*Endocrinology*, 2025, **166**, bqaf028
https://doi.org/10.1210/endocr/bqaf028
Advance access publication 21 February 2025
**Mini-Review**

# GLP-1 Receptor Agonists: Promising Therapeutic Targets for Alcohol Use Disorder

**Elisabet Jerlhag**[1]

[1]Department of Pharmacology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, SE-405 30 Gothenburg, Sweden

**Correspondence:** Elisabet Jerlhag, MSc, PhD, Department of Pharmacology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Medicinaregatan 13A, SE-405 30 Gothenburg, Sweden. Email: Elisabet.Jerlhag@pharm.gu.se.

## Abstract

Glucagon-like peptide-1 (GLP-1) is abundant in the circulation, and it is well-known to regulate glucose homeostasis, feeding, and body weight. GLP-1 receptor agonists are therefore approved for treating type 2 diabetes and obesity. However, more recent research has demonstrated that GLP-1 acts within the brain to modulate reward responses, thereby highlighting GLP-1 as a potential target for addiction. Specifically, preclinical studies demonstrated that GLP-1 receptor agonists decrease alcohol intake, reduce the motivation to consume alcohol, and prevent relapse drinking by potentially lowering alcohol-induced reward. These preclinical results have been confirmed and extended in human studies in which GLP-1 receptor agonists reduce alcohol intake in patients with alcohol use disorder (AUD) who have a regular weight or comorbidity of obesity or type 2 diabetes. On a similar note, genetic variations in genes encoding for the GLP-1 receptor are associated with AUD and heavy drinking. The central mechanisms by which GLP-1 regulates alcohol-related behaviors are not fully defined, but may involve areas central to reward as well as regions projecting to these reward areas, such as the nucleus tractus solitarius of the brainstem. Together, existing preclinical and clinical data suggest that GLP-1 is involved in the AUD process and implies its role as a tentative treatment for AUD.

**Key Words:** appetite-regulatory hormones, gut–brain axis, alcohol, drugs of abuse, dopamine, reward, addiction, dependence

**Abbreviations:** AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; DPP-IV, dipeptidyl peptidase-IV; Ex4, Exendin-4; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; LDTg, laterodorsal tegmental area; NAc, nucleus accumbens; NTS, nucleus tractus solitarius; SNP, single nucleotide polymorphism; VTA, ventral tegmental area.

## Glucagon-Like Peptide-1

The neurobiological underpinnings of alcohol use disorder (AUD) are complex, and the gut–brain axis has gained recent attention. The bidirectional communication of this axis includes appetite-regulatory peptides such as glucagon-like peptide-1 (GLP-1). GLP-1 is produced by L-cells in the intestines (1) as well as preproglucagon-containing neurons of the nucleus tractus solitarius (NTS) (2). The physiological properties of GLP-1 are vast, and include a reduction in feeding, both the hedonic and homeostatic aspects (for review see (3)). GLP-1 receptor (GLP-1R) agonists, which are approved for type 2 diabetes due to their regulation of glucose-dependent insulin secretion, have also been approved for obesity owing to their ability to reduce body weight in both rodents and humans (for review see (3)). As GLP-1 is rapidly degraded by dipeptidyl peptidase-IV (DPP-IV), agonists at the GLP-1R with longer half-life have been developed. To date, GLP-1R agonists that are short- (exenatide, Exendin-4, Ex4; injected twice a day), moderate- (liraglutide, injected daily), and long-acting (semaglutide and dulaglutide; administered weekly) are clinically available. The findings that GLP-1R is expressed throughout the body, including the brain (2, 4-6), indicate that the approved GLP-1R agonist may have both peripheral and central effects. As summarized in the present mini-review, central effect that has gained recent interest is the ability of GLP-1R agonists to reduce alcohol-related responses. While such findings were demonstrated initially in rodents, more recent studies also show similar effects in humans, which is illustrated in Fig. 1, and references are summarized in Fig. 2. The search for relevant articles included in the present mini-review was based on keywords, and all selected articles were quality checked.

## GLP-1R Agonists Reduce Alcohol Consumption in Animals and Man

### Preclinical Studies

As escalated alcohol intake over time contributes to the development of AUD (7), the impact of GLP-1R agonists thereof may be of interest when identifying novel treatments for AUD (Fig. 1). While the initial publication revealed a reduction in alcohol intake after acute systemic injection of Ex4 (8), additional studies found a similar outcome by more long-acting GLP-1R agonists. Specifically, in male rats exposed to 12 weeks of alcohol an acute Ex4 injection decreased alcohol consumption (8), a reduction most profound in high-alcohol–consuming male rats (9, 10). Moreover, a lower intravenous self-administration of alcohol was observed in males treated with Ex4 (11). Although these initial studies demonstrated a

**Received:** 19 August 2024. **Editorial Decision:** 7 February 2025. **Corrected and Typeset:** 5 March 2025

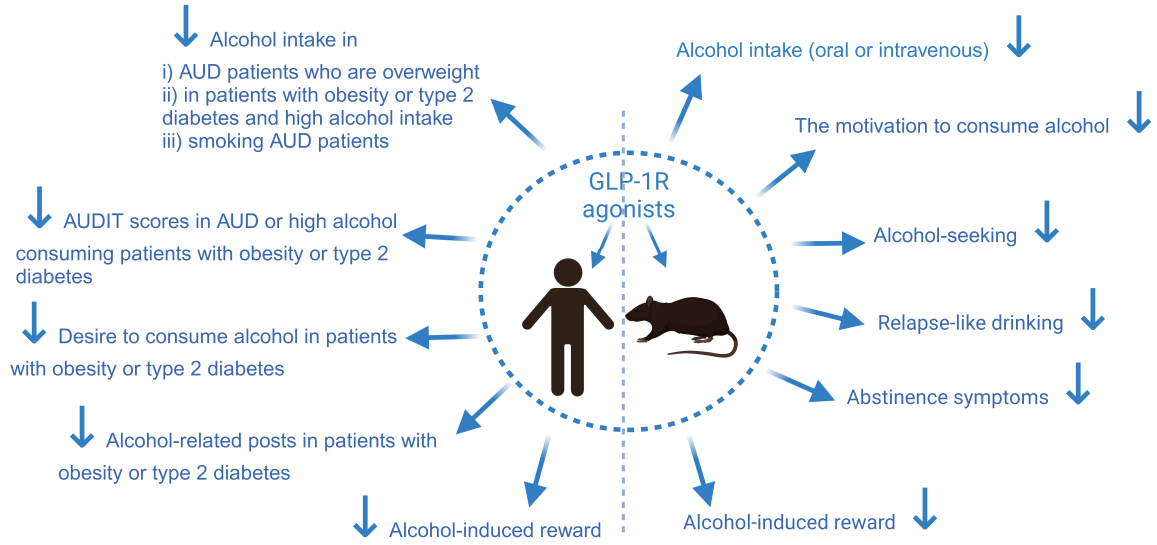


**Figure 1.** Schematic illustration on preclinical and clinical studies. Summary of how GLP-1 receptor (GLP-1R) agonists influence alcohol-related responses in animals (to the right) and humans (to the left). AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; ↓ decrease. The illustration was created with BioRender.com.

treatment reduction in male rodents, more recent studies showed that a lower alcohol intake after Ex4 is observed in both group-housed male mice (12) and nonhuman primates (vervet monkeys) (13). Not only did the systemic Ex4 injection lower the alcohol intake, but also changed the drinking pattern. This is evident as Ex4 reduced the number of drinking bouts and increased the time to first drink (12). These data are further corroborated as local administration of Ex4 into the ventral tegmental area (VTA) prevented the ability of ghrelin, a well-known orexigenic peptide, to increase alcohol intake in the intermittent access model as well as the operant responding for alcohol (14). Long-term alcohol consumption is associated with other negative health consequences, including hepatic steatosis, another aspect improved by Ex4 (15).

In addition to Ex4, the moderate-acting GLP-1R agonist, liraglutide, decreased the alcohol intake and alcohol preference across species, as the intake was lower after liraglutide in male rats (16), male mice (16, 17), and nonhuman primates (vervet monkeys) (13). Moreover, these effects are observed after both acute and repeated liraglutide injections (13, 16, 17).

Dulaglutide was the first long-acting GLP-1R agonist demonstrated to reduce alcohol consumption in male and female rats, with more beneficial treatment effects in males than in females (18). Specifically, both lowered alcohol intake and preference were found during 5 or 9 weeks of weekly dulaglutide treatments, and the treatment effect was sustained for an additional 3 weeks beyond treatment discontinuation (18). The second long-acting GLP-1R found to impact alcohol intake was semaglutide, also known by the brand names Ozempic and Wegovy. The beneficial effects of semaglutide include its higher affinity and potency at the GLP-1R as well as its availability as a weekly per-oral formulation (for review see (19)). An initial study revealed lower alcohol intake in male rats treated acutely with semaglutide than in those treated with vehicle (17). Subsequently, acute and repeated injections of semaglutide dose-dependently reduced alcohol intake and the preference for alcohol in both male and female rats, an effect more profound in females (20, 21). On a similar note, semaglutide lowered binge drinking in mice and rats (22) and alcohol intake in alcohol-preferring male vervet monkeys (23). It should be further noted that the long-acting agonist has the most profound effect without causing tolerance development (16, 18, 20, 24).

These preclinical data demonstrated a critical role for GLP-1R in controlling alcohol consumption, but the impact of GLP-1 has been less studied. Obtained data on circulating GLP-1 are contradictory. Indeed, systemic injection of GLP-1 reduced alcohol intake (9), whereas alcohol intake remained unchanged after the elevation of endogenous GLP-1 levels, achieved either by enhancing the release or by decreasing degradation (though inhibition of DPP-IV) (17). On the other hand, no studies have so far explored the ability of enhanced central GLP-1 release to influence alcohol intake in rodents. Yet another approach has been used to study the impact of endogenous GLP-1 within the brain on alcohol intake, in which endogenous GLP-1 release is blocked by local infusion of a GLP-1R antagonist (Ex9). Specifically in these studies, local infusion of a GLP-1R antagonist (Ex9) has been found to elevate alcohol intake (9, 17), indicating that central endogenous GLP-1 may regulate alcohol drinking. However, future studies using central vs peripheral DPP-IV inhibitors are warranted to disentangle the impact of and tentative discrepancy between central and peripheral GLP-1 on alcohol intake.

While escalated alcohol intake over time is an important aspect of AUD, the motivation to consume alcohol is another central factor for AUD that is reduced by GLP-1R agonists. Supportively, Ex4 dose-dependently (25) diminished the drive to consume alcohol of male rats when tested in the operant self-administration model (8, 25). On a similar note, systemic Ex4 administration reduced operant self-administration of alcohol in male mice, whereas the ability of Ex4 to lower the motivation to consume alcohol was less pronounced in female mice (26). On a similar note, seeking alcohol in the progressive ration test was attenuated by systemic Ex4 injection in rats (8) and male mice (26), whereas Ex4 did not influence the alcohol-seeking female mice (26). Together these data further highlight the sex-diverging differences related to GLP-1R

| | GLP-1R | Outcome | References |
|---|---|---|---|
| **Preclinical studies** | Ex4<br>Liraglutide<br>Dulaglutide<br>Semaglutide | Decreased alcohol consumption | (8-10, 12, 13)<br>(13, 16, 17)<br>(18)<br>(17, 20-23) |
| | Ex4 | Lower intravenous self-administration of alcohol | (11) |
| | Ex4<br>Liraglutide | Reduced motivation to consume alcohol | (8, 25)<br>(16) |
| | Ex4 | Alcohol-seeking | (8, 26) |
| | Ex4<br>Liraglutide<br>AC3174<br>Semaglutide | Relapse-like drinking | (12, 16)<br>(29)<br>(24)<br>(20) |
| | Liraglutide | Abstinence symptoms | (29, 30) |
| | Ex4<br>Liraglutide<br>Semaglutide | Attenuation of alcohol-induced reward | (8)<br>(16)<br>(20) |
| **Clinical studies** | **GLP-1R** | **Outcome** | **References** |
| | GLP-1R agonists | Reduced desire to consume alcohol, interest in alcohol, and alcohol consumption in patients treated for obesity or diabetes type 2 | (38) |
| | | Lowered alcohol-related events posted online in patients treated for obesity or diabetes type 2 | (37) |
| | Exenatide (Ex4) | Decreased alcohol intake in overweight alcohol use disorder (AUD) patients | (35) |
| | Liraglutide | Lowered self-reported alcohol intake in patients with type 2 diabetes | (32) |
| | Dulaglutide | Decreased alcohol intake in smoking AUD patients | (36) |
| | Semaglutide | Lowered binge drinking, Alcohol Use Disorders Identification Test (AUDIT) scores, and self-reported alcohol intake in overweight individuals with high alcohol intake | (39) |
| | | Reduced the AUDIT scores in overweight patients with AUD co-morbidity | (40) |
| | | Reduced alcohol-related posts in social media among overweight individuals and those with type 2 diabetes | (39) |
| | | Reduction in stimulatory and sedative effects | (39) |

**Figure 2.** Summary of preclinical and clinical references. Summary of preclinical and clinical studies demonstrating that GLP-1 receptor (GLP-1R) agonists reduce alcohol-related outcomes in animals and humans, including the references linked to these studies. Ex4, Exendin-4.

agonists and alcohol. The mechanisms underlying these observed sex differences in response to GLP-1R agonists are not yet fully understood but may be linked to sex hormones. Research suggests that estrogen can affect responses to these agonists in studies on feeding behavior (27, 28). Additionally, pharmacokinetic differences and sex-specific

molecular mechanisms may also be significant factors. Moreover, GLP-1R expression may vary between sexes, including differences in specific brain regions and cell types within those regions. As Ex4, liraglutide suppressed the motivation to consume alcohol in alcohol-preferring male rats (sP rats) when it is being injected repeatedly (16).

Another factor substantially contributing to the complexity of AUD is relapse drinking, which is commonly observed after periods of abstinence (ie, white periods). In animals, this can be studied using the alcohol deprivation model in which alcohol is deprived before being reintroduced. Using this model, acute systemic injection of Ex4 prevented relapse drinking in male rats (16) as well as socially housed male mice (12). Likewise, in male mice relapse drinking was suppressed by liraglutide (29), AC3174, another GLP-1R agonist (24), and by semaglutide (20). During withdrawal, both mice and rats display abstinence symptoms that are alleviated by systemic injection of liraglutide (29, 30). While the motivation to consume alcohol and relapse drinking has not been studied in relation to central GLP-1, elevation of GLP-1 in the periphery (by DPP-IV inhibitor) has been found to diminish the abstinence symptoms observed during withdrawal (31).

In summary, these preclinical studies revealed that GLP-1R agonists lowered alcohol intake, the motivation to consume alcohol, alcohol-seeking, relapse-drinking, and abstinence symptoms (Figs. 1 and 2). Moreover, these effects are observed by all tested GLP-1R agonists and across different strains, species, and sexes. While these preclinical studies reveal that the receptor controls these AUD-related behaviors, future studies should explore the impact of GLP-1 in the blood and brain for such behaviors.

## Clinical Studies

While these preclinical studies have pinpointed that GLP-1R activation controls various aspects of the AUD cycle, more recent clinical studies have revealed an effect on alcohol consumption in humans (Fig. 1). The first link between GLP-1R and alcohol was observed in a small, preliminary pilot study of patients with type 2 diabetes who self-reported lower alcohol intake after liraglutide treatment (32). Further evidence was provided by a human genetic study in which an association between single nucleotide polymorphisms (SNPs) of the GLP-1R genes and AUD diagnosis was demonstrated in 2 separate population cohorts of patients with AUD with regular weight (24). This study further revealed a positive correlation between SNPs of the GLP-1R genes and intravenous self-administration of alcohol and breath alcohol concentrations in alcohol-consuming individuals (24). Others later corroborated these human genetic findings in a population of regular-weight individuals with low- and high-risk alcohol consumption, since an association between polymorphisms of the GLP-1R gene and Alcohol Use Disorders Identification Test (AUDIT) scores was found (33). One brain area of interest for the interaction between GLP-1R and alcohol was the hippocampus, as the expression of GLP-1R therein was higher in patients with AUD than in controls (34). Furthermore, the right globus pallidus blood oxygen level–dependent response to monetary reward was associated with SNPs in the GLP-1R genes in alcohol-consuming individuals (24). A randomized clinical trial provided further evidence of the interaction between GLP-1 and alcohol, as daily injections of exenatide caused a reduction in alcohol intake in overweight patients with AUD, an effect not observed in individuals with regular weight (35). On a similar note, a randomized clinical trial assessed dulaglutide's effectiveness in reducing alcohol intake among smoking patients with AUD who varied in weight but were predominantly obese (36). In this study, the alcohol intake was decreased by 12 weeks of dulaglutide treatment, an effect obtained independent of smoking status, baseline alcohol consumption, or body weight (36). The interaction between GLP-1R and alcohol was further found in a nationwide cohort study investigating the risk of alcohol-related events in patients with a prescription of GLP-1-based therapies (37). This register-based study revealed that the alcohol-related events were lowered by GLP-1R agonists than in DPP-IV inhibitors (37). However, the impact on weight was not reported in this study, including both individuals with type 2 diabetes or with obesity (37). Furthermore, a social media study analyzing anonymous online reports demonstrated that individuals, without reported weight, on GLP-1R agonist treatment self-report a lower incidence of desire to consume alcohol, interest in alcohol, and alcohol consumption (38). Similarly, machine learning analysis of social media posts revealed that semaglutide reduced alcohol-related posts—such as expressions of desire, craving, and negative effects—among overweight individuals and those with type 2 diabetes who consume high levels of alcohol (39). Furthermore, binge drinking, AUDIT scores, and self-reported alcohol intake were reduced by semaglutide compared with both the control group and the baseline measurements taken before treatment initiation in overweight individuals with high alcohol intake (39). The observed reduction in alcohol intake in these overweight patients consuming high amounts of alcohol might be associated with semaglutide's ability to reduce alcohol's stimulatory and sedative effects (39). In a small sample of overweight patients with AUD comorbidity, semaglutide lowered the AUDIT scores (40). While most of these studies report that GLP-1R agonists profoundly reduce alcohol drinking in overweight patients with AUD, the outcomes in individuals of regular weight are understudied. Therefore, the effects of these GLP-1R agonists on alcohol intake in individuals with regular weight vs obesity should be compared in randomized clinical trials. It should be further noted that there are some discrepancies in the preclinical and clinical work conducted so far, as animals of regular weight and mostly humans with overweight have been studied. It is therefore arguable that additional preclinical studies in overweight animals should be conducted. Since these preclinical and clinical studies are still in the early stages, firm conclusions about which patient groups may respond best remain undetermined. One could however speculate that appetite-regulatory peptides, known to regulate feeding and alcohol intake, are more important in a subpopulation of patients with obesity and AUD comorbidities rather than other subtypes.

While the impact of elevated endogenous GLP-1 levels on alcohol intake has not been studied, 1 study revealed that the GLP-1 levels are similar between control and patients with AUD (41) and that alcohol ingestion (peroral and intravenous) reduces GLP-1 in serum (34). Additionally, in a placebo-controlled crossover study in women, alcohol ingestion lowered the circulating levels of GLP-1 independent of the body weight (42).

Conclusively, these human data reveal that GLP-1R agonists reduce alcohol intake and alcohol-related events in individuals who heavily drink alcohol or are alcohol dependent (Fig. 2). While most of these studies demonstrate an effect in

overweight individuals or those with type 2 diabetes, the impact of weight on treatment response remains to be elucidated in detail. Although a reduction in alcohol intake is observed after GLP-1R activation, the specific neuronal circuits and mechanisms underlying this effect remain to be defined in humans, as they also do in rodents.

## Tentative Causes of the Reduced Alcohol Intake by GLP-1R Agonists

It has been demonstrated that alcohol's rewarding properties contribute to escalated alcohol consumption as well as relapse drinking (for review see (7)) and possess an enhanced risk of later AUD diagnosis (43). It has therefore been speculated that alcohol's rewarding properties are suppressed by GLP-1R agonists and that this contributes to a reduction in alcohol consumption. This hypothesis is mainly supported by preclinical studies reflecting alcohol's rewarding properties (Fig. 1), including dopamine release in the nucleus accumbens (NAc), locomotor stimulation, and reward in the conditioned place preference test (44-48).

Ex4 was the first GLP-1R agonist found to attenuate alcohol's rewarding properties in male mice, as systemic administration of Ex4 blocked the alcohol-induced dopamine release in NAc (8), locomotor stimulation (8), and reward in the conditioned place preference test (8, 9). It was thereafter shown that both liraglutide (16) and semaglutide (20) suppress the rewarding properties of alcohol. These findings translate to overweight patients who consume alcohol, as alcohol's stimulatory effects are attenuated by semaglutide in this patient population (39).

Suppression of memory of alcohol's rewarding properties is another aspect of importance for the manifestation of AUD. Indeed, both Ex4 and GLP-1 blocked the memory of alcohol reward in the CPP test; liraglutide did not influence this behavior (8, 9, 16), but diminished the memory impairments observed at long-term alcohol exposure (29).

Another tentative factor that might influence the treatment outcome is the ability of higher doses of GLP-1R agonist to cause nausea (49). Malaises is however an unlikely contributing factor to reduced alcohol intake as lower doses without nauseating properties (49-54) that do not condition for aversion (51) or influence water intake were used in the alcohol studies. Sedation and anhedonia are other unlikely factors contributing to reduced alcohol intake as neither of the GLP-1R agonists influences locomotor activity or dopamine in the NAc shell per se. Although higher doses of GLP-1R agonists alter plasma corticosterone (55), the GLP-1R agonists used in the alcohol studies were in a dose range that does not alter corticosterone in plasma (56, 57). Another tentative factor that might contribute to reduced alcohol intake are changes in alcohol metabolism, although unlikely as neither Ex4 nor liraglutide influences the blood alcohol concentrations obtained after alcohol injection (8, 16).

## Brain Regions of Interest

Most studies exploring mechanisms that might contribute to GLP-1R agonists' ability to reduce alcohol-related behaviors have used Ex4. As such, findings from central and peripheral GLP-1R knockout mice concluded that Ex4 acts via central GLP-1R (58). Specifically, the ability of systemic Ex4 to reduce alcohol intake was diminished in mice with a knockout of central but not peripheral GLP-1R, whereas the opposite was seen for food intake suppressed by Ex4 (58). Several GLP-1R-expressing brain regions appear important for the interaction between alcohol and GLP-1R, where initial studies focused on brain regions central to reward.

One of these is the laterodorsal tegmental area (LDTg); when infused into LDTg, Ex4 ablated the alcohol-induced reward and lowered alcohol consumption (59). The VTA is a heterogeneous region targeted by cholinergic projections from the LDTg, and different subparts of the VTA appear to modulate alcohol-related responses differently. Indeed, local infusion of Ex4 into the anterior region did not affect any alcohol-related behaviors, whereas infusion into the posterior region modulated some but not all of these responses (9, 59-61). Dopaminergic neurons of the VTA project to the NAc, and GLP-1R expressed in this area seems to participate in modulation of alcohol-related responses. Specifically, both fluorescently tagged Ex4 (62) and semaglutide (20) were detected in this region when administered systemically. Moreover, the rewarding properties of alcohol, alcohol intake (59), and operant self-administration of alcohol (63) were suppressed after Ex4 infusion into this area. Further support was provided from electrophysiological recordings of NAc slices, in which both Ex4 and liraglutide, but not dulaglutide, reduced excitatory neurotransmission in the NAc, without affecting inhibitory neurotransmission (64). While the neurotransmitters in the NAc participating in the suppressed alcohol-related responses remain to be characterized in detail, recent studies have found that both semaglutide and Ex4 enhance the metabolism of dopamine (20) and that Ex4 reduces the release of the neuromodulators serine, glycine, and taurine (65).

While GLP-1R in reward-related areas has been found to modulate alcohol-related responses, other regions protecting these reward areas may be of relevance. One of these is the NTS, known to express GLP-1R and project preproglucagon (a marker of GLP-1 production) containing neurons to areas central to the reward (eg, LDTg, VTA, and NAc) (66). Administering Ex4 directly into the NTS of male rodents successfully diminished the rewarding effects of alcohol and led to a marked decrease in their alcohol intake (67). GLP-1R-expressing brain regions that regulate alcohol-related responses also include the lateral hypothalamus, lateral septum, and hippocampus (29, 63). On the contrary, activation of GLP-1R in the arcuate nucleus, paraventricular nucleus, basolateral amygdala, or putamen did not regulate alcohol-related responses and may thus be less important to control alcohol's effects (60, 63). It should however be emphasized that GLP-1Rs are expressed throughout the brain, and additional GLP-1R-expressing brain regions may control alcohol-related responses, a tentative subject for future studies. It should be further emphasized that GLP-1R in these brain regions has been identified as important for alcohol-related responses through studies involving localized brain infusions. Moreover, it should be considered that the ability of GLP-1R agonists to pass the blood–brain barrier varies, and their ability to activate different brain regions may vary (68, 69). It is also plausible that the different GLP-1R agonists do not target areas identified by local infusions, and this should be elucidated in future studies. Another factor that might influence the regions targeted by the GLP-1R agonist is that blood–brain penetration is influenced by exposure to alcohol. Future studies should therefore address the possibility that the different

GLP-1R agonists act via different neuronal circuits to regulate alcohol-related responses in alcohol-naïve vs alcohol-exposed rodents.

## Summary and Future Directions

While these preclinical and clinical studies show promising outcomes of GLP-1R agonists on alcohol-related responses, the ability of each of these agonists to reduce alcohol consumption in overweight and regular-weight patients with AUD should be tested in randomized clinical trials, an aspect currently being investigated in several studies using semaglutide. Given the positive outcomes observed in rodents at low doses, this effect should be evaluated in detail in humans, raising the possibility of fewer side effects associated with using low doses. Although more recent preclinical studies have included female studies, this aspect has been omitted to a large extent, raising the need for additional studies on female subjects. It should be further noted that GLP-1R agonists decrease the intake of various drugs of abuse in rodents (for review see (70)) and that the use of multiple drugs is common (for review see (71)). Together these findings raise the possibility that the GLP-1R agonists may reduce the intake of several addictive drugs, which is a tentative subject for future studies. Although the single use of 1 gut–brain peptide has beneficial effects, more recent studies reveal that combining gut–brain peptides synergistically reduces body weight, thereby transforming the treatment of obesity (72). However, the effects of gut–brain peptide combinations on alcohol-related responses remain largely unexamined, and future studies should investigate this potential interaction.

## Funding

The mini-review is supported by grants from the Swedish Research Council (2023-2600).

## Disclosures

While E.J. has obtained funding that supports the writing of the present mini-review, these financial considerations have had no impact on writing of or the interpretation of the studies included in the mini-review. Thus, E.J. has no conflict of interest to declare.

## Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## References

1. Novak U, Wilks A, Buell G, McEwen S. Identical mRNA for preproglucagon in pancreas and gut. *Eur J Biochem*. 1987;164(3):553-558.
2. Alvarez E, Roncero I, Chowen JA, Thorens B, Blázquez E. Expression of the glucagon-like peptide-1 receptor gene in rat brain. *J Neurochem*. 1996;66(3):920-927.
3. Srivastava G, Apovian C. Future pharmacotherapy for obesity: new anti-obesity drugs on the horizon. *Curr Obes Rep*. 2018;7(2):147-161.
4. Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. *J Comp Neurol*. 1999;403(2):261-280.
5. Jensen CB, Pyke C, Rasch MG, Dahl AB, Knudsen LB, Secher A. Characterization of the glucagonlike peptide-1 receptor in male mouse brain using a novel antibody and in situ hybridization. *Endocrinology*. 2018;159(2):665-675.
6. Pyke C, Heller RS, Kirk RK, *et al*. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology*. 2014;155(4):1280-1290.
7. Koob GF. Neurocircuitry of alcohol addiction: synthesis from animal models. *Handb Clin Neurol*. 2014;125:33-54.
8. Egecioglu E, Steensland P, Fredriksson I, Feltmann K, Engel JA, Jerlhag E. The glucagon-like peptide 1 analogue exendin-4 attenuates alcohol mediated behaviors in rodents. *Psychoneuroendocrinology*. 2013;38(8):1259-1270.
9. Shirazi RH, Dickson SL, Skibicka KP. Gut peptide GLP-1 and its analogue, exendin-4, decrease alcohol intake and reward. *PLoS One*. 2013;8(4):e61965.
10. Davis JF, Schurdak JD, Magrisso IJ, *et al*. Gastric bypass surgery attenuates ethanol consumption in ethanol-preferring rats. *Biol Psychiatry*. 2012;72(5):354-360.
11. Sørensen G, Caine SB, Thomsen M. Effects of the GLP-1 agonist exendin-4 on intravenous ethanol self-administration in mice. *Alcohol Clin Exp Res*. 2016;40(10):2247-2252.
12. Thomsen M, Dencker D, Wörtwein G, *et al*. The glucagon-like peptide 1 receptor agonist exendin-4 decreases relapse-like drinking in socially housed mice. *Pharmacol Biochem Behav*. 2017;160:14-20.
13. Thomsen M, Holst JJ, Molander A, Linnet K, Ptito M, Fink-Jensen A. Effects of glucagon-like peptide 1 analogs on alcohol intake in alcohol-preferring vervet monkeys. *Psychopharmacology (Berl)*. 2019;236(2):603-611.
14. Brigande AM, Darwich JG, Currie PJ. Mesolimbic exendin-4 attenuates reward salience evoked by neuropeptide Y and ghrelin. *Behav Brain Res*. 2023;440:114249.
15. Mahalingam S, Bellamkonda R, Arumugam MK, *et al*. Glucagon-like peptide 1 receptor agonist, exendin-4, reduces alcohol-associated fatty liver disease. *Biochem Pharmacol*. 2023;213:115613.
16. Vallöf D, Maccioni P, Colombo G, *et al*. The glucagon-like peptide 1 receptor agonist liraglutide attenuates the reinforcing properties of alcohol in rodents. *Addict Biol*. 2016;21(2):422-437.
17. Marty VN, Farokhnia M, Munier JJ, Mulpuri Y, Leggio L, Spigelman I. Long-acting glucagon-like peptide-1 receptor agonists suppress voluntary alcohol intake in male Wistar rats. *Front Neurosci*. 2020;14:599646.
18. Vallöf D, Kalafateli AL, Jerlhag E. Long-term treatment with a glucagon-like peptide-1 receptor agonist reduces ethanol intake in male and female rats. *Transl Psychiatry*. 2020;10(1):238.
19. Bucheit JD, Pamulapati LG, Carter N, Malloy K, Dixon DL, Sisson EM. Oral semaglutide: a review of the first oral glucagon-like peptide 1 receptor agonist. *Diabetes Technol Ther*. 2020;22(1):10-18.
20. Aranäs C, Edvardsson CE, Shevchouk OT, *et al*. Semaglutide reduces alcohol intake and relapse-like drinking in male and female rats. *EBioMedicine*. 2023;93:104642.
21. Aranäs C, Blid Sköldheden S, Jerlhag E. Antismoking agents do not contribute synergistically to semaglutide's ability to reduce alcohol intake in rats. *Front Pharmacol*. 2023;14:1180512.
22. Chuong V, Farokhnia M, Khom S, *et al*. The glucagon-like peptide-1 (GLP-1) analogue semaglutide reduces alcohol drinking and modulates central GABA neurotransmission. *JCI Insight*. 2023;8(12):e170671.
23. Fink-Jensen A, Wörtwein G, Klausen MK, *et al*. Effect of the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide on alcohol consumption in alcohol-preferring male vervet monkeys. *Psychopharmacology (Berl)*. 2025;242(1):63-70.
24. Suchankova P, Yan J, Schwandt ML, *et al*. The glucagon-like peptide-1 receptor as a potential treatment target in alcohol use disorder: evidence from human genetic association studies and a mouse model of alcohol dependence. *Transl Psychiatry*. 2015;5(6):e583.

25. Bornebusch AB, Fink-Jensen A, Wörtwein G, Seeley RJ, Thomsen M. Glucagon-like peptide-1 receptor agonist treatment does not reduce abuse-related effects of opioid drugs. *eNeuro*. 2019;6(2): ENEURO.0443-18.2019.
26. Díaz-Megido C, Thomsen M. Sex-dependent divergence in the effects of GLP-1 agonist exendin-4 on alcohol reinforcement and reinstatement in C57BL/6J mice. *Psychopharmacology (Berl)*. 2023;240(6):1287-1298.
27. Asarian L, Abegg K, Geary N, Schiesser M, Lutz TA, Bueter M. Estradiol increases body weight loss and gut-peptide satiation after Roux-en-Y gastric bypass in ovariectomized rats. *Gastroenterology*. 2012;143(2):325-327.e2.
28. Richard JE, Anderberg RH, López-Ferreras L, Olandersson K, Skibicka KP. Sex and estrogens alter the action of glucagon-like peptide-1 on reward. *Biol Sex Differ*. 2016;7:6.
29. Liu W, Wang Z, Wang W, Wang Z, Xing Y, Hölscher C. Liraglutide reduces alcohol consumption, anxiety, memory impairment, and synapse loss in alcohol dependent mice. *Neurochem Res*. 2024;49(4):1061-1075.
30. Sharma AN, Pise A, Sharma JN, Shukla P. Glucagon-like peptide-1 (GLP-1) receptor agonist prevents development of tolerance to anti-anxiety effect of ethanol and withdrawal-induced anxiety in rats. *Metab Brain Dis*. 2015;30(3):719-730.
31. Sharma AN, Pise A, Sharma JN, Shukla P. Dipeptidyl-peptidase IV (DPP-IV) inhibitor delays tolerance to anxiolytic effect of ethanol and withdrawal-induced anxiety in rats. *Metab Brain Dis*. 2015;30(3):659-667.
32. Kalra S, Kalra B, Sharma A. Change in alcohol consumption following liraglutide initiation: a real life experience. Paper presented at: 71st Anerican diabetes association confernace; 2011:2019-P.
33. Farokhnia M, Fede SJ, Grodin EN, *et al*. Differential association between the GLP1R gene variants and brain functional connectivity according to the severity of alcohol use. *Sci Rep*. 2022;12(1):13027.
34. Farokhnia M, Browning BD, Crozier ME, Sun H, Akhlaghi F, Leggio L. The glucagon-like peptide-1 system is modulated by acute and chronic alcohol exposure: findings from human laboratory experiments and a post-mortem brain study. *Addict Biol*. 2022;27(5): e13211.
35. Klausen MK, Jensen ME, Møller M, *et al*. Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. *JCI Insight*. 2022;7(19):e159863.
36. Probst L, Monnerat S, Vogt DR, *et al*. Effects of dulaglutide on alcohol consumption during smoking cessation. *JCI Insight*. 2023;8(22):e170419.
37. Wium-Andersen IK, Wium-Andersen MK, Fink-Jensen A, Rungby J, Jørgensen MB, Osler M. Use of GLP-1 receptor agonists and subsequent risk of alcohol-related events. A nationwide register-based cohort and self-controlled case series study. *Basic Clin Pharmacol Toxicol*. 2022;131(5):372-379.
38. Bremmer MP, Hendershot CS. 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. *J Stud Alcohol Drugs*. 2024;85(1):5-11.
39. Quddos F, Hubshman Z, Tegge A, *et al*. Semaglutide and tirzepatide reduce alcohol consumption in individuals with obesity. *Sci Rep*. 2023;13(1):20998.
40. Richards JR, Dorand MF, Royal K, Mnajjed L, Paszkowiak M, Simmons WK. Significant decrease in alcohol use disorder symptoms secondary to semaglutide therapy for weight loss: a case series. *J Clin Psychiatry*. 2023;85(1):23m15068.
41. Olsson Y, Hodzic K, Wass C, *et al*. Free-access intravenous alcohol self-administration in social drinkers and individuals with alcohol use disorder: evaluation of relationships with phosphatidylethanol and self-reported alcohol consumption. *Alcohol Clin Exp Res (Hoboken)*. 2023;47(8):1453-1466.
42. Molina-Castro M, Seyedsadjadi N, Nieto D, Leggio L, Rowitz B, Pepino MY. The glucagon-like peptide-1 and other endocrine responses to alcohol ingestion in women with versus without metabolic surgery. *Addict Biol*. 2024;29(10):e13441.
43. King A, Vena A, Hasin DS, deWit H, O'Connor SJ, Cao D. Subjective responses to alcohol in the development and maintenance of alcohol use disorder. *Am J Psychiatry*. 2021;178(6): 560-571.
44. Engel JA, Fahlke C, Hulthe P, *et al*. Biochemical and behavioral evidence for an interaction between ethanol and calcium channel antagonists. *J Neural Transm*. 1988;74(3):181-193.
45. Imperato A, Di Chiara G. Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. *J Pharmacol Exp Ther*. 1986;239(1):219-228.
46. Blomqvist O, Söderpalm B, Engel JA. Ethanol-induced locomotor activity: involvement of central nicotinic acetylcholine receptors? *Brain Res Bull*. 1992;29(2):173-178.
47. Engel J, Strömbom U, Svensson TH, Waldeck B. Suppression by alpha-methyltyrosine of ethanol-induced locomotor stimulation: partial reversal by L-dopa. *Psychopharmacologia*. 1974;37(3): 275-279.
48. Boileau I, Assaad JM, Pihl RO, *et al*. Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse*. 2003;49(4): 226-231.
49. Kanoski SE, Rupprecht LE, Fortin SM, De Jonghe BC, Hayes MR. The role of nausea in food intake and body weight suppression by peripheral GLP-1 receptor agonists, exendin-4 and liraglutide. *Neuropharmacology*. 2012;62(5-6):1916-1927.
50. Mietlicki-Baase EG, Ortinski PI, Rupprecht LE, *et al*. The food intake-suppressive effects of glucagon-like peptide-1 receptor signaling in the ventral tegmental area are mediated by AMPA/kainate receptors. *Am J Physiol Endocrinol Metab*. 2013;305(11): E1367-E1374.
51. Cagniard B, Murphy NP. Affective taste responses in the presence of reward- and aversion-conditioned stimuli and their relationship to psychomotor sensitization and place conditioning. *Behav Brain Res*. 2012;236(1):289-294.
52. Rodriguez JA, Fehrentz JA, Martinez J, Ben Haj Salah K, Wellman PJ. The GHR-R antagonist JMV 2959 neither induces malaise nor alters the malaise property of LiCl in the adult male rat. *Physiol Behav*. 2018;183:46-48.
53. Mietlicki-Baase EG, McGrath LE, Koch-Laskowski K, *et al*. Amylin receptor activation in the ventral tegmental area reduces motivated ingestive behavior. *Neuropharmacology*. 2017;123:67-79.
54. Baisley SK, Baldo BA. Amylin receptor signaling in the nucleus accumbens negatively modulates mu-opioid-driven feeding. *Neuropsychopharmacology*. 2014;39(13):3009-3017.
55. Guerrero-Hreins E, Goldstone AP, Brown RM, Sumithran P. The therapeutic potential of GLP-1 analogues for stress-related eating and role of GLP-1 in stress, emotion and mood: a review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;110:110303.
56. Vestlund J, Jerlhag E. The glucagon-like peptide-1 receptor agonist, exendin-4, reduces sexual interaction behaviors in a brain site-specific manner in sexually naive male mice. *Horm Behav*. 2020;124:104778.
57. Vestlund J, Jerlhag E. Glucagon-like peptide-1 receptors and sexual behaviors in male mice. *Psychoneuroendocrinology*. 2020;117: 104687.
58. Sirohi S, Schurdak JD, Seeley RJ, Benoit SC, Davis JF. Central & peripheral glucagon-like peptide-1 receptor signaling differentially regulate addictive behaviors. *Physiol Behav*. 2016;161:140-144.
59. Vallöf D, Kalafateli AL, Jerlhag E. Brain region specific glucagon-like peptide-1 receptors regulate alcohol-induced behaviors in rodents. *Psychoneuroendocrinology*. 2019;103:284-295.
60. Colvin KJ, Killen HS, Kanter MJ, Halperin MC, Engel L, Currie PJ. Brain site-specific inhibitory effects of the GLP-1 analogue exendin-4 on alcohol intake and operant responding for palatable food. *Int J Mol Sci*. 2020;21(24):9710.
61. Dixon TN, McNally GP, Ong ZY. Glucagon-like peptide-1 receptor signaling in the ventral tegmental area reduces alcohol self-administration in male rats. *Alcohol Clin Exp Res*. 2020;44(10): 2118-2129.

62. Hernandez NS, O'Donovan B, Ortinski PI, Schmidt HD. Activation of glucagon-like peptide-1 receptors in the nucleus accumbens attenuates cocaine seeking in rats. *Addict Biol*. 2019;24(2):170-181.
63. Allingbjerg ML, Hansen SN, Secher A, Thomsen M. Glucagon-like peptide-1 receptors in nucleus accumbens, ventral hippocampus, and lateral septum reduce alcohol reinforcement in mice. *Exp Clin Psychopharmacol*. 2023;31(3):612-620.
64. Vestlund J, Bergquist F, Licheri V, Adermark L, Jerlhag E. Activation of glucagon-like peptide-1 receptors and skilled reach foraging. *Addict Biol*. 2020;26(3):e12953.
65. Edvardsson CE, Vestlund J, Ericson M, Jerlhag E. The GLP-1 receptor agonist exendin-4 reduces taurine and glycine in nucleus accumbens of male rats, an effect tentatively involving the nucleus tractus solitarius. *Front Pharmacol*. 2024;15:1439203.
66. Rinaman L. Ascending projections from the caudal visceral nucleus of the solitary tract to brain regions involved in food intake and energy expenditure. *Brain Res*. 2010;1350:18-34.
67. Vallöf D, Vestlund J, Jerlhag E. Glucagon-like peptide-1 receptors within the nucleus of the solitary tract regulate alcohol-mediated behaviors in rodents. *Neuropharmacology*. 2019;149:124-132.
68. Gu G, Roland B, Tomaselli K, Dolman CS, Lowe C, Heilig JS. Glucagon-like peptide-1 in the rat brain: distribution of expression and functional implication. *J Comp Neurol*. 2013;521(10):2235-2261.
69. Salinas CBG, Lu TT, Gabery S, *et al*. Integrated brain atlas for unbiased mapping of nervous system effects following liraglutide treatment. *Sci Rep*. 2018;8(1):10310.
70. Jerlhag E. The therapeutic potential of glucagon-like peptide-1 for persons with addictions based on findings from preclinical and clinical studies. *Front Pharmacol*. 2023;14:1063033.
71. Compton WM, Valentino RJ, DuPont RL. Polysubstance use in the U.S. opioid crisis. *Mol Psychiatry*. 2021;26(1):41-50.
72. Kusminski CM, Perez-Tilve D, Müller TD, DiMarchi RD, Tschöp MH, Scherer PE. Transforming obesity: the advancement of multireceptor drugs. *Cell*. 2024;187(15):3829-3853.