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# The Role of GLP-1 Analogues in Treating Substance Use Disorders: A Scoping Review Study

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VÄSTRA GÖTALANDSREGIONEN

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**Summary**

**Introduction:**

This study delves into the burgeoning field of research surrounding the potential role of Glucagon-Like Peptide-1 (GLP-1) in substance-use disorders (SUD). Substance-use disorders pose a significant global health burden, affecting millions of individuals and impacting various facets of society. From the intricate neurobiological mechanisms to clinical implications, this review encompasses a broad spectrum of perspectives, shedding light on the complex interplay between GLP-1 and substance use disorders.

**Aim:**

The aim of this study is to provide an overview of the current scientific literature on substance use disorder and GLP-1 analogues.

**Methods:**

This study was conducted as a scoping review study using two databases, Pubmed and Scopus. The data collection was structured according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines and was conducted according to a method previously described by Arksey and O'Malley.

**Results:**

The review included two randomized controlled trials (RCTs), two clinical trials, two observational studies, and eight review articles, primarily involving alcohol use disorder (AUD). The overall pattern indicates a greater reliance on review articles for interpreting the role of GLP-1 in addiction, with a notable lack of robust primary research, such as more RCTs. Most of the articles concentrate on AUD.

**Conclusion:**

The emerging research at the intersection of metabolic and addiction sciences shows potential for GLP-1 receptor agonists in treating substance use disorders. However, this potential is primarily based on early preclinical studies, making the current evidence insufficient for clinical application. Additionally, more rigorous and long-term studies, including RCTs, are required to confirm these findings and potentially revolutionize future addiction treatment approaches.

**Abbreviations:**

AUD: Alcohol use disorder

AUDIT: Alcohol use disorders identification test

BMI: Body mass index

CNS: Central nervous system

CUD: Cocaine use disorder

GLP-1: Glucagon like peptide 1

IV: Intravenous

NAs: Nucleus accumbens

NRT: Nicotine replacement therapy

PPG: Preproglucagon gene

RCT: Randomized control trial

SUD: Substance use disorder

VTA: Ventral tegmental area

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# 1. Introduction

## 1.1. Substance-Related Disorders: A Global Challenge

Substance-related disorders represent a pervasive and complex global challenge, encompassing a range of conditions characterized by the recurrent use of substances despite adverse consequences (1-6). From alcohol and tobacco to illicit drugs and prescription medications, substance abuse and addiction affect individuals across all demographics and regions, posing significant public health, social, and economic burdens.

The prevalence of substance-related disorders is widespread, with millions of people worldwide grappling with the repercussions of addiction (2, 6, 7). Not only do these disorders have profound impacts on the individuals directly affected, but they also extend to their families, communities and society at broad. Substance abuse contributes to a myriad of health issues, including mental health disorders, infectious diseases and chronic medical conditions, exacerbating healthcare disparities and straining healthcare systems globally (8).

The impact of substance-related disorders on global health underscores the necessity for a nuanced understanding of the mechanisms at play and the identification of potential therapeutic targets (2, 5, 6, 9, 10). In this context, the mesolimbic dopamine reward pathway takes center stage (11).

## 1.2. The mesolimbic dopamine reward pathway: Motivational circuit

Moving from substance abuse to neurobiological mechanisms, the mesolimbic dopamine reward pathway is believed to be an essential regulatory component in addiction (11). The mesolimbic dopamine reward system is a complex neural circuitry in the brain that plays a crucial role in processing rewarding and reinforcing stimuli (2, 6, 11). The pathway primarily involves dopaminergic neurons that originate in the ventral tegmental area (VTA), located in the midbrain. These dopaminergic neurons project to various brain regions, with a major projection to the nucleus accumbens (NAc), a core part of the brain's reward system (11). This system is integral to understanding motivation, pleasure and the development of addictive behaviors (11).

## 1.3. Glucagon-Like Peptide-1 (GLP-1): An Overview

Activation of glucagon-like peptide-1 receptors results in various physiological and metabolic responses, such as increased insulin secretion, inhibition of gastric emptying, inhibition of glucagon secretion and reduced food intake (12). Today, GLP-1 receptor agonists are approved for the treatment of type II diabetes mellitus and obesity (6, 12).

GLP-1 is a peptide, primarily produced by the L cells in the small intestine but also in the central nervous system (CNS) in the nucleus tractus solitarius (NTS) of the caudal brainstem (2, 3, 6, 11-13). The preproglucagon (PPG) gene is responsible for the synthesis of GLP-1, which is then released into the bloodstream and the central nervous system. Notably, PPG-expressing neurons in the NTS project to various midbrain and forebrain areas, including the ventral tegmental area (VTA) and nucleus accumbens (NAc), implicated in the mesolimbic dopamine reward system (11).

Central GLP-1 receptor activation contributes to the reduction of food intake proposedly by modulating the hedonic value of palatable food through direct

interactions with the mesolimbic reward system (6). GLP-1 receptors in the CNS play a role in the so called, brain-gut communication between the gut and the brain (3, 7, 12). This interaction influences satiety, food intake regulation and potentially behaviors associated with substance use.

The exploration of GLP-1 beyond its traditional metabolic actions has opened avenues for research into its influence on neural circuits associated with substance-related behaviors and addiction (6, 14, 15).

## 1.4. Role in Addiction:

Substance abuse, including drugs and alcohol, can hijack the mesolimbic dopamine reward pathway, leading to increased dopamine release and reinforcing addictive behaviors (6, 11). These substances can directly or indirectly stimulate the release of dopamine in the NAc, creating a surge in pleasurable sensations. This artificially elevated dopamine signal reinforces the association between drug use and reward, promoting the formation of strong memories and cravings (11).

Repeated drug exposure leads to neuroadaptations in the mesolimbic pathway, altering its normal functioning (11). The prefrontal cortex, which is connected to the mesolimbic pathway, plays a role in assessing risks and rewards, but in addiction, this regulatory mechanism is compromised (1, 12).

It is believed that further exploring the mesolimbic dopamine pathway's connection to addiction could potentially facilitate the development of effective treatments (1-3, 6, 9, 11, 12).

Studies indicate that GLP-1 receptor agonists could be effective in treating addiction due to their influence on the mesolimbic dopamine reward system (1, 3, 7, 11). When GLP-1 receptors are activated they can directly influence the activity of dopamine neurons (11). This modulation decreases the dopamine release that is typically stimulated by rewarding stimuli, including

addictive substances. It has been hypothesized that by reducing the dopamine surge, GLP-1 may decrease the reward or pleasure associated with such stimuli, potentially reducing addictive behaviors.

The potential clinical applications of GLP-1 agonists in treating addiction disorders are based on these mechanisms of action (1-3, 6, 9, 11, 12).

# 2. Aim

The aim of this study was to provide an overview of the current scientific literature on substance use disorders and GLP-1 analogues.

# 3. Research question

1. Does treatment with GLP-1 analogues influence clinical outcomes in substance abuse?

# 4. Materials and Method

## 4.1. Study design:

This study was conducted as a scoping review study, according to Arksey and O'Malley (16). The data collection was structured according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (17). Quality assessment of the included studies is not part of a scoping literature review.

## 4.2. Eligibility criteria:

To be included, studies had to report on the use of GLP-1 receptor agonists on substance-use related effects of alcohol, nicotine or other drugs. There were no limitations on study design, type of substance, type of GLP-1 receptor agonist or demographics. Only literature written in English was included. Studies that were performed on animals were excluded. Studies regarding food addiction were excluded since it is not considered to be a part of substance abuse disorders.

The observed period in which studies were published was set between 2014-2024 to focus the effort on the most pertinent and manageable body of literature, as well as to ensure the information is current and relevant to today's understanding of the topic.

## 4.3. Information sources:

A detailed search was performed to summarize published data related to GLP-1 analogues and substance use disorders using two databases; PubMed and Scopus. The search strategy was formed together with a research

librarian at the University of Gothenburg and the search day was January 30, 2024.

## 4.4. Literature search:

The search strategy consisted of the following terms: (Substance-Related Disorders OR substance abuse OR addiction OR cocaine OR tobacco OR nicotine OR smoking OR alcohol OR amphetamine OR cannabis OR opioids OR narcotics) AND (GLP-1 OR Semaglutide OR Ozempic OR Liraglutide OR Victoza OR Exenatide OR Glucagon-Like Peptide 1) with filters Human and English language as well as range from 2014-2024. The same search terms were used in both PubMed and Scopus database.

All identified articles were first categorized for appropriateness as *relevant/maybe/not relevant* by assessing title. Selected *relevant* and *maybe* articles were categorized once more into *relevant/not relevant* based on the abstract. The remaining articles were read in full text and evaluated based on specified inclusion and exclusion criteria.

## 4.5. Ethical consideration in included studies:

Ethical approval was not necessary for this study, as it solely relies on literature from previously conducted studies. No primary data was collected for the study. All the included studies declared that they had obtained ethical approval before the studies were conducted. Research on SUDs often involves vulnerable populations who may be at higher risk of coercion or undue influence. Informed consent, protecting vulnerable populations, balancing risks and benefits as well as maintaining data privacy and confidentiality should also be included. Long-term follow-up, transparency in reporting and managing conflicts of interest are also crucial.

# 5. Results

A total of 14 studies were included in this scoping review, selected from 377 initially identified through the literature search on January 30, 2024. Out of these 377 articles, 274 articles were excluded based on title and an additional 12 articles were removed due to duplication. The remaining 91 articles underwent abstract screening, resulting in 68 being dismissed as irrelevant. Ultimately, 21 articles were reviewed in full text, and 7 were excluded based on the criteria outlined in the flowchart.

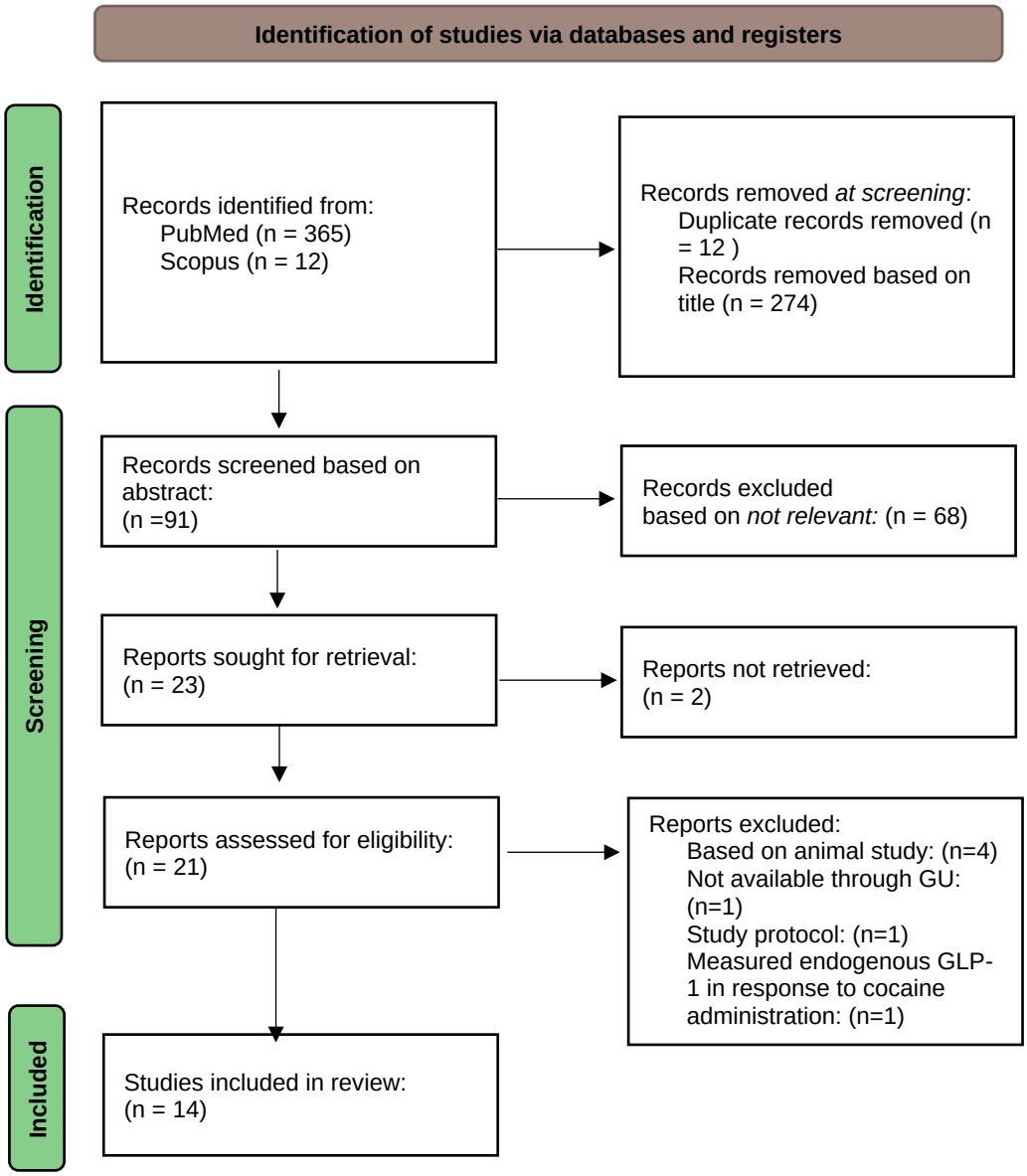


*Figure 1 (17): presentation of data collection*

*Table 1. presentation of the included studies*

| Article | Year of publication & study design | Aim | Number of participants, sex, age | Substance of abuse and dose | GLP-1 analogue and dose | Main result |
|---|---|---|---|---|---|---|
| **J. A. Engel and E. Jerlhag** - Role of appetite-regulating peptides in the pathophysiology of addiction: implications for pharmacotherapy **(7)** | 2014 Review article | Examines the potential of targeting GLP-1 receptors as novel approaches for the pharmacological treatment of addiction. | N/A | Alcohol + psychostimulants | Exanitide, Luraglutide, | GLP-1 may represent a novel target for development of pharmacological treatment strategies for addictive behaviors. Highlights the need for further research. |
| **I. A. Reddy, G. D. Stanwood and A. Galli** - Moving beyond energy homeostasis: new roles for glucagon-like peptide-1 in food and drug reward**(12)** | 2014 Review article | Explore GLP-1's potential as a mediator in the control of eating behaviors and its influence on the rewarding effects of drugs of abuse, including psychostimulants and alcohol. | N/A | Alcohol + psychostimulants | Exanitide, Liraglutide | The article hypothesizes that GLP-1 might modulate dopamine homeostasis within the mesolimbic reward system, impacting both food and drug reward processing. |
| **E. Jerlhag** - GLP-1 signaling and alcohol-mediated behaviors; preclinical and clinical evidence**(1)** | 2018 Review article | This article provides a review of the role of GLP-1 in regulating alcohol consumption and potentially treating AUD. | N/A | Alcohol + other substances in general | Liraglutide | Clinical evidence, though limited, suggests that GLP-1 receptor gene variations are associated with alcohol addiction, GLP-1 receptor agonists may reduce alcohol intake in patients with type-2 |

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| | | | | | | diabetes and that plasma levels of GLP-1 are associated with the subjective response to cocaine. |
| **N. S. Hernandez and H. D. Schmidt**<br>- Central GLP-1 receptors: Novel molecular targets for cocaine use disorder**(6)** | 2019<br>Review article | The article synthesizes a body of preclinical evidence suggesting that GLP-1 receptor agonists could potentially be repurposed to treat cocaine use disorder (CUD). | N/A | Cocaine | Unspecified | Indicates that GLP-1 receptor activation can reduce cocaine intake, decrease cocaine's rewarding effects and attenuate relapse-like behaviors. |
| **E. Jerlhag**<br>- Gut-brain axis and addictive disorders: A review with focus on alcohol and drugs of abuse**(3)** | 2019<br>Review article | Highlight potential of gut-brain peptides in the treatment of AUD and other addictive disorders. | N/A | Alcohol | Unspecified | It emphasizes the complexity of addiction as a multi-faceted disorder that may benefit from targeted pharmacotherapies aimed at the gut-brain axis. |
| **G. A. Angarita, D. et al.**<br>- Testing the effects of the GLP-1 receptor agonist exenatide on cocaine self-administration and subjective responses in humans with cocaine use disorder**(5)** | 2021<br>Clinical trial | Investigate the effect of Exenatide on self-administration and subjective effects of cocaine among individuals with CUD. | F: 1<br>Total: 13<br>30-55 years | IV- cocaine every 20 min, ascending dose regimen of 4, 8, and 16 mg/70 kg. | Exanitide 5 µg single-dose | *Primary behavioral outcomes:* Pre-treatment with exenatide did not change numbers of cocaine infusions in comparison to pre-treatment with placebo.<br>*Primary subjective effects (VAS self-ratings):*<br>Exenatide did not change primary subjective outcomes of |

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| | | | | | | cocaine-induced subjective effects of euphoria/high nor wanting cocaine compared to placebo |
| **L. Yammine et al.**<br>- Exenatide Adjunct to Nicotine Patch Facilitates Smoking Cessation and May Reduce Post-Cessation Weight Gain: A Pilot Randomized Controlled Trial**(18)** | 2021<br>RCT-pilot study | Examine the efficacy of extended-release Exenatide combined with NRT for smoking cessation, craving, and withdrawal symptoms, with post-cessation body weight as a secondary outcome. | F: 25<br>Total: 82<br>Intervention group: 41<br>Control group: 41<br>18-75 years | Tobacco | Exenatide 2 mg once weekly for 6 weeks | Extended-release Exenatide added to the nicotine patch, reduced abstinence and mitigated post-cessation body weight gain compared to patch alone. Exenatide increased the risk for smoking abstinence compared to placebo (46.3% and 26.8%, respectively). |
| **M. K. Klausen et al.**<br>- The role of glucagon-like peptide 1 (GLP-1) in addictive disorders**(2)** | 2022<br>Review article | Explore the potential of GLP-1 receptor agonists as an innovative treatment strategy for addictive disorders. | N/A | N/A | N/A | Explores the connection between metabolic regulation and addiction neuroscience, advocating for further research to move from preclinical findings to clinical practice. |
| **L. Leggio et al.**<br>- GLP-1 receptor agonists are promising but unproven treatments for alcohol and substance use disorders**(14)** | 2023<br>Review article | Evaluate the potential of GLP-1 receptor agonists as treatments for AUD and SUD. | N/A | Alcohol + other substances in general | Semaglutide | Emphasizes the gap between the preclinical research and the need for conclusive clinical trial data before these treatments can be widely recommended for addiction treatment. |

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| **M. Leslie**<br>- Hot weight loss drugs tested against addiction**(15)** | 2023<br>Review article | Shed light upon preclinical results | N/A | Alcohol + other substances in general | Unspecified | Emphasizes the gap between preclinical findings and results of ongoing clinical trials to fully understand the potential and mechanisms of GLP-1 receptor agonists in treating SUD. |
| **F. Quddos et al.**<br>- Semaglutide and Tirzepatide reduce alcohol consumption in individuals with obesity**(9)** | 2023<br>Clinical study | Explore the potential efficacy of GLP-1-agonists in reducing alcohol intake among individuals with obesity (BMI>30), being current alcohol drinkers and taking GLP-1 agonists for >30 days (interventions group) compared to individuals not taking GLP-1 (control group). | F: 124<br>Total: 153<br>Intervention group: 106<br>Control group: 47<br>~40 years | Alcohol | Semaglutide and Tirzepatide | *Change in alcohol consumption:* statistically significant lower alcohol consumption in intervention group compared to control group<br><br>*The effects of alcohol intoxication:* reduced in intervention group compared to control group |
| **L. Probst et al.**<br>- Effects of dulaglutide on alcohol consumption during smoking cessation**(13)** | 2023<br>Double-blind RCT | Primary goal to assess the difference in alcohol consumption after 12 weeks of treatment with Dulaglutide on individuals undergoing treatment for smoking-cessation | F: 92<br>Total: 155<br>Intervention group: 76<br>Control group: 75<br>33-53 years | Alcohol | Dulaglutide | *Week 12 Dulaglutide group:* 29 % less alcohol consumption compared to placebo<br><br>*Week 12 Dulaglutide group adjusted for education:* 36 % less alcohol consumption compared to placebo |

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| | | compared to a placebo. | | | | *Subgroup heavy drinkers:* no difference in alcohol consumption compared to placebo |
| **J. R. Richards et al.** - Significant Decrease in Alcohol Use Disorder Symptoms Secondary to Semaglutide Therapy for Weight Loss: A Case Series**(4)** | 2023 Observational study-descriptive Case series | Investigate the impact of Semaglutide therapy, prescribed for weight loss, on the alcohol intake of patients with positive screenings, using AUDIT, for AUD. | F: 5 Total: 6 24-60 years | Alcohol | Semaglutide 0,25-1 mg weekly over 1-9 months period | The mean AUDIT score at intake was 14,0 ± 3,9 with a mean follow up AUDIT of 4,5 ± 2,0. The mean decrease in AUDIT score with Semaglutide was statistically significant relative to a null hypothesis of no change (mean [SD] change= 9,5 [2,7], P< 0,001) |
| **M. P. Bremmer and C. S. Hendershot** - Social Media as Pharmacovigilance: The Potential for Patient Reports to Inform Clinical Research on Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists for Substance Use Disorders**(10)** | 2024 Observational study-descriptive Case series | Seeks to uncover patient-reported effects of GLP-1 receptor agonists on alcohol consumption by analyzing social media posts, thereby offering an innovative approach to support traditional drug development processes. | F: Unspecified M: Unspecified Total: 1 503 Age N/A | Alcohol | Semaglutide | Reduced drinking quantity 31%, Lost interest in alcohol 28,5%, Aversive responses while drinking 26,3%, Reduction in craving 10,4%, No change in alcohol effects 11,7%. |

Table abbreviations: AUD: Alcohol use disorder, AUDIT: Alcohol Use Disorders Identification Test, BMI: Body mass index, CUD: Cocaine use disorder, GLP-1: Glucagon like peptide 1, IV: Intravenous, N/A: Not applicable, NRT: Nicotine replacement therapy, RCT: Randomized control trial, SUD: Substance use disorder

## 5.1. General overview:

The table provides an overview of the research articles. In summary there are two RCT- studies, two clinical trials, two observational studies and the remaining eight articles are review articles discussing the potential and theoretical applications of GLP-1 analogues in treating various addictions.

The overall pattern indicates a greater reliance on review articles for interpreting the role of GLP-1 in addiction, with a notable lack of robust primary research such as more randomized controlled trials. Most of the articles concentrate on AUD with ten articles dedicated to this topic (1, 3, 4, 7, 9, 10, 12-15). Two articles address cocaine use disorder (CUD) (5, 6) and one focuses on tobacco use (18). Additionally, there is one review article included in the table that is exploring the potential of GLP-1 receptor agonists as innovative treatment for addictive disorders (14).

## 5.2. GLP-1 receptor agonists and alcohol use disorder:

The majority of review articles have examined the potential of GLP-1 agonists in AUD (1, 3, 7, 12, 14, 15). The findings suggest a potential role for GLP-1 agonists in treating AUD, but few studies provide clinically significant evidence supporting reduced alcohol intake and altered subjective responses to alcohol. One clinical trial suggested that patients treated with Semaglutide or Tirzepatide for weight loss also exhibited improvement in AUD symptoms such as statistically significant lower alcohol consumption in intervention group compared to control group and reduced alcohol intoxication in intervention group compared to control group (9). This was demonstrated by the mean AUDIT score dropping from 11 to 4 with Semaglutide and from 8 to 3 with Tirzepatide after starting the medication. Additionally, the number of drinks consumed in the past 30 days decreased from 4.5 to 2 drinks with Semaglutide and from 4 to 1 drink with Tirzepatide after initiating the treatment.

Two observational studies have been conducted (4, 10). One study investigated the impact of Semaglutide therapy initially prescribed for weight loss, on the alcohol intake of patients with positive screenings. This study reported a mean decrease in AUDIT score with Semaglutide (4). Another study based on 1 503 patient-reported effects using social media, stated reduced drinking quantity in 31%, lost interest in alcohol in 28,5%, aversive responses while drinking in 26,3%, reduction in craving in 10,4% as well as no change in alcohol effects in 11,7%.

One double blinded-RCT was conducted, investigating the impact of Dulaglutide on AUD during smoking cessation and revealed a 29% decrease in alcohol consumption in intervention group compared to placebo, suggesting that GLP-1 receptor agonists might help reduce alcohol intake in humans undergoing smoking cessation (13). Furthermore, it also implicated that in the subgroup heavy drinkers, there was no difference in alcohol consumption compared to placebo.

## 5.3. GLP-1 receptor agonist and cocaine use disorder:

There is one clinical trial investigating the effect of Exenatide on self-administration and subjective effects of cocaine among individuals with CUD (5). It reported that Exenatide did not significantly alter the primary subjective outcomes related to cocaine-induced effects, such as euphoria or the desire for cocaine, when compared to a placebo. One review article synthesizes a body of preclinical evidence suggesting that GLP-1 receptor agonists could potentially be used to treat CUD (6).

## 5.4. GLP-1 receptor agonist and tobacco use:

One of the articles, a pilot randomized controlled trial conducted by Yammine et al. (2021) (18), evaluated the efficacy of extended-release Exenatide, when combined with NRT for smoking cessation. It found that the combination of Exenatide with NRT was effective in improving

smoking cessation rates, reducing craving and withdrawal symptoms as well as controlling weight gain post-cessation. However, it also showed that Exenatide increased the risk for smoking abstinence compared to placebo (46.3% and 26.8%, respectively).

## 5.5. Proposed mechanism of action:

Across the articles, the proposed mechanisms by which GLP-1 receptor agonists exert their effects on substance use involve modulation of the mesolimbic dopamine system, which is central to the brain's reward pathways. By influencing this system, GLP-1 receptor agonists may reduce the reinforcing effects of drugs and alcohol (1, 2, 6, 7, 10, 12, 13, 18). None of the included studies demonstrated a change in the proposed signaling pathway.

# 6. Discussion:

This scoping review study has explored the current body of literature regarding GLP-1 receptor agonists in the treatment of substance use disorders from 2014 to 2024. The findings across the articles suggest a potential role for GLP-1 receptor agonists in the treatment of various SUDs with primary results revealing an expanding evidence base that suggests GLP-1 receptor agonists may be effective in treating AUD and tobacco dependence, though the findings are less consistent for CUD (1-3, 6, 7, 10, 12-15, 18).

This review aligns with existing research suggesting the potential benefits of GLP-1 receptor agonists in SUD treatment. Preclinical studies indicate that GLP-1 receptor activation can modulate dopamine release in the NAc (6, 11, 12). This modulation may influence the rewarding properties of drugs and substances, potentially impacting the development and maintenance of addictive behaviors. It is believed GLP-1 analogs spur addiction in part by quelling activity of this system and the same mechanism could explain why people who take the medications report they are less motivated to drink alcohol and smoke (15). While the preclinical data are promising, particularly in reducing alcohol and cocaine use in animal models (19, 20), further research is necessary to translate these preclinical findings into practical and systematic clinical guidelines for treating SUD.

Quddos F et al. (9) have shown statistically significant reductions in alcohol consumption and intoxication, particularly with Semaglutide and Tirzepatide. The reduction in the number of drinks consumed over the past 30 days reinforces the effectiveness of these treatments. Patients reported a decrease from 4.5 to 2 drinks with Semaglutide and from 4 to 1 drink with Tirzepatide. This significant decline in alcohol consumption could imply that these medications could lead to tangible behavioral changes. However, the self-report nature of this study is subject to selection bias, as individuals

who experience both positive and negative effects are more likely to report them than those who experience no effect. Also, this study only included individuals with obesity limiting the results to this population.

Additionally, an observational study reported decreased alcohol intake among patients prescribed Semaglutide for weight loss (4). However, a double-blinded RCT with Dulaglutide highlighted the need for further investigation into the variability of responses among different subgroups of AUD patients, especially heavy drinkers (13). One multi-cohort observational study explored the potential of the GLP-1 receptor as a therapeutic target for alcohol use disorder by examining the genetic association between GLP-1 receptor variants and AUD, evaluating how GLP-1 receptor variants influence alcohol consumption behavior, investigating their effects on brain activity related to reward, and testing the efficacy of GLP-1 receptor agonism in reducing alcohol intake (19). Participants with a specific genetic variant of the GLP-1 receptor administered significantly more alcohol to themselves and had higher breath alcohol concentrations. This could suggest that individual genetic differences could determine the therapeutic effectiveness of these drugs, making personalized medicine a consideration in the treatment of AUD. Identifying specific genetic markers associated with positive responses to GLP-1 receptor agonists could therefore lead to more targeted and effective interventions for individuals struggling with alcohol dependence.

The role of GLP-1 receptor agonists in CUD treatment remains unclear. While a clinical trial with Exenatide did not show significant changes in cocaine-induced euphoria or desire (5), preclinical evidence suggests potential benefits. Notably, a study found decreased GLP-1 levels following intravenous cocaine use, correlating with increased heart rate and euphoria (20). These findings suggest that GLP-1 receptor agonists might mitigate some subjective effects of cocaine by normalizing GLP-1 levels, though more research is needed to confirm these effects and more robust clinical

research, such as RCTs, are needed to evaluate the effects of GLP-1 receptor agonists and its effect on CUD.

For tobacco dependence, a pilot RCT demonstrated that combining Exenatide with NRT significantly improved smoking cessation rates compared to NRT alone (18). This suggests that GLP-1 receptor agonists could enhance existing smoking cessation strategies by addressing withdrawal symptoms and weight gain associated with quitting smoking. A factor to consider is that in the pursuit of alternative reinforces, individuals quitting smoking may increase their consumption of alcohol (21).

Nonetheless, potential side-effects and the mechanism of action in the proposed signaling pathway mechanisms remains an area for future research to explore. On the other hand, GLP-1 receptor agonists are widely prescribed in the treatment for diabetes and obesity, providing a substantial base of clinical experience with these medications. Research in the field lack the discussion on potential differences between various GLP-1 analogues preventing the ability to offer individualized treatment options in the field of SUD. To identify the role of GLP-1 agonists in the treatment of SUD further studies are needed to elucidate which patients would benefit and whether GLP-1 agonists improve long-term abstinence. Another aspect to take into consideration is the potent placebo response, which is often the case in addiction treatment (22). Preclinical data suggest that GLP-1 can attenuate withdrawal, as experiments with GLP-1 agonists reduced withdrawal-induced anxiety in rodents (23, 24). This has not yet been demonstrated in human studies from the articles included in this scoping review, highlighting a potential field for future research.

Overall, the field exhibits a significant discrepancy between the volume of review articles and original studies, pointing to a foundational gap in research. This predominance of review articles over RCTs could indicate a research landscape marked by high interest, yet the foundational research

appears insufficient to support the level of interpretation required for clinical application.

The choice of methodology in this study, particularly the reliance on literature reviews, comes with inherent limitations. Literature reviews synthesize existing data rather than generating new empirical findings, which can sometimes lead to gaps in knowledge that only primary research can fill. While a literature review offers a comprehensive overview of the current understanding and trends within a field, it may also reinforce existing biases in the literature and is limited by the quality and scope of the studies reviewed. Conducting a RCT would provide more definitive evidence on the effectiveness of GLP-1 receptor agonists in treating SUD.

Given these considerations, while an RCT is the standard method for future research, it is not currently practical due to the extensive resources and time that would be required for now. However, an alternative approach could involve conducting more small-scale observational studies on patients currently receiving GLP-1 receptor agonist treatment for conditions like obesity and diabetes who also have concurrent SUD. Literature reviews alone will not generate new knowledge; to advance our understanding, it is essential to gather empirical observations from actual patients. These observational studies could provide important insights and pave the way for more comprehensive research endeavors.

# 7. Conclusion

In conclusion, GLP-1 receptor agonists show promise in reducing alcohol consumption and enhancing smoking cessation programs, though their impact on CUD is less clear. Future research should focus on conducting RCTs to confirm the efficacy of these treatments and explore the mechanisms underlying their effects. Clinicians should remain informed about emerging evidence and consider the potential benefits and risks of GLP-1 receptor agonists in treating SUDs. Overall, while promising, the application of GLP-1 receptor agonists in SUD treatment requires further investigation to fully understand their therapeutic potential and ensure safe and effective clinical use. Long-term data with extended follow-up periods are essential.

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