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Review

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

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ABSTRACT

*Background:* Increasing evidence suggests that GLP-1 receptor agonists (GLP-1RA) have a potential use in addiction treatment. Few studies have assessed the impact of GLP-1RA on substance use disorder (SUD), particularly in humans. The study aimed to do systematic review of clinical trials to assess GLP-1RA's effect on reducing SUD in patients.

*Methods:* The scientific literature was reviewed using the MEDLINE, Scopus and Cochrane Library databases, following PRISMA guidelines. Studies including patients with a diagnosis of SU who were treated with GLP-1RA were selected. The primary outcome was GLP-1RA's therapeutic effect on SUD, and the secondary outcomes were therapeutic effects of GLP-1RA on weight, BMI and HbA1c.

*Results:* 1218 studies were retrieved, resulting in 507 papers after title and abstract screening. Following full-text review, only 5 articles met inclusion criteria. We incorporated a total of 630 participants utilizing Exenatide (n=3) and Dulaglutide (n=2) as GLP-1RAs. Therapeutic effect of GLP-1RA on SUD was assessed in 5 studies, with 3 demonstrating a significant decrease in SUD (alcohol and nicotine). GLP-1RA's impact on body weight, BMI, and HbA1c, was reported in 3 studies. These revealed a notable reduction in these parameters among the GLP-1RA treated group.

*Conclusion:* This review will give an overview of current new findings in human studies; we suggest that the effects of GLP-1RA in SUD is a possible new option of therapy in addiction medicine.

## 1. Introduction

Globally, an estimated 39.5 million people are affected from substance use (SU) (World Drug Report, 2023) and in 2021 alone, 5.8 percent of the world's population - or 296 million people - used drugs, an increase of about 23 percent from the previous 10 years. Approximately five million people are affected from cocaine use disorder (CUD) (Peacock et al., 2018; Klausen et al., 2022a), whose deaths from overdose are rapidly increasing and exceed opioid overdose deaths (Kampman). In addition, the World Health Organization (WHO) indicates that 280 million people are affected from alcohol use disorder (AUD) (Alcohol, 2024), but only 1 in 5 people have received drug treatment, with the situation worsening in the previous years due to the pandemic (World Drug Report, 2023). AUD is responsible for high mortality due to medical complications, injury (Carvalho et al., 2019) and suicide (Borges et al., 2017). In fact, according to WHO, alcohol causes 5.3 percent of deaths worldwide and, overall, 5.1 percent of the global burden of disease and injury – measured in Disability Adjusted Life Years (DALYs) – is attributable to alcohol consumption. Excessive alcohol use results in significant social and economic losses for individuals and society at large causing death and disability in young adults (Alcohol, 2024). As with alcohol, tobacco is one of the leading causes of premature death, and globally, 940 million men and 193 million women smoked tobacco in 2019 (The tobacco atlas, 2024). Despite available treatment options for smoking cessation, the relapse rate is around 95–98 % (Prochaska and Benowitz, 2016). Specifically,

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chronic psychoactive SU is characterized by a transition from recreational drug use to compulsive and disordered use. The prevailing scientific consensus has identified addiction as a chronic disease, codified as substance use disorder (SUD). SUDs are characterized by pharmacological effects of tolerance and withdrawal, as well as a core set of behavioral components defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). These can be grouped into three main categories: improbability to control SU; social distress; and risky SU (Poisson et al., 2021).

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted, in response to meal ingestion, by intestinal L cells (Creutzfeldt, 1979). Its function is to stimulate insulin release from pancreatic β-cells, lowering glucose levels (Hayes et al., 2014; Müller et al., 2019), slowing gastric emptying and promoting satiety (Tang-Christensen et al., 1998; Turton et al., 1996; Langhans, 2000; Alhadeff et al., 2012; Mietlicki-Baase et al., 2017; Wang et al., 2015). Therefore, GLP-1 receptor analogs (GLP-1RA) were developed to treat patients with type 2 diabetes mellitus and subsequently used in patients with obesity with good results (Maselli and Camilleri, 2021). Currently GLP-1RAs are approved by the FDA for the treatment of these two conditions (Kreymann et al., 1987; Srivastava and Apovian, 2018) that pose major public health concerns.

GLP-1 is a peptide hormone mainly secreted by 3 tissues in the human body: enteroendocrine L cells in the distal intestine, alpha cells in the pancreas, and the central nervous system (Zhao et al., 2021), participating in the regulation of glucose homeostasis through its interaction with GLP-1R. GLP-1RA are a class of drugs initially used in patients with type 2 diabetes with expanding clinical indications. The therapeutic application and potential value of GLP-1RA for several diseases represents a research hotspot. Their clinical effects, in addition to glucose reduction, include decrease of blood pressure and weight loss, protection against major cardiovascular disease, and reduction of cardiovascular mortality (Brown et al., 2021a). Furthermore, GLP-1RAs play a neuroprotective effect by stimulating the differentiation of nerve cells and inhibiting neuroinflammation (Pelle et al., 2023). Other studies underway are analyzing the correlation between the function of GLP-1RAs and the development and progression of tumors (Zhao et al., 2021).

GLP-1RA are highly likely to act on the brain through the humoral pathway in addition to the neural pathway, where they could remain in the brain for several hours as they are stable, and exert effects similar to those induced by the brain-derived GLP-1 (Katsurada and Yada, 2016). Previous studies on murine models have shown that peripheral liraglutide GLP-1 directly stimulates pro-opiomelanocortin/cocaine- and amphetamine-stimulated transcript neurons, and indirectly inhibits neurotransmission to neuropeptide Y/Agouti-related peptide neurons through gamma-aminobutyric acid-dependent signals (Katsurada and Yada, 2016, 2016; Isbil-Buyukcoskun and Gulec, 2004).

Animal model studies have highlighted a potential role of these drugs in the treatment of Parkinson's disease, Alzheimer's diseases, dementia (Dahiya et al., 2022; Bi et al., 2023).

The GLP-1R, a stimulatory G-protein receptor, is expressed in several discrete CNS nuclei including the hypothalamus and hindbrain (Martinou et al., 2022). Importantly, GLP-1Rs are expressed in key brain areas controlling reward and motivated behaviors that include the ventral tegmental area (VTA) and the nucleus accumbens (NAc); their role within these brain areas, however, remains largely unknown. The VTA and its dopaminergic projections to the NAc orchestrate goal-oriented motivation. It is also becoming increasingly clear that addictive drugs can hijack the reward system, a system originally evolved to motivate drive toward natural rewards. Although the brain centers of reward control are neuroanatomically separate, they are not entirely disconnected from the classical homeostatic centers and, under physiological conditions, bidirectional communication occurs between the two regions (Martinou et al., 2022). Many of the classical hormones that regulate feeding directly impact mesolimbic VTA/NAc neurons, such as GLP-1 (Martinou et al., 2022). GLP-1RA drugs, whose receptors are expressed in brain regions thought to be involved in reward and addiction (Cork et al., 2015; Jensen et al., 2020; Rinaman, 2010), have been found to reduce SUD and addiction-like symptoms in preclinical studies. Addiction-like symptoms include escalation of SU, neurocognitive deficits, tolerance, exaggerated motivation for drugs, increased reinstatement of drug seeking after extinction' effect and preference for drug over nondrug rewards (Vanderschuren and Ahmed, 2021). Animal studies have reported discordant results with respect to the regulation of addiction behaviors by GLP-1RA (Bornebusch et al., 2019; Sirohi et al., 2016). Bornebusch et al. in their study on rodents demonstrated that GLP-1RA decreased oral alcohol self-administration but did not attenuated the addiction related behavioral effects of opioids (Bornebusch et al., 2019). Sirohi et al (Sirohi et al., 2016). studied alcohol intake, amphetamine reinforcement and hedonic feeding on rodents. First, the effect of EX-4 pretreatment on the expression of amphetamine-induced conditioned place preference (Amp-CPP) was examined in the FLOX and GLP-1R KD(Nestin) mice. Next, alcohol intake (10 % v/v) was evaluated in FLOX and GLP-1R KD(Nestin) mice following saline or EX-4 injections. Finally, they ~~we~~ assessed the effects of EX-4 pretreatment on hedonic feeding behavior (Sirohi et al., 2016). Results indicate that Amp-CPP was completely blocked in the FLOX mice, but not in the GLP-1R KD(Nestin) mice following EX-4 pretreatment. Ex-4 pretreatment selectively blocked alcohol consumption in the FLOX mice, but was ineffective in altering alcohol intake in the GLP-1R KD(Nestin) mice. Notably, hedonic feeding was partially blocked in the GLP-1R KD(Nestin) mice, whereas it was abolished in the FLOX mice. The present study provides critical insights regarding the nature by which GLP-1 signaling controls reinforced behaviors and underscores the importance of both peripheral and central GLP-1R signaling for the regulation of addictive disorders. Correspondingly, recent studies are testing the use of GLP-1RAs for the treatment of AUD (Farokhnia et al., 2022), tobacco use disorder (Lengsfeld et al., 2023a; Yammine et al., 2021) and other SUDs (Leslie, 2023a). Therefore, the purpose of our work was to conduct a systematic review of clinical papers published to date regarding the use of GLP-1RA in patients with addictions, evaluating therapeutic response and efficacy on SUD.

## 2. Material and methods

### 2.1. Study design

A systematic review was conducted in keeping with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2021). This work was recorded on PROSPERO, International prospective register of systematic reviews (ID: CRD42024500110). The included population consisted of human patients, $\geq$ 18 years old who have been treated with GLP-1RA and who have been diagnosed with SUDs. Outcomes of interest included patient characteristics and different types of SUDs.

### 2.2. Search strategies

An electronic search of the in MEDLINE, Scopus and Cochrane Library (Wiley) databases was performed on March 15, 2024, looking for relevant studies that could be included in this study. The search was performed by setting the following terms: "GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONISTS [MeSH terms]" AND "substance use [MeSH terms]" OR "substance abuse [MeSH terms]" OR "cocaine use [MeSH terms]" OR "alcohol use [MeSH terms]" OR "tobacco use [MeSH terms]" OR "caffeine use [MeSH terms]" OR "hallucinogens use [MeSH terms]" OR "volatile solvents use [MeSH terms]" OR "cannabinoid use [MeSH terms] " OR "hypnotics use [MeSH terms]" OR "opioids use [MeSH terms]". The Boolean operator "AND" was used to combine parts of the subject terms and "OR" was used to expand the search. Two independent reviewers (SM and NP) screened titles and abstracts, assessed full-text versions, and extracted data. Disagreements were resolved by

re-extraction or third-party adjudication.

### 2.3. Data extraction and quality assessment

The literature search was performed by two independent reviewers (SM and NP) using a predefined search strategy. Duplicate studies were removed manually. Each reviewer then examined the titles, abstracts and/or full texts of included manuscripts to ensure that all inclusion criteria were met before extracting the following data: first author's name, year of publication, study design, country of origin, number of patients included, type of GLP-1RA, measurement tool, patients' characteristics, dose and duration of GLP-1RA treatment, clinical efficacy of GLP-1RA treatment on SUD.

### 2.4. Inclusion and exclusion criteria

We defined our study eligibility using the populations-interventions-comparators-outcomes (PICO) study design framework. Population: Adults with SUD per the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), International Classification of Diseases 10th Revision (ICD-10) or other classification. We included all patients regardless of psychiatric comorbidities, age, gender, body mass index (BMI) and education. Interventions: treatment with GLP-1RA. Comparator: RCT or placebo-controlled clinical trials. Outcomes: Alcohol, tobacco or psychoactive SUD (total abstinence and reduced use). We excluded non-English studies, animal studies, abstracts, review articles, case reports or case series including less than 10 subjects; editorials or letters, studies not evaluating the use of GLP-1-RAs on SUD-related effects; patient age $< 18$. Where overlapping studies were identified or suspected, the more recent or informative study was included for analysis.

### 2.5. Primary and secondary outcomes

The primary outcome of the present study was to determine the relationship between the therapeutic effect of GLP-1RA and the decrease in SUD in patients. Secondary outcomes included the effects of GLP-1RA on body weight, BMI, glycated hemoglobin levels. Primary outcome was defined at the time of the first studies' selection, while secondary outcomes were included following title and abstract review in order to capture a complete and accurate representation of the patient characteristics that have been evaluated by current literature.

### 2.6. Risk of bias assessment

The Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to rate risk of bias for non-randomized included studies (Sterne et al., 2016). Thus, the Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) is the recommended tool to assess the risk of bias in randomized trials included in Cochrane Reviews (Sterne et al., 2019). RoB 2 is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct, and reporting. Within each domain, a series of questions ('signaling questions') aim to elicit information about features of the trial that are relevant to risk of bias. A proposed judgement about the risk of bias arising from each domain is generated by an algorithm, based on answers to the signaling questions. Judgement can be 'Low' or 'High' risk of bias or can express 'Some concerns'.

### 2.7. Statistical analysis

Patients' characteristics and outcomes were summarized and described as means ± standard deviation or median (IQRs) for continuous variables or percentages for categorical variables. Secondary outcomes were qualitatively analyzed due to heterogeneity of outcome reporting in the included studies.

## 3. Results

### 3.1. Study selection

A total of 1218 studies were retrieved, and 507 unique results remained for the initial title and abstract screening. Results were screened and 39 manuscripts underwent full-text review. Finally, only 5 articles met full inclusion criteria (Fig. 1). Studies included 5 randomized, placebo controlled trials (Lengsfeld et al., 2023a; Yammine et al., 2021; Angarita et al., 2021; Klausen et al., 2022b; Probst et al., 2023). Table 1 reports the types of SUD in the included studies, according to DSM-5TR (alcohol in 2 studies, cocaine in 1, nicotine in 2). Two studies were carried out in the United States. SUD diagnosis was conducted using DSM-5 criteria (n=1), AUDIT (n=1), FAGERSTROM test (n=1) or medical examination (n=2) (Table 1).

### 3.2. Risk of bias assessment

There was low to moderate risk of bias in the included study according to the RoB 2. Overall, 1 of the included studies had low risk of bias for all the items (Yammine et al., 2021), one study had low or moderate risk in all items (Lengsfeld et al., 2023a), while 3 studies had high risk for bias for 1 or more items (Angarita et al., 2021; Klausen et al., 2022b; Probst et al., 2023) (Table 2).

### 3.3. Study characteristics

Across the 5 studies, a total of 630 participants were included. The GLP-1RAs used were Exenatide (n=3) and Dulaglutide (n=2), as shown in Table 3. The trial duration ranged from 6 to 26 weeks. All the studies (n=5) were RCT, and almost all of them took place in outpatient settings (n=4).

### 3.4. Patients' and diseases' characteristics

In Table 3, patient characteristics are reported, including age, sex, educational level, psychiatric comorbidities, and BMI. Three studies included persons with co-occurring psychiatric disorders.

### 3.5. Outcomes

Table 4 reports the outcomes. The primary outcome (relationship between the therapeutic effect of GLP-1RA and the decrease of SUD) was reported by 5 studies, and 2 of them detected a significant effect of GLP-1RA on decreasing SUD (alcohol in 1 study, nicotine in 1) (Yammine et al., 2021; Klausen et al., 2022b; Probst et al., 2023). One study did not detect a significant effect of GLP-1RA on alcohol use, but found an effect in a subgroup of participants who were obese (Klausen et al., 2022b). One study did not show any significant effect of the administration of GLP-1RA on subjective effects of cocaine or cocaine administration (Angarita et al., 2021) and the latter did not find significant differences of dulaglutide on smoking abstinence rate (Lengsfeld et al., 2023a).

Secondary outcomes included the effects of GLP-1RA on body weight, BMI, glycated hemoglobin levels and were reported by 4 studies, showing a significant reduction of body weight, BMI and glycated hemoglobin levels in the GLP-1RA treated group.

## 4. Discussion

The present systematic review highlights the potential role of GLP-1RA in the treatment of SUDs. The published evidence consists of five randomized trials, analyzing the effects of exenatide and dulaglutide on alcohol, nicotine and cocaine use. Two out of five studies detected a significant decrease in the SUD in the treated group versus the placebo group, one study detected a decrease only in a subset of participants, and two studies did not find a significant difference on cocaine and tobacco

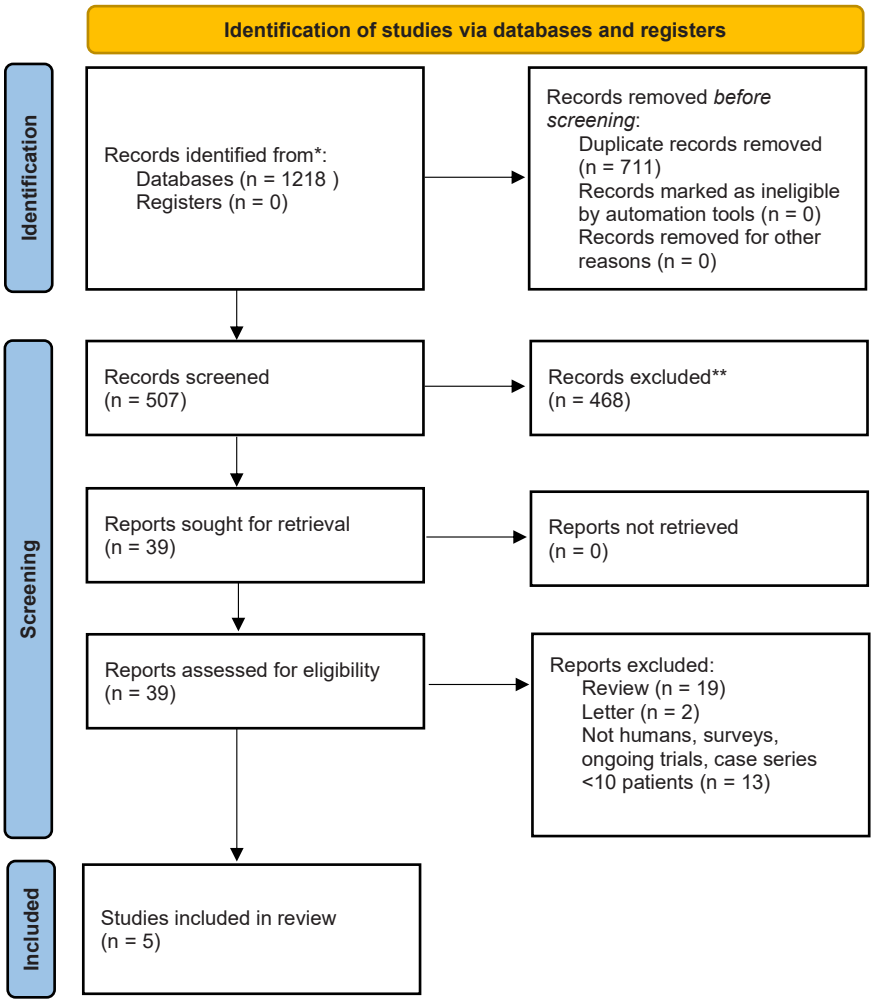


**Fig. 1.** "flow chart of the search process according to the PRISMA guidelines". *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

**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

use (Angarita et al., 2021). The study on cocaine use (Angarita et al.) however had several limitations and differences with the first three papers (Yammine et al., 2021; Klausen et al., 2022b; Probst et al., 2023). The paper by Angarita et al (Angarita et al., 2021). included only 13 patients, with administration of exenatide limited to one single dose and using as outcomes two different endpoints: number of cocaine "infusions" (button presses by the included subjects associated with a cocaine injection) and subjective cocaine effects using computerized VAS self-ratings. On the other hand, in 3 RCTs the treatment with GLP-1RA was administered for longer periods ranging from 6 to 26 weeks and had a significant effect on alcohol and nicotine use. The study by Lengsfeld et al (Lengsfeld et al., 2023a). reported no effect of

**Table 2**
Methodological quality evaluation of the included non-randomized studies according to RoB-2.

| Author | Domain 1 | Domain 2 (first part) | Domain 2 (second part) | Domain 3 | Domain 4 | Domain 5 |
|---|---|---|---|---|---|---|
| Yammine | Low | Low | Low | Low | Low | Low |
| Angarita | Low | Low | Low | High | Low | High |
| Klausen | Low | High | Low | Low | Low | Low |
| Probst | Low | Low | High | Low | High | Low |
| Lengsfeld | Low | Low | Moderate | Moderate | Low | Low |

Domain 1: risk of bias arising from the randomization process
Domain 2 (first part): risk of bias due to deviation from the intending intervention (effect of assignment to intervention)
Domain 3 (second part): risk of bias due to deviations from the intending intervention (effect of adhering to intervention)
Domain 3: missing outcome data
Domain 4: risk of bias in measurement of the outcome
Domain 5: risk of bias selection of the reported result

**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)
**: Median (Interquartile Range)
***: data reports the number of patients (percentage) with BMI>29.9
BMI: Body mass index
Sc: subcutaneous
GLP-1RA: Glucagon-like peptide-1 Receptor Agonist
NA: Not assessed
#: >29.9 BMI

dulaglutide on tobacco abstinence rates but an effect on prevention of post-cessation weight gain and decreased HbA1c levels. Also the other 2 studies (Klausen et al., 2022b; Yammine et al., 2023) providing the information demonstrated additional beneficial effects in weight and BMI reduction and glycated hemoglobin reduction. Adverse events were mainly gastrointestinal symptoms, and the rate of serious events was not different compared to placebo (Klausen et al., 2022b).

These results suggest a potential role of GLP-1RA in the management of patients with SUDs, even if the number of relevant published study is still low, the results are not fully concordant and concern only ethanol and nicotine. In 3 of the included randomized trials, the effects of GLP-1RA were present despite different types of GLP-1RA, doses and duration of treatment, which lasted a minimum of 6 weeks. The results of the systematic review are not discordant with the results of small case studies, such as that of Richards et al (Richards et al., 2023)., which demonstrated the potential of GLP-1RA in the treatment of AUD in 6 patients. The study by Richards et al (Richards et al., 2023). is a retrospective chart review; the authors identified patients treated with semaglutide for weight loss who also had positive screenings for hazardous alcohol use with AUDIT test. Following treatment with semaglutide all 6 patients had a significant decrease of AUDIT scores and AUD symptoms.

The reward circuit and related structures may participate in the interactions between the GLP-1 pathway and psychoactive substances. Primarily, the literature has largely endorsed a relationship between obesity and SUD, postulating that exposure to highly palatable foods increases key neuroendocrine signals, which remodel brain reward circuits to reinforce pathological eating behaviors (Brutman et al., 2019; Bliss and Whiteside, 2018). Highly palatable foods interact with brain reward circuits to promote intake, just as would happen at the neurobiological level with SUD (Martinelli et al., 2024). Neuroscience studies of rats with obesity observe typical neurobiological features of addiction in their brain systems, which result from behaviors similar to addiction to foods rich in fat and sugar (Brown et al., 2021b).

However, because GLP-1R expression is widespread throughout the brain, it is very likely that other brain areas participate in these

**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. |

SUD: Substance Use Disorder
GLP-1RA: Glucagon-like peptide-1 Receptor Agonist
NA: Not assessed

interactions (Jerlhag, 2023). A further priority of upcoming studies will be to define the key neurocircuits involved and confirm or deny the potential utility of GLP-1RA in the context of SUDs. Furthermore, future research on GLP-1RA treatment in patients with SUD can fill the gaps regarding optimal duration of pharmacotherapy, maintenance and dose titration strategies, and ways to improve pharmacotherapy utilization. More knowledge is needed about chronic and prolonged effects of different GLP-1RA, as well as the effect on other psychoactive substances not yet studied, such as amphetamines, opioids, and benzodiazepines. In addition, further studies are needed to identify the patients or subtypes of patients with various addictions who might benefit from treatment with these drugs: for example, the possibility that polymorphisms in GLP-1R genes affect the results of GLP-1RA treatment on alcohol consumption in patients with AUD.

We underline that other clinical trials (Yammine et al., 2023; Lengsfeld et al., 2023b; Antonsen et al., 2018 Jul 16; Leslie, 2023b) have been designed, registered on clinicaltrial.gov and are ongoing and in the future further data may more accurately delineate the role of GLP-1RA in the management of substance use disorder.

### 4.1. Strengths and limitations

The strengths of this systematic review include a careful methodology in accordance with the most accredited guidelines. However, several limitations should be highlighted. Given the relative novelty of the study topic, the results are limited by the amount of data that could be extracted. Only 5 studies were identified, although there were no restrictions on the time frame. However, the restriction to human studies, completed clinical trials, and English-language studies only limited the number of included articles. Furthermore, the studies had a high degree of heterogeneity, concerning the type of substance, the characteristics of the included patients, the type and doses of the GLP-1RA administration limiting the possibility to perform a meta-analysis among studies. However given the lack of standardized protocols for RCTs in this area, this heterogeneity was unavoidable and was not a specific limitation of this review. We underscore that the results of this review should be viewed with some caution with respect to the primary outcome, i.e., characterization of the effect of GLP-1RA on SU-related behaviors, because of the different types of GLP-1RA used in the various studies, dosages, and treatment durations. Nevertheless, this systematic review is a first step to encourage new studies and insights on the topic.

## 5. Conclusion

In conclusion, current clinical trials indicate a potential role of GLP-1RA to treat patients with SUDs.

The literature review showed uneven results, with a positive effect on decreasing substance use in some studies and no effect in others. It is desirable that further randomized studies be conducted on homogeneous groups of patients affected by SUD (stratified according to the type of substance use disorder) in which the effect of GLP-1RA is tested.

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## Statement of human and animal rights and informed Consent

In the studies included in this review, the study-related procedures were performed in accordance with the Declaration of Helsinki. Participants enrolled in each study provided voluntary written informed consent.

## CRediT authorship contribution statement

**Silvia Martinelli:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mattia Longaroni:** Writing – review & editing, Validation, Software, Resources, Project administration, Methodology, Formal analysis, Data curation. **Alessandro Mazzotta:** Writing – review & editing, Visualization, Validation, Software, Resources, Project administration, Methodology, Formal analysis, Data curation. **Niccolo Petrucciani:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation.

## Declaration of Competing Interest

None

All authors declare no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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