Effect of Glucagon-Like Peptide-1 (GLP-1) Agonists on Pain & Addiction

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Use of GLP-1 Agonists for Treating Substance Use Disorders and Behavioral Addiction

What is GLP-1? Where is it made?

- Glucagon-like peptide-1 is a natural hormone produced in the intestinal L-cells of the ileum and colon in response to food intake
- GLP-1 is produced to a smaller degree by the pancreatic alpha cells
- GLP-1 is also made in the brain in the nucleus of the solitary tract, and plays a role in regulating appetite and metabolism

When is GLP-1 released?

- GLP is released with 10-15 minutes after eating a meal with high levels of glucose, fat, or protein.
- GLP-1 remains elevated for several hours after eating

What does GLP-1 do?

- Stimulates insulin secretion from pancreas to lower blood sugar levels
- Slows gastric emptying from the stomach into the intestines. This reduces hunger and **increases satiety**, leading to weight loss
- GLP=1 has been shown to reduce risk of heart attacks, strokes, kidney damage
- GLP-1 receptor agonists mimic the effect of the natural hormone GLP-1, by binding to the same receptors

What are the common GLP-1 receptor agonist medications?

- Semaglutide (Ozempic and Wegovy)
- Tirzepatide (Mounjaro and Zepbound)
- Dulaglutide (Trulicity)
- Liraglutide (Victoza and Saxenda)

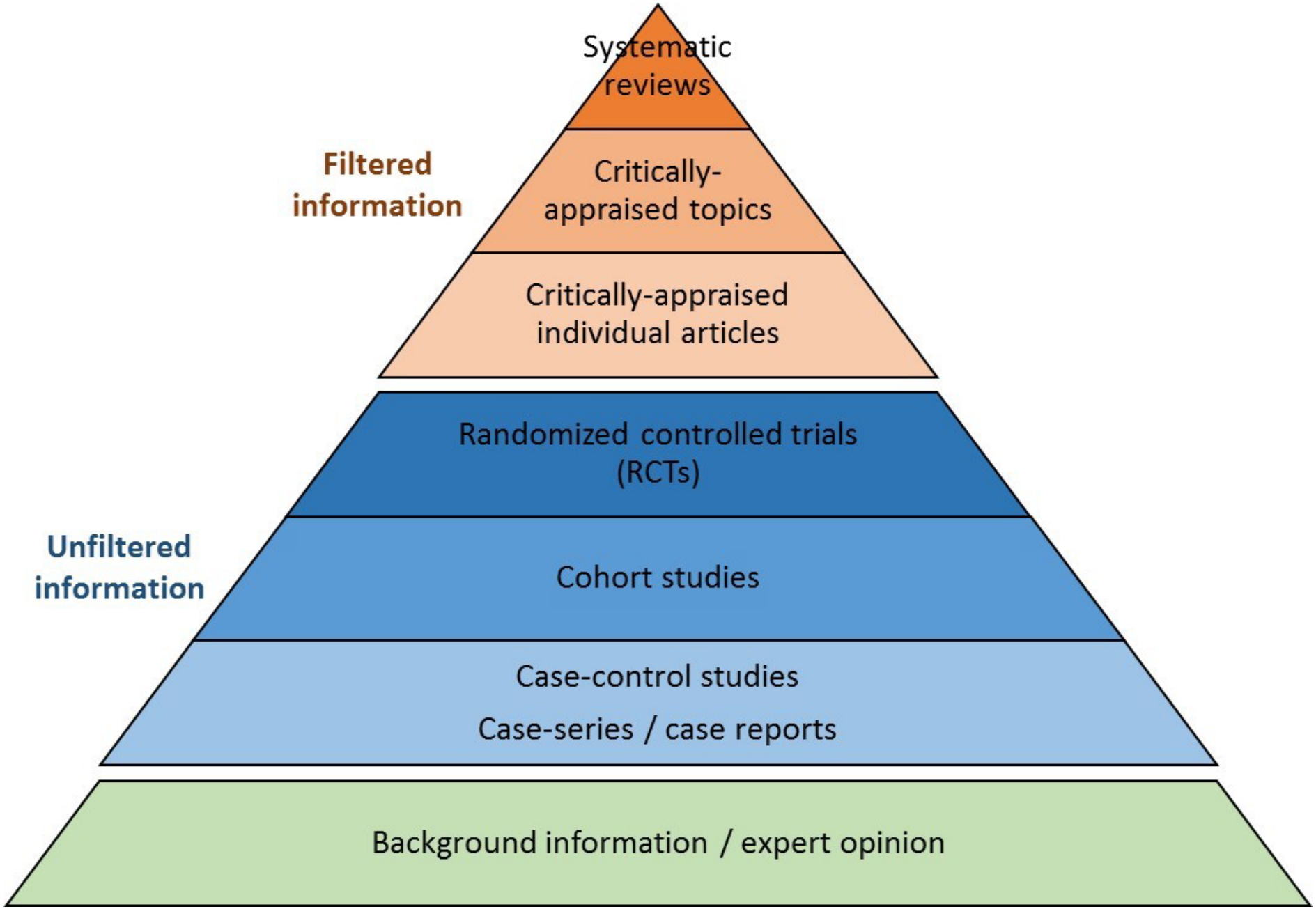
What are the FDA approved indications for GLP-1 agonists?

- Type II Diabetes Mellitus
- Chronic weight management
- Tirzepatide (Zepbound) received FDA approval to treat moderate to severe obstructive sleep apnea in December 2024
- Semaglutide (Ozempic) received FDA-approval for treatment of diabetic nephropathy in January 2025

Novel Directions

- Semaglutide was linked with a significant reduction if risk of Alzheimer's disease in patients with Type 2 diabetes of 40-70%, and Novo is running two phase III trials testing this, with results expected later this year
- Increasing interest in using GLP-1 agonists in psychiatry and addiction medicine

1. Obesity and addiction could potentially share dysregulated dopaminergic pathways, leading to heightened sensitivity to rewards and impaired self-control and stress-reactivity
    a. Patients report suggest that GLP-1 is blunting the pleasure response across the board, and many patients report less desire to drink or smoke after starting GLP-1 agonists. This could be related to the dopamine signaling pathway in the nucleus accumbens.
2. In December 2024, Eli Lilly CEO David Ricks stated that they will start studying Zepbound as a treatment for alcohol and drug addiction. He stated “These medications may be called anti-hedonics, aiming to reduce the desire cycle”. (Endpoint News)
3. Novo Nordisk stated in March 2025 that they have an ongoing Phase II trial including Semaglutide in patients with alcoholic liver disease with a primary endpoint of treating liver damage and a secondary endpoint of alcohol consumption. (Biospace)


Systematic reviews
Filtered information
Critically-appraised topics
Critically-appraised individual articles
Randomized controlled trials (RCTs)
Unfiltered information
Cohort studies
Case-control studies
Case-series / case reports
Background information / expert opinion

Review

Potential role of glucagon-like peptide-1 (GLP-1) receptor agonists in substance use disorder: A systematic review of randomized trials

Silvia Martinelli [a,b], Alessandro Mazzotta [c], Mattia Longaroni [d], Niccolò Petrucciani [e,*]

Therapeutic effect of GLP-1RA on SUD was assessed **in 5 studies**, with 3 demonstrating a significant decrease in SUD (alcohol and nicotine).

November 2024

Table 1
Design and characteristics of the included studies.

References	Country	Inclusion period	Design	Purpose of the study	Nature and size of the sample	Measurement tool
Yammine, 2021	US	2016–2019	RCT	Effect of GLP−1Ra treatment on tobacco use	82 tobacco smokers included: 41 placebo; 41 GLP−1RA	Medical examination
Angarita, 2021	US	2014–2018	RCTdb	Effect of GLP−1Ra treatment on cocaine use	13 patients with cocaine use disorder	Self-report assessment; DSM−5; urine screening of drugs
Klausen, 2022	Denmark	2017–2019	RCTdb	Effect of GLP−1Ra treatment on alcohol use	127 patients with alcohol use disorder included: 65 placebo; 62 GLP−1RA	AUDIT; CIWA-Ar; ICD−10; DSM−5
Probst, 2023	Switzerland	2017–2022	RCT	Effect of GLP−1Ra treatment on alcohol use	151 patients with alcohol use included: 75 placebo; 76 GLP−1RA	Medical examination; assessment of median and IQR of alcohol consumption
Lengsfeld, 2023	Switzerland	2017–2020	RCTdb	Effect of GLP−1Ra treatment on tobacco use	255 patients with tobacco use included: 128 placebo; 127 GLP−1RA	Fagerstroem test

RCT: Randomized placebo controlled clinical trial
RCTdb: Randomized, double-blind, placebo controlled clinical trial
GLP-1RA: Glucagon-like peptide-1 Receptor Agonist
IQR: interquartile range

Table 3
Patients' characteristics and type of GLP-1Ra treatment.

Author	Age*	Female sex, n (%)	BMI*	Psychiatric comorbidities*	Higher Education, n (%)	Type of GLP-1Ra treatment
Yammine, 2021	51.1(9.2) tot; 51 (9.1) placebo; 51.2 (9.4) GLP−1RA	25(30.5) tot; 13(31.7) placebo; 12(29.3) GLP−1RA	NA	8.5(6.1) tot; 8.3(6.4) placebo; 8.6(5.9) GLP−1RA	5(6.1) tot; 2(4.9) placebo; 3(7.3) GLP−1RA	EXENATIDE (2 mg sc, once a week for 6 weeks)
Angarita, 2021	45±7 tot	1 (7.7 %)	28±4	NA	12±1* tot (years of education)	EXENATIDE (5 mcg sc – 3 h before cocaine self administration)
Klausen, 2022	52.5 (10) placebo; 52.1(10.8) GLP−1RA	26 (40) placebo; 25(40.3) GLP−1RA	26.7(4.6) placebo; 26.7(5.2) GLP−1RA	NA	32 (50) placebo; 26(41.9) GLP−1RA	EXENATIDE (2 mg sc, once a week for 26 weeks)
Probst, 2023	42 (33-53)** tot; 43(33–51.5)** placebo; 41(33–54.2)** GLP−1RA	92(60.9) tot; 41(54.7) placebo; 51(67.1) GLP−1RA	#119(90.8)*** tot; #60[87]*** placebo; #59(95.2)*** GLP−1RA	44(29.1) tot; 20(26.7) placebo; 24(31.6) GLP−1RA	74 (49) tot; 30 (40) placebo; 44(57.9) GLP−1RA	DULAGLUTIDE (sc at initial dose of 0.75 mg/0.5 mL in the first week and increased to 1.5 mg/0.5 mL in the following weeks until the end of treatment, for 12 weeks)
Langsfeld, 2023	43.2(13.1)* tot; 43.2(13.1)* placebo; 42.7(13.8) *GLP−1RA	155(60.8) tot; 72(56.3) placebo; 83(65.4) GLP−1RA	27.1(5.0) tot; 27.1(5.0) placebo; 27.1(5.1) GLP−1RA	71(27.8) tot; 35(27.3) placebo; 36(28.3) GLP−1RA	NA	DULAGLUTIDE (sc at initial dose of 0.75 mg/0.5 mL in the first week and increased to 1.5 mg/0.5 mL in the following weeks until the end of treatment, for 12 weeks)

* Mean (SD)

Table 4
Patients' outcomes rates and associated factors.

Author	Patients included n.	Effect on patients' decreasing SUD	Effect on secondary outcomes	Follow-up period	Medical Factors associated with SUD	Factors associated with SUD	Safety Measures
Yammine, 2021	82 tot; 41 placebo; 41 GLP−1RA	Exenatide increased smoking abstinence compared to placebo (46.3 % and 26.8 %, respectively), (risk ratio [RR] = 1.70; 95 % credible interval = [0.96, 3.27]; PP = 96.5 %).	Post-cessation body weight was 5.6 pounds lower in the exenatide group (193.6, 95 % CrI [190.0, 197.1]) than the placebo group (199.2, 95 % CrI [194.9, 203.4]) (PP = 97.4 %).	6 weeks	In a good health	Years of regular smoking, mean ± SD 27.0 ± 11.8	Adverse events were reported in 4(9.5 %) and 1 (2.3 %) of participants in the exenatide and placebo groups, respectively.
Angarita, 2021	13	Exenatide had NO effect on administration and subjective effects of cocaine (4.4 ± 0.8 vs. 4.0 ± 0.8; F (1,12)=1.73, p=0.21)	Both Exenatide and cocaine decreased levels of GLP−1 and insulin ($p = 0.03$, $p = 0.02$, $p < 0.0001$, $p < 0.0001$)	1 day	In a good health	Lifetime years of cocaine use (mean ± SD) 22 ± 10;	No serious adverse events. Exenatide did not produce hypoglycemia in any subject during cocaine sessions.

Klausen, 2022	127 tot, 65 placebo; 62 GLP−1RA	There were no significant differences in decreasing number of heavy drinking days and total alcohol intake between the enaxatide versus placebo group. In a subgroup analysis of obese patients with a BMI greater than 30 kg/m2 (n = 30), Exenatide reduced heavy drinking days by 23.6 percentage points (95 % CI, –44.4 to –2.7, P = 0.034) and reduced total alcohol intake per 30 days by 1205 g (95 % CI, –2206 to –204, P = 0.026) relative to placebo	Exenatide group had a reduction in BMI of 0.95 (95 % CI, –1.6 to –0.3, P = 0.006), glycated hemoglobin (HbA1c) of 1.6 mmol/mol (95 % CI, –2.8 to –0.4, P = 0.011)	26 weeks + 6-month follow-up	NA	Heavy drinking days (mean SD): Placebo 17.3 (8.5); Exenatide Group 16.7 (8.2)	Adverse events were mainly gastrointestinal, body weight loss, fatigue, and injection site reactions. Serious adverse events were reported almost equally between the 2 groups (Exenatide 24.2 % vs. placebo 18.5 %)
Probst, 2023	151 tot; 76 placebo; 75 GLP−1RA	At week 12, participants in the dulaglutide group drank an estimated 29 % less (baseline alcohol intake adjusted relative effect = 0.71, 95 % CI 0.52–0.97, P = 0.04) than participants in the placebo group.	NA	12 weeks	Cancer, pulmonal, cardiovascular, gastrointestinal, metabolic, neurological disease	Nicotine consumption: cigarettes per day 20.0 [15.0–20.0]; Substance use 16 (10.6); Alcohol consumption: standard glasses of alcohol per week 3.0 [2.0–7.0]	Gastrointestinal symptoms are common minor side effects
Langsfeld, 2023	255 tot; 128 placebo; 127 GLP−1RA	At week 12, 63 % (80/127) participants in the dulaglutide group and 65 % (83/128) on placebo treatment were abstinent, with no difference between the groups	Wight reduction (−1 kg, SD 2.7) and decrease of median HbA1c levels (change 0.0, IQR −0.2, 0.2) on dulaglutide treatment	12 weeks	Cancer, pulmonal, cardiovascular, gastrointestinal, osteoporosis and neurological disease	Mean Fagerstroem score was 7.0 points (SD 5.0) and median lifetime smoking exposure was 20 pack years (IQR 11.0, 35.0)	Gastrointestinal symptoms are common in both groups: 90 % (114/127) on dulaglutide group and 81 % (81/128) on placebo group. Other adverse events were mild to moderate, in particular upper respiratory tract infections.

Alcohol Use Disorder

JAMA Psychiatry | Original Investigation

Once-Weekly Semaglutide in Adults With Alcohol Use Disorder
A Randomized Clinical Trial

Christian S. Hendershot, PhD; Michael P. Bremmer, MA; Michael B. Paladino, BS; Georgios Kostantinis, BA; Thomas A. Gilmore, BA; Neil R. Sullivan, BA; Amanda C. Tow, MD, PhD; Sarah S. Dermody, PhD, CPsych; Mark A. Prince, PhD; Robyn Jordan, MD, PhD; Sherry A. McKee, PhD; Paul J. Fletcher, PhD; Eric D. Claus, PhD; Klara R. Klein, MD, PhD

February 2025

JAMA Psychiatry

RCT: Once-Weekly Semaglutide in Adults with Alcohol Use Disorder

POPULATION

14 Men, 34 Women

Non–treatment-seeking adults meeting criteria for alcohol use disorder

Mean (SD) age, 39.9 (10.6) y

SETTINGS / LOCATIONS

1 US academic medical center

INTERVENTION

48 Participants randomized and analyzed

24 Semaglutide
Once-weekly semaglutide

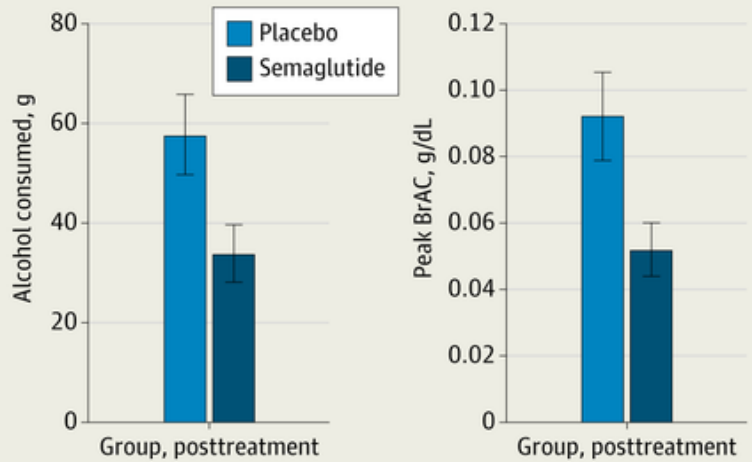
24 Placebo
Placebo injections

PRIMARY OUTCOME

Estimated alcohol consumed over 120 min during laboratory self-administration (estimated alcohol consumed in grams and peak breath alcohol concentration [BrAC] in g/dL)

FINDINGS

Among participants consuming alcohol in a laboratory session following 8 wk of treatment, those in the semaglutide group drank significantly less alcohol than those in the placebo group



Mean (SD) alcohol consumed: Semaglutide: 33.62 (20.72) g; placebo: 57.19 (28.15) g
Mean (SD) peak BrAC: Semaglutide: 0.052 (0.029) g/dL; placebo: 0.092 (0.046) g/dL
Effect sizes: Alcohol consumed: β, −0.48; 95% CI, −0.85 to −0.11; *P* = .01; peak BrAC: β, −0.46; 95% CI, −0.87 to −0.06; *P* = .03

Hendershot CS, Bremmer MP, Paladino MB, et al. Once-weekly semaglutide in adults with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry*. Published online February 12, 2025. doi:10.1001/jamapsychiatry.2024.4789

Hendershot et al

- Mechanism thought to involve central modulation of reward pathways and dopamine signaling

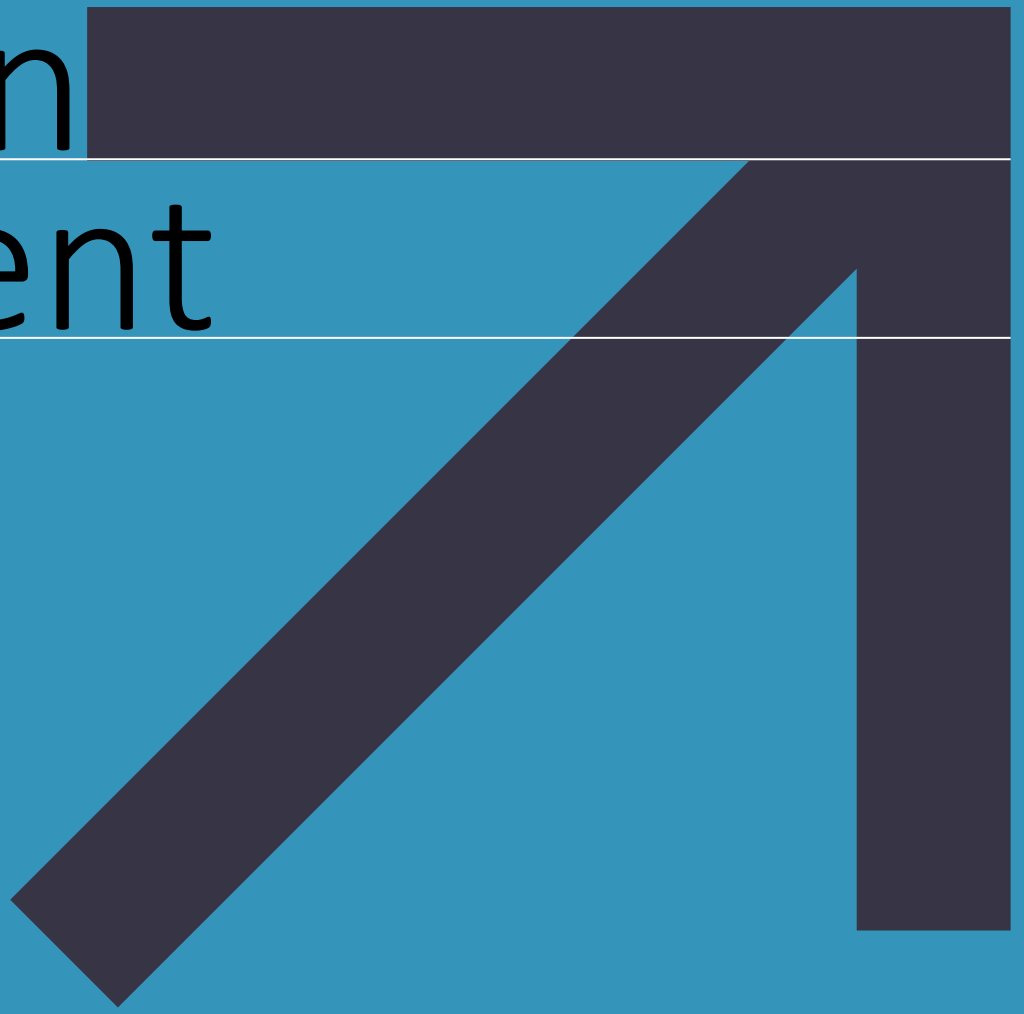
Alcohol Use Disorder:

- Retrospective cohort study of over 200,000 patients with AUD in from 2006 - 2023
- Semaglutide and liraglutide are associated with a substantially decreased risk of AUD-related hospitalizations and may outperform currently approved AUD medications in certain populations, particularly those with comorbid obesity or type 2 diabetes (Lähteenvuo et. Al 2024)

Opioid Use Disorder

- Preclinical studies in rodent models show that liraglutide reduces opioid self-administration, cue-induced and drug-induced heroin seek, and relapse-like behavior. These results were found without compromising opioid analgesia. These effects are mediate via GLP-1 receptors in nucleus accumbens and related reward circuitry (Evans et al 2022 and Zhang et al 2020)

Role of GLP-1A in PainMangagement



GLP 1

GLP-1 receptor agonists, originally developed for diabetes, due to their regulator of glucose and lipid metabolism.

In recent years, have become a focal point in the medical community due to their innovative treatment mechanisms, robust therapeutic efficacy, and expansive development prospects.

GLP-1A now being explored for pain management because of their neuroprotective and anti-inflammatory effects.

The Purpose

This brief presentation will discuss the direct and indirect effects of GLP-1A and as it relates to the field of Pain Management.

We will discuss the current literature of preclinical and clinical evidence of seven pain modalities: including inflammatory pain, osteoarthritis, visceral pain, neuropathic pain, diabetic neuropathy, cancer pain and headache,

We will also discuss underlying biological mechanisms of GLP-1RAs as therapeutic agents for pain suffering

Indirect: Weight Loss

RCT N=156 between 18 and 74 y/o with KOA and a BMI ≥27. Patients were randomly assigned to liraglutide 3 mg/d or placebo for 52 wk. The coprimary outcomes were changes in body weight and the Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscale from week 0 to 52.

From week 0 to 52 there was a significant difference in body weight between the liraglutide and placebo group (mean changes: -2.8 and +1.2 kg, respectively; group difference, 3.9 kg; 95% CI: -6.9, -1.0; P = 0.008). **There was, however, no group difference in KOOS pain (mean changes: 0.4 and -0.6 points, respectively; group difference, 0.9 points; 95% CI: -3.9, 5.7; P = 0.71).** Treatment-emergent adverse events related to the gastrointestinal system were experienced by **50.2%** and 39.2% of patients in the liraglutide and placebo groups, respectively.

(https://pubmed.ncbi.nlm.nih.gov/33471039/)

Indirect: Weight Loss

68-week, double-blind, randomized, placebo-controlled trial at 61 sites in 11 countries. N = 407. The mean age was 56 y/o, the mean BMI 40.3, and the mean WOMAC pain score 70.9. A total of 81.6% of the participants were women. **The mean change in body weight from baseline to week 68 was -13.7% with semaglutide and -3.2% with placebo (P<0.001). The mean change in the WOMAC pain score at week 68 was -41.7 points with semaglutide and -27.5 points with placebo (P<0.001). Participants in the semaglutide group had a greater improvement in SF-36 physical-function score than those in the placebo group (mean change, 12.0 points vs. 6.5 points; P<0.001).** Adverse events that led to permanent discontinuation of the trial regimen occurred in 6.7% of the participants in the semaglutide group and in 3.0% in the placebo group, with gastrointestinal disorders being the most common reason for discontinuation.

(https://www.nejm.org/doi/full/10.1056/NEJMoa2403664?utm_source=openevidence)

Ongoing Trials

Study Overview

Brief Summary

The purpose of this study is to evaluate the efficacy and safety of retatrutide in participants who have obesity or overweight (J1I-MC-GZBJ master protocol) including subsets of participants who have knee osteoarthritis (OA) (J1I-MC-GOA1) or who have obstructive sleep apnea (OSA) (J1I-MC-GSA1). This study will last about 89 weeks and will include up to 24 visits. Addendum (2) is optional and available to approximately 500 participants to continue treatment with retatrutide for up to an additional 24 weeks.

(https://clinicaltrials.gov/study/NCT05929066)

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Percent Change From Baseline in Body Weight		Baseline, Week 80
Change from Baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale Score for GOA1 Subset		Baseline, Week 80
Change from Baseline in Apnea-Hypopnea Index (AHI) Events Per Hour for GSA1 Subset		Baseline, Week 80
Percent Change from Baseline in Body Weight to		Baseline, Week 104

Reduction of Inflammatory Markers

Meta-analysis included 52 eligible RCTs (n = 4734) with a median follow-up of 24 weeks, a mean age of 54.13 years, 44.46% females, body mass index (BMI) 29.80 kg/m2, glycated haemoglobin (HbA1c) 8.28% and diabetes duration 7.27 years. GLP-1 RAs treatment, compared to placebo or conventional diabetes therapies (including oral medicine and insulin), **resulted in significant reductions in CRP, TNF-α, IL-6, IL-1β and leptin (standard mean difference [SMD] -0.63 [-1.03, -0.23]; SMD -0.92 [-1.57, -0.27]; SMD -0.76 [-1.32, -0.20], SMD -3.89 [-6.56, -1.22], SMD -0.67 [-1.09, -0.26], respectively), as well as significant increases in adiponectin (SMD 0.69 [0.19, 1.19]).**

(https://pubmed.ncbi.nlm.nih.gov/40230207/)

Narrative Review

Review | Open access | Published: 27 February 2025

Advances in GLP-1 receptor agonists for pain treatment and their future potential

Yongtao He, Biao Xu, Mengna Zhang, Dan Chen, Shuyuan Wu, Jie Gao, Yongpeng Liu, Zixin Zhang, Junzhe Kuang & Quan Fang

The Journal of Headache and Pain **26**, Article number: 46 (2025) | Cite this article

Inflammatory pain, Osteoarthritis
Visceral pain (IBS)
Neuropathic pain, diabetic neuropathy
Cancer pain
Headache

(https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-025-01979-4#Sec11)

Inflammatory Pain & OA

Preclinical evidence: In rodent models, GLP-1 receptor agonists (e.g., liraglutide, exenatide) reduced joint inflammation and hyperalgesia. This is thought to occur through:

Decreased proinflammatory cytokine expression (e.g., TNF-α, IL-1β).

Suppression of NF-κB signaling in synovial tissue.

(https://www.nature.com/articles/s41598-022-05323-7)

Possible cartilage-protective effects (via chondrocyte survival and ECM stabilization).

(https://www.nature.com/articles/s41419-017-0217-y)

Human data: Clinical studies in OA patients are limited. Some trials show pain reduction (see previous Indirect: Weight Loss Slides)

Visceral Pain (IBS)

Animal models: GLP-1RAs reduce visceral hypersensitivity (visceral hypersensitivity is a hallmark biological feature of IBS) in chemically induced colitis and post-infectious IBS models.
Mechanisms may involve modulation of:
Spinal pain transmission
Gut motility and secretion
Enteric neuron excitability

It was reported that GLP-1R was expressed in colonic mucosal nerve fibers and showed increased expression in biopsies from individuals with IBS).
(https://pubmed.ncbi.nlm.nih.gov/29813107/)
A rat model of IBS, intraperitoneal administration of exendin-4 normalized stress-induced defecation and visceral pain sensitivity (https://pubmed.ncbi.nlm.nih.gov/31602785/)
Another model of induced visceral hypersensitivity, liraglutide effectively reduced visceral

Visceral Pain (IBS)

Animal models cont:

It was reported that GLP-1R was expressed in colonic mucosal nerve fibers and showed increased expression in biopsies from individuals with IBS).
(https://pubmed.ncbi.nlm.nih.gov/29813107/)

A rat model of IBS, intraperitoneal administration of **exendin-4 normalized stress-induced defecation and visceral pain sensitivity**
(https://pubmed.ncbi.nlm.nih.gov/31602785/)

Another model of induced visceral hypersensitivity, liraglutide effectively **reduced visceral allodynia by suppressing pro-inflammatory cytokine (IL6)** production and improving colonic barrier integrity
(https://pubmed.ncbi.nlm.nih.gov/28440889/)

Visceral Pain (IBS)

Clinical studies:
An RTC in IBS patients (n=166), randomly assigned to receive single subcutaneous injections of ROSE-010 100µg (GLP1 analog), 300µg and placebo in a cross-over design. **Results showed dose- and time-dependent reduction in pain and bloating in twice as many ROSE-010 patients then placebo**, but only in female patients, suggesting potential sex-specific effects (The authors discuss possible links to estrogen modulation of GLP-1 receptors in the CNS and gut).
ROSE-010 was most effective in patients with **constipation-dominant IBS (IBS-C) and mixed IBS**, with significantly less pain relief observed in patients with diarrhea-dominant or unspecified IBS.
(https://pubmed.ncbi.nlm.nih.gov/18945254/)
(https://pubmed.ncbi.nlm.nih.gov/35234561/)

Neuropathic Pain

Preclinical studies:

GLP-1RAs reduced thermal and mechanical allodynia in diabetic mice and rats.

Suggested mechanisms include:

Downregulation of TRPV1, a pain-associated ion channel.

Upregulation of antioxidant enzymes and anti-apoptotic proteins in peripheral nerves.

Restoration of nerve conduction velocity and preservation of myelinated fibers.

Neuropathic Pain

Clinical evidence:
RTC (n=42) showed that in individuals with T2DM undergoing intensive glycemic control, **exenatide treatment significantly increased nerve regeneration and improved the severity of pain, based on questionnaire responses.**
(https://pubmed.ncbi.nlm.nih.gov/33714226/)

Neuropathic Pain

Clinical evidence:
Another clinical study showed participants (n=22) with DPN underwent nerve ultrasonography, neuropathy symptom scoring, and nerve conduction studies before and after one month of GLP-1RA therapy (semaglutide or dulaglutide).
Results revealed **significant reductions in tibial nerve cross-sectional area (an indicator of nerve swelling) in 86% and 93% participants at 1 and 3 months respectively, and 32% achieving normal nerve morphology. Improvements in neuropathy severity scores and sensory nerve conduction were observed, and follow-up at three months indicated sustained improvements.** These benefits appeared **independent of changes in glycated hemoglobin or BMI**, suggesting a **direct** neuroprotective effect of GLP-1RAs (https://pubmed.ncbi.nlm.nih.gov/38189936/)

Cancer Pain

Rodent studies using bone cancer pain models have shown that intrathecal administration of GLP-1RAs:
Reduces nociceptive responses via β-endorphin release from spinal microglia or astrocytes.
Inhibits central sensitization via PI3K-Akt and MAPK pathway regulation.
(https://pubmed.ncbi.nlm.nih.gov/24719110/)
(https://pubmed.ncbi.nlm.nih.gov/25247855/)

However, no clinical trials have tested GLP-1RAs in cancer pain or opioid-sparing strategies in oncology.

Headaches

Preclinical Studies:

In vitro experiments using LPS-stimulated BV-2 microglia confirmed that liraglutide decreased the protein levels of IL-1β and TNF-α (https://pubmed.ncbi.nlm.nih.gov/34325647/)

Another study demonstrated that liraglutide alleviated CM-associated hyperalgesia by inhibiting CGRP, phosphorylated ERK (p-ERK), and c-fos protein levels in the TNC, with a concurrent increase in IL-10 release (https://pubmed.ncbi.nlm.nih.gov/37442520/)

Headaches

Observational evidence:
Case report of GLP-1RA discontinuation leading to rapid weight gain and subsequent onset of IIH symptoms. (The patient stopped duraglutide abruptly due to lack of insurance coverage and regained the weight she had lost within a month. She subsequently developed IIH)
(https://pmc.ncbi.nlm.nih.gov/articles/PMC11156736/)

Headaches

On the other hand, weight loss from **GLP-1RA therapy has been associated with symptom resolution in IIH**. An open-label, single-center, case-control pilot study investigated the effects of GLP-1RAs in individuals with idiopathic intracranial hypertension and obesity. The intervention group (n = 13) received semaglutide or liraglutide alongside standard body weight management, while the control group (n = 26) underwent standard weight management alone. **After six months, participants in the GLP-1RA-treated group achieved significantly greater weight loss compared to the control group. This weight reduction was accompanied by fewer headache days and a decreased requirement for acetazolamide (Median reduction in MHD was significantly higher in the GLP-1-RA group (-4 [-10.5, 0.5] vs. 0 [-3, 1]; p = 0.02), and the 50% responder rate was 76.9% vs. 40.0% (p = 0.04))**

(https://pubmed.ncbi.nlm.nih.gov/37460968/)

Headaches

Randomized, placebo-controlled trial (n=15) further evaluated the effect of exenatide on ICP in women with IIH. **Exenatide significantly reduced ICP at 2.5 h, 24 h, and 12 weeks compared to placebo, with no significant weight loss observed in the exenatide group.** This indicates a **direct effect** of exenatide on ICP modulation, likely mediated by its action at the choroid plexus. Additionally, mean monthly headache days were significantly reduced in the exenatide group compared to placebo, further supporting its therapeutic potential
(https://pubmed.ncbi.nlm.nih.gov/36907221/)

Conclusion

Clinical evidence is limited, especially in cancer pain and many neuropathic pain syndromes.
Difficult to distinguish direct analgesic effects from secondary benefits like weight loss in obesity-linked pain conditions.
Heterogeneous responses (e.g. gender differences in IBS).
Risks of abrupt cessation, such as rebound IIH upon stopping therapy.
Lack of phase III trials, definitive dosing guidelines, and studies on long-term safety and combinatorial approaches with existing therapies

Thank You!

Questions?

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