Heavy Hitters: Glucagon-like peptide-1 (GLP-1) receptor agonists for addiction treatment

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GLP-1 receptor agonists for addiction treatment

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Michael Weaver, MD, DFASAM

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Nancy Shenoi, MD

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Learning Objectives

1. Recall mechanisms of action and current clinical use of glucagon-like peptide-1 (GLP-1) receptor agonist medications.
2. Recognize pre-clinical and human subject research evidence for utility of GLP-1 agonists in treatment of substance use disorders.
3. Discuss potential clinical use of GLP-1 agonist medications for treatment of addiction to nicotine, stimulants, alcohol, and other substances.

Overview of GLP-1 Agonists

Nancy Shenoi, MD

What are GLP-1 Receptor Agonists?

- Emulate GLP-1, an endogenous incretin hormone and satiation factor
- Approved to treat type 2 diabetes mellitus and obesity
- Low risk of hypoglycemia
- Lower the chance of cardiovascular events and are recommended for individuals with history of clinical ASCVD
  - Semaglutide recently FDA-approved for reducing the risk of major adverse cardiovascular events in patients with CVD and either obesity or overweight
- Lower all cause mortality

Mullur et al *J Endocrinology* 2024

Advantages of GLP-1 Receptor Agonists

- Can improve left ventricular ejection fraction, myocardial contractility, coronary blood flow, cardiac output, and endothelial function
- Decrease pancreatic apoptosis and stimulate pancreatic cell proliferation

Mullur et al *J Endocrinology* 2024

Metabolism & Elimination

- Primary metabolism in kidneys and liver
- Poor oral availability, most are delivered by subcutaneous injection
- Renal elimination

Mullur et al *J Endocrinology* 2024

Adverse Effects & Contraindications

- Common side effects: nausea, vomiting, diarrhea, AKI
- Delayed gastric emptying increases risk of aspiration
- Increased risk of pancreatitis and medullary thyroid cancer
- Contraindications
  - Pregnancy
  - Personal/family history of medullary thyroid cancer and MEN2
  - Allergic/hypersensitivity reactions to medication
- Compounded medications are not regulated by the FDA
  - Dosing variability and increased risk of side effects and overdose

Mullur et al *J Endocrinology* 2024

GLP1 Agonists and Addiction: Putative Mechanisms

- Activation of GLP-1 receptors in the ventral tegmental area and nucleus accumbens reduces dopamine release in response to addictive substances, decreasing cravings and reinforcement.
- GLP-1 Receptor agonists impact hypothalamic signaling pathways regulating impulse control, reducing compulsive drug-seeking
- GLP-1 RAs are anti-inflammatory and neuroprotective, significant as chronic substance use is associated with neuroinflammation and oxidative stress

Jerlhag, Elizabet. *International Review of Neurobiology*. 2024
Badulescu et al. *Physiology & Behavior.* 2024
Bhalla el al. *Neuroscience & Biobehavioral Reviews*. *2022*

Hypothesized Effects at Different Brain Regions

Brain Region	Effect of GLP-1 Agonists
Mesolimbic dopamine system (Ventral Tegmental Area and Nucleus Accumbens)	⬇ Reduces dopamine release, decreasing reward response to addictive substances.
	⬇ Lowers drug-seeking behavior by dampening reinforcement mechanisms.
Hypothalamus	⬇ Suppresses cravings and compulsive behaviors by modulating appetite and impulse control pathways.
Prefrontal Cortex	⬆ Enhances executive function and decision-making, reducing relapse risk.
Amygdala	⬇ Reduces neuroinflammation and stress-related drug-seeking behaviors.

GLP-1 agonists for substance use disorders: pre-clinical (animal) evidence

Michael Weaver, MD

Pre-clinical evidence

- GLP-1 agonists reduce addiction-related behaviors in rodents and primates

Alcohol

- Alcohol is currently the most investigated substance for effects of GLP-1 agonists
- Several studies demonstrated reductions in alcohol-induced conditioned place preference (CPP) in rodents (mice and rats)
  - CPP is when an animal exhibits a clear preference for an environment associated with a positive reinforcing substance
  - Animal spends more time in the place where it received the substance compared to the place where it received the placebo
- GLP-1 agonist administration also reduced alcohol consumption in alcohol-preferring non-human primates (vervet monkeys)
- Other studies showed that boosting endogenous GLP-1 may not be sufficient to reduce alcohol drinking in rats

Bruns N VI, et al *Pharmacol Res* 2024

Cocaine

- Limited research has been done on stimulants, primarily for cocaine
- Experimental (not FDA-approved) GLP-1 agonist compound in rats reduced cocaine self-administration
- Chronic daily injections prevented reinstatement of cocaine-induced CPP
- Preclinical studies have consistently demonstrated a reduction in the rewarding and reinforcing effects of both cocaine and amphetamine
- Clinical research is necessary at this stage

Bruns N VI, et al *Pharmacol Res* 2024

Opioids

- Repeated doses of liraglutide (brand-name Victoza) reduced heroin self-administration in rats
- Experimental GLP-1 agonist compound in rats reduced fentanyl and oxycodone self-administration
- Limited research on GLP-1 agonists for opioid use
- Early results are encouraging

Bruns N VI, et al *Pharmacol Res* 2024

Nicotine

- GLP-1 agonists reduced nicotine intake in mice and withdrawal symptoms in rats

Bruns N VI, et al *Pharmacol Res* 2024

GLP-1 agonists for substance use disorders: Questions for a Researcher

Luba Yammine, PhD

Frequently Asked Questions

- What do we know about GLP-1RA and nicotine use?
- What prompted you to do this research?
- How do GLP-1RA therapies help with smoking cessation?
- Are you concerned about hypoglycemia? Other potential side effects?
- Are you currently running any clinical trials?
- What about off-label use of GLP-1RA for smoking cessation and addictions in general?

What do we know about GLP-1RA and nicotine use?

Preclinical studies on GLP-1RA and Nicotine

- GLP-1RA
  - block expression of conditioned place preference
  - attenuate nicotine-induced locomotor activation, nicotine self-administration, and nicotine-evoked dopamine release in NAc
  - reduce nicotine withdrawal induced hyperphagia and weight gain

Source: *1.Egeciouglu et al (2013)*
2.Tuesta et al (2017)
3.Herman et al (2023)
4.Falk et al (2023)

Clinical studies

- Exenatide 2mg once weekly adjunct to nicotine patch X 6 weeks (n=84)
  - 46.3% abstinence with exenatide, 26.8% abstinence with placebo
  - **Post-cessation body weight: exenatide: -0.22 kg, placebo +1.3 kg**
- Dulaglutide 1.5 mg once weekly adjunct to varenicline X 12 weeks (n=255)
  - 63% abstinence with dulaglutide, 65% abstinence with placebo
  - **Post-cessation body weight: dulaglutide** -1kg [SD=2.7]), placebo +1.9kg [SD=2.4]
- Semaglutide once weekly X 8 weeks (0.25 mg X 4 weeks, 0.5 mg X 4 weeks
  - Greater declines in cigarettes per day in the semaglutide group (vs placebo)
  - **Change in body weight: semaglutide: -5.05%, placebo, +0.18%**

Source: *5.Yammine et al (2021)*
6.Lengsfeld et al (2023)
7. Hendershot et al (2025)

Clinical studies

- **NCT05530577:** Semaglutide once weekly up to 1 mg/week X 9 weeks (n=48)

- **NCT03712098**: liraglutide 3 mg daily X 32 weeks (n=40)

Additional Evidence

- Analyses of EHR data from patients with type 2 diabetes (T2D):
  - compared to patients who used other medications for T2D, patients who used GLP-1RA were less likely to receive a diagnosis of nicotine misuse
  - In patients with T2D and comorbid tobacco smoking - compared to patients who used other medications for T2D, GLP-1RA use was associated with less healthcare utilization for tobacco use disorder
- Analysis of social media posts
  - 23% of nicotine related comments stated complete cessation of nicotine intake

Source: *8.De Giorgi et al (2024)*
9.Wang et al (2024)
10.Arilotta et al (2024)

In Summary….

- Promising preclinical and epidemiological data
- Completed RCTs are few, with variable findings related to smoking
- Positive impact on preventing post-cessation weight gain
- Further clinical research is needed

What prompted you to do this research?

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PLOS | ONE

The Glucagon-Like Peptide 1 Analogue, Exendin-4, Attenuates the Rewarding Properties of Psychostimulant Drugs in Mice

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Gut Peptide GLP-1 and Its Analogue, Exendin-4, Decrease Alcohol Intake and Reward

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The Glucagon-Like Peptide 1 Analogue Exendin-4 Attenuates the Nicotine-Induced Locomotor Stimulation, Accumbal Dopamine Release, Conditioned Place Preference as well as the Expression of Locomotor Sensitization in Mice

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GLP-1 analog attenuates cocaine reward

Devon L. Graham,[1] Kevin Erreger,[2,3] Aurelio Galli,[2,3,*] and Gregg D. Stanwood[1,3,*]

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PMCID: PMC5049632
PMID: 26303264

The glucagon-like peptide 1 receptor agonist liraglutide attenuates the reinforcing properties of alcohol in rodents

Daniel Vallöf,[1] Paola Maccioni,[2] Giancarlo Colombo,[2] Minja Mandrapa,[1] Julia Winsa Jörnulf,[1] Emil Egecioglu,[3] Jörgen A. Engel,[1] and Elisabet Jerlhag[1]

Source: *1.Egeciouglu et al (2013)*
11. Egeciouslu et al (2013)
12.Shirazi et al (2013)
13. Vallof et al (2016)
14. Graham et al (2013)

How do these medications help with smoking cessation?

Hypothesized Mechanisms and Therapeutic Effects

- Modulation of dopamine release → decrease in reward
- Activation in medial habenular pathways → aversive effects of nicotine
- Other??

Is hypoglycemia a concern?
Other potential side effects?

- **GI side effects**
- Hypoglycemia
- Excessive weight loss?
- Other??

Source: *15. Xie et al (2024)*
16. Sodhi et al (2023)

Ongoing studies

- R01 DA053241 (**NCT05610800**): A Randomized Controlled Trial of Exenatide as an Adjunct to Nicotine Patch for Smoking Cessation and Prevention of Post-Cessation Weight Gain (PI: Yammine, Co-PI: Verrico)

- Novo Nordisk Investigator Initiated Trial (**NCT06173778**): A Randomized Controlled Trial of Once-Weekly Semaglutide for Limiting Post-Smoking Cessation Weight Gain in Adult Smokers with Overweight/Obesity (PI: Yammine, Co-PI: Leidy)

What about off-label use of GLP-1RAs for smoking cessation and addictions in general?

- Unknowns
  - GLP-1RA, dosing, treatment duration, sustainability of effects, safety considerations
  - Monotherapy vs adjunct to smoking cessation treatments
  - Suitable patient candidates
- Patients with comorbid tobacco use prescribed GLP-1RA for FDA-approved indications may experience additional benefits related to tobacco use (reduction in nicotine intake or complete cessation)

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THANK YOU

GLP-1 agonists for substance use disorders: Human studies (other than tobacco)

Michael Weaver, MD

Human research other than tobacco

- Clinical studies involving humans
  - Epidemiological data from electronic health records
  - Open-label studies of medication
  - Placebo-controlled randomized trials

Alcohol

- Analysis of social media posts from patients on GLP-1 agonists for diabetes or obesity
  - Showed reduction in alcohol craving and use
- Retrospective EHR review
  - Showed that semaglutide reduced the risk of development of alcohol use disorder (AUD) in patients with obesity and/or diabetes
- Randomized controlled trial
  - Exenatide had no effect on drinking in patients with AUD
  - Reduced drinking in patients with AUD and comorbid obesity
- More research is necessary to establish whether obesity moderates GLP-1RA treatment effects on AUD (and SUD more generally)
- Multiple ongoing studies of GLP-1RAs for AUD

Hendershot, et al *JAMA Psychiatry* 2025

Cocaine

- Pilot study of exenatide administration
  - 13 human subjects with cocaine use disorder with a single dose of each
  - No effect on cocaine self-administration or euphoria
- Exenatide as treatment for cocaine use disorder
  - Open-label trial for 3 weeks in 3 patients with cocaine use disorder
  - 1 subject of 3 achieved sustained abstinence
- Ongoing study of exenatide for 6 weeks on cocaine self-administration and subjective effects
- More research is necessary

Bruns N VI, et al *Pharmacol Res* 2024

Opioids

- Clinical study of liraglutide
  - Reduced cravings for heroin in patients with opioid use disorder who had already been admitted to an addiction treatment facility
- Limited research on GLP-1 agonists for opioid use
- Early results are encouraging
- Several ongoing studies of GLP-1RAs for OUD

Bruns N VI, et al *Pharmacol Res* 2024

Cannabis

- Retrospective electronic health record review
  - Showed that semaglutide reduced the risk of cannabis use disorder

- Recent epidemiologic study showed that compared with usual care, use of GLP-1 agonists was associated with a reduced risk of SUD (alcohol, opioids, stimulants, and cannabis)

Bruns N VI, et al *Pharmacol Res* 2024
Xie, et al *Nat Med* 2025

Current state of GLP-1 agonist research in SUD

- GLP-1 agonists may be useful across several different classes of substances
  - Similar to naltrexone for alcohol as well as opioid use disorder
  - Likely to see more research on effects across a variety of substances
- Significant gaps in knowledge about the role of GLP-1 agonists for patients with addiction
- Rigorous clinical trials are needed to establish the efficacy of GLP-1 agonists for treating different classes of SUD

What the future holds

- Additional research questions
  - Optimal duration of therapy
  - Titration strategies
  - Sustainability of effects
  - Safety considerations
  - Mechanism of action
- Further areas of interest
  - Equitable access to these medications
  - Incorporation into future clinical practice

Ethical Issues involving GLP-1 Receptor Agonists

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Equitable Access to GLP-1 Agonists Globally

- World Obesity Federation has identified gaps in obesity treatment in low- and middle-income countries and in rural areas.
- Only 4 countries offer insurance coverage for obesity treatment: Brazil, Chile, United States, Canada
- Canada's universal health care system and lower prices for diabetes medications enhance accessibility
- The Inflation Reduction Act of 2022 allowed Medicare to negotiate the price with 10 costly medications without a generic
  - no GLP-1 agonists are on this list

Azizi et al. *Circulation (AHA/ASA Journal).* 2024

Domestic Disparities in GLP-1 Agonist Adoption

- 5-year study of those with commercial insurance revealed that among those with diabetes, there were lower rates of GLP-1 RA use among Asian, Black, and Hispanic individuals and those with lower household income
- Another study using the TriNetX EHR network found that non-White groups had lower odds of receiving tirzepatide and semaglutide prescriptions and Asians & Native American/Pacific Islanders had significantly lower odds of receiving dulaglutide
- Possible causes include: limited healthcare access, provider biases, and gaps in insurance coverage, all of which affect equitable T2D treatment.
- These are all factors that could be pertinent to people with SUDs in addition to known challenges faced by people with active substance use disorders:
  - Risk of co-occurring psychiatric disorders, unemployment, addiction related stigma

Eberly et al. *JAMA Health Forum.* 2021.

Ethical Access

- GLP-1 agonist access is at this time already limited for patients with diabetes and obesity, meaning that obtaining these medications for SUD treatment if FDA approved, may potentially be challenging and costly for patients with SUDs
  - Added layer of provider bias about the indications for prescription
- Diversion for cosmetic purposes would then affect care of those with SUDs as well
- Evidence based guidelines for ”rational drug use” of GLP-1 RAs would then be necessary
- Investing in patient-education and public health initiatives to raise awareness of indications for GLP1 agonists and prevent off-label marketing is important

Kukhareva et al. *medRXiv.* 2024.
Echeverry-Guerrero et al. *Pharmacoepidemiology.* 2024.

Impact on Mental Health

- GLP-1 RAs are thought to regulate neuroinflammation and hormones involved in mood and appetite regulation such as cortisol and thyroid hormone
  - when a person stops the medication, depression symptoms may return
  - GLP-1 RAs affect GABA neurotransmission and may be pro anxiogenic
- Weight loss helps people with self efficacy, likely a positive prognostic factor also in SUD treatment
- Some reports exist of Liraglutide and Semaglutide GLP-1 receptor agonists triggering suicidal thoughts, self-injury, and depression, but pre-existing risk factors for depression or suicidal ideation may be present such as family history, trauma history, and other medications.
- Phase 4 surveillance is still ongoing for most GLP-1 receptor agonists

Arillotta et al. *Brain Sciences.* 2023

Obesity and stigma

- GLP-1 agonist medications risk medicalizing weight and increasing weight stigma
  - Ex: Concept of “taking the easy way out” for bariatric surgery patients could extend to those receiving GLP-1 receptor agonists
- Social identity threat perspective- heavier individuals may feel pathologized by medical profession
- Weight inclusive care-avoid weight stigma and focus on improving metabolic syndrome comorbidities and adopting healthy behaviors

Tomiyama, Janet. *Annals of Behavioral Medicine*. 2025

When People May Benefit

- Exploratory analyses revealed that exenatide significantly reduced heavy drinking days and total alcohol intake in a subgroup of obese patients (BMI > 30 kg/m2).
- The use of semaglutide and liraglutide among obese or T2DM patients with AUD was associated with a substantially decreased risk of hospitalization due to AUD
- Exenatide increased the risk for smoking abstinence compared to placebo among prediabetics and those who were overweight
  - It reduced end-of-treatment craving in the overall sample and withdrawal among abstainers.
  - Exenatide offset increases to post-cessation body weight

Klaussen et al, *JCI Insight.* 2022
Lähteenvuo et al, *JAMA Psychiatry. 2025*
Yammine et al, *Nicotine Tob. Research.* 2021

Therefore…

Those with obesity or Type 2 diabetes mellitus and a comorbid substance use disorder may have additional benefit from GLP-1 receptor agonists

What should we do?

- While GLP-1 RAs are undergoing further exploration, we *have* FDA approved treatments for nicotine use disorder, alcohol use disorder, and opioid use disorder that should be prescribed
- Most people with substance use disorders don't receive addiction treatment
  - As of 2021, only 1 in 5 people with opioid use disorder received buprenorphine-naloxone, naltrexone, or methadone
- Failing to offer these medications is a missed opportunity

Jones et al, *JAMA Network Open.* 2023.

Takeaways

- We do not endorse GLP-1 RA use for substance use disorder treatment but encourage use of existing FDA-approved treatments for SUDs.
- Patients with an existing FDA-approved indication for GLP-1 RAs with a comorbid SUD may have increased benefit from GLP-1 RAs
- Greater education and awareness of people stigmatized from obesity, diabetes, or addiction can help with health equity

Questions?

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