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REVIEW ARTICLE

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Psychiatric effects of GLP-1 receptor agonists: A systematic review of emerging evidence

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Abstract

This systematic review examines the current literature on glucagon-like peptide-1 receptor agonists (GLP-1RAs)-associated psychiatric manifestations, including depression, suicidality, eating disorders, substance use disorders (SUD) and schizophrenia spectrum disorders. A comprehensive literature search was conducted to identify studies evaluating the association between GLP-1RAs and psychiatric outcomes. The electronic databases systematically searched were PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Embase and Web of Science. GLP-1RAs are increasingly recognised for their potential neuropsychiatric effects beyond glycaemic control and weight loss. Findings suggest modest antidepressant effects, inconsistent associations with suicidality and potential therapeutic benefit in disorders of reward regulation. These findings are constrained by limited sample diversity, variability in outcome measures and the consistent underrepresentation of individuals with psychiatric comorbidities, factors that warrant targeted future research. This review highlights key findings on the neuropsychiatric effects of GLP-1RAs. The heterogeneity among the studies in terms of dosing, clinical indications and baseline psychiatric status complicates interpretation, but preliminary evidence suggests modest antidepressant effects and potential therapeutic roles in eating and SUD. Concerns regarding suicidality remain unresolved. In schizophrenia, GLP-1RAs provide clear metabolic benefits but have not demonstrated consistent effects on psychiatric symptomatology.

KEYWORDS

GLP-1, systematic review, type 2 diabetes, weight control

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of medications primarily developed for the treatment of type 2 diabetes

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mellitus (T2DM) and, more recently, obesity management.[1] Their therapeutic efficacy derives from multiple mechanisms, including glucose-dependent insulin secretion, delayed gastric emptying and central appetite modulation.[2,3] In recent years, the focus on GLP-1RAs has expanded beyond glycemic and weight control to include increasing research into their potential effects on central nervous system (CNS) pathways, including roles in mood regulation, neuroinflammation and cognitive function.[2] This evolving understanding has spurred investigations into their neuropsychiatric implications, yet the underlying mechanisms and clinical relevance remain incompletely defined.

The expression of GLP-1 receptors in brain regions such as the amygdala, hippocampus and nucleus accumbens—areas critical for mood, stress and reward processing—provides a biological rationale for their potential neuropsychiatric effects.[4] Preclinical models demonstrate that GLP-1 signalling influences hypothalamic–pituitary–adrenal (HPA) axis activity and dopaminergic neurotransmission, supporting a mechanistic basis for effects on affective and compulsive behaviours.[5] These findings have prompted growing investigation into the potential utility of GLP-1RAs in a range of psychiatric conditions, including mood, anxiety and substance use disorders (SUD).[6]

Despite these mechanistic insights, clinical evidence on the psychiatric effects of GLP-1RAs remains limited and frequently inconsistent. Some studies suggest antidepressant or anxiolytic effects,[7] while others report potential adverse outcomes, including emotional blunting and suicidality.[8] Moreover, the routine exclusion of individuals with significant psychiatric comorbidities from GLP-1RA clinical trials limits the generalisability of findings and perpetuates an evidence gap for high-risk populations.[9]

Given the increasing off-label use of GLP-1RAs for weight management and the high prevalence of psychiatric comorbidities among individuals with metabolic disease, evaluating their neuropsychiatric safety and therapeutic potential is essential.[10] This systematic review synthesises existing literature on GLP-1RA-associated psychiatric manifestations, including depression, suicidality, anxiety, eating disorders, SUD and schizophrenia spectrum disorders. We critically evaluate the quality and consistency of available evidence, identify key methodological limitations and outline priorities for future research.

2 | MATERIALS AND METHODS

2.1 | Search strategy

A comprehensive literature search was conducted to identify studies evaluating the association between GLP-1RAs and psychiatric outcomes. The following electronic databases were systematically searched: PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase and Web of Science. Searches incorporated controlled vocabulary (e.g., Medical Subject Headings and Emtree) and Boolean operators. Search terms included population-specific keywords and drug names, such as 'GLP-1 receptor agonist,' 'exenatide,' 'semaglutide' and 'liraglutide,' in combination with intervention-related terms like 'GLP-1RA therapy' and 'GLP-1 analogs.' Comparator terms included 'non-GLP-1 treatments,' 'insulin' and 'metformin,' and outcome-related terms encompassed 'psychiatric symptoms,' 'major depressive disorder,' 'generalized anxiety disorder' and other mental health diagnoses. Supplementary searches were conducted by reviewing reference lists of included articles, relevant systematic reviews and grey literature sources, including conference abstracts and organisational reports. The Boolean search strategy was designed to ensure broad coverage of relevant psychiatric outcomes across databases.

2.2 | Inclusion and exclusion criteria

Study selection was guided by predefined inclusion and exclusion criteria to ensure methodological rigour and relevance. Eligible studies included randomised controlled trials (RCTs), non-RCTs, controlled before-and-after studies and observational designs (cross-sectional, cohort and case–control) that incorporated control or comparator groups. Meta-analyses that addressed the primary or secondary outcomes of interest were also included to capture aggregated findings across studies. Primary outcomes included the prevalence and clinical characteristics of psychiatric conditions among individuals treated with GLP-1RAs, compared to those receiving no treatment or alternative antidiabetic therapies. Studies investigating potential pathophysiological mechanisms linking GLP-1RAs use and psychiatric disorders, particularly major depressive disorder and generalised anxiety disorder (GAD), were also considered. Secondary outcomes included the impact of new-onset psychiatric illness on clinical prognosis, treatment comparisons and recovery trajectories following GLP-1RAs exposure. No restrictions were applied based on publication year or language. Both peer-reviewed and unpublished literature were eligible for inclusion. Studies were excluded if they were irrelevant to the research question, those that lacked appropriate psychiatric outcome measures, or did not provide sufficient data for analysis.

2.3 | Quality assessment

To evaluate the validity and methodological rigour of the studies included, standardised assessment tools were applied. The Cochrane Risk of Bias tool was used to assess RCTs, and the ROBINS-I tool was applied to non-randomised studies. These frameworks enabled a systematic evaluation of potential biases related to study design, participant selection, intervention fidelity and outcome reporting. This quality appraisal process helped ensure that conclusions drawn from the review were grounded in methodologically sound and high-quality evidence. Results of this assessment can be found in Tables S1 and S2.

2.4 | Data extraction

Key data were systematically extracted from each study using a standardised data collection protocol. Extracted variables included study

design, sample size, participant characteristics, intervention details, comparators and reported psychiatric outcomes. Where appropriate, a meta-analysis was performed using a random-effects model to synthesise quantitative findings. When meta-analysis was precluded by substantial heterogeneity, a narrative synthesis was undertaken to qualitatively summarise the findings. Subgroup analyses explored variation by demographic characteristics, study quality and specific psychiatric outcome categories. Sensitivity analyses were also conducted to assess the influence of methodological differences on the robustness of the overall findings.

3 | RESULTS

As seen in Figure 1, 38 studies were ultimately included in this review. A summary of key characteristics of each study can be found in Table S1.

3.1 | Depression

GLP-1RAs may have modest antidepressant effects. A meta-analysis combining RCTs and cohort studies ($n = 2071$) reported a small but statistically significant reduction in depression rating scale scores among individuals receiving GLP-1RAs (standardized mean difference ≈ -0.12, $p < 0.01$), with more pronounced effects observed among individuals with T2DM.[11] Proposed mechanisms include central activation of preproglucagon-expressing neurons in the nucleus tractus solitarius and stimulation of corticotropin-releasing hormone-producing neurons in the hypothalamus, linking GLP-1 signalling to modulation of the HPA axis.[12]

However, evidence regarding the psychiatric safety profile of GLP-1RAs remains mixed. A large community-based cohort study using post-marketing surveillance data identified a significant association between GLP-1RA use and increased psychiatric risk, reporting a 195% increased risk of major depressive disorder and a 106% increased risk of suicidal behaviour among individuals with obesity treated with liraglutide or semaglutide.[13] These findings highlight the importance of comprehensive psychiatric assessment and monitoring when initiating GLP-1RA therapy, particularly in populations at elevated risk.

In contrast, a target trial emulation study utilising US Medicare data compared older adults with type 2 diabetes who initiated GLP-1RAs with those who began treatment with either sodium-glucose cotransporter-2 (SGLT2) inhibitors or dipeptidyl peptidase-4 (DPP-4) inhibitors. Among 14 665 matched pairs of GLP-1RA and SGLT2 inhibitor users, there was no statistically significant difference in the risk of incident depression (hazard ratio [HR] 1.07, 95% confidence interval [CI]: 0.98–1.18). However, among 13 711 matched pairs comparing GLP-1RA and DPP-4 inhibitor users, GLP-1RA initiation was associated with a significantly reduced risk of depression (HR 0.90, 95% CI: 0.82–0.98).[14] These findings suggest that the psychiatric effects of GLP-1RAs may differ based on the comparator medication class.

A meta-analysis of 80 randomised clinical trials including 107 860 participants found no significant association between GLP-1RA use and either serious psychiatric adverse events (log relative risk [RR] $= -0.02$; 95% CI: -0.20 to 0.17; $p = 0.87$) or nonserious events (log[RR] $= -0.03$; 95% CI: -0.21 to 0.16; $p = 0.76$) compared to placebo. No significant change in depressive symptoms was observed (Hedges' $g = 0.02$; 95% CI: -0.51 to 0.55; $p = 0.94$).[15] Consistent with these findings, a large post hoc analysis of the STEP 1, 2, 3 and 5 trials reported a statistically significant but clinically negligible reduction in depressive symptoms among individuals without major psychiatric illness treated with semaglutide (estimated treatment difference: -0.56; 95% CI: -0.75 to -0.37; $p < 0.001$).[16] In contrast, GLP-1RA use was associated with small but statistically significant improvements in restrained eating ($g = 0.35$; 95% CI: 0.13–0.57; $p = 0.002$) and emotional eating ($g = 0.32$; 95% CI: 0.11–0.54; $p = 0.003$). Improvements were also observed in quality of life across mental ($g = 0.15$), physical ($g = 0.20$), diabetes-related ($g = 0.23$) and weight-related ($g = 0.27$) domains.[15,16] Interestingly, the improvements in quality of life occurred independent of the degree of weight loss, possibly suggesting these improvements are from mechanisms beyond weight reduction alone.[16]

3.2 | Suicidality

The association between GLP-1RA therapy and suicidality remains uncertain and controversial. A large cohort study conducted in Sweden and Denmark found no statistically significant increase in suicidality associated with GLP-1RA exposure; the upper bound of the CI corresponded to an absolute risk of 0.16 events per 1000 person-years.[17] A meta-analysis of four studies reported a non-significant relative risk of 0.568 (95% CI: 0.077–4.205). Substantial heterogeneity was observed across studies ($I^2 = 98\%$), likely reflecting differences in study design, populations and outcome ascertainment. The extremely wide prediction interval (0.001–218.938) further underscores the high degree of uncertainty and variability in effect estimates. However, pharmacovigilance data suggest a potential increased risk of suicidal ideation with semaglutide use in individuals concurrently prescribed antidepressants or benzodiazepines, with reported odds ratios (ROR) of 4.45 and 4.07, respectively.[18]

3.3 | Eating disorders

GLP-1RAs have shown promise in reducing binge eating behaviours. A systematic review of five studies reported significant improvements in body weight, body mass index, waist circumference and Binge Eating Scale (BES) scores among individuals treated with GLP-1RAs, particularly dulaglutide and semaglutide.[19] Participants treated with GLP-1RAs showed a greater reduction in BES scores compared to controls, with a mean difference of -8.14 points.[19] The study also referenced additional research demonstrating reductions in compulsive and emotional eating behaviours. However, most included

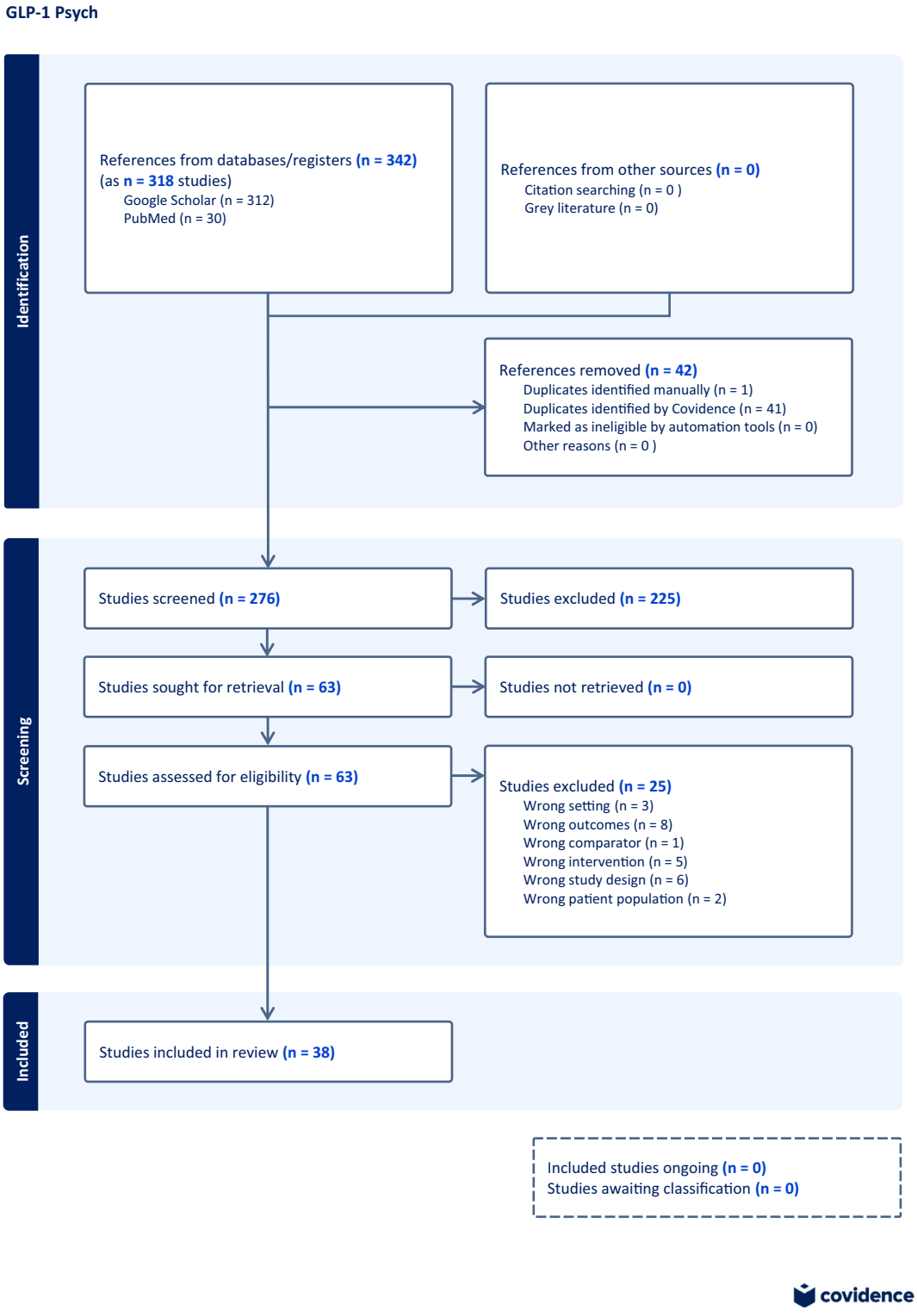

FIGURE 1 Study selection preffered reporting items for systematic reviews and meta-analyses diagram.

studies focused on individuals diagnosed with binge eating disorder (BED). Further research is needed to determine whether GLP-1RA treatment may be effective for individuals with other eating disorders. Preclinical studies suggest that GLP-1 and serotonin co-modulate hypothalamic appetite regulation via alpha-melanocyte-stimulating hormone (α-MSH) signalling, supporting further investigation into potential applications in anorexia nervosa and bulimia nervosa.[20]

3.4 | Substance use disorders

Evidence supporting the use of GLP-1RAs in the treatment of SUD is limited but emerging. In a RCT, exenatide was found to reduce neural reward responses to alcohol cues but did not lead to a significant overall reduction in alcohol consumption.[21] However, participants in the exenatide group experienced a statistically significant reduction in heavy drinking days (23.6%) and total alcohol consumption (1205 g over 30 days) compared to placebo. The study sample was racially homogenous, consisting of White participants and marked by a high attrition rate (54.3%).

Among individuals with obesity, exenatide treatment was associated with significant reductions in alcohol consumption. A subsequent RCT found that dulaglutide reduced alcohol intake by 29% over 12 weeks, corresponding to a mean change of −1.4 drinks per day compared to −0.1 in the placebo group.[22] Evidence for GLP-1RAs in tobacco use disorder is mixed. One RCT reported increased smoking abstinence with exenatide, while another found no significant benefit with dulaglutide.[23,24] These preliminary findings underscore the need for further RCTs across diverse SUD populations.

3.5 | Schizophrenia spectrum and other psychotic disorders

In individuals living with schizophrenia, GLP-1RAs have primarily been studied for their metabolic benefits. Preclinical studies suggest that liraglutide may exert cognitive and antipsychotic effects through dopaminergic modulation and neurotrophic signalling. However, human studies remain limited and have yielded inconclusive findings. In a RCT, 12 weeks of weekly exenatide did not significantly improve cognitive performance in individuals with schizophrenia.[25,26] Meta-analyses have found no evidence that GLP-1RAs exacerbate psychotic symptoms. For example, Bak et al. reported no change in psychopathology severity with exenatide or liraglutide treatment,[27] and Almeida et al. found no association between GLP-1RA exposure and antipsychotic medication use across multiple study designs.[28] These findings have been further corroborated by more recent studies. Vu et al. reported no adverse psychiatric events among diabetic patients prescribed metformin and antipsychotics concurrently taking semaglutide for weight loss.[29] A prospective, non-randomised pilot study conducted by Campforts et al. found that patients on semaglutide due to antipsychotic-induced weight gain experienced an improvement in their quality of life and a reduction in their psychiatric symptoms.[30] While GLP-1RAs appear to be psychiatrically safe in this population, definitive evidence of therapeutic benefit remains lacking.

3.6 | Anxiety disorders

Beyond their metabolic effects, GLP-1RAs have been investigated for their potential impact on anxiety disorders, including GAD. Findings to date are mixed, with some studies suggesting anxiolytic effects and others raising concerns about possible adverse outcomes.

A large-scale observational study using data from over 11 million adults with obesity found that GLP-1RA users had a significantly increased risk of developing psychiatric conditions compared to non-users. Specifically, GLP-1RA users demonstrated a 108% increased risk of anxiety disorders, a 195% higher risk of major depressive disorder and a 106% increased risk of suicidal behaviour.[13] These associations remained consistent across demographic subgroups and specific GLP-1RAs, including semaglutide and liraglutide. Similarly, a pharmacovigilance analysis of the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) identified a statistically significant association between GLP-1RAs and reported psychiatric adverse events.[31] Anxiety, nervousness and insomnia were among the most frequently reported psychiatric adverse events, with a small increase in reporting frequency (ROR = 1.04).[31]

In contrast, several studies suggest that GLP-1RAs may confer some protective effects against anxiety. A population-based cohort study reported a lower risk of anxiety among individuals with T2DM treated with GLP-1RAs compared to non-users.[32] These findings were supported by a meta-analysis demonstrating significant reductions in depression and anxiety scale scores among GLP-1RA users compared to controls.[11] Additionally, a study of semaglutide use in individuals with T2DM found no increased risk of anxiety or depression and reported a lower risk of cognitive impairment.[33]

These contradictory findings underscore the complex and potentially bidirectional relationship between GLP-1RAs and psychiatric outcomes. Heterogeneity in study design, patient populations and specific GLP-1RAs examined likely contributes to these inconsistencies. Further large-scale, prospective studies are needed to elucidate the psychiatric risk–benefit profile of GLP-1RAs across diverse clinical populations.

4 | DISCUSSION

This systematic review underscores a growing body of evidence indicating that GLP-1RAs may exert clinically meaningful effects on neuropsychiatric health. Initially developed for glycaemic control and more recently approved for obesity management, GLP-1RAs exhibit CNS activity that intersects with neurobiological pathways involved in mood regulation, reward processing and cognitive function. These pleiotropic effects warrant critical evaluation, especially as GLP-1RAs are increasingly prescribed to diverse clinical populations, many of whom have co-occurring psychiatric conditions (Table 1).

4.1 | Mechanistic considerations

GLP-1 is synthesised peripherally by intestinal L-cells and centrally by preproglucagon (PPG) neurons in the nucleus tractus solitarius.[12] Centrally acting GLP-1RAs are capable of crossing the blood–brain barrier and binding to receptors in limbic and hypothalamic regions involved in appetite regulation, stress response and affective processing.[12] Preclinical studies in rodents demonstrate that GLP-1 signalling

TABLE 1 Summary of the evidence.

Condition	Evidence summary	Studies cited
Depression	Meta-analytic data suggest a small but statistically significant reduction in depressive symptoms, with greater effect sizes observed in individuals with type 2 diabetes mellitus. Findings from large observational cohorts are mixed, with some demonstrating no difference in risk compared to active comparators, and others reporting increased incidence of major depressive disorder in populations with obesity. Improvements in quality-of-life metrics have been observed independent of weight reduction.	11,13–16
Suicidality	Large population-based studies and meta-analyses generally do not demonstrate a statistically significant increase in suicidal ideation or behaviour. Pharmacovigilance data suggest a potential increased risk among individuals concurrently prescribed antidepressants or benzodiazepines.	17,18
Eating disorders	GLP-1RA therapy, particularly dulaglutide and semaglutide, has been associated with significant reductions in binge eating behaviours, weight and related anthropometric measures, with data primarily derived from individuals with binge eating disorder. Evidence for other eating disorders is limited.	19,20
Substance use disorders	Randomised controlled trials demonstrate reductions in alcohol consumption and heavy drinking days with exenatide and dulaglutide. Data on tobacco use disorder are mixed, with some trials indicating increased abstinence and others showing no effect.	21–24
Schizophrenia spectrum and other psychotic disorders	No evidence of exacerbation of psychotic symptoms. Some studies report improvements in quality of life and psychiatric symptom burden in patients with antipsychotic-induced weight gain receiving semaglutide.	25–30
Anxiety disorders	Evidence is inconsistent. Large cohort data in obese populations indicate increased risk of anxiety disorders, whereas studies in type 2 diabetes mellitus populations and meta-analyses report reduced risk or no significant association.	11,13,31–33

Abbreviation: GLP-1RA, glucagon-like peptide-1 receptor agonists.

modulates corticotropin-releasing hormone neurons in the paraventricular nucleus of the hypothalamus and dopaminergic neurons in the ventral tegmental area, implicating GLP-1 in HPA axis regulation and attenuation of reward salience. These neuroendocrine mechanisms may underlie observed improvements in binge eating behaviours and support the potential utility of GLP-1RAs in conditions characterised by hedonic dysregulation, including substance use and mood disorders. These mechanistic pathways offer plausible explanations for both therapeutic effects and adverse psychiatric outcomes, such as anxiety, emotional blunting or dysphoria. However, the extent to which these central mechanisms directly mediate psychiatric symptom changes remains unclear. More in-depth investigation is needed to clarify how GLP-1R activation in specific brain regions contributes to both beneficial and adverse effects across affective and compulsive spectrum disorders.

4.2 | Depression and mood disorders

The relationship between GLP-1RAs and depression remains complex and incompletely understood. Although proposed mechanisms—such as modulation of the HPA axis and central GLP-1 receptor signalling—suggest potential antidepressant effects, clinical findings remain inconsistent. This discrepancy may reflect an incomplete understanding of how GLP-1-mediated neuroendocrine signalling translates into mood-related outcomes in humans, particularly given evidence of bidirectional HPA axis effects and variability in individual neurobiological vulnerability. A large post-marketing cohort study reported a substantially increased risk of depression, anxiety and suicidal behaviour among individuals with obesity treated with liraglutide or semaglutide, raising important safety concerns.[26] In contrast, a target trial emulation using U.S. Medicare data found no increased risk of depression among GLP-1RA users compared to those initiating SGLT2 inhibitors, and a modestly reduced risk relative to users of DPP-4 inhibitors.[27] Additionally, a comprehensive meta-analysis of 80 randomised controlled trials involving over 100 000 participants found no significant increase in psychiatric adverse events or depressive symptoms with GLP-1RA use and reported improvements in quality of life and emotional regulation.[28]

These discrepant findings likely reflect heterogeneity in study design, comparator drug classes and baseline psychiatric risk across study populations. Moreover, most RCTs were not designed or powered to assess psychiatric outcomes and frequently excluded individuals with moderate to severe mood disorders, thereby limiting the generalisability of findings. It remains unclear whether improvements in depressive symptoms reflect a direct neuropsychotropic effect of GLP-1RAs or are secondary to indirect benefits such as improved glycaemic control, weight loss and reductions in systemic inflammation. This distinction is particularly important given the well-established bidirectional relationship between diabetes and depression, wherein poor glycaemic control can exacerbate depressive symptoms, and depression can impair diabetes self-management.

4.3 | Suicidality and neuropsychiatric risk

Reports of suicidality associated with GLP-1RA use have raised considerable concern, particularly amid widespread off-label prescribing for weight loss. However, large-scale pharmacoepidemiologic studies have not demonstrated a statistically significant association to date. Specifically, a meta-analysis of randomised controlled trials completed in 2024 did not find an increase in suicides or suicidal behaviour.[34] Notably, some data suggest a potential risk signal among individuals concurrently using antidepressants or benzodiazepines—groups already at elevated baseline psychiatric risk.[18] This observation raises important questions about potential pharmacodynamic interactions and underlying neurobiological vulnerability. Understanding whether suicidality reflects a direct mechanistic effect—such as dysregulated stress response or limbic modulation—or is a downstream consequence of rapid weight loss, metabolic shifts or medication interactions remains an important area for future research. The absence of a robust safety signal should not be interpreted as evidence of safety in high-risk populations, and clinicians should exercise caution when prescribing GLP-1RAs to individuals with a history of suicidality or severe mood disorders. Regulatory agencies may need to consider population-specific monitoring recommendations as the use of GLP-1RAs continues to expand.

4.4 | Eating disorders and reward dysregulation

GLP-1RAs show promising early evidence for reducing compulsive eating behaviours, particularly in individuals with BED. These findings align with preclinical research demonstrating that GLP-1 analogues reduce the salience of food-related cues and attenuate mesolimbic dopamine signalling. Notably, reductions in BES scores have been observed independent of weight loss, suggesting a potential direct effect on reward-related neural pathways. These therapeutic implications may extend beyond BED to include individuals with bulimia nervosa, night eating syndrome or addictive-like eating phenotypes, who may benefit from targeted GLP-1RA therapy. However, caution is warranted in individuals with anorexia nervosa or restrictive eating patterns, where further appetite suppression could exacerbate underlying psychopathology.

4.5 | Substance use disorders

Preliminary findings suggest that GLP-1RAs may attenuate craving and reduce substance use in alcohol and nicotine use disorders, potentially through central GLP-1R-dependent modulation of dopaminergic signalling in the nucleus accumbens.[21,23,24] Differential effects observed between individuals with and without obesity suggest a complex interaction between metabolic status and central reward processing. Notably, while one study reported increased smoking abstinence rates with exenatide, subsequent trials have failed to replicate these findings in larger or more diverse populations. Replication in multisite RCTs with rigorous assessment of craving, substance use and relapse risk will be essential to determine the clinical utility of GLP-1RAs in addiction medicine.

4.6 | Schizophrenia spectrum and other psychotic disorders

In individuals with schizophrenia spectrum disorders, the primary clinical interest in GLP-1RAs has focused on mitigating antipsychotic-induced metabolic side effects.[26,27,35] Although animal models have suggested that GLP-1 signalling may enhance cognitive function and attenuate positive psychotic symptoms through dopaminergic modulation, these effects have not been consistently replicated in human studies.[36,37] Moreover, cognitive benefits observed in preclinical models may not translate to the complex neurobiology of chronic schizophrenia.[37] Given the established safety and tolerability of GLP-1RAs in this population, further investigation is warranted. However, additional research is needed to clarify whether observed improvements in psychiatric symptoms are attributable to direct neuropsychotropic effects or arise indirectly through metabolic stabilisation, reward normalisation or inflammation reduction.[27,29,30,38]

4.7 | Anxiety disorders

In addition to clinical outcomes, preclinical studies provide insight into the neurobiological mechanisms through which GLP-1RAs may influence anxiety and mood regulation. Animal models have shown that GLP-1 and its analogues, such as exendin-4, can induce anxiety-like behaviours in rodents.[4] These effects are thought to be mediated through GLP-1's activation of the HPA axis and its engagement of brain regions involved in emotion regulation.[4] For example, GLP-1 signalling within the amygdala and hypothalamus has been shown to modulate stress reactivity and anxiety-related phenotypes. Some preclinical findings suggest that GLP-1 signalling exerts both anxiogenic and antidepressant effects, depending on dosage, exposure duration and the specific neural targets engaged.[4] This bidirectional activity complicates the interpretation of psychiatric outcomes in humans and may help explain the variability observed in clinical studies. These findings underscore the importance of identifying dose-dependent and circuit-specific mechanisms in humans, as differential engagement of stress-related versus reward-related neural pathways may help explain the heterogeneous anxiety-related outcomes observed in clinical settings.

5 | CONCLUSION

This review highlights key findings from the current literature on the neuropsychiatric effects of GLP-1RAs. Most examined studies did not enroll participants with diagnosed psychiatric disorders or evaluate structured psychiatric outcomes as primary endpoints. Follow-up

periods were generally short, limiting conclusions about long-term psychiatric safety and treatment durability. The heterogeneity among the studies in terms of dosing, clinical indications and baseline psychiatric status further complicates interpretation.

Although preliminary evidence suggests modest antidepressant effects and potential therapeutic roles in eating and SUD, concerns regarding suicidality remain unresolved. In schizophrenia, GLP-1RAs provide clear metabolic benefits but have not demonstrated consistent effects on psychiatric symptomatology.

6 | LIMITATIONS OF REVIEW

Several limitations characterise the current literature on the psychiatric effects of GLP-1RAs. Many studies excluded individuals with significant psychiatric comorbidities, including those with active suicidal ideation or mood stabilisation disorders, thereby limiting generalisability and leaving the effects of GLP-1RAs on high-risk populations largely unknown. This omission is particularly concerning given the neuropsychiatric adverse effects that have been reported in post-marketing surveillance and preliminary clinical observations. Considerable heterogeneity across study designs—including variations in dosing regimens, treatment durations, populations studied and outcome assessments—further complicates synthesis and limits the ability to draw cohesive conclusions or conduct meaningful meta-analyses. Additionally, short follow-up periods restrict insight into the long-term psychiatric safety and durability of any potential therapeutic effects. Confounding effects from the concurrent use of medications such as antidepressants or benzodiazepines also complicate interpretation, making it difficult to attribute observed outcomes specifically to GLP-1RA exposure. Although some studies report potential antidepressant or anxiolytic effects, the evidence remains inconsistent and preliminary, while concerns about adverse psychiatric outcomes, including suicidality, remain insufficiently addressed. Mechanistic understanding is also limited; most hypotheses about CNS involvement remain speculative due to a lack of integrated neurobiological or mechanistic studies. Finally, the exclusion of high-risk populations introduces selection bias, and the likelihood of publication bias, whereby studies reporting favourable outcomes are overrepresented, further constrains the interpretability and clinical applicability of the existing literature.

7 | FUTURE RESEARCH DIRECTIONS

To address these limitations, future research should prioritise randomised controlled trials consisting of diverse, representative patient populations that are explicitly designed to assess psychiatric outcomes using structured clinical interviews and validated symptom rating scales. Longitudinal studies with extended follow-up are essential to evaluate long-term neuropsychiatric safety, particularly with respect to suicidality, mood stabilisation and compulsive behaviours. Stratified research by sex, ethnic group, period of life, metabolic status and psychiatric history could help identify subgroups most likely to benefit from (or be vulnerable to) GLP-1RA treatment. Mechanistic studies exploring CNS interactions, such as GLP-1 signalling within the HPA axis and dopaminergic circuits, may elucidate the biological pathways underlying the psychiatric effects observed in clinical populations. Research examining off-label use in psychiatric populations, such as those with major depressive disorder, anxiety disorders and obsessive-compulsive spectrum disorders, may help clarify the broader therapeutic potential of GLP-1RAs.

Given ongoing concerns regarding suicidality, future trials should incorporate rigorous adverse event monitoring, especially for individuals concurrently using psychotropic medications, to ensure safe prescribing practices and inform regulatory oversight as GLP-1RA use continues to expand. Clinicians should perform monthly check-ins by using validated tools to assess depression and suicidality among patients enrolled in these clinical trials. Patients and caregivers should be provided appropriate psychoeducation to report adverse symptoms such as mood lability, appetite changes and suicidal ideation. As articulated earlier, future studies should include patient populations with marked comorbidities and pharmacovigilance to better elucidate the risk of GLP-1RA administration.

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CONFLICT OF INTEREST STATEMENT

All authors state no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this systematic review are openly available in the following electronic databases: PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and Web of Science.

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REFERENCES

1. Drucker DJ. The biology of incretin hormones. *Cell Metab*. 2006;3(3):153-165 (in English). doi:10.1016/j.cmet.2006.01.004
2. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002 (in English). doi:10.1056/NEJMoa2032183
3. Nauck MA, Meier JJ. Incretin hormones: their role in health and disease. *Diabetes Obes Metab*. 2018;20(suppl 1):5-21 (in English). doi:10.1111/dom.13129

4. Anderberg RH, Richard JE, Hansson C, Nissbrandt H, Bergquist F, Skibicka KP. LP-1 is both anxiogenic and antidepressant; divergent effects of acute and chronic GLP-1 on emotionality. *Psychoneuroendocrinology*. 2016;65:54-66. doi:10.1016/j.psyneuen.2015.11.021
5. Shirazi RH, Dickson SL, Skibicka KP. Gut peptide GLP-1 and its analogue, exendin-4, decrease alcohol intake and reward. *PLoS One*. 2013;8(4):e61965 (in English). doi:10.1371/journal.pone.0061965
6. van Bloemendaal L, IJzerman RG, Ten Kulve JS, et al. GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. *Diabetes*. 2014;63(12):4186-4196. doi:10.2337/db14-0849
7. Mansur RB, Lee Y, Zhou AJ, et al. The effect of GLP-1 receptor agonists on mood and cognition: a systematic review and meta-analysis of randomized controlled trials. *CNS Spectr*. 2021;26(4):417-427. doi:10.1017/S1092852921000420
8. European Medicines Agency. Statement on ongoing review of GLP-1 receptor agonists. EMA website. 2023. Accessed August 3, 2025. https://www.ema.europa.eu/en/
9. Kirkman SKB. Psychiatric exclusion criteria in obesity and diabetes clinical trials: a missed opportunity? *Obesity (Silver Spring)*. 2020;28(8):1470-1471. doi:10.1002/oby.22883
10. Pan A, Keum N, Okereke OI, et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes Care*. 2012;35(5):1171-1180 (in English). doi:10.2337/dc11-2055
11. Chen X, Zhao P, Wang W, Guo L, Pan Q. The antidepressant effects of GLP-1 receptor agonists: a systematic review and meta-analysis. *Am J Geriatr Psychiatry*. 2024;32(1):117-127 (in English). doi:10.1016/j.jagp.2023.08.010
12. Detka J, Głombik K. Insights into a possible role of glucagon-like peptide-1 receptor agonists in the treatment of depression. *Pharmacol Rep*. 2021;73(4):1020-1032 (in English). doi:10.1007/s43440-021-00274-8
13. Kornelius E, Huang JY, Lo SC, Huang CN, Yang YS. The risk of depression, anxiety, and suicidal behavior in patients with obesity on glucagon like peptide-1 receptor agonist therapy. *Sci Rep*. 2024;14(1):24433 (in English). doi:10.1038/s41598-024-75965-2
14. Tang H, Lu Y, Donahoo WT, et al. Glucagon-like peptide-1 receptor agonists and risk for depression in older adults with type 2 diabetes: a target trial emulation study. *Ann Intern Med*. 2025;178(3):315-326 (in English). doi:10.7326/ANNALS-24-01347
15. Pierret ACS, Mizuno Y, Saunders P, et al. Glucagon-like peptide 1 receptor agonists and mental health: a systematic review and meta-analysis. *JAMA Psychiatry*. 2025;82:643-653. doi:10.1001/jamapsychiatry.2025.0679 (in English).
16. Wadden TA, Brown GK, Egebjerg C, et al. Psychiatric safety of semaglutide for weight management in people without known major psychopathology: post hoc analysis of the STEP 1, 2, 3, and 5 trials. *JAMA Intern Med*. 2024;184(11):1290-1300. doi:10.1001/jamainternmed.2024.4346
17. Ueda P, Söderling J, Wintzell V, et al. GLP-1 receptor agonist use and risk of suicide death. *JAMA Intern Med*. 2024;184(11):1301-1312. doi:10.1001/jamainternmed.2024.4369
18. Bushi G, Khatib MN, Rohilla S, et al. Association of GLP-1 receptor agonists with risk of suicidal ideation and behaviour: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2025;41(2):e70037 (in English). doi:10.1002/dmrr.70037
19. Radkhah H, Rahimipour Anaraki S, Parhizkar Roudsari P, et al. The impact of glucagon-like peptide-1 (GLP-1) agonists in the treatment of eating disorders: a systematic review and meta-analysis. *Eat Weight Disord*. 2025;30(1):10 (in English). doi:10.1007/s40519-025-01720-9
20. Aoun L, Almardini S, Saliba F, et al. GLP-1 receptor agonists: a novel pharmacotherapy for binge eating (binge eating disorder and bulimia nervosa)? A systematic review. *J Clin Transl Endocrinol*. 2024;35:100333 (in English). doi:10.1016/j.jcte.2024.100333
21. Klausen MK, Thomsen M, Wortwein G, Fink-Jensen A. The role of glucagon-like peptide 1 (GLP-1) in addictive disorders. *Br J Pharmacol*. 2022;179(4):625-641 (in English). doi:10.1111/bph.15677
22. Leggio L, Hendershot CS, Farokhnia M, et al. GLP-1 receptor agonists are promising but unproven treatments for alcohol and substance use disorders. *Nat Med*. 2023;29(12):2993-2995 (in English). doi:10.1038/s41591-023-02634-8
23. Martinelli S, Mazzotta A, Longaroni M, Petrucciani N. Potential role of glucagon-like peptide-1 (GLP-1) receptor agonists in substance use disorder: a systematic review of randomized trials. *Drug Alcohol Depend*. 2024;264:112424 (in English). doi:10.1016/j.drugalcdep.2024.112424
24. Probst L, Monnerat S, Vogt DR, et al. Effects of dulaglutide on alcohol consumption during smoking cessation. *JCI Insight*. 2023;8(22):e170419 (in English). doi:10.1172/jci.insight.170419
25. Gill H, Lieberman JM, DiVincenzo JD, et al. Evaluating the use of glucagon-like peptide 1 for the treatment of cognitive dysfunction in individuals with mood disorders. *Curr Treat Options Psychiatry*. 2022;9:331-345.
26. Bak M, Campforts B, Domen P, van Amelsvoort T, Drukker M. Glucagon-like peptide agonists for weight management in antipsychotic-induced weight gain: a systematic review and meta-analysis. *Acta Psychiatr Scand*. 2024;150(6):516-529 (in English). doi:10.1111/acps.13734
27. Menon T, Lee S, Gong XY, et al. A systematic review on the efficacy of GLP-1 receptor agonists in mitigating psychotropic drug-related weight gain. *Curr Treat Options Psychiatry*. 2024;29:331-345.
28. Almeida OP, Fong Z, Hill Almeida LM, Sanfilippo FM, Page A, Etherton-Beer C. Cross-sectional, case-control and longitudinal associations between exposure to glucagon-like peptide-1 receptor agonists and the dispensing of antidepressants. *Diabetes Obes Metab*. 2024;26(7):2925-2932 (in English). doi:10.1111/dom.15616
29. Vu C, Thai R, Dike D, Sydner B. Semaglutide plus metformin versus metformin alone for antipsychotic-induced weight gain in patients with type 2 diabetes mellitus. *Psychiatry Q*. 2025. doi:10.1007/s11126-025-10137-7
30. Campforts B, Drukker M, van Amelsvoort T, Bak M. Management of obesity with semaglutide or metformin in patients with antipsychotic-induced weight gain (MOSA): a non-randomised open-label pilot study. *BMC Psychiatry*. 2024;24:865. doi:10.1186/s12888-024-06317-7
31. Chen W, Cai P, Zou W, Fu Z. Psychiatric adverse events associated with GLP-1 receptor agonists: a real-world pharmacovigilance study based on the FDA adverse event reporting system database. *Front Endocrinol*. 2024;15:1330936. doi:10.3389/fendo.2024.1330936
32. Tsai WH, Sung FC, Chiu LT, Shih YH, Tsai MC, Wu SI. Decreased risk of anxiety in diabetic patients receiving glucagon-like peptide-1 receptor agonist: a nationwide, population-based cohort study. *Front Pharmacol*. 2022;13:765446 (in English). doi:10.3389/fphar.2022.765446
33. De Giorgi R, Koychev I, Adler AI, et al. 12-month neurological and psychiatric outcomes of semaglutide use for type 2 diabetes: a propensity-score matched cohort study. *EClinicalMedicine*. 2024;74:102726 (in English). doi:10.1016/j.eclinm.2024.102726
34. Silverii GA, Marinelli C, Mannucci E, Rotella F. Glucagon-like peptide-1 receptor agonists and mental health: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2024;26(6):2505-2508. doi:10.1111/dom.15538
35. Trott M, Arnautovska U, Siskind D. GLP-1 receptor agonists and weight loss in schizophrenia – past, present, and future. *Curr Opin Psychiatry*. 2024;37(5):363-369 (in English). doi:10.1097/YCO.0000000000000952
36. Camkurt MA, Lavagnino L, Zhang XY, Teixeira AL. Liraglutide for psychiatric disorders: clinical evidence and challenges. *Horm Mol Biol Clin Investig*. 2018;36(2):20180031. doi:10.1515/hmbci-2018-0031
37. Tempia Valenta S, Nicastri A, Perazza F, et al. The impact of GLP-1 receptor agonists (GLP-1 RAs) on mental health: a systematic review. *Curr Treat Options Psychiatry*. 2025;68(Suppl 1):S982. doi:10.1192/j.eurpsy.2025.1993

38. Acar AŞ, Erbaş O. Glucagon-like peptide-1 and psychiatric disorder. *JEBMS*. 2021;2(2):106-115. doi:10.5606/jebms.2021.75645

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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