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Authors' Affiliation:
Collegium Medicum at Jan Kochanowski University in Kielce, Poland

***Corresponding author:**
Milena Kędzierska,
Collegium Medicum at Jan Kochanowski University in Kielce, Poland,
e-mail: kedzierska.milena19@gmail.com
Orcid: 0009-0008-0980-3543

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GLP-1 analogues in the treatment of alcohol dependence: a new direction in pharmacotherapy – a literature review

Milena Kędzierska*

ABSTRACT

Alcohol use disorder (AUD) is a widespread health issue that leads to serious complications for both the body and the mind. Because current treatments often fail to prevent relapse, researchers are looking for new ways to treat the condition. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which are standard treatments for diabetes and obesity, are now becoming a focus in addiction medicine. In this review, we investigate how these drugs affect the reward system in the brain and whether they can help reduce alcohol abuse. Preclinical studies in animal models clearly show that activation of GLP-1 receptors in key brain regions, such as the nucleus accumbens (NAcc) and the ventral tegmental area (VTA), attenuates the reinforcing effects of alcohol and reduces voluntary alcohol intake. Importantly, preliminary clinical data—including reviews of medical records and case reports—confirm these observations. They indicate that patients taking these medications experience a reduced desire to drink alcohol and are less likely to engage in alcohol-related incidents. Although the results of studies on the effects of semaglutide and liraglutide are encouraging, it should be emphasized that the current evidence is largely derived from small study groups or retrospective observations and therefore requires rigorous verification. GLP-1 analogs represent a highly promising, innovative therapeutic target for AUD; however, their routine (off-label) use requires validation in large, randomized, multicenter clinical trials to precisely determine the safety profile and establish guidelines for future therapies.

Keywords: "alcohol use disorder" (AUD), "GLP-1 receptor agonist," "semaglutide," "liraglutide," "reward system," "dopamine".

1. INTRODUCTION

Alcohol use disorder (AUD) has become one of the most stubborn public health crises we face. It's estimated that roughly half a billion people—over 400 million, to be exact—are currently struggling with it, which is why it remains a primary driver of global illness and death. The disorder itself is a gradual slide: it starts with a loss of control and quickly spirals into compulsive drinking. When a patient tries to stop drinking, they fall into an emotional trap. Abstinence often triggers states that are impossible to overcome. Physically, things are also very bad—alcohol literally destroys the heart and liver and increases the risk of cancer (Nasrollahizadeh et al.,

2026). Finally, we must consider the broader context. The families of these individuals go through hell, and society pays the price in the form of rising accident and suicide rates (Zheng et al., 2025).

Although psychosocial interventions remain the cornerstone of AUD treatment, pharmacotherapy provides essential support. Currently, there are very few medications officially approved by the FDA and the EMA. This group includes disulfiram, acamprosate, and naltrexone, and in the case of the EMA, also nalmefene (Nasrollahizadeh et al., 2026). Although the above methods may be helpful, their effectiveness is not always satisfactory, meaning that a significant number of patients do not experience a significant improvement (Zheng et al., 2025). The best evidence of the limitations of modern medicine in this area is the relapse rate, which exceeds 70% as early as the first year after the start of therapy. All of this underscores how desperately we need new molecular targets and more effective tools in the fight against addiction (Nasrollahizadeh et al., 2026).

Although these therapies are currently in use, their long-term efficacy is limited, and many patients do not see significant improvement (Zheng et al., 2025). Relapse rates—which exceed 70% in the first year—clearly highlight how limited our current treatment options really are. This disparity between clinical need and current outcomes compels us to look beyond conventional methods; we urgently need to identify new molecular targets and broaden our therapeutic approaches (Nasrollahizadeh et al., 2026).

Recent years have seen a major shift in research as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) emerge as a novel strategy for treating addiction. Although drugs like semaglutide, liraglutide, dulaglutide, and exenatide were originally developed to address metabolic conditions—namely, obesity and type 2 diabetes—their clinical utility is now being re-evaluated through a psychiatric lens (Zheng et al., 2025; Brunchmann et al., 2019). The mechanism driving this interest is their ability to mimic endogenous incretin hormones (Nasrollahizadeh et al., 2026). This redirection in research is largely driven by a single, critical finding: GLP-1 receptors are expressed within the mesolimbic reward system—specifically in the ventral tegmental area (VTA) and the nucleus accumbens (NAc). The discovery of these receptors in key reward circuits provides a neurobiological basis for suggesting that these agents can modulate addictive behaviors (Zheng et al., 2025). Incretin drugs—by interacting with these specific sites—seem to modify mesolimbic dopamine signaling; this process effectively lowers the "pull" of addictive substances (Völker et al., 2026). Preclinical studies and preliminary reports on patients point to a similar finding—GLP-1 agonists have been shown to inhibit the activity of reward centers. This mechanism appears to be the cause of the noticeable decrease in the desire to drink observed in recent studies (Nasrollahizadeh et al., 2026).

Given these promising reports, the aim of this study is to synthesize the current knowledge regarding the repurposing of GLP-1 receptor agonists in psychiatry. The main research hypothesis posits that GLP-1 receptor agonists constitute a safe and effective therapeutic strategy for reducing alcohol consumption and alleviating alcohol cravings in patients with AUD. This review will assess the mechanisms of action, efficacy, and limitations of this modern approach, seeking to answer the question of whether metabolic drugs may change the standards of addiction treatment in the near future.

2. REVIEW METHODS

The search strategy included the following keywords: “glucagon-like peptide-1,” “GLP-1 receptor agonists,” “alcohol use disorder,” “alcohol drinking,” “semaglutide,” and “liraglutide.” Databases, including PubMed, the Cochrane Library, and Scopus, were searched to cover the biological and physiological basis of the relationship between GLP-1 analogs and alcohol use disorder (AUD), with a particular focus on the mechanisms through which these drugs affect the brain’s reward system. Inclusion and exclusion criteria: I chose to limit my analysis to full-text English articles published between January 2016 and January 2026. I picked this ten-year window because the research into using incretin drugs for psychiatric purposes has really exploded during this time. For my review, I prioritized high-quality evidence—specifically systematic reviews, meta-analyses, and randomized controlled trials (RCTs). I also included key in vivo animal studies, as I found they were essential to explaining the neurobiological and molecular mechanisms underlying the effects of GLP-1 analogs on the central nervous system. I intentionally weeded out any papers that didn't provide a clear scientific link between the drug's mechanism and actual alcohol-related behaviors. Likewise, if I couldn't get my hands on the full text, or if a study wasn't strictly focused on the link between GLP-1 agonists and AUD, I simply left it out of the review.

Study Selection and Data Extraction

All the information presented in this paper comes from peer-reviewed scientific studies that met these criteria. My initial database search identified 129 records. Then, 57 articles were selected for full-text evaluation. Based on the inclusion and exclusion rules, 13 publications were included in the final text synthesis. Figure 1 shows the entire selection process in a standard PRISMA flow diagram.

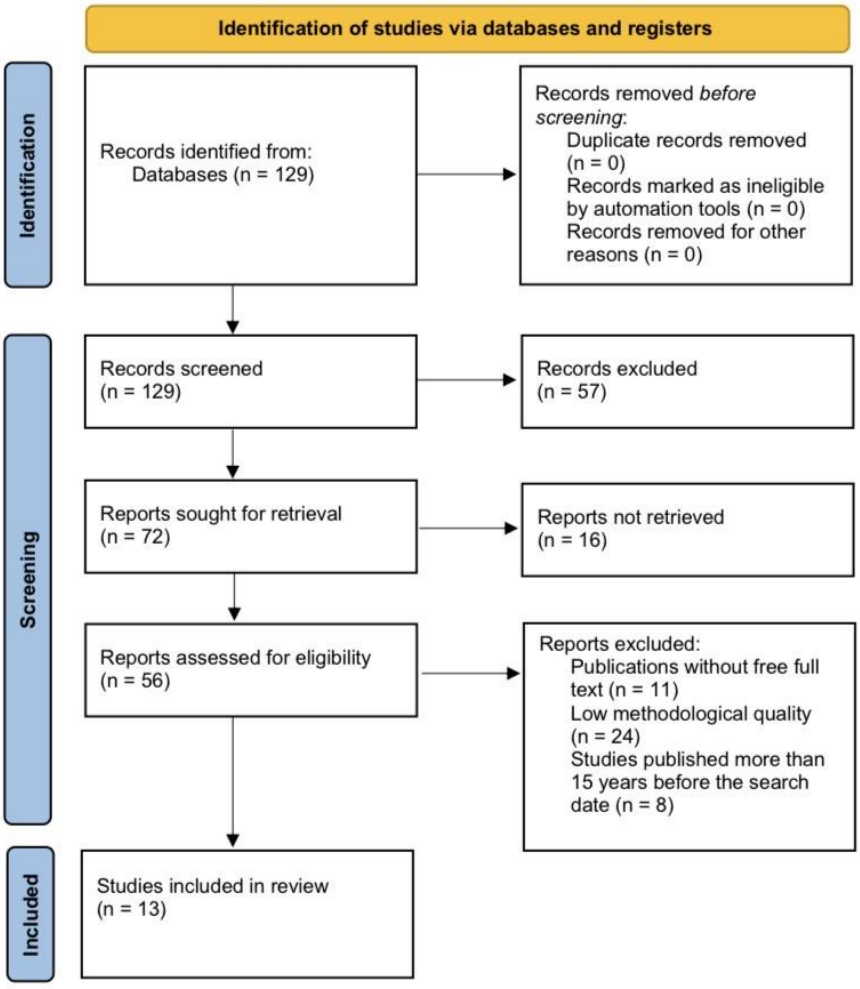

Figure 1. PRISMA flowchart

3. RESULTS AND DISCUSSION

The Pathophysiology of Alcohol Addiction and the Reward System and GLP-1 System

The Neurobiology of AUD

Understanding the mechanisms of alcohol addiction requires examining neurobiological processes, particularly the dopaminergic pathway. The mesolimbic dopamine system, commonly referred to as the reward center, plays a key role in the development of alcohol use disorder (AUD) (Vallöf et al., 2016). This system primarily consists of dopaminergic neurons in the ventral tegmental area (VTA), which project to the nucleus accumbens (NAcc), the amygdala, the hippocampus, the prefrontal cortex, and the dorsal striatum. It is within the mesolimbic system that the desire ("wanting") to consume an addictive substance is generated. When alcohol and other substances enter the system, they strongly stimulate VTA neurons, increasing dopamine levels in the nucleus accumbens—this conditions the brain to seek the rewarding properties of alcohol (Klausen et al., 2025). Because these properties are so potent, they serve as a primary catalyst for the escalation of consumption and are frequently responsible for driving relapse (Jerlhag, 2025).

Distribution of GLP-1 receptors in the CNS

While it is common to think of the incretin system only in terms of digestion or metabolic balance, GLP-1 receptors are surprisingly widespread—especially throughout the brain (Jerlhag, 2025). We have solid evidence from both animal models and human post-mortem samples that these receptors occupy key sites in the reward circuit: the VTA, NAcc, amygdala, thalamus, and hypothalamus, among others. It's also notable that GLP-1 is not purely "gut-derived." Locally, synthesis occurs in the brainstem—specifically in the nucleus of the solitary tract (NTS)—from which it forms direct neural connections to the VTA and NAcc (Klausen et al., 2025). The real

challenge begins when we administer these analogs peripherally, as they must contend with the blood-brain barrier. It's not a straightforward process; the molecule itself determines whether or not it actually gets through (Jerlhag, 2025). Take liraglutide, for instance—researchers have clearly shown that it crosses the blood-brain barrier to target regions such as the arcuate nucleus in the hypothalamus (Klausen et al., 2025). Furthermore, GLP-1 circulating in the peripheral blood may also indirectly affect the brain by activating vagal afferents, which transmit signals to the NTS and, from there, to the VTA and NAcc (Vallöf et al., 2015).

Mechanism of Action

The physiological functions of peptides such as GLP-1 include regulating food intake, promoting satiety, and suppressing hunger, all of which are mediated by receptors in the NTS, hypothalamus, and amygdala (Vallöf et al., 2015). However, more recent evidence suggests that these peptides act much more broadly in the brain, modulating reward center responses beyond mere homeostasis (Jerlhag, 2025). It has been demonstrated that GLP-1-sensitive mechanisms regulate reward processes in general, attenuating non-caloric reward, for example, that induced by chemicals and addictive substances. Activation of the GLP-1 system using drugs such as liraglutide or exenatide effectively and directly inhibits alcohol-induced dopamine release in the nucleus accumbens (NAcc) in animal models, suppressing the rewarding effects of alcohol (Vallöf et al., 2015). This phenomenon has been confirmed, among other things, in the conditioned place preference (CPP) test (Jerlhag, 2025). It's worth noting that GLP-1 agonists don't lower basal dopamine levels; they only step in to dial back the pathologically high spikes that come from substance use (Klausen et al., 2025). This shows how GLP-1 analogs do double duty—they balance metabolic satiety and, at the same time, work on the mesolimbic pathway. By doing this, they essentially make the brain "full" or satisfied, reducing the rewarding impact of alcohol to a point where it's no longer the primary driver (Vallöf et al., 2015).

GLP-1 Analogs in Animal Models (Preclinical Studies)

Effects on Alcohol Consumption and Seeking

The use of GLP-1 receptor agonists leads to an effective reduction in voluntary alcohol consumption, as demonstrated in a variety of animal models. The therapeutic potential of analogs such as liraglutide, exenatide, and AC3174 is well-supported by preclinical rodent data. These studies consistently demonstrate reduced ethanol intake, a result replicated across both operant self-administration models and two-bottle free-choice experiments. More recent experiments demonstrate that acute and chronic administration of the long-acting analog semaglutide significantly reduces alcohol consumption and preference in a dose-dependent manner in rats of both sexes. There's a nuance here regarding sex differences—specifically with dulaglutide, which seems to hit harder in males when it comes to suppressing alcohol intake, leaving a less clear impact in females. It's also encouraging that we aren't just looking at rodent data here; primate studies have started to paint a similarly positive picture. In studies involving savanna cats, it was shown that liraglutide, and to a lesser extent exenatide, significantly reduce voluntary alcohol consumption without causing adverse effects such as vomiting.

Impact on Relapse

The phenomenon of returning to drinking after a period of enforced abstinence can be successfully studied in animals using the so-called alcohol deprivation model, which accurately mirrors relapses in humans. Acute semaglutide therapy effectively prevented relapse in both male and female rats that had undergone prior deprivation. The drug blocked increased alcohol consumption at both 24 and 48 hours after alcohol was made available again. A systematic review of preclinical studies indicates that other GLP-1 analogs under investigation, such as liraglutide, AC3174, and exenatide, are also effective in preventing relapse in rodents following a period of interrupted ethanol exposure (Aranäs et al., 2023).

In vivo molecular mechanisms

Alcohol consumption induces a strong response from the mesolimbic system, which in male mice manifests as increased locomotor activity and enhanced dopamine release in the shell region of the nucleus accumbens (NAcS). In vivo microdialysis studies revealed that semaglutide administered prior to alcohol exposure effectively suppresses this dopamine release in the NAcS and completely abolishes alcohol-induced hyperlocomotion. Semaglutide appears to influence dopamine turnover specifically during alcohol exposure. This is evidenced by a significant spike in metabolites—namely DOPAC and HVA—within the nucleus accumbens, suggesting a direct metabolic effect. This accelerated dopamine breakdown is due to increased gene expression for the MAOA and COMT enzymes, induced by semaglutide therapy in animals exposed to alcohol. The underlying mechanism is reinforced by studies using

intraventricular injections. When researchers delivered exenatide directly into brain structures—specifically the ventral tegmental area (VTA) or the nucleus accumbens (NAcc)—they observed a clear inhibition of alcohol-seeking behaviors. Direct evidence for the central action of these drugs is the physical detection of fluorescently labeled semaglutide (CY3-semaglutide) in the shell region of the nucleus accumbens following its systemic administration in alcohol-consuming rats of both sexes (Thomsen et al., 2019).

Clinical Observations in Humans and Ongoing Clinical Trials

Retrospective Studies and Case Reports

Everything started with some chance observations—clinicians noticed that patients treated for obesity or type 2 diabetes suddenly changed their attitude toward alcohol. It turned out to be more than just a passing observation; massive sets of electronic health records confirmed that putting patients on incretin-based therapy actually changes their habits regarding substance use (Qeadan et al., 2025). Consider the results from a large study that tracked obese patients over a full year. Semaglutide came out on top, showing a 50–56% drop in substance use. That's a significant gap compared with the standard results for naltrexone or topiramate. What's more, this wasn't just a trend among those with obesity; patients managing type 2 diabetes saw the exact same results, no matter their BMI (Wang et al., 2024). This holds steady even at the "big data" level. Across U.S. records covering 100 million-plus lives, AUD patients on GIP/GLP-1 RAs ended up with a 50% lower rate of acute alcohol intoxication (Qeadan et al., 2024). In addition to the statistics, what we hear from the patients themselves is also important. They often describe a rather unique phenomenon: they simply lost their desire for alcohol all of a sudden. It's not that they're fighting temptation—they simply don't feel the need. This change in attitude is largely why these patients are less likely to engage in drinking binges (Wang et al., 2024).

Randomized clinical trials (RCTs)

Randomized clinical trials (RCTs) are of fundamental importance for validating observational data, as they allow for an objective assessment of efficacy. In the most recent study evaluating the effect of weekly low-dose semaglutide injections on a group of patients with AUD, a significant reduction in alcohol consumption and a decrease in peak breath alcohol concentration (BrAC) were demonstrated under laboratory self-administration conditions. In a 9-week outpatient trial, semaglutide didn't stop people from drinking entirely, but it did make a difference: participants reported fewer cravings and drank less whenever they did consume alcohol (Hendershot et al., 2025). Exenatide's track record is more nuanced. While an earlier study using it as an add-on to behavioral therapy failed to show a broad benefit over a placebo, the results shifted in subgroup analysis. Specifically, patients struggling with obesity (BMI > 30) saw a genuine reduction in both their heavy drinking days and total alcohol consumption (Klausen et al., 2022).

The neurological data here is compelling. fMRI scans show clearly that exenatide dampens the brain's reaction to alcohol-related triggers—specifically in the ventral striatum and the septum—which points to a central shutdown of the reward pathways. We also have SPECT imaging data to support this. The lower dopamine transporter availability observed in the striatum confirms the drug's impact on dopaminergic transmission pathways (Klausen et al., 2022). Table 1 summarizes the most important data from preclinical and clinical studies on the effects of GLP-1 receptor agonists on reducing alcohol consumption and inhibiting the neural processes underlying addiction.

Table 1. Summary of scientific evidence regarding the impact of selected GLP-1 receptor agonists on the reduction of alcohol consumption.

Drug	Research Model	Key Observations	Source
Semaglutide	Rats (both sexes)	Reduced alcohol intake and preference; relapse prevention	Nasrollahizadeh et al., 2026
Semaglutide	Humans (AUD)	Reduced alcohol consumption and peak breath alcohol concentration	Hendershot et al., 2025
Liraglutide	Animals (rodents/primates)	Decreased voluntary alcohol intake without adverse effects	Vallöf et al., 2015; Klausen et al., 2025
Exenatide	Humans (BMI > 30)	Reduced heavy drinking days and total alcohol consumption	Klausen et al., 2022

Safety Profile

Any assessment of the safety profile of GLP-1 agonists in individuals with AUD must take into account the specific health burdens of this patient group, including the risk of organ damage resulting from long-term addiction. Among adverse events in these clinical trials, gastrointestinal complaints were by far the most common. Participants frequently reported nausea, vomiting, and reduced appetite, which effectively triggered a marked decrease in their body weight (Klausen et al., 2022). A mild profile of these types of adverse effects was also observed in trials using semaglutide, where no serious adverse events or dangerous drug interactions with alcohol itself were reported (Hendershot et al., 2025). A significant concern in the population of alcohol abusers, who are at high baseline risk for acute pancreatitis, was the fear that incretin therapy might trigger this condition. Nevertheless, clinical trials of exenatide in patients with AUD did not show increased serum pancreatic enzyme levels or cases of acute pancreatitis in the study group (Klausen et al., 2022). Drugs in this class are also considered promising for individuals with cirrhosis, and because some are primarily eliminated via the kidneys, they may represent a safe option for patients with alcoholic liver disease. However, it should be noted that due to weight loss and gastrointestinal side effects, their intended use in a population of often malnourished patients with AUD will require close clinical monitoring (Klausen et al., 2022).

4. CONCLUSION

The accumulated data allow for a clear answer to the objective of this study: GLP-1 analogs represent a highly promising, innovative therapeutic target in the treatment of alcohol use disorder (AUD). However, it must be emphasized that their routine use outside approved metabolic indications (off-label) requires definitive confirmation through large, randomized, multicenter clinical trials.

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Authors' Contributions

The author has read and agreed with the published version of the manuscript.

Informed consent

Not applicable.

Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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