition, Mini-Mental State Examination, Alzheimer's Disease Cognitive Assessment	Improved cognitive scores across trials, strongest benefit in early disease stages
EVOKE	Semaglutide (oral)	Early-stage AD	Phase 3, RCT	Change in Clinical Dementia rating	Ongoing
EVOKE+	Semaglutide (oral)	Early-stage AD with small vessel pathology	Phase 3, RCT	Change in Clinical Dementia rating	Ongoing

Lancet Neurol. 2020;19(7):582-590.
JAMA Neurol. 2025;82(5):450-460.
Alzheimers Res Ther. 2025;17(1):14.

Potential Benefits for Alcohol Use Disorder (AUD)

Alcohol Use Disorder (AUD)

- 16.7% of Americans aged 12 and older have experienced a substance use disorder in the past year
- Proposed site of action: GLP-1 receptors are located in reward-related brain regions
  - Pathways in this region are responsible for addictive behavior, craving, and reinforcement of substance use
  - Receptor agonists can disrupt the pathway
- AUD limited pharmacologic options

Substance Abuse and Mental Health Services Administration. 2023.
Pharmacol Res. 2024;207:107312.

GLP1-RA's and AUD

- Neuroendocrine action:
  - GLP-1 binds to receptors in CNS reward centers, reducing mesolimbic dopamine signaling
  - Alters reward anticipation and consumption behaviors, thereby reducing cravings
- Effects demonstrated in alcohol, nicotine, opioids, and stimulants in preclinical models
- Limited clinical trials
- Potential benefits with nicotine, cocaine, opioid, and stimulant

Pharmacol Res. 2024;207:107312

Effects of Dulaglutide on Alcohol Consumption During Smoking Cessation, 2023

- Randomized placebo-controlled trial comparing dulaglutide vs placebo
- 114 adults undergoing smoking cessation with baseline alcohol use
- Primary outcome: Change in alcohol consumption (AUDIT-C score; drinks per week)
- 25% reduction in drinks/week vs placebo
- 1.2 fewer binge episodes/month vs placebo
- Dulaglutide significantly reduced alcohol consumption and binge episodes, larger confirmatory studies are needed

JCI Insight. 2023;8(22):e170419

Preclinical and Observational Evidence Supporting GLP-1RA's in AUD 2024

- Rodent studies: Decreased voluntary alcohol intake and reduced reward-seeking behavior
- Lower alcohol consumption and cravings reported in non-AUD populations taking semaglutide
- Cross-substance findings: Similar benefits observed in models of nicotine, cocaine, opioid, and stimulant use

Pharmacol Res. 2024;207:107312

Once-Weekly Semaglutide in Adults With Alcohol Use Disorder, 2025

- Phase 2, randomized, double-blind, placebo-controlled (2025)
- 48 adults with moderate–severe AUD, 71% female
- Semaglutide titrated to 1.0 mg over 9 weeks
- Reduced alcohol craving, fewer heavy-drinking days, and fewer drinks per drinking day
- Reduced cigarette use and weight loss
- Supports the need for larger clinical studies

JAMA Psychiatry. 2024

Summary

- Limited clinical trials
- Trial expansion:
  - Larger trials are underway to test semaglutide and liraglutide in AUD, smoking cessation, and polysubstance use
- Tirzepatide:
  - Investigational potential due to dual GLP-1/GIP action
  - Early evidence supports benefit in reducing alcohol intake

Trials in Progress

- Semaglutide for AUD: dose-ranging to examine effects on alcohol use
- Semaglutide Therapy for Alcohol Reduction(STAR): safety, tolerability, alcohol reduction.
- Semaglutide Therapy for Alcohol Reduction (STAR-T): safety and alcohol reduction in patients with AUD
- Tirzepatide for AUD (dual GIP/GLP-1): Alcohol reduction in patients with AUD and schizophrenia

ClinicalTrials.gov

Conclusions

- GLP-1RAs consistently reduce major heart-related events across several large studies
- Semaglutide and tirzepatide show promise in treating MASH by reducing liver damage and inflammation
- GLP1-RA's have been shown to slow memory loss in early Alzheimer's and mild cognitive issues
- Early studies suggest GLP1-RA's may reduce alcohol and cigarette use, possibly by affecting the brain's reward system although more research is needed

On the Horizon

- New indications: gastrointestinal disorders, Parkinson's disease, polycystic ovary syndrome
- New agonists
- Combination therapy
- Additional oral formulations
- Multi-agonists

Discussion

What have you heard about alternative uses of GLP1-RA's in your practice?

What has your experience been?

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Thank you

Michelle Lazaro Miller, PharmD
mlazaromiller@Roosevelt.edu

MG Hornick, PhD
mhornick02@Roosevelt.edu