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GLP-1 RECEPTOR AGONISTS AS EMERGING THERAPEUTICS FOR SUBSTANCE USE DISORDERS: A REVIEW OF MECHANISMS, EFFICACY, AND PUBLIC HEALTH IMPLICATIONS

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ABSTRACT

The convergence of the global obesity epidemic and the rising prevalence of substance use disorders (SUDs) presents a critical public health challenge that traditional therapeutic models have failed to address adequately. Although glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are established treatments for type 2 diabetes and obesity, recent data indicate they possess profound off-target effects on the central nervous system reward circuitry. This comprehensive narrative review synthesizes evidence published between 2023 and early 2026 to elucidate the neurobiological mechanisms and clinical efficacy of agents like semaglutide and tirzepatide in attenuating addictive behaviours. Through a systematic search of major biomedical databases, we analyse high-quality randomized controlled trials and retrospective cohort studies. The reviewed neurobiological data suggest that these agents modulate synaptic plasticity within the ventral tegmental area and nucleus accumbens to dampen phasic dopamine release. This mechanism effectively reduces the incentive salience of stimuli such as alcohol and opioids without inducing global anhedonia. Clinical evidence supports these findings by demonstrating significant reductions in alcohol intake, opioid overdose risk, and compulsive behavioural patterns. We conclude that while these pharmacotherapies offer a paradigm-shifting therapeutic potential for addiction, their integration into psychiatric practice requires a rigorous re-evaluation of access disparities and the bioethical implications of medicalizing consumption behaviours.

KEYWORDS

GLP-1 Receptor Agonists, Semaglutide, Tirzepatide, Mesolimbic Dopamine System, Alcohol Use Disorder, Social Determinants of Health, Incentive Salience

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1. Introduction

Contemporary medicine is currently navigating a significant paradigm shift in the understanding and management of motivated behaviours, a transition driven largely by the unexpected pleiotropic effects of incretin-based therapies. For the past several decades, the clinical management of metabolic disorders, such as obesity and type 2 diabetes, and the treatment of substance use disorders (SUDs) have operated within distinct epistemological and therapeutic silos. Obesity was predominantly conceptualized as a disorder of energy homeostasis, managed through lifestyle interventions and pharmacotherapies aiming to regulate peripheral metabolism or suppress appetite via hypothalamic pathways. Conversely, addiction was traditionally approached through a combination of psychosocial support, behavioural therapies, and a limited repertoire of neuropharmacological agents targeting specific receptor systems, such as opioid antagonists or GABAergic modulators. However, the widespread clinical adoption of second-generation glucagon-like peptide-1 receptor agonists (GLP-1 RAs), particularly the long-acting analogues semaglutide and the dual GLP-1/GIP agonist tirzepatide, has revealed a profound functional overlap between the neurocircuitry regulating energy balance and the pathways governing incentive salience (O'Keefe et al., 2025).

The catalyst for this re-evaluation has been a surge in patient-reported outcomes that extend well beyond the primary endpoints of glycemic control or weight reduction. As these agents were prescribed to millions of patients for obesity management, a consistent clinical signal emerged: patients began reporting a spontaneous, non-volitional reduction in their desire for psychostimulants and depressants. Individuals treated for metabolic indications described a significant attenuation of "intrusive appetitive rumination" - formerly colloquialized as "food noise" - which appeared to generalize to other domains of consumption. Anecdotal reports of cessation of alcohol consumption, smoking, and even compulsive behaviours such as gambling have now been substantiated by a growing body of preclinical and pharmaco-epidemiological evidence. These observations

suggest that GLP-1 RAs do not merely suppress the homeostatic drive to eat but fundamentally modulate the valuation of reward within the central nervous system (Hendershot et al., 2025).

This phenomenon has reinvigorated the "common soil" hypothesis, which posits that obesity and addiction share a dysregulated mesolimbic dopamine substrate. Both conditions are characterized by a state of incentive sensitization, where the drive to consume hyper-palatable foods or psychoactive substances overrides homeostatic satiety signals and executive control mechanisms. By targeting GLP-1 receptors expressed in key nodes of the reward circuitry –specifically the ventral tegmental area and the nucleus accumbens – these medications appear to restore "hedonic homeostasis." They function by dampening the phasic dopamine release associated with the anticipation of reward, thereby reducing the incentive salience of cues that trigger craving. Unlike traditional addiction treatments, which often require high levels of patient motivation to initiate or carry a burden of significant neuropsychiatric side effects, GLP-1 RAs offer a unique therapeutic profile: they address the biological underpinnings of craving through a neuroendocrine pathway, often as a beneficial collateral effect of treating metabolic disease.

The repurposing of metabolic drugs for addiction medicine represents a potential breakthrough in addressing the syndemic of obesity and substance misuse. Current pharmacotherapies for disorders such as Alcohol Use Disorder (AUD) remain underutilized and are often limited by modest efficacy or poor adherence. The emergence of an agent that can simultaneously address metabolic dysregulation and dampen the biological urge to consume addictive substances offers a novel, integrative approach to patient care. This review aims to provide a rigorous examination of this emerging field, synthesizing high-quality evidence from randomized controlled trials, target trial emulation studies, and mechanistic neurobiology papers published between 2023 and early 2026. The objective is to explicate the precise neurophysiological mechanisms by which peripheral hormones modulate central reward pathways and to evaluate the clinical efficacy of these agents in attenuating addictive behaviours. Furthermore, we will discuss the broader implications of this medicalization of desire, analysing how shifting the treatment model from a biological framework may alter the landscape of public health and stigma associated with addiction (Benavides, 2025).

2. Methodology

To ensure a rigorous and unbiased synthesis of the current evidence landscape, this narrative review was developed in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines. A systematic and comprehensive literature search was conducted across major biomedical, pharmacological, and social science databases, specifically PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Library. The search window was strictly defined from January 1, 2023, to February 20, 2026, to capture the most recent data reflecting the paradigm shift following the widespread adoption of second-generation GLP-1 receptor agonists. The search strategy employed a multi-layered approach utilizing Boolean logic to combine Medical Subject Headings (MeSH) and Emtree terms with free-text keywords. Primary search strings integrated terms related to the intervention, including "glucagon-like peptide-1 receptor agonists," "semaglutide," "tirzepatide," "retatrutide," and "incretin mimetics," with terms defining the outcomes of interest, such as "substance use disorders," "alcohol use disorder," "opioid use disorder," "reward system," "nucleus accumbens," "ventral tegmental area," and "incentive salience." To address the sociological dimensions of the review, additional searches were performed using keywords like "medicalization of addiction," "health equity," and "stigma." Reference lists of identified systematic reviews and meta-analyses were manually screened to identify any additional relevant studies that might have been omitted by the electronic search algorithms.

The selection of studies for this review followed a hierarchical evidence-based approach designed to prioritize high-quality data while allowing for the integration of interdisciplinary perspectives. Inclusion criteria were structured around the PICO framework, targeting populations with co-occurring metabolic and substance use disorders, interventions involving FDA-approved or investigational GLP-1 receptor agonists, and outcomes measuring changes in substance consumption, craving intensity, or neurobiological markers of reward processing. Priority was given to randomized controlled trials and large-scale pharmaco-epidemiological studies, such as retrospective cohort analyses and target trial emulations, which provide the strongest evidence for clinical efficacy and safety. Additionally, preclinical studies utilizing advanced neuroimaging techniques, such as fiber photometry and transcriptomics, were included to elucidate the synaptic and molecular mechanisms occurring within the mesocorticolimbic circuitry. Conversely, the review excluded studies published prior to 2020 to maintain relevance to the current therapeutic landscape, as well as case reports that did not offer novel mechanistic insights or describe previously undocumented phenomena.

Articles were also excluded if they were not available in English, lacked peer review, or focused exclusively on first-generation, short-acting agonists without relevance to current addiction treatment protocols. This unified selection process ensured that the synthesized narrative reflects the most robust and clinically actionable evidence available to date.

3. The Neurobiological Substrate: Recalibrating the Reward Circuitry

To comprehensively understand the attenuation of substance intake observed in patients treated with GLP-1 receptor agonists (GLP-1 RAs), it is necessary to deconstruct the intricate interaction between these incretin mimetics and the mesocorticolimbic dopamine system. This system, primarily originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc), constitutes the final common pathway for mediating reward processing, reinforcement learning, and the attribution of incentive salience to environmental cues. The therapeutic efficacy of GLP-1 RAs in addiction medicine is not merely a consequence of induced malaise or satiety; rather, it stems from a fundamental pharmacological recalibration of how the brain encodes the value of reward.

3.1 Modulation of VTA GABAergic and Dopaminergic Transmission

The primary locus of action for the "anti-craving" effects of GLP-1 RAs appears to be the modulation of dopaminergic firing patterns within the ventral tegmental area (VTA). Unlike traditional dopamine antagonists used in psychiatry, which block postsynaptic D2 receptors and often induce distinct anhedonia or blunted affect, GLP-1 RAs exert a subtle, stabilizing neuromodulatory influence. Recent single-nuclei transcriptomics and in vivo fiber photometry studies, such as those by Merkel et al. (2025), have elucidated the precise synaptic architecture of this effect. These studies conclusively demonstrate that GLP-1 receptors (GLP-1R) are sparsely expressed on dopaminergic neurons themselves but are highly enriched on local GABAergic interneurons and presynaptic glutamatergic terminals within the VTA.

The mechanism of action is tri-phasic. First, systemic administration of agents like semaglutide results in the activation of GLP-1Rs on these local GABAergic interneurons. Second, this activation potentiates the excitatory glutamatergic drive onto these interneurons, significantly increasing their firing rate. Third, this elevated GABAergic tone exerts a powerful inhibitory control ("braking") over the projecting dopamine neurons. Consequently, this circuit selectively attenuates phasic dopamine release – the rapid, high-amplitude spikes in dopamine concentration that typically occur in response to unpredicted rewards or potent pharmacological stimuli such as alcohol, cocaine, or hyperpalatable foods. Crucially, research by Kooij et al. (2024) utilizing advanced dopamine sensing dynamics indicates that while the anticipatory, cue-driven dopamine spikes (associated with "wanting" or craving) are dampened, the tonic dopamine firing – the baseline activity essential for general motivation, motor control, and background reward processing – remains largely preserved or is even slightly enhanced during the consumption phase ("liking"). This dissociation between the anticipatory drive and the consummatory pleasure is vital for the clinical safety profile of these drugs; it explains why patients report a liberation from the compulsion to consume substances without suffering from the profound depressive states or loss of joy in daily activities that often accompany direct dopaminergic blockade.

3.2 Synaptic Plasticity in the Nucleus Accumbens and Lateral Septum

Beyond the midbrain VTA, GLP-1 RAs exert profound effects on synaptic plasticity within the forebrain, specifically in the Nucleus Accumbens (NAc) Core and the Lateral Septum (LS). Chronic exposure to addictive substances induces pathological neuroadaptations, most notably an alteration in the ratio of AMPA to NMDA glutamate receptors (AMPA/NMDA ratio) on medium spiny neurons (MSNs). This synaptic potentiation solidifies drug-seeking habits and heightens sensitivity to relapse triggers. Preclinical data suggests that GLP-1 receptor activation can normalize this AMPA/NMDA ratio, effectively "erasing" or weakening the synaptic trace of drug conditioning, thereby reducing the ability of drug-associated cues (e.g., the sight of alcohol) to trigger automatic seeking behaviour.

Furthermore, a pivotal study by Edvardsson et al. (2026) identified a novel, previously underappreciated inhibitory circuit involving the lateral septum (LS). The LS serves as a critical relay station integrating contextual information from the hippocampus with motivational signals from the VTA. The study demonstrated that tirzepatide-induced activation of GLP-1 signalling in the LS suppresses the rewarding effects of alcohol by modulating downstream dopaminergic output via a specific GABA-A receptor-dependent mechanism. Interestingly, this research highlighted significant sexual dimorphism in the neurobiology of

addiction: long-term alcohol consumption was found to upregulate GLP-1R expression in the LS of male subjects but not females, suggesting that while the therapeutic target remains valid for both sexes, the molecular trajectory of recovery may differ. By engaging this septal "brake" on the reward system, GLP-1 RAs provide a context-dependent suppression of reward seeking, preventing the hyper-activation of the mesolimbic pathway in environments previously associated with substance use.

3.3 The Synergistic Role of GIP and Dual Agonism

The introduction of tirzepatide, a dual agonist targeting both the GLP-1 receptor and the glucose-dependent insulinotropic polypeptide (GIP) receptor, adds a layer of synergistic complexity to addiction pharmacotherapy. While GLP-1 receptors are densely concentrated in the VTA, NAc, and LS, GIP receptors exhibit a distinct distribution pattern, with significant expression in the hypothalamus and regions regulating neuroinflammation. Emerging evidence indicates that GIP receptor activation may complement GLP-1 signalling through two distinct pathways. First, GIP agonism appears to enhance metabolic efficacy and systemic insulin sensitivity, which may indirectly support cognitive function and impulse control, reversing the "metabolic cognitive syndrome" often seen in chronic substance users. Second, and perhaps more importantly, GIP signalling has potent anti-neuroinflammatory properties. Chronic substance use is associated with significant glial activation and neuroinflammation, which drives craving and cognitive deficits. By mitigating this neuroinflammatory response, the GIP component of dual agonists may prevent the neuronal damage that perpetuates the cycle of addiction and withdrawal (Henney et al., 2026).

4. Clinical Efficacy in Substance Use Disorders: Evidence from 2024–2026

The translation of preclinical findings into clinical practice has accelerated significantly, yielding a body of evidence that supports the repurposing of incretin-based therapies for addiction medicine. Recent data, spanning from rigorous randomized controlled trials to extensive pharmaco-epidemiological analyses, delineate a clear therapeutic potential for GLP-1 receptor agonists in modulating consumption behaviours across various substance classes.

4.1 Alcohol Use Disorder (AUD): Randomized Trials and Real-World Evidence

Alcohol Use Disorder represents the domain with the most advanced clinical validation for GLP-1 receptor agonists. A pivotal development in this area is the Phase 2 randomized, double-blind, placebo-controlled trial conducted by Hendershot et al., published in JAMA Psychiatry in 2025. This study evaluated the efficacy of once-weekly semaglutide in non-treatment-seeking adults with AUD. The results demonstrated that while semaglutide did not significantly alter the absolute number of drinking days, it produced a marked reduction in the quantity of alcohol consumed per drinking episode. Specifically, the study reported medium-to-large effect sizes for the reduction in grams of alcohol consumed during laboratory self-administration tasks (β = -0.48; P =.01) and a significant decrease in peak breath alcohol concentration (β = -0.46; P =.03). Furthermore, semaglutide treatment was associated with a significant reduction in subjective craving intensity and the frequency of heavy drinking days over the study period. These findings suggest a harm-reduction mechanism wherein the medication enhances bio-behavioural satiety signals, facilitating a shift from loss-of-control bingeing to more moderated consumption patterns (Hendershot et al., 2025).

Complementing this interventional data, large-scale real-world evidence has reinforced the association between incretin therapy and reduced alcohol pathology. A retrospective cohort study by Wang et al. (2024), published in Nature Communications, analysed electronic health records of over 83,000 patients with obesity. The analysis revealed that treatment with semaglutide was associated with a 50% to 56% lower risk for both the incidence and recurrence of AUD over a 12-month follow-up period compared to other anti-obesity medications, including naltrexone and topiramate. This protective effect was consistent across stratifications by gender, age, and diabetic status, suggesting a robust neurobiological effect independent of glycemic control. Further comparative efficacy data were provided by Henney et al. (2026) in a target trial emulation published in Diabetes, Obesity and Metabolism. This study, utilizing a database of over 120 million patients, compared the incidence of AUD among patients treated with various GLP-1 RAs versus DPP-4 inhibitors. The results highlighted a hierarchy of efficacy, with the dual GLP-1/GIP agonist tirzepatide demonstrating a superior hazard ratio (HR) of 0.47 for incident AUD, compared to an HR of 0.68 for semaglutide. Notably, older generation agents such as liraglutide and dulaglutide did not show a statistically significant reduction in this analysis, pointing towards the necessity of high-potency receptor activation or synergistic GIP agonism for effective modulation of reward circuitry (Henney et al., 2026).

4.2 Opioid Use Disorder (OUD): Risk Mitigation and Overdose Prevention

In the context of the opioid crisis, emerging pharmaco-epidemiological data indicate a potentially life-saving role for GLP-1 receptor agonists. A retrospective cohort study by Wang et al. (2024), published in JAMA Network Open, employed a target trial emulation design to assess opioid overdose risk among patients with type 2 diabetes and co-occurring OUD. The investigators found that patients prescribed semaglutide had a significantly lower risk of opioid overdose compared to those treated with other antidiabetic agents, including insulin and metformin. The hazard ratios for overdose ranged from 0.32 to 0.58, indicating a risk reduction of approximately 42% to 68%. This finding is clinically profound, suggesting that semaglutide may exert a neuroprotective effect or sufficiently dampen opioid craving to prevent the administration of lethal doses. While randomized clinical trials are currently underway to corroborate these observational findings, the magnitude of the reported association supports the integration of GLP-1 RAs as adjunctive therapies in medication-assisted treatment protocols for OUD (Wang et al., 2024).

4.3 Behavioural Addictions and Nicotine Dependence

The therapeutic scope of GLP-1 RAs appears to extend to behavioural addictions and other chemical dependencies, supporting the concept of a trans-diagnostic mechanism of action. Regarding nicotine dependence, the trial by Hendershot et al. (2025) noted a secondary outcome wherein semaglutide treatment predicted greater relative reductions in cigarettes smoked per day among concurrent smokers. In the realm of behavioural addictions, Arillotta et al. (2024) conducted a mixed-methods analysis published in Brain Sciences, examining patient-reported outcomes regarding compulsive behaviours. The study identified that approximately 21.35% of relevant reports described a cessation or significant interruption of compulsive shopping behaviours following the initiation of GLP-1 RA therapy. Patients described a restoration of impulse control and a diminution of the intrusive urge to spend, analogous to the reduction in appetitive rumination. O'Keefe et al. (2025) further synthesized these findings in Progress in Cardiovascular Diseases, categorizing tirzepatide and semaglutide as broad-spectrum "anti-consumption agents" that modulate the valuation of reward in the nucleus accumbens, thereby facilitating rational decision-making in the presence of potent environmental cues (O'Keefe et al., 2025; Arillotta et al., 2024).

5. Public Health Implications: The Pleiotropic Impact of Metabolic Pharmacotherapy on Addiction

The serendipitous discovery that glucagon-like peptide-1 receptor agonists (GLP-1 RAs), originally designed for glycemic control and weight management, exert a potent suppressive effect on the desire for psychostimulants and depressants represents a potential watershed moment in public health. This phenomenon, often described in clinical literature as a beneficial off-target effect, suggests that the pharmacological management of obesity may concurrently address the biological underpinnings of the addiction epidemic. As data from randomized trials and large-scale retrospective cohorts accumulate, it becomes increasingly evident that these agents function as broad-spectrum modulators of consumptive behaviour, challenging the historical siloing of metabolic and psychiatric care. The intersection of the obesity epidemic and the prevalence of substance use disorders creates a syndemic burden on healthcare systems, which these medications are uniquely positioned to alleviate by targeting the shared neurobiological substrate of reward dysregulation.

The concept of GLP-1 RAs as "anti-consumption agents," as proposed by O'Keefe et al. (2025), provides a framework for understanding their societal utility beyond weight loss. In an environment characterized by the ubiquity of hyper-palatable foods, readily available alcohol, and other reinforcing stimuli, the mesolimbic dopamine system is frequently in a state of chronic hyper-activation. By dampening the incentive salience of these stimuli within the nucleus accumbens and ventral tegmental area, GLP-1 RAs essentially recalibrate the reward threshold, allowing individuals to navigate an obesogenic and addictive environment with restored executive control. This mechanism has profound implications for preventative medicine. If a significant proportion of the population currently treated for obesity with these agents also experiences a non-volitional reduction in alcohol and nicotine intake, the downstream effects on population health metrics – such as rates of alcoholic liver disease, cardiovascular events associated with smoking, and alcohol-related trauma – could be substantial. The retrospective data from Wang et al. (2024), indicating a 50% to 56% reduction in the incidence of alcohol use disorder diagnoses among patients treated with semaglutide, supports the hypothesis that widespread adoption of these therapies could function as a passive, large-scale intervention for substance misuse.

Furthermore, the integration of GLP-1 RAs into addiction treatment paradigms offers a pragmatic shift toward harm reduction rather than a strict abstinence-only model. The randomized clinical trial data from Hendershot et al. (2025) indicated that while semaglutide did not necessarily lead to total abstinence, it significantly reduced the quantity of alcohol consumed per drinking episode and the frequency of heavy drinking days. This aligns with modern addiction medicine goals, where reducing the harms associated with binge behaviours is a clinically valid endpoint. For public health systems, a medication that reduces the intensity of binges could lead to a measurable decrease in acute emergency room visits for alcohol intoxication and opioid overdoses. The findings by Wang et al. (2024), which showed a hazard ratio of 0.32 to 0.58 for opioid overdose among patients with comorbid type 2 diabetes and opioid use disorder treated with semaglutide, underscore this potential. Such a significant reduction in overdose risk suggests that these metabolic drugs could serve as critical adjuncts to existing medication-assisted treatments, potentially stabilizing patients who have been refractory to standard interventions.

However, the deployment of these "dual-purpose" medications introduces significant challenges regarding health equity and access. As noted in the analyses by Benavides (2025), the high cost of GLP-1 RAs creates a stratification of health outcomes based on socioeconomic status. Individuals with comprehensive insurance coverage or financial means can access a treatment that simultaneously manages metabolic health and reduces the biological drive for addictive substances, thereby compounding their health advantages. Conversely, marginalized populations, who historically suffer disproportionately from the comorbidities of obesity, alcohol use disorder, and tobacco dependence, face significant barriers to access. If the "anti-addiction" benefits of these drugs remain an exclusive privilege of the wealthy due to pricing structures and insurance formularies that segregate metabolic and behavioural health indications, existing health disparities will likely widen. The current regulatory landscape, where these drugs are approved for obesity but not yet for addiction, creates a complex scenario where clinicians must navigate off-label prescribing, often leaving the most vulnerable patients without coverage for what could be a life-saving intervention.

Ultimately, the emergence of GLP-1 RAs as potential therapeutics for substance use disorders forces a re-evaluation of how healthcare systems value preventative behavioural health. The reduction in "food noise" and substance craving reported by patients represents a biological liberation from compulsive consumption patterns that drive chronic disease. While the economic burden of these medications is high, cost-effectiveness models must begin to account for the aggregate savings from avoided addiction-related morbidity, such as liver cirrhosis treatments, cancer therapies related to alcohol and smoking, and the societal costs of untreated substance use disorders. Future health policy will need to address how to equitably integrate these metabolic therapies into psychiatric care, recognizing that treating the biological dysregulation of the reward system is a valid and necessary component of public health strategy. The transition from viewing addiction solely as a behavioural issue to treating it as a modifiable neuroendocrine disorder marks a significant evolution in medical practice, promising a more holistic approach to human health and well-being.

6. Discussion

The findings synthesized in this review underscore a pivotal moment in addiction medicine, driven by the repurposing of metabolic pharmacotherapies. The convergence of preclinical models, real-world data, and randomized clinical trials provides a compelling case for the efficacy of GLP-1 receptor agonists (GLP-1 RAs) in modulating addictive behaviours. The primary mechanism appears to be the restoration of hedonic homeostasis through the dampening of phasic dopamine release in the ventral tegmental area and nucleus accumbens, as detailed in recent neurobiological studies (Merkel et al., 2025; Kooij et al., 2024). This neuroadaptive recalibration effectively reduces the incentive salience of drug-associated cues without inducing general anhedonia, a critical distinction that separates these agents from traditional dopamine antagonists which often compromise patient quality of life.

Clinically, the data support a broad spectrum of efficacy. In the domain of Alcohol Use Disorder (AUD), the results from the randomized trial by Hendershot et al. (2025) and the large-scale retrospective analyses by Wang et al. (2024) and Henney et al. (2026) align to suggest that GLP-1 RAs, particularly semaglutide and tirzepatide, significantly reduce alcohol consumption, heavy drinking days, and the incidence of AUD diagnosis. The superiority of tirzepatide over semaglutide in preventing AUD onset highlights the potential synergistic benefit of dual GLP-1/GIP receptor agonism, suggesting that broader metabolic engagement may enhance neurobehavioural outcomes (Henney et al., 2026). Furthermore, the substantial reduction in opioid overdose risk observed by Wang et al. (2024) points to a potentially life-saving application in the opioid crisis,

positioning these drugs not merely as anti-craving agents but as critical components of harm reduction strategies.

However, the enthusiasm for these therapeutic advances must be tempered by significant challenges regarding access and equity. The medicalization of addiction treatment, while destigmatizing in its biological framing, risks exacerbating health disparities if these high-cost medications remain accessible primarily to the wealthy. As Benavides (2025) argues, relying on expensive proprietary drugs to solve public health crises can inadvertently sideline structural interventions needed to address the root causes of addiction, such as social determinants of health. Moreover, the long-term neuropsychiatric safety profile requires continued vigilance. Although the FDA's 2026 update found no causal link to suicidality, ongoing monitoring is essential to ensure that the suppression of reward processing does not lead to subtle forms of affective blunting or anhedonia in vulnerable populations.

Future research directions should focus on elucidating the precise patient phenotypes most likely to benefit from GLP-1 RA therapy, potentially through pharmacogenomic profiling or biomarkers of metabolic dysfunction. Additionally, longitudinal studies are needed to determine the durability of the anti-addiction effects following treatment discontinuation and to explore the efficacy of next-generation agents like retatrutide. Ultimately, the integration of GLP-1 RAs into addiction psychiatry represents a shift towards a more holistic, neuro-metabolic model of care, promising improved outcomes for patients with co-occurring metabolic and substance use disorders.

7. Conclusions

The comprehensive synthesis of peer-reviewed literature published between 2023 and 2026 solidifies the status of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as a breakthrough class of therapeutics that transcends their original metabolic indications. The evidence unequivocally demonstrates that agents such as semaglutide and tirzepatide exert a specific, targeted modulatory effect on the central nervous system's reward circuitry, which is distinct from their peripheral effects on satiety. Neurobiological data have clarified the precise mechanism of action: by activating GLP-1 receptors expressed on GABAergic interneurons in the ventral tegmental area and altering synaptic plasticity in the nucleus accumbens and lateral septum, these drugs dampen the phasic dopamine release associated with drug anticipation and "wanting" (Merkel et al., 2025; Edvardsson et al., 2026). Crucially, this modulation appears to preserve the tonic dopamine signalling necessary for general motivation and reward perception ("liking"), thereby offering a therapeutic profile that avoids the anhedonia and dysphoria often associated with traditional dopamine antagonists (Kooij et al., 2024).

Clinically, the transition from preclinical models to human efficacy has been robust. The randomized controlled trial by Hendershot et al. (2025) provides high-quality evidence that semaglutide significantly reduces alcohol consumption and craving intensity in individuals with Alcohol Use Disorder (AUD), validating a harm-reduction model where the goal is a shift toward moderated intake rather than immediate abstinence. Furthermore, large-scale pharmaco-epidemiological analyses have revealed a profound public health potential, demonstrating a 42–68% reduction in opioid overdose risk among patients treated with GLP-1 RAs (Wang et al., 2024) and a lower incidence of new AUD diagnoses, particularly with the dual agonist tirzepatide (Henney et al., 2026). Emerging data also suggest a trans-diagnostic efficacy, extending to behavioural impulse control disorders such as compulsive shopping, positioning these drugs as broad-spectrum "anti-consumption" agents (Arillotta et al., 2024).

Despite this promising clinical horizon, the integration of GLP-1 RAs into standard addiction psychiatry faces significant barriers related to healthcare infrastructure and equity. The high cost of these biologic therapies creates a risk of stratifying recovery outcomes based on socioeconomic status, potentially limiting access to this life-saving innovation to patients with substantial financial resources or specific insurance coverage (Benavides, 2025). Moreover, while current regulatory safety reviews have found no causal link between GLP-1 RAs and suicidality, the long-term neuropsychiatric implications of chronically dampening reward sensitivity require ongoing pharmacovigilance (FDA, 2026). Future research must prioritize longitudinal studies to assess the durability of treatment effects after discontinuation and explore the potential of next-generation multi-agonists. Ultimately, the adoption of GLP-1 RAs represents a paradigm shift toward a neuro-metabolic model of addiction treatment, offering a potent biological tool to address the syndemic of obesity and substance use disorders.

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