

A current grasp of GLP-1 receptor agonists for addiction: emerging therapeutic potential

RM Moosa-Bathey 

Department of Pharmaceutical Sciences, Tshwane University of Technology, South Africa

Corresponding author, email: batteym@tut.ac.za

Abstract

Glucagon-like peptide-1 (GLP-1) receptor agonists have gained prominence for their role in managing type 2 diabetes and obesity. Recently, their potential in addressing substance use disorders has attracted significant interest. GLP-1 receptor agonists exert effects on reward-related neural pathways, suggesting their utility in modulating addiction-related behaviours. This article examines the mechanisms through which GLP-1 receptor agonists impact on addiction, summarises preclinical and clinical studies, and explores their therapeutic potential for abuse of substances such as alcohol, nicotine, opioids and stimulants. Despite promising findings, challenges remain, including understanding optimal dosing, long-term safety and individual variability. Future research directions are outlined to establish GLP-1 receptor agonists as a novel therapeutic option for addiction.

Keywords: glucagon-like peptide-1 (GLP-1) receptor agonists, addiction, reward-related neural pathways

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<https://doi.org/10.36303/SAPJ.2615>

Introduction

Addiction is a complex neuropsychiatric disorder characterised by compulsive substance use despite harmful consequences.¹ Current treatments, including behavioural therapies and pharmacological agents, often have suboptimal outcomes owing to high relapse rates and limited efficacy.¹ This has driven the search for novel therapeutic targets, with the glucagon-like peptide-1 (GLP-1) system emerging as a promising candidate.²

GLP-1 is a gut-derived peptide that plays a crucial role in glucose metabolism and appetite regulation.² However, its influence extends beyond metabolic functions, as recent studies have indicated its involvement in the reward pathways associated with addiction. The GLP-1 analogue exendin-4 attenuates nicotine-induced locomotor stimulation and dopamine release in the nucleus accumbens (NAc), a critical region for reward processing.³ This suggests that GLP-1 receptor activation may mitigate the reinforcing properties of nicotine, thereby influencing addiction-related behaviours.³ Furthermore, the expression of locomotor sensitisation, which reflects neurochemical alterations related to craving and compulsive drug use, was also reduced by exendin-4, highlighting the potential of GLP-1 in addiction treatment.⁴

Mechanisms of action in addiction

GLP-1 receptor agonists influence addiction through multiple mechanisms.

- *Reward pathway modulation:* GLP-1 receptors are expressed in the ventral tegmental area and NAc, regions critical for reward processing.³ Activation of these receptors reduces dopamine release, dampening the reinforcing effects of addictive substances.³

- *Stress and anxiety reduction:* GLP-1 receptor agonists attenuate stress-induced relapse by modulating hypothalamic-pituitary-adrenal (HPA) axis activity.⁵
- *Appetite and craving regulation:* By acting on the hypothalamus, GLP-1 receptor agonists reduce cravings and consumption of rewarding substances, including food and drugs.²

The mechanisms underlying GLP-1's effects on addiction are complex and multifaceted. It is proposed that GLP-1 signalling modulates reward circuitry by influencing dopamine homeostasis and reducing the rewarding effects of psychostimulants and alcohol.⁶ Additionally, the importance of understanding the neurobiological mechanisms that govern GLP-1's effects on addiction has been emphasised, suggesting that the GLP-1 pathway may play a significant role in regulating alcohol and drug consumption patterns.⁷ Furthermore, the role of genetic and individual variations in response to GLP-1 receptor agonists cannot be overlooked. The potential variations associated with gender and genetic differences that may influence the efficacy of GLP-1 receptor agonists in treating addictive disorders have been discussed.⁸ In terms of behavioural addictions, a decrease in excessive buying was mentioned in 21.35% of comments, while numerous people claimed an increase in their sexual drive and libido.⁸ The current mixed-methods approach seemed to be a helpful tool for understanding complicated subjects such as how GLP-1 receptor agonists affect problems linked to drug and non-substance addiction; certain benefits related to the effects of GLP-1 receptor agonists on mental health might also be deduced from this.⁸ Overall, it seemed that GLP-1 receptor agonists could be able to address substance seeking as well as maladaptive/addictive behaviours, although further empirical studies are required.⁸ This underscores the importance of personalised approaches in addiction treatment, as individual differences may significantly affect treatment outcomes.⁸

Predclinical evidence

Animal studies have provided robust evidence for the efficacy of GLP-1 receptor agonists in addiction models.

- **Alcohol:** Exenatide and liraglutide have been shown to reduce alcohol intake and preference in rodent models by attenuating reward-related dopamine signalling.⁹ In addition to nicotine, GLP-1 receptor agonists have shown promise in modulating alcohol consumption.⁹ It was reported that liraglutide, another GLP-1 receptor agonist, attenuates the reinforcing properties of alcohol in rodent models.⁹ The study found that liraglutide delayed withdrawal-induced anxiety and reduced tolerance to the anxiolytic effects of alcohol, suggesting a multifaceted role of GLP-1 in alcohol use disorders.⁹ This aligns with findings that noted that GLP-1 and its analogue exendin-4 decrease alcohol intake and reward, further supporting the hypothesis that GLP-1 receptor activation can influence alcohol-related behaviours.¹⁰ The convergence of GLP-1's effects on both nicotine and alcohol suggests a broader application of GLP-1 receptor agonists in treating various substance use disorders (SUDs).¹⁰
- **Nicotine:** GLP-1 receptor agonists decrease nicotine self-administration and conditioned place preference, suggesting reduced reinforcing effects.¹¹ Studies utilising GLP-1 receptor agonists such as exendin-4 have demonstrated a reduction in the rewarding effects of nicotine, as evidenced by decreased locomotor stimulation and conditioned place preference in rodent models.¹¹ These findings suggest that GLP-1 receptor activation may attenuate the dopaminergic responses typically associated with nicotine, thereby diminishing its reinforcing

properties.¹² Furthermore, administration of GLP-1 into the interpeduncular nucleus has been shown to decrease nicotine intake without inducing malaise, indicating a specific action on nicotine reward pathways rather than general aversion.²

- **Opioids:** Preclinical data suggest that GLP-1 receptor agonists diminish opioid-induced euphoria and prevent relapse behaviours. Research indicates that GLP-1 receptor agonists such as exenatide have been studied for their effects on opioid-related behaviours. For instance, while some studies have shown that GLP-1 receptor stimulation can enhance corticotropin-releasing factor (CRF) signalling, which is involved in stress and addiction pathways, the direct impact of GLP-1 on opioid abuse-related effects remains contentious.¹³ It was found that treatment with GLP-1 receptor agonists did not significantly reduce the abuse-related effects of opioid drugs in animal models, suggesting that while GLP-1 may have a role in addiction, it does not uniformly mitigate the reinforcing properties of opioids.¹³ This finding highlights the complexity of the interactions between GLP-1 signalling and opioid addiction.
- **Stimulants:** In cocaine and amphetamine models, GLP-1 receptor agonists suppress drug-seeking behaviours and relapse. Cocaine addiction represents another area where GLP-1 receptor agonists have demonstrated efficacy. It was found that central GLP-1 receptor activation modulates cocaine-evoked phasic dopamine signalling in the NAc core, indicating that GLP-1 can influence the dopaminergic pathways associated with cocaine reinforcement.¹⁴ Similarly, it was shown that exendin-4 reduces cocaine self-administration in mice, implicating the GLP-1 system in modulating cocaine's effects on behaviour

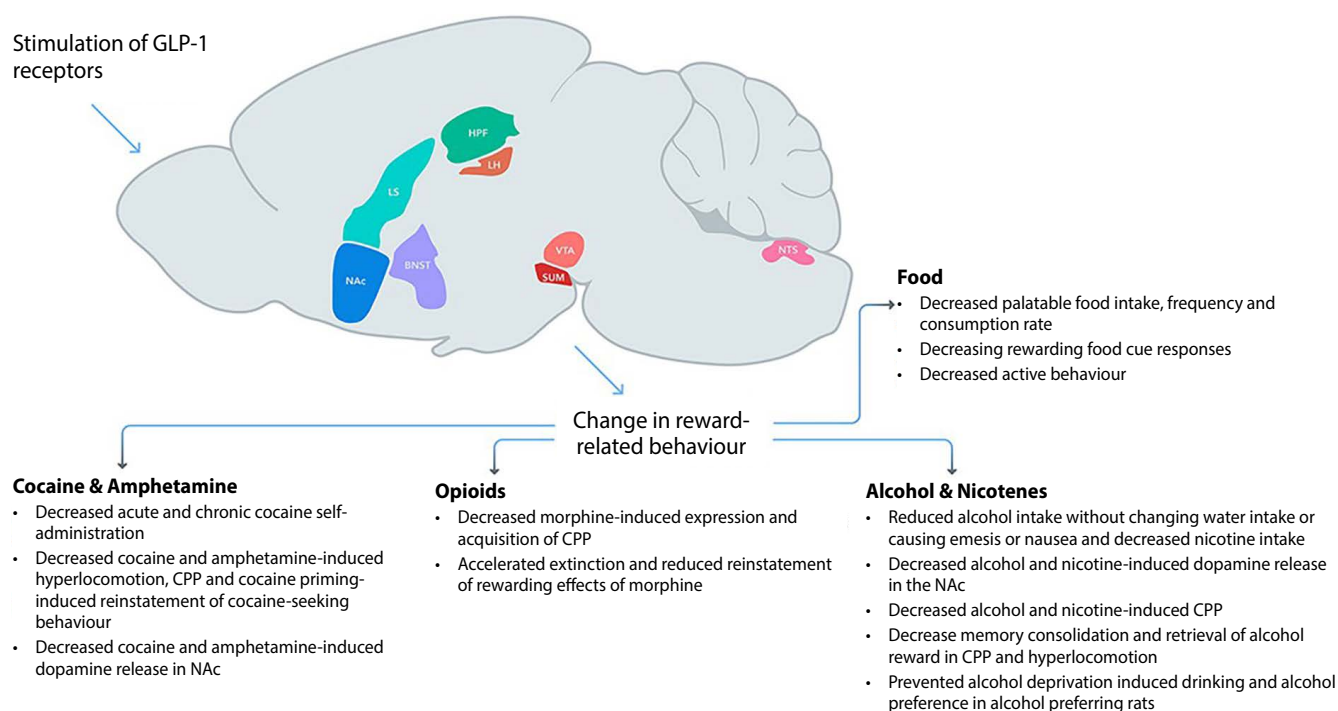


Figure 1: Schematic drawing of reversed reward responses after GLP-1 modulation²

GLP-1 – glucagon-like peptide-1, CPP – conditioned place preference, NAc – nucleus accumbens

and dopamine homeostasis.¹⁵ These findings underscore the potential of GLP-1 receptor agonists as therapeutic agents for cocaine addiction.¹⁶ Figure 1 depicts reversed reward responses after GLP-1 modulation.

Clinical evidence

While clinical trials on GLP-1 receptor agonists for addiction are limited, early findings are promising. Research into the therapeutic potential of GLP-1 receptor agonists, particularly semaglutide, for treating SUDs, including alcohol and cannabis use disorders, is gaining momentum. Ongoing trials are evaluating semaglutide for alcohol use disorder, with preliminary data indicating a reduction in binge drinking episodes. Several ongoing clinical trials aim to evaluate the efficacy of semaglutide in reducing alcohol consumption and aiding smoking cessation, reflecting a broader interest in the role of GLP-1 in addiction treatment.¹⁷ Preliminary findings suggest that patients receiving semaglutide report a decreased interest in consuming addictive substances, including alcohol and tobacco, which aligns with the drug's known effects on appetite regulation and reward pathways in the brain.¹⁸

There is growing optimism surrounding the broader benefits of GLP-1 medications, which have already shown remarkable success in treating obesity. Recent findings suggest that these drugs may also be effective in addressing addiction. A placebo-controlled clinical trial conducted by researchers at the University of North Carolina, Chapel Hill, recently provided compelling evidence: 48 adults with alcohol use disorder received weekly low-dose injections of semaglutide – commercially known as Ozempic and Wegovy – for nine weeks. The treatment led to a notable reduction in both alcohol consumption and cravings.¹⁹ Building on these promising results, Eli Lilly is set to launch trials targeting alcohol addiction, smoking, and potentially other forms of substance abuse using its own GLP-1 agents. Similarly, Novo Nordisk has announced its plans to explore these new therapeutic applications.

Challenges and limitations

Despite the promising findings regarding the role of GLP-1 in addiction, some studies have reported mixed results. Bornebusch et al.¹³ found that GLP-1 receptor agonist treatment did not reduce the abuse-related effects of opioid drugs, suggesting that the efficacy of GLP-1 in addiction may vary depending on the substance involved. This finding highlights the need for further research to delineate the specific mechanisms through which GLP-1 receptor activation influences different types of addiction.

- **Dosing and tolerability:** The optimal dosing regimens for GLP-1 receptor agonists in the context of addiction treatment remain unclear, as doses effective for metabolic disorders may not translate directly. For instance, while liraglutide is commonly used at doses of 1.2–1.8 mg for diabetes management, its efficacy and tolerability at these doses for addiction treatment have not been thoroughly established.²⁰ This uncertainty necessitates further research to determine appropriate dosing

strategies that maximise therapeutic benefits while minimising adverse effects.

- **Long-term safety:** Chronic use of GLP-1 receptor agonists requires further evaluation, particularly in populations with SUDs. While these medications have been shown to be generally safe in the context of diabetes and obesity, their long-term effects on individuals with SUDs are not well understood. Concerns regarding potential adverse effects, such as gastrointestinal issues and the risk of pancreatitis, highlight the need for ongoing monitoring and research to ensure the safety of these agents in vulnerable populations.^{21,22}
- **Individual variability:** Genetic and behavioural factors may significantly influence treatment outcomes with GLP-1 receptor agonists. Variability in individual responses to these medications can be attributed to genetic polymorphisms that affect drug metabolism and receptor sensitivity.²³ Additionally, behavioural factors, such as the presence of comorbid mental health disorders, can impact on the efficacy of treatment. Personalised approaches that consider these individual differences are essential for optimising treatment outcomes and enhancing adherence to therapy.^{21,24}
- **Mechanistic complexity:** The precise interaction between GLP-1 signalling and addiction-related pathways warrants further exploration. While existing studies suggest that GLP-1 receptor activation can modulate dopaminergic signalling in the brain's reward pathways, the underlying mechanisms remain complex and are not fully understood.²⁵ Further research is needed to elucidate how GLP-1 receptor agonists interact with other neurobiological systems involved in addiction, which could inform the development of more effective treatment strategies.²⁶

Future directions

- **Expanded clinical trials:** Large-scale, randomised controlled trials are essential to confirm the efficacy of GLP-1 receptor agonists across various substances, including alcohol, nicotine, and other drugs of abuse. Current studies primarily focus on metabolic disorders, and while preliminary data suggest benefits in addiction treatment, robust clinical evidence is needed to establish these agents as standard therapeutic options. Trials should encompass diverse populations, including those with comorbidities, to assess the generalisability of findings. For instance, a multi-site trial could evaluate the effects of liraglutide on alcohol use disorder, comparing outcomes with standard treatment protocols.
- **Combination therapies:** Investigating GLP-1 receptor agonists in combination with existing pharmacotherapies may enhance treatment outcomes for individuals with SUDs. Combining GLP-1 receptor agonists with medications such as naltrexone or varenicline could provide synergistic effects, targeting multiple pathways involved in addiction. For instance, a study examining the combined effects of GLP-1 receptor agonists and traditional anti-addiction medications could provide insights into improved efficacy and reduced relapse rates. This approach may also help mitigate withdrawal symptoms and cravings,

enhancing overall treatment adherence.

- **Biomarker development:** Identifying biomarkers for predicting treatment response to GLP-1 receptor agonists could enable personalised interventions tailored to individual patient profiles. Genetic, epigenetic and neurobiological markers may help determine which patients are most likely to benefit from GLP-1 therapy. For instance, research into genetic polymorphisms affecting GLP-1 receptor sensitivity could inform treatment decisions and optimise dosing strategies. Developing a biomarker panel could facilitate early identification of patients at risk of poor treatment outcomes, allowing for timely adjustments to therapeutic approaches.
- **Broader applications:** Exploring the use of GLP-1 receptor agonists for behavioural addictions, such as gambling or food addiction, may reveal additional therapeutic applications. Given the role of the reward system in both substance use and behavioural addictions, GLP-1 receptor agonists could potentially modulate cravings and impulsivity associated with these behaviours. Future studies should investigate the efficacy of GLP-1 receptor agonists in reducing compulsive behaviours and improving self-control in individuals with behavioural addictions. This line of research could expand the therapeutic landscape for GLP-1 receptor agonists beyond traditional SUDs.

Discussion

GLP-1 receptor agonists represent a novel and promising approach for treating addiction by targeting the underlying neurobiological mechanisms of reward and craving. While preclinical and preliminary clinical data are encouraging, further research is essential to address current limitations and translate these findings into clinical practice. The integration of GLP-1 agonists into addiction treatment could revolutionise care, offering hope to individuals struggling with SUDs.

The exploration of GLP-1 receptor agonists in the context of addiction, particularly opioid addiction, presents a promising avenue for future research. Given the neurobiological mechanisms that underlie addiction, GLP-1 receptor agonists may offer novel therapeutic strategies for managing opioid use disorder and potentially other SUDs. One of the key future directions involves investigating the specific mechanisms through which GLP-1 receptors influence opioid-related behaviours. For instance, studies have demonstrated that GLP-1 receptor agonists, such as exendin-4, can reduce reinstatement of heroin-seeking behaviour in animal models, suggesting that GLP-1 signalling may play a critical role in modulating cravings and relapse.²⁷

Future research should focus on elucidating the neurocircuitry involved, particularly in areas such as the NAc and the ventral tegmental area, where GLP-1 receptors are known to be expressed and may interact with dopaminergic pathways.⁴ Understanding these interactions could lead to targeted pharmacotherapies that effectively reduce opioid cravings and withdrawal symptoms. Additionally, the potential for GLP-1 receptor agonists to be used in combination with existing treatments for opioid use disorder warrants further exploration. For instance, integrating GLP-1 receptor agonists with standard of care for opioid dependence

could enhance treatment efficacy and improve patient outcomes. This approach is supported by findings that GLP-1 receptor activation can influence reward pathways associated with various addictive substances, including alcohol and nicotine.²⁸ Clinical trials assessing the efficacy of GLP-1 receptor agonists as adjunct therapies in opioid use disorder treatment protocols could therefore provide valuable insights into their therapeutic potential. Moreover, the role of GLP-1 in modulating stress responses and its interaction with the HPA axis could be another important area of investigation. Research has indicated that GLP-1 receptor stimulation can enhance CRF signalling, which is implicated in stress and addiction pathways.¹³ Understanding how GLP-1 influences stress-related behaviours in the context of opioid addiction could lead to innovative strategies for managing stress-induced relapse.

Conclusion

The future directions for research on GLP-1 in addiction are multifaceted, encompassing mechanistic studies, clinical trials, and the development of novel compounds. By advancing our understanding of GLP-1 signalling in the context of addiction, we can pave the way for innovative therapeutic strategies that address the complex challenges associated with SUDs. GLP-1 receptor agonists, originally developed for managing type 2 diabetes and obesity, have shown promising potential in the treatment of addiction. Preclinical and emerging clinical studies suggest that GLP-1 receptor agonists can modulate reward pathways in the brain, particularly by reducing the reinforcing effects of addictive substances such as alcohol, nicotine and opioids.¹⁹ These agents act on the mesolimbic dopamine system, reducing cravings, drug-seeking behaviour and relapse risk. While research is still in early stages, GLP-1 receptor agonists represent a novel and potentially transformative therapeutic avenue for addressing SUDs, particularly in individuals with coexisting metabolic conditions. Continued investigation is essential to validate efficacy, safety and optimal dosing in diverse populations.

Acknowledgements

None.

Conflict of interest

The author has no conflict of interest.

Funding source

None.

Ethical approval

Not applicable.

ORCID

RM Moosa-Bathey  <https://orcid.org/0000-0002-1953-143X>

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