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GLP-1 AGONISTS IN PSYCHIATRY — A NEW THERAPEUTIC DIRECTION FOR DEPRESSION, ADDICTIONS, AND EATING DISORDERS

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), originally developed for the treatment of type 2 diabetes mellitus and obesity, are increasingly being investigated for their potential relevance to psychiatric disorders. Accumulating preclinical and clinical evidence indicates that GLP-1 signaling extends beyond metabolic regulation and may influence central mechanisms implicated in mood regulation, motivational processing, compulsive reward-seeking, and interoceptive control. This review synthesizes current mechanistic, preclinical, clinical, and registry-based evidence concerning the possible role of GLP-1 RAs in psychiatry, with particular emphasis on major depressive disorder, substance use disorders, and eating disorders. The biological rationale for their psychiatric relevance is supported by evidence of GLP-1-mediated signaling through circumventricular organs, vagal–brainstem pathways, and selected central nervous system regions, including hypothalamic, hippocampal, and mesolimbic reward-related circuits. Proposed mechanisms include modulation of reward salience, attenuation of neuroinflammatory signaling, improvement of metabolic-inflammatory burden, and enhancement of neuroplastic processes.

The clinical evidence remains heterogeneous and indication-specific. In depression, the most consistent findings relate to cognitive and motivational domains, particularly in patients with major depressive disorder and coexisting overweight or obesity, whereas broader evidence from metabolic trials suggests modest reductions in depressive symptoms without establishing disorder-specific antidepressant efficacy. In substance use disorders, alcohol use disorder currently represents the most advanced area of investigation, with semaglutide demonstrating favorable outcomes in a phase 2 trial, while exenatide showed no overall reduction in heavy drinking but reduced alcohol cue reactivity and suggested potential benefit in obese participants. Evidence for nicotine use disorder is mixed, and data concerning opioid and stimulant use disorders remain preliminary. In eating disorders, binge-eating phenotypes appear to be the most plausible therapeutic target, whereas evidence for bulimia nervosa is limited and anorexia-spectrum disorders raise important safety concerns due to appetite suppression and weight loss. Overall, the safety profile of GLP-1 RAs in psychiatric populations appears broadly consistent with their established metabolic use, with gastrointestinal adverse effects predominating; however, psychiatric monitoring remains advisable because observational safety data are not fully concordant. Current evidence supports further diagnosis-specific randomized controlled trials but does not yet justify routine psychiatric prescribing outside carefully selected clinical contexts or research settings.

KEYWORDS

GLP-1 Receptor Agonists, Substance Use Disorders, Eating Disorders, Neuroinflammation, Psychiatry

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1. Introduction

GLP-1 RAs have traditionally been regarded as metabolic agents used in the management of type 2 diabetes mellitus and obesity (Drucker, 2024).

In recent years, however, their potential relevance to psychiatry has attracted growing scientific attention (Pierret et al., 2025). This interest reflects the convergence of metabolic, inflammatory, and neurobiological perspectives on mental disorders (Paul et al., 2023). Major depressive disorder, substance use disorders, and eating disorders are frequently accompanied by obesity, insulin resistance, dysregulated appetite signaling, and low-grade systemic inflammation (Aoun et al., 2024). These shared biological disturbances suggest that agents acting on metabolic and gut–brain pathways may have effects that extend beyond weight reduction and glycemic control (Beutler, 2026; Xie et al., 2025).

The biological rationale for investigating GLP-1 RAs in psychiatry is supported by the recognition of GLP-1 as a gut–brain signaling system (Beutler, 2026). GLP-1 signaling is involved not only in satiety, glucose homeostasis, and gastrointestinal motility, but also in neural processes related to reward valuation, motivational drive, cue reactivity, and learned reinforcement (Beutler, 2026; Eren-Yazicioglu et al., 2020). These processes are highly relevant to psychiatric phenotypes characterized by anhedonia, compulsive consumption, craving, binge eating, and impaired interoceptive regulation (Aoun et al., 2024; Eren-Yazicioglu

et al., 2020). Consequently, the psychiatric effects of GLP-1 RAs may be conceptualized not as nonspecific mood enhancement, but as modulation of neurobehavioral systems that contribute to symptom maintenance across several diagnostic categories (Pierret et al., 2025).

From a pharmacological perspective, currently available GLP-1 RAs, including liraglutide, semaglutide, dulaglutide, and exenatide, differ in molecular structure, half-life, albumin binding, route of administration, and degree of central nervous system exposure (Knudsen & Lau, 2019). Nevertheless, they share the ability to activate GLP-1 receptors expressed in peripheral metabolic tissues as well as in brain regions implicated in appetite regulation, reward processing, stress responsivity, and cognition (Eren-Yazicioglu et al., 2020; West et al., 2025). Importantly, current evidence does not support a simple distinction between agents that “cross” or “do not cross” the blood–brain barrier (West et al., 2025). Rather, central GLP-1 RA effects appear to involve a combination of selective brain access, signaling through circumventricular organs, arcuate nucleus engagement, vagal–brainstem pathways, and downstream modulation of mesolimbic and cortical networks. This more nuanced model is clinically important, because psychiatric effects may occur even when diffuse whole-brain drug penetration is limited (West et al., 2025).

The expanding clinical use of GLP-1 RAs has also generated observations that are relevant to psychiatric research (Pierret et al., 2025). Reports of reduced alcohol intake, diminished nicotine craving, changes in appetite-related intrusive thoughts, and improvement in some mood or cognitive domains have stimulated formal investigation of these agents in depression, addiction, and eating-disorder phenotypes (Hendershot et al., 2025; Pierret et al., 2025). However, the current evidence remains heterogeneous and should be interpreted cautiously. Many available studies were conducted in metabolically selected populations, used non-psychiatric primary endpoints, or relied on observational designs (Pierret et al., 2025; Sa et al., 2026). Therefore, it remains uncertain whether observed psychiatric effects reflect direct central mechanisms, indirect benefits of improved metabolic health, or an interaction between both pathways (Kim, 2025; Pierret et al., 2025).

Accordingly, the central question is not whether GLP-1 RAs should be classified as conventional psychiatric drugs, but whether they can modify biological and behavioral processes that sustain specific psychiatric phenotypes.

2. Methodology

This review was designed as a literature-based narrative synthesis. Its aim was to provide an overview of the emerging psychiatric relevance of glucagon-like peptide-1 receptor agonists, with particular emphasis on depression, substance use disorders, and eating disorders. The literature search focused primarily on English-language publications published between 2015 and May 26, 2026. Earlier seminal studies were also included when they were necessary to clarify key mechanistic concepts, including GLP-1 neuroanatomy, blood–brain barrier permeability, gut–brain signaling, and reward-circuit modulation.

The evidence base was identified mainly through PubMed and PubMed Central, supplemented by clinical trial registry records from ClinicalTrials.gov and EudraCT where ongoing or unpublished psychiatric trials were relevant to the scope of the review. Search terms included combinations of “GLP-1 receptor agonist,” “semaglutide,” “liraglutide,” “exenatide,” “dulaglutide,” “depression,” “major depressive disorder,” “substance use disorder,” “alcohol use disorder,” “nicotine dependence,” “opioid use disorder,” “stimulant use disorder,” “binge eating disorder,” “bulimia nervosa,” “anorexia nervosa,” “reward,” “craving,” “neuroinflammation,” and “psychiatric safety.

Studies were considered eligible for inclusion if they addressed GLP-1 RA pharmacology or one of the psychiatric domains relevant to this review. Eligible sources included mechanistic studies examining central or peripheral GLP-1 signaling with psychiatric relevance, preclinical studies assessing mood-, reward-, or addiction-related outcomes, randomized clinical trials, prospective observational or registry-based studies, systematic reviews, meta-analyses, and relevant case reports in areas where higher-quality evidence was limited. Particular priority was given to primary human studies, especially randomized controlled trials and large cohort or registry-based analyses. Reviews were used mainly to contextualize mechanisms, summarize broader trends, or identify gaps in the literature.

3. Pharmacology of GLP-1 Agonists

Endogenous glucagon-like peptide-1 is synthesized primarily by enteroendocrine L-cells of the distal intestine and by preproglucagon-expressing neurons located in the nucleus tractus solitarius (Müller et al., 2019). GLP-1 RAs prolong incretin signaling by resisting degradation by dipeptidyl peptidase-4 (DPP-4) and, depending on the specific compound, by structural modifications such as fatty-acid acylation, albumin binding, Fc fusion, or formulation-based half-life extension (Drucker, 2018; Knudsen & Lau, 2019). Their established peripheral actions include glucose-dependent stimulation of insulin secretion, suppression of glucagon release, delayed gastric emptying, and enhancement of satiety (Drucker, 2018). Through these mechanisms, GLP-1 RAs may indirectly influence psychiatric outcomes by improving glycemic control, reducing adiposity, attenuating systemic inflammation, ameliorating obesity-related sleep-disordered breathing, and decreasing illness-related psychosocial burden (Drucker, 2018; Pierret et al., 2025).

Nevertheless, the psychiatric relevance of GLP-1 signaling cannot be explained solely by peripheral metabolic improvement (Kabahizi et al., 2022; Pierret et al., 2025). Receptor-mapping studies and translational evidence indicate that GLP-1 pathways also modulate central processes within hypothalamic, hindbrain, hippocampal, and mesolimbic reward-related circuits. These neural systems are implicated in appetite regulation, craving, reinforcement learning, effort-based decision-making, interoception, and emotional regulation (Eren-Yazicioglu et al., 2020; Kabahizi et al., 2022). Such findings provide a mechanistic basis for considering GLP-1 RAs as potential modulators of psychiatric phenotypes characterized by dysregulated reward processing, compulsive consumption, anhedonia, and impaired motivational control (Aoun et al., 2024; Eren-Yazicioglu et al., 2020).

The extent and route of central nervous system engagement by GLP-1 RAs remain complex (Beutler, 2026). Seminal fluorescent-tracer studies demonstrated that peripherally administered liraglutide can localize to circumventricular organs and selected hypothalamic regions, including the arcuate nucleus and paraventricular nucleus (Secher et al., 2014). Subsequent blood–brain barrier kinetic studies suggested limited but measurable brain uptake for several incretin-based agents, including liraglutide and semaglutide; however, this uptake does not appear to reflect uniform capillary transport across all brain regions (Beutler, 2026). Current evidence therefore supports a more nuanced model in which central GLP-1 RA effects arise through a combination of selective blood–brain barrier transit, access to circumventricular organs, vagal–brainstem signaling, and downstream recruitment of distributed hypothalamic, mesolimbic, and cortical networks (Beutler, 2026; Secher et al., 2014).

This distinction is particularly relevant for psychiatry, because clinically meaningful neurobehavioral effects may occur even in the absence of widespread whole-brain drug penetration (De Giorgi et al., 2025). Human imaging studies further support this translational plausibility by demonstrating that liraglutide can alter neural responses to highly palatable food cues (Farr et al., 2016). In addition, detection of GLP-1 receptors in the human brain strengthens the rationale for investigating these agents in psychiatric conditions involving altered reward salience, craving, appetite-related cognition, and emotional regulation (De Giorgi et al., 2025; Farr et al., 2016).

The psychiatric relevance of GLP-1 signaling appears to involve three major biological pathways: modulation of reward-related circuits, regulation of neuroinflammatory responses, and support of neuroplasticity (De Giorgi et al., 2025). First, GLP-1-producing neurons located in the nucleus tractus solitarius project to key mesolimbic structures, including the ventral tegmental area and nucleus accumbens, which are central to reinforcement learning, cue salience, and motivational drive. Experimental activation of GLP-1 receptors within these regions has been shown to reduce the intake of highly palatable food and attenuate alcohol- and cocaine-related reinforcement, suggesting that GLP-1 receptor agonists may influence compulsive consumption and craving-related behaviors (Eren-Yazicioglu et al., 2020).

Second, GLP-1 receptor activation may affect psychiatric symptoms through anti-inflammatory mechanisms (De Giorgi et al., 2025; Diz-Chaves et al., 2022). In preclinical models, GLP-1 signaling suppresses microglial activation and reduces the production of pro-inflammatory cytokines, including pathways associated with inflammasome activation (Diz-Chaves et al., 2022). These effects are particularly relevant to depression, where low-grade inflammation, altered cytokine signaling, and NLRP3 inflammasome activity have been implicated in symptom persistence and reduced treatment response (De Giorgi et al., 2025).

Moreover, GLP-1 signaling may contribute to neuroplasticity and cognitive-emotional regulation. Experimental studies have linked GLP-1 receptor activation with modulation of CREB/BDNF signaling, enhancement of adult neurogenesis, and preservation of synaptic plasticity, especially within hippocampal circuits. These mechanisms provide a plausible biological basis for the potential effects of GLP-1 receptor agonists on anhedonia, cognitive dysfunction, stress vulnerability, and impaired emotional learning (De Giorgi et al., 2025).

3.1. Depression

The evidence supporting a potential role of GLP-1 receptor agonists in depression is strongest at the preclinical level (De Giorgi et al., 2025). In corticosterone-induced models of depression, liraglutide has been shown to reduce depressive- and anxiety-like behaviors while improving hippocampal neuroplasticity (Weina et al., 2018). Similarly, in diabetic and chronic-stress models, liraglutide and semaglutide have been associated with improvements in depressive-like behavior, cognitive performance, or both (De Giorgi et al., 2025; Piątkowska-Chmiel et al., 2025). These effects have been linked to modulation of hippocampal signaling, gut–brain axis pathways, and inflammatory mechanisms (De Giorgi et al., 2025). Intranasal lixisenatide has also been reported to attenuate emotional symptoms in a mouse model of depression through CREB-mediated adult hippocampal neurogenesis (Ren et al., 2021). Collectively, these findings support the biological plausibility of GLP-1 receptor agonism across several depression-relevant domains, including anhedonia-like behavior, anxiety-like behavior, cognitive impairment, neuroinflammation, and impaired neuroplasticity (De Giorgi et al., 2025).

A 2024 systematic review and meta-analysis found that adults treated with GLP-1 receptor agonists had significantly lower depression rating scores than control participants (Chen et al., 2024). However, most of the included trials were designed primarily for metabolic rather than psychiatric outcomes, making it difficult to determine whether the observed improvements reflected direct central effects, indirect benefits of weight loss and improved metabolic health, or a combination of both (Chen et al., 2024; Pierret et al., 2025). More clinically informative data come from recent randomized studies of semaglutide in patients with major depressive disorder and overweight or obesity (Badulescu et al., 2026; Gill et al., 2026). In a 16-week randomized trial of oral semaglutide, the primary executive-function endpoint was not met; nevertheless, global cognitive performance improved and the intervention was generally well tolerated (Badulescu et al., 2026). A preregistered secondary analysis of the same trial found that semaglutide increased willingness to exert effort for reward and reduced effort sensitivity, suggesting a potentially relevant effect on motivational deficits in depression (Gill et al., 2026). These findings indicate a possible domain-specific benefit in cognition and reward-related motivation, but they do not yet establish GLP-1 receptor agonists as effective antidepressant treatments for core syndrome-level major depressive disorder (Badulescu et al., 2026; Gill et al., 2026; Pierret et al., 2025).

Psychiatric safety data in patients with depression remain mixed, particularly in observational research (Pierret et al., 2025). Large meta-analyses of randomized placebo-controlled trials have not demonstrated an overall increase in psychiatric adverse events, and regulatory reviews by the European Medicines Agency and the U.S. Food and Drug Administration have not found evidence supporting a causal association between GLP-1 receptor agonists and suicidal ideation or self-injurious behavior (*Meeting Highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 April 2024 | European Medicines Agency (EMA)*, 2024; Pierret et al., 2025; Research, 2026). In contrast, some observational and pharmacovigilance studies have reported higher rates of depression, anxiety, or broader psychiatric diagnoses, and individual case reports have described mood worsening during semaglutide treatment (Pierret et al., 2025; Tobaiqy & Elkout, 2024). The most methodologically cautious interpretation is that randomized controlled data currently provide stronger reassurance regarding causality, whereas observational findings may be influenced by confounding by indication, baseline psychiatric vulnerability, differential prescribing patterns, and surveillance bias (Pierret et al., 2025; Research, 2026). Therefore, GLP-1 receptor agonists should not be considered contraindicated solely on psychiatric safety grounds, but their use in patients with active or recurrent depression should include careful baseline assessment and follow-up monitoring of mood, anxiety symptoms, and suicidal ideation (*Meeting Highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 April 2024 | European Medicines Agency (EMA)*, 2024; Research, 2026).

3.2. Substance Use Disorders

Preclinical studies have shown that GLP-1 receptor activation can attenuate several addiction-related behaviors (Klausen, Thomsen, et al., 2022). In rodent models, exendin-4 reduced cocaine self-administration, while GLP-1 receptor agonism decreased alcohol reward, heroin-seeking behavior, and amphetamine-induced behavioral activation (Sørensen et al., 2015). More recent studies with liraglutide have also demonstrated reductions in heroin self-administration and drug-induced reinstatement, supporting the hypothesis that GLP-1 receptor agonists may influence relapse-related mechanisms (Douton et al., 2022; Klausen, Thomsen, et al., 2022). Overall, the preclinical evidence is broad and internally consistent, indicating that addictive disorders represent biologically plausible targets for this therapeutic class (Klausen, Thomsen, et al., 2022; Leggio et al., 2023). However, translation into human populations remains at an early stage (Leggio et al., 2023).

Among substance-related indications, alcohol use disorder currently has the strongest clinical support (Hendershot et al., 2025; Klausen, Jensen, et al., 2022). In a randomized controlled trial published in 2022, exenatide did not significantly reduce heavy drinking days in the overall sample of 127 patients with alcohol use disorder compared with placebo. However, it attenuated alcohol cue reactivity in the ventral striatum and septal area, and exploratory subgroup analyses suggested reductions in heavy drinking and total alcohol intake among participants with obesity (Klausen, Jensen, et al., 2022). More recently, a 2025 phase 2 trial of low-dose semaglutide in 48 adults with alcohol use disorder reported more encouraging findings. Semaglutide reduced alcohol consumption during a laboratory self-administration task, decreased drinks per drinking day, lowered weekly craving, and predicted greater reductions in heavy drinking over time. Nevertheless, it did not significantly reduce average drinks per calendar day or the total number of drinking days (Hendershot et al., 2025).

Observational studies further support the potential relevance of GLP-1 receptor agonists in alcohol and broader substance use outcomes, although they should not be interpreted as definitive evidence of efficacy (Cai et al., 2026; Lähteenvuo et al., 2025). Registry-based analyses have associated semaglutide and liraglutide with reduced hospitalization for alcohol use disorder (Lähteenvuo et al., 2025). A large 2026 Veterans Affairs target-trial emulation also reported lower incident risks of alcohol, nicotine, opioid, cocaine, and cannabis use disorders, as well as lower overdose and mortality rates among individuals with pre-existing substance use disorders. These findings are important for hypothesis generation and suggest possible transdiagnostic effects across addictive disorders (Cai et al., 2026). However, they remain vulnerable to residual confounding, including differences in baseline metabolic status, obesity, health-care engagement, prescribing patterns, and illness severity (Cai et al., 2026; Lähteenvuo et al., 2025). It is also possible that metabolic phenotype moderates treatment response, as suggested by exploratory findings in alcohol use disorder (Klausen, Jensen, et al., 2022; Lähteenvuo et al., 2025).

The evidence for nicotine use disorder is mixed but clinically relevant, particularly because post-cessation weight gain is a major barrier to sustained smoking abstinence (Lüthi et al., 2024). In a pilot trial, exenatide added to nicotine replacement therapy improved smoking abstinence, reduced craving and withdrawal symptoms, and lowered post-cessation weight gain among participants who achieved abstinence (Yammine et al., 2021). In contrast, dulaglutide did not improve abstinence rates in a randomized smoking-cessation study, although it reduced post-cessation weight gain and improved glycemic indices (Lengsfeld et al., 2023). Follow-up data at 12 months likewise failed to demonstrate a sustained abstinence advantage (Lüthi et al., 2024). Taken together, these findings suggest that GLP-1 receptor agonists may be more appropriately considered as adjunctive agents targeting craving, withdrawal-related appetite changes, and weight control rather than as established smoking-cessation monotherapies (Lengsfeld et al., 2023; Lüthi et al., 2024; Yammine et al., 2021).

For stimulant and opioid use disorders, the current human evidence remains insufficient (Patil et al., 2026). In cocaine use disorder, acute pretreatment with exenatide did not significantly alter cocaine self-administration, subjective euphoria, or drug wanting in a small human laboratory study. However, the study evaluated only a single low-dose acute exposure, which limits conclusions regarding the potential effects of chronic administration, higher doses, or longer treatment duration (Angarita et al., 2021). In opioid use disorder, clinical evidence remains at an early stage, and the potential therapeutic role of GLP-1 receptor agonists has not yet been established in completed randomized efficacy trials (Freet et al., 2025; Patil et al., 2026). Nevertheless, ongoing registered trials are now evaluating semaglutide for illicit opioid use, and additional studies are examining GLP-1 receptor agonists in cocaine use disorder (Freet et al., 2025; Grigson, 2025; Patil et al., 2026; Suzuki, 2025). Therefore, the most cautious interpretation is not that GLP-1 receptor agonists are ineffective for opioid or stimulant use disorders, but rather that the available human evidence is underpowered, incompletely dosed, and too preliminary to support routine clinical use at present (Angarita et al., 2021; Freet et al., 2025; Patil et al., 2026).

3.3. Eating Disorders

Current evidence on GLP-1 receptor agonists in eating disorders indicates the greatest potential benefit in binge-eating phenotypes, whereas their use in restrictive-spectrum disorders raises substantial clinical concerns (Bartel et al., 2024; Radkhah et al., 2025). Early studies involving patients with obesity and either subclinical or syndromal binge eating suggested that liraglutide may reduce binge-eating behavior while also producing expected metabolic benefits (Allison et al., 2023; Radkhah et al., 2025). However, the available data remain limited (Bartel et al., 2024; Radkhah et al., 2025). In a 2023 pilot randomized controlled trial evaluating liraglutide 3.0 mg/day in binge-eating disorder, 27 participants were enrolled. Although both the liraglutide and placebo groups showed reductions in objective binge-eating episodes, liraglutide did not significantly outperform placebo on the primary binge-frequency endpoint or remission rates. It did, however, result in significantly greater weight loss (Allison et al., 2023). This distinction is clinically important, as it suggests that GLP-1 receptor agonists in binge-eating disorder may exert more consistent effects on appetite regulation and weight-related outcomes than on the broader psychopathological features of the disorder, particularly when used as monotherapy and over short treatment periods (Allison et al., 2023; Radkhah et al., 2025).

Findings from other studies of binge-eating phenotypes are somewhat more encouraging (Radkhah et al., 2025). In patients with type 2 diabetes and binge-eating disorder, dulaglutide 1.5 mg once weekly was reported to be superior to gliclazide in a pilot study, reducing binge-eating episodes while also improving body weight and metabolic parameters (Da Porto et al., 2020). A retrospective cohort study of semaglutide likewise reported greater reductions in Binge Eating Scale scores compared with other anti-obesity pharmacotherapies, generating considerable interest in its potential role in the management of binge-eating symptoms (J. Richards et al., 2023). Recent reviews published between 2024 and 2025 have reached broadly similar conclusions: GLP-1 receptor agonists are biologically plausible candidates for reducing binge eating, but current findings are derived mainly from small pilot studies, retrospective cohorts, mixed obesity and binge-eating samples, and short follow-up periods. Thus, although the results are promising, the overall evidence base remains methodologically fragile and insufficient to support firm clinical recommendations (Bartel et al., 2024; Radkhah et al., 2025).

In bulimia nervosa, available data are considerably weaker and consist mainly of case-based observations (Aoun et al., 2024). One frequently cited case report described remission of bulimia nervosa symptoms and depressive symptoms shortly after liraglutide was added to ongoing metformin therapy in a patient with polycystic ovary syndrome and reactive hypoglycemia (Perez-Cheron, 2018). Such observations are mechanistically interesting, particularly in cases where binge-purge behavior appears closely linked to hunger dysregulation, glycemic instability, or insulin-related metabolic disturbances (Aoun et al., 2024; Perez-Cheron, 2018). However, isolated case reports cannot establish efficacy, define appropriate patient selection, or justify generalization to the broader bulimia nervosa population. Bulimia nervosa therefore remains an important unresolved area within this field (Aoun et al., 2024; Bartel et al., 2024).

Findings in anorexia-spectrum disorders suggest a substantially different clinical picture (Bartel et al., 2024; J. R. Richards & Khalsa, 2024). Rather than indicating therapeutic benefit, recent reports have raised concerns about semaglutide misuse and possible worsening of restrictive eating psychopathology, including in atypical anorexia nervosa (J. R. Richards & Khalsa, 2024). These observations support a strongly cautious approach. In restrictive eating disorders, GLP-1 receptor agonists may obscure illness severity, reinforce caloric restriction, accelerate clinically significant weight loss, and complicate nutritional rehabilitation. Consequently, the same appetite-suppressing and weight-reducing properties that may be therapeutically useful in binge-eating disorder may be harmful in anorexia-spectrum conditions. GLP-1 receptor agonists should therefore be used with particular caution in patients with current or past restrictive eating pathology, and their use in this population should not be considered without careful psychiatric and nutritional assessment (Bartel et al., 2024; J. R. Richards & Khalsa, 2024).

4. Discussion

Overall, current evidence supports the interpretation of GLP-1 receptor agonists as potential transdiagnostic psychometabolic agents rather than as substitutes for established psychiatric pharmacotherapy (Bartel et al., 2024; Pierret et al., 2025). Their relevance appears greatest in clinical phenotypes in which metabolic dysfunction, inflammation, interoceptive dysregulation, and reward processing are closely interconnected (Pierret et al., 2025; Radkhah et al., 2025). This may explain why the most promising findings have emerged in alcohol use disorder and binge-eating phenotypes, where craving, cue reactivity, impaired control over consummatory behavior, and metabolic abnormalities frequently coexist (Hendershot et al., 2025; Radkhah et al., 2025). By contrast, major depressive disorder without significant metabolic burden, cognitive impairment, or reward-related dysfunction may not represent the subgroup most likely to benefit from GLP-1 receptor agonism. The recent semaglutide trials in major depressive disorder, which demonstrated signals in cognition and effort-based reward valuation rather than a clear syndrome-level antidepressant effect, are consistent with this interpretation (Badulescu et al., 2026; Gill et al., 2026).

A second important theme is that metabolic status may function as an effect modifier rather than merely a background clinical characteristic (De Giorgi et al., 2025; Klausen, Jensen, et al., 2022). In the exenatide trial in alcohol use disorder, exploratory benefits were concentrated among participants with obesity (Klausen, Jensen, et al., 2022). Similarly, the Toronto semaglutide trial in major depressive disorder enrolled individuals with a body mass index of at least 25 kg/m², and much of the observational evidence derives from populations with obesity or type 2 diabetes (Badulescu et al., 2026). These findings raise an important clinical and scientific question: do GLP-1 receptor agonists act directly on psychiatric circuits regardless of metabolic phenotype, or are their effects most pronounced when insulin resistance, adipose-tissue inflammation, altered satiety signaling, and reward dysregulation coexist? At present, this question remains unresolved (De Giorgi et al., 2025). However, the balance of evidence suggests that patients with metabolic vulnerability may represent a particularly relevant target population (De Giorgi et al., 2025; Klausen, Jensen, et al., 2022). Future trials should therefore consider stratification or enrichment based on obesity, insulin resistance, inflammatory biomarkers, and behavioral features such as high cue reactivity, pronounced craving, or impaired effort-based motivation (De Giorgi et al., 2025; Gill et al., 2026; Hendershot et al., 2025).

A third important issue concerns whether the psychiatric effects observed with GLP-1 receptor agonists reflect direct central mechanisms or secondary consequences of improved physical health (De Giorgi et al., 2025). In depression, improvements in glycemic control, weight reduction, amelioration of sleep-disordered breathing, reduced cardiometabolic symptom burden, and decreased weight-related distress may all contribute to mood improvement independently of direct receptor-mediated effects in the brain (De Giorgi et al., 2025; Pierret et al., 2025). However, a purely indirect explanation is unlikely to be sufficient (De Giorgi et al., 2025; Farr et al., 2016). Randomized studies have reported changes in effort-based decision-making and alcohol self-administration, while neuroimaging studies have demonstrated altered reward-related brain responses following GLP-1 receptor agonist exposure (Farr et al., 2016; Gill et al., 2026; Hendershot et al., 2025). The most plausible interpretation is therefore that both mechanisms are relevant: direct modulation of neural circuits involved in reward, motivation, and interoception, together with indirect benefits resulting from reduced psychometabolic burden. This dual mechanism may be clinically advantageous, particularly in patients whose psychiatric symptoms are closely intertwined with obesity, insulin resistance, or type 2 diabetes (De Giorgi et al., 2025; Pierret et al., 2025).

The use of GLP-1 receptor agonists in eating disorders requires an especially nuanced clinical approach (Bartel et al., 2024). In binge-eating disorder, where impaired satiety, heightened food-cue salience, and recurrent loss of control over eating are central clinical features, GLP-1 receptor agonists represent biologically coherent therapeutic candidates (Aoun et al., 2024; Radkhah et al., 2025). In contrast, in anorexia-spectrum disorders, where caloric restriction and weight loss may themselves become pathologically reinforcing, the same pharmacological properties may be harmful (Bartel et al., 2024; J. R. Richards & Khalsa, 2024). This apparent contrast does not reflect an inconsistency in the mechanism of action, but rather the importance of diagnosis-specific application. Future psychiatric research should therefore avoid asking whether GLP-1 receptor agonists are broadly “beneficial” or “harmful” for eating disorders as a single category (Bartel et al., 2024). A more clinically meaningful question is which eating-disorder phenotype is being treated, at what stage of illness, under what level of nutritional supervision, and within what psychotherapeutic framework (Bartel et al., 2024; J. R. Richards & Khalsa, 2024).

The future research agenda is increasingly reflected in ongoing clinical trial registries (De Giorgi et al., 2025; Patil et al., 2026; Vinberg, 2026). Recent published trials and protocols, together with ongoing registered

studies, have evaluated or are evaluating semaglutide in major depressive disorder with overweight or obesity, alcohol use disorder, opioid use disorder, cocaine use disorder, smoking cessation, and GLP-1-based interventions in binge-eating phenotypes (De Giorgi et al., 2025; Freet et al., 2025; Hendershot et al., 2025; Johns Hopkins University, 2025; University of North Carolina, Chapel Hill, 2025; Vinberg, 2026). Future trials should prioritize longer follow-up, appropriate psychiatric comparators, standardized measures of craving and reward processing, concurrent assessment of psychiatric and metabolic outcomes, relapse-prevention endpoints, and prespecified moderation analyses by body mass index, insulin resistance, sex, baseline inflammation, and reward-related dysfunction (De Giorgi et al., 2025; Gill et al., 2026). Until such data become available, off-label psychiatric use of GLP-1 receptor agonists should remain selective, transparent, and closely monitored (Bartel et al., 2024; J. R. Richards & Khalsa, 2024).

5. Conclusions

GLP-1 receptor agonists represent one of the most biologically plausible psychometabolic therapeutic classes currently being investigated for potential psychiatric applications. Their relevance extends beyond the regulation of satiety and metabolic homeostasis, as GLP-1 signaling also appears to influence reward processing, neuroinflammatory pathways, and neuroplastic mechanisms implicated in depression, addictive disorders, and binge-eating phenotypes. However, biological plausibility alone is insufficient to establish clinical efficacy.

Current evidence supports a cautious, graded interpretation. In depression, the available findings are promising but not yet definitive, with the clearest effects observed in cognitive and motivational domains rather than in broad remission of the depressive syndrome. In substance use disorders, alcohol use disorder currently has the strongest human evidence, whereas findings in nicotine use disorder remain mixed and appear most relevant to adjunctive treatment contexts. Opioid and stimulant use disorders remain early-stage translational targets. In eating disorders, binge-eating disorder represents the most promising phenotype, while bulimia nervosa remains insufficiently studied and anorexia-spectrum conditions require particular caution because of the appetite-suppressing and weight-reducing properties of this drug class.

The most balanced current position is therefore neither premature enthusiasm nor dismissal of their psychiatric potential. GLP-1 receptor agonists should not yet be regarded as established psychiatric treatments. Still, they are credible candidates for the next phase of psychometabolic drug repurposing, particularly in patients whose symptoms are linked to metabolic, inflammatory, and reward-related dysfunction. Their future role in psychiatry will depend on whether ongoing and future trials can demonstrate durable benefits on diagnosis-specific psychiatric outcomes, identify subgroups most likely to respond, and establish long-term safety in populations vulnerable to restrictive eating, dehydration, nutritional compromise, and psychiatric relapse.

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