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Glucagon-Like Peptide-1 Receptor Agonist potential in AUD treatment. Neurobiological Mechanisms and Clinical Evidence

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ABSTRACT

Alcohol Use Disorder (AUD) constitutes a significant global health challenge, with standard pharmacological treatments constrained by limited long-term efficacy and poor patient adherence. Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs), originally used in the management of diabetes, have recently been identified as potential treatment for AUD due to their influence on the gut-brain axis and mesolimbic reward circuit. This review synthesizes evidence from a systematic search of PubMed and Scopus (January 2010 to July 2025), with emphasis on contemporary GLP-1 RAs such as Semaglutide, Liraglutide, and Exenatide. Preclinical studies consistently show that GLP-1 RAs reduce alcohol intake, motivation, and relapse-like behaviors in animal models by modulating dopaminergic signalling in the structures of the reward system. Cohorts and early randomized clinical trials provide indications that GLP-1 RAs treatment results in a reduction in the prevalence of Heavy Drinking Days and craving, potentially induced by the cross-reward effect. Although the safety profile appears favorable, most of the evidence comes from retrospective data and pilot studies. In summary, GLP-1 RAs are a promising intervention for AUD. However, there is still a requirement for large-scale randomized controlled trials with standardized abstinence endpoints to establish their efficacy and future clinical utility.

Keywords: Alcohol Use Disorder, Addiction, Reward circuit, Semaglutide, GLP-1 Receptor agonist, Craving

1. INTRODUCTION

Alcohol Use Disorder (AUD) is a chronic condition representing a significant public health problem. According to the WHO, it is a reason for millions of deaths annually worldwide. It is defined by impaired control over alcohol intake despite negative social or health consequences. The medications currently available in the standard pharmacological treatment of AUD, such as naltrexone (an opioid receptor antagonist) and acamprosate (a GABA/ NMDA modulator), although valuable, are

characterized by limited long-term efficacy and a low rate of patient adherence. This therapeutic gap reinforces the urgent need for the identification of new, both safe and effective molecules targeted at the underlying neurobiological addiction mechanism.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs), widely used in the management of type 2 diabetes and obesity (e.g., Liraglutide, Semaglutide), are emerging as a promising and innovative drug class. Their therapeutic rationale is grounded in their involvement in the gut-brain axis and in the expression of GLP-1 Receptors within the reward system, localized in key mesolimbic structures (Vallöf et al., 2019; Keller et al., 2022) (including the Ventral Tegmental Area and the Nucleus Accumbens), which constitute a critical addiction pathway (Farokhnia et al., 2022). This review analyzes the current state of knowledge regarding the therapeutic potential of GLP-1 RAs in the treatment of Alcohol Use Disorder.

2. REVIEW METHODS

We conducted a literature review using the Web of Science, PubMed, Cochrane Library, and Scopus. We covered publications from January 2010 to July 2025, focusing on modern GLP-1 RAs (Liraglutide, Semaglutide, Exenatide). The review scope was defined by the application of multiple complementary search platforms and keywords. Various search engines and keywords like "GLP-1 agonist", "Semaglutide", "Liraglutide", "Alcohol Use Disorder", "alcohol consumption", "craving", "addiction", and "reward circuit" were utilized. We analyzed original clinical, large cohort, or registry studies examining associations between GLP-1 RAs use and AUD, craving, and overall alcohol intake, and Peer-reviewed systematic reviews and meta-analyses. We excluded studies focused exclusively on other substance addictions or solely on the metabolic effects of GLP-1 RAs without behavioral context, or that lacked an appropriate control group (except for large cohort studies). We also excluded in vitro studies, letters to the editor, opinions, and conference abstracts without full peer review (Figure 1).

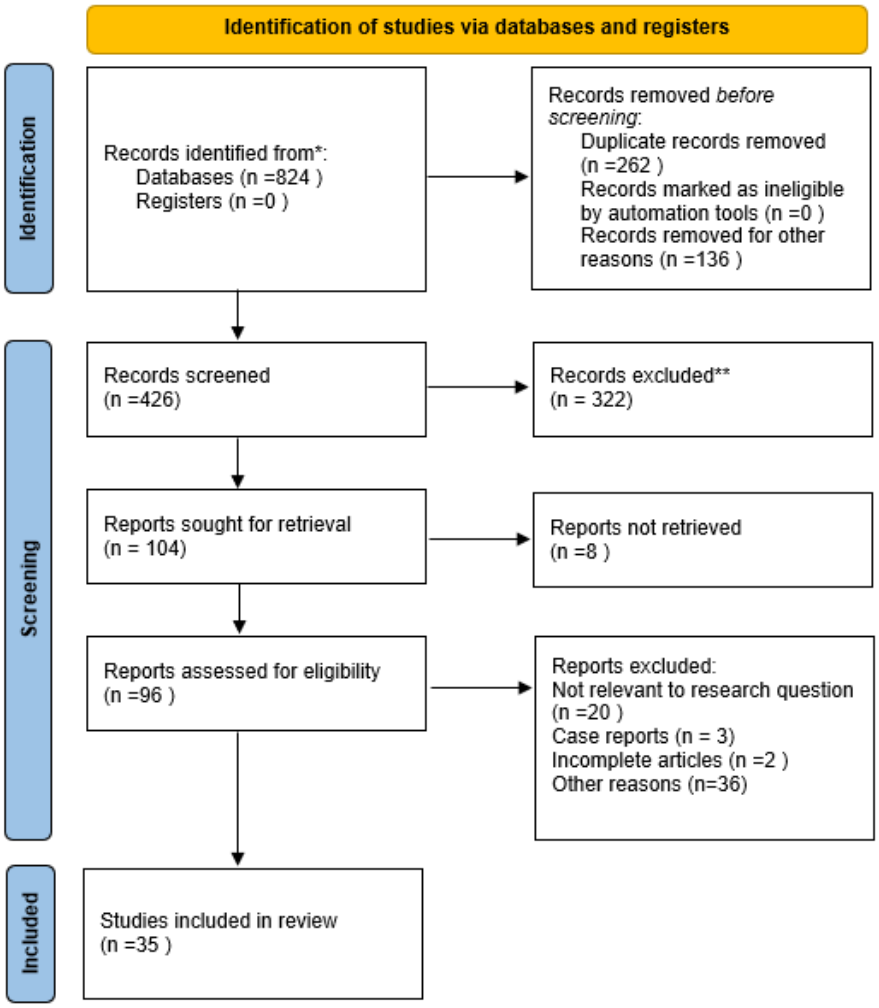

Figure 1. PRISMA flowchart

3. RESULTS AND DISCUSSION

Physiological Basis of GLP-1 and Mechanisms in AUD

Glucagon-like peptide 1 is an endogenous molecule released from the intestines and neurons in the brainstem (NTS). Its action is mediated by the activation of the GLP-1 receptor (GLP-1R), a G protein-coupled receptor. Endogenous GLP-1 has a short half-life and is rapidly inactivated by the enzyme Dipeptidyl Peptidase-4 (DPP-4). GLP-1 Receptor Agonists are synthetic analogs that, in addition to mimicking the natural hormone's effects, exhibit decreased resistance to degradation by DPP-4, resulting in prolonged half-life and convenient dosing. In the context of alcohol addiction, the presence and function of GLP-1 receptors in the Central Nervous System (CNS) are of key importance (Table 1).

Table 1. GLP-1R Location and Its Relevance in AUD

Anatomical Location	Key Physiological Function	Role in Alcohol Use Disorder (AUD)
Ventral Tegmental Area (VTA)	Source of dopaminergic neurons, reward, and motivation integration.	GLP-1R activation reduces the excitability of dopaminergic neurons, suppressing the dopamine (DA) surge induced by alcohol.
Nucleus Accumbens (NAc)	Crucial for the sensation of the reward, euphoria, and positive reinforcement.	Decreased DA release in the NAc weakens the hedonic and motivational value of alcohol.
Nucleus of the Solitary Tract (NTS)	A crucial element of the Dorsal Vagal Complex (DVC). It processes visceral sensory inputs (satiety, taste) and transmits them to higher brain regions.	It acts as a 'gateway' for signals from the gut-brain axis. Stimulation of GLP-1R in the NTS inhibits alcohol-seeking behaviors, likely by interpreting its consumption as a signal of satiety or metabolic discomfort.
Hypothalamus	Regulation of energy homeostasis, appetite, and control of the HPA (stress) axis.	Regulates the stress response via the HPA axis; crucial for preventing stress-induced relapse and mediates the cross-reward effect.
Amygdala	Processing of emotions, fear, and assigning emotional significance to stimuli.	Modulates the emotional importance of reward-related cues and reduces withdrawal anxiety, which drives negative reinforcement drinking.
Prefrontal Cortex and Hippocampus	Executive Function (decision-making, impulse control), contextual memory, and learning.	Enhances impulse control and decision-making (PFC). Weakens the influence of contextual memory (Hippocampus) that triggers craving and relapse.

This broad distribution, including not only reward centers but also the hindbrain and limbic structures, provides a strong basis for the hypothesis that pharmacological activation of GLP-1R can modulate behaviors associated with substance abuse, including alcohol. GLP-1 receptor agonists (GLP-1 RAs) exert their influence via mechanisms that are far more intricate than what was earlier assumed. Specifically, while the involvement of the Ventral Tegmental Area (VTA)has been recognized, recent research suggests that GLP-1 receptors located directly in the Nucleus Accumbens (NAc) also play an important role in reducing alcohol-induced reward (Allingbjerg et al., 2023).

Moreover, the neurobiological mechanism is not solely based on reduced neuronal excitability; dopamine transporter (DAT) regulation constitutes another important factor. This mechanism attenuates the dopaminergic peak commonly induced by alcohol by altering the dopamine clearance, thereby reducing alcohol's reward value (Jensen et al., 2020). In addition, GLP-1 RAs are linked to the Nucleus of the Solitary Tract (NTS) located in the Rhombencephalon, which plays a role in integrating peripheral signals to restrain alcohol-seeking behaviors (Vallöf et al., 2019; Keller et al., 2022). By influencing specific structures in the limbic system, such as the ventral hippocampus and lateral septum, which regulate anxiety and emotional responses as well as through the general HPA axis, they modulate stress-related drinking (Allingbjerg et al., 2023; Cruz et al., 2024).

This modulation of the mesolimbic and homeostatic systems by GLP-1 RAs is not specific solely to ethanol. The neural circuits governing energy balance and reward processing largely overlap as alcohol, cocaine, sugar, and fat utilize similar dopaminergic

pathways (Sekar et al., 2017). Because of GLP-1 RAs action on this convergent neurocircuitry, targeting the VTA, NAc, and hypothalamus, they suppress the motivational drive regardless of the stimulus. This simultaneous reduction in the desire for different stimuli, such as palatable food and alcohol, is well known as the cross-reward effect.

Preclinical Evidence

Preclinical studies in animal models (rodents and primates) have provided solid and repeatable evidence that GLP-1 RAs can modulate behaviors associated with alcohol abuse through central reward mechanisms.

1. Reduction of Consumption and Motivation

Administration of GLP-1 Receptor Agonists, including Exenatide, Liraglutide, and Semaglutide, led to a significant decrease in the quantity of alcohol consumed. In the Intravenous Self-Administration (IVSA) paradigm, GLP-1 receptor activation markedly reduced the number of ethanol injections in mice. Similarly, in oral alcohol intake models in rats, GLP-1 agonists lowered total intake (Marty et al., 2020) and reduced alcohol preference over water (Shirazi et al., 2013). The explicit decline in alcohol consumption had no notable effect on overall fluid intake or the animals' locomotor activity, suggesting that, rather than a result of general malaise, it was caused by a mechanism specific to reward and motivation.

In operant conditioning tests requiring the animal to perform work (e.g., press a lever) to obtain alcohol, these drugs decreased the motivation to consume alcohol (measured by a reduction in lever presses). Moreover, the administration of Exenatide caused attenuation of alcohol-induced conditioned place preference (CPP) (Shirazi et al., 2013; Abtahi et al., 2018), indicating a reduction in the rewarding effects and a weakening of the positive associations of alcohol. In the relapse-like drinking model, administration of GLP-1 RAs to alcohol deprived rats prevented the reinstatement of cue- and stress-induced alcohol-seeking behaviors (Aranäs et al., 2023). This prevention of relapse highlights a critical benefit for long-term treatment efficacy.

2. Central Action

Direct microinjections of GLP-1 agonists into key brain regions, such as the Ventral Tegmental Area (VTA), were sufficient to reduce alcohol self-administration (Jerlhag, 2020). It has also been demonstrated that GLP-1 receptors localized in other structures of the reward circuitry- the Nucleus Accumbens (NAc), lateral septum, and ventral hippocampus- contribute to reducing the rewarding effects of alcohol upon activation (Allingbjerg et al., 2023).

Microdialysis studies show that GLP-1 receptor activation inhibits the dopamine elevation in the Nucleus Accumbens (NAc) normally induced by alcohol consumption (Vallöf et al., 2016). These studies indicate that GLP-1 RAs directly influence the structures of the reward pathway and addiction mechanisms.

Semaglutide also cut down on "binge-like" drinking in both male and female rodents (Aranäs et al., 2023), which is significant given the sex differences in the pathophysiology of addiction. Furthermore, these drugs significantly reduced alcohol consumption in other animal models, such as alcohol-preferring male vervet monkeys (Thomsen et al., 2019), confirming the translatability of these findings to primates and potentially to humans.

Clinical Evidence

While preclinical studies have provided strong mechanistic evidence, clinical evidence for the therapeutic potential of GLP-1 RAs in treating Alcohol Use Disorder (AUD) is still evolving. The current landscape relies mainly on secondary analyses of obesity or diabetes trials, extensive observational cohort studies, and a growing number of direct randomized clinical trials (RCTs). The available literature currently provides a promising therapeutic signal.

Secondary Analyses and Observational Studies

Initial indications of the potential of GLP-1 RAs emerged from observations of patients treated with these drugs for type 2 diabetes or obesity. Patients frequently reported a spontaneous loss of pleasure not only from food but also from other potentially rewarding substances such as nicotine and alcohol. These observations were supported by large retrospective cohort studies that exploit Electronic Health Records (EHRs) and national registers, in one of which patients receiving Semaglutide-based treatment had a significantly lower incidence of AUD and a consequently decreased risk of relapse than those in the active control group (Wang et al., 2024). A

recent cohort study (Liu et al., 2024) showed that GLP-1 RAs administration is associated with a decrease in alcohol-related hospitalizations, providing further evidence of the real-world potential of these agents.

Randomized Clinical Trials and Meta-Analyses

Direct clinical trials are beginning to confirm primary findings from observational studies. In a randomized trial, mainly directed towards hepatic health, patients with Alcohol-Associated Liver Disease (ALD) who received Semaglutide-based treatment reported a marked decline in craving that was reflected in the ethanol intake. A pivotal Randomized Clinical Trial with Exenatide reported a statistically significant decrease in Heavy Drinking Days (HDD) amongst the intervention group in comparison to a placebo group, although no relevant difference in overall abstinence rates or total consumption across the entire cohort group was found. fMRI data collected in this RCT suggest attenuation of alcohol cue reactivity in brain reward centers (Klausen et al., 2022), which is also supported by the evidence that alcohol exposure modulates the endogenous GLP-1 system, underlaying a biological basis for the intervention (Farokhnia et al., 2022). Systematic reviews and meta-analyses summarizing available data indicate a strong correlation between therapy based on GLP-1 receptor agonists and a reduction in both alcohol craving and the prevalence of excessive drinking episodes, evaluated through standardized diagnostic tools such as the AUDIT scale (Fink-Jensen et al., 2025).

Clinical and Safety Profile

GLP-1 RAs are considered a well-tolerated group of drugs among the AUD population. Their ability to simultaneously improve weight control and glycemic regulation amounts to a significant clinical advantage, given the high co-occurrence of AUD and obesity, as well as the other metabolic conditions. Mostly reported side effects mainly concern the gastrointestinal system (nausea, diarrhea) and, due to their transient nature, rarely require treatment discontinuation.

Limitations and Future Directions

Given the promising results, expanding the direction and scale of the research is essential. Most accessible clinical evidence is derived mainly from small pilot studies and retrospective/cohort analyses where AUD was not the primary endpoint. There is still a lack of large, long-term, double-masked, randomized controlled trials (RCTs) conducted exclusively in populations free of comorbidity, using uniform, clinically relevant endpoints, such as total alcohol abstinence.

Future studies must assess the long-term efficacy and safety of GLP-1R analogues in AUD and determine the optimal dose and duration to achieve the best clinical outcomes. Research should also involve the next-generation dual and triple agonists, which may offer greater effects, and directly compare GLP-1 RAs with approved AUD treatments such as naltrexone and acamprosate.

4. CONCLUSION

Evidence from preclinical and emerging clinical data identifies GLP-1 RAs as an encouraging pharmacological intervention for Alcohol Use Disorder (AUD). Their therapeutic value is supported by in vivo studies showing modulation of the central reward system in various ways, including inhibition of dopamine signaling. Translational evidence points out that agents such as Semaglutide and Exenatide have significant potential to reduce craving and Heavy Drinking Days. Although the effectiveness and safety profile appear favorable, current clinical validation relies mainly on pilot studies and secondary analyses. To enable future clinical integration, upcoming studies have to focus on large-scale, long-term RCTs with standardized endpoints based on abstinence, including populations with and without metabolic comorbidities. Regardless of these limitations, available evidence positions GLP-1 RAs as an up-and-coming option to tackle unmet medical needs in alcohol dependence.

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Authors' Contributions

Paulina Wądołowska: Conceptualization, supervising, writing- rough preparation
Patryk Pindlowski: Formal analysis, investigation
Ewelina Komorowska: Writing- rough preparation
Jakub Szyszkowski: Project administration

Zuzanna Zgrzywa: Conceptualization
Brygida Tucka: Resources, literature review
Natalia Kriese: Methodology, literature review
Izabella Zawadzka: Conceptualization, methodology
Bartłomiej Kowalski: Investigation, editing
Jakub Jaworski: Editing

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Conflict of interest
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Data and materials availability
All data associated with this study will be available based on reasonable request to the corresponding author.

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