METABOLISM ENDOCRINOLOGY AND OBESITY

Cite as: Archiv EuroMedica. 2026. 16; 1. DOI 10.35630/2026/16/Iss.1.005

Received 12 December 2025;
Accepted 4 February 2026;
Published 12 February 2026

GLP-1 RECEPTOR AGONISTS AND DEPRESSION IN OBESITY: CURRENT EVIDENCE

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ABSTRACT

BACKGROUND

Obesity is closely associated with depression and emotional distress. Glucagon like peptide 1 receptor agonists have become widely used for obesity treatment, raising concerns about their potential psychiatric effects. While randomized controlled trials generally report neutral or mildly favorable mood outcomes, real world studies and pharmacovigilance data suggest heterogeneous signals, creating uncertainty regarding psychiatric safety.

AIMS

To critically assess the association between GLP 1 receptor agonist therapy and depressive symptoms in adults with obesity by comparing evidence from randomized trials, real world observational studies, pharmacovigilance databases, and qualitative research published between 2022 and 2025.

METHODS

A narrative review was conducted using PubMed. Original studies involving adults with overweight or obesity treated with GLP 1 receptor agonists and reporting psychiatric outcomes were included. Randomized trials, observational cohorts, pharmacovigilance analyses, and qualitative studies were synthesized narratively due to methodological heterogeneity.

RESULTS

Randomized controlled trials consistently showed no increased risk of depression or suicidal ideation and, in some

cases, modest mood improvement in selected populations without major psychiatric comorbidity. In contrast, real world and pharmacovigilance data revealed heterogeneous findings, including signals of depressive symptoms and anxiety in subsets of patients, limited by confounding and reporting bias. Qualitative evidence demonstrated substantial interindividual variability in emotional responses to treatment.

CONCLUSIONS

Current evidence does not support a causal association between GLP 1 receptor agonist therapy and clinically significant depression in adults with obesity. Discrepancies between data sources are largely attributable to methodological differences and population selection. Individualized assessment and clinical vigilance remain warranted, particularly in patients with underlying psychological vulnerability.

Keywords: GLP 1 receptor agonists; obesity; depression; psychiatric safety; real world evidence; pharmacovigilance; qualitative research

1. INTRODUCTION

Obesity represents a major global health challenge and is strongly associated with an increased prevalence of mood disorders, particularly depression [1]. Epidemiological studies consistently show that individuals with obesity are more likely to develop depressive symptoms compared with the general population, a bidirectional relationship driven by biological, psychological, and social mechanisms. Chronic low-grade inflammation, dysregulation of appetite-regulating neurocircuits, body image dissatisfaction, and societal stigma contribute to significant psychiatric burden in this population, leading to reduced quality of life and impaired functioning [2–4]. As the prevalence of obesity continues to rise worldwide, understanding the interplay between metabolic and mental health outcomes has become increasingly important in clinical practice.

In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as one of the most effective pharmacological treatments for obesity. Agents such as semaglutide and liraglutide not only induce substantial weight loss but also improve glycaemic control and reduce obesity-related comorbidities [5,6]. Their rapid adoption in clinical and real-world settings, alongside increased media visibility, has contributed to widespread interest in their physiological, behavioural, and psychological effects. It should be noted, however, that media narratives often coexist with persistent barriers and stigma in accessing treatment. [7] Although clinical trials generally report favourable safety profiles, including stable or slightly improved mood indicators in participants without baseline psychiatric disorders [8,9], accumulating real-world data and pharmacovigilance reports have raised concerns about potential depressive symptoms, anxiety, or suicidal ideation emerging during treatment with GLP-1 RAs [10–12].

These contrasting observations- reassuring evidence from randomized trials versus emerging psychiatric signals in post-marketing settings have generated an urgent need to critically examine the current state of knowledge. The pathophysiological plausibility of GLP-1 related mood effects adds further complexity. GLP-1 interacts with central nervous system pathways involved in appetite regulation, reward processing, and emotional regulation, suggesting both potential antidepressant and depressogenic mechanisms depending on individual vulnerability, dose, treatment duration, and the psychosocial context of weight loss [13–15].

Given these uncertainties, and the rapidly expanding use of GLP-1 RAs in obesity management, a synthesis of recent evidence is essential to guide clinicians, researchers, and policymakers. This narrative review aims to integrate findings from randomized controlled trials, real-world observational studies, pharmacovigilance databases, and qualitative research published between 2022 and 2025. The objective is to provide a balanced and critical assessment of whether GLP-1 receptor agonists influence depressive symptoms in adults with obesity, to explore possible mechanisms underlying these effects, and to identify gaps requiring further investigation.

RELEVANCE

The relevance of the article is determined by the combination of three factors. Obesity is closely associated with depressive disorders and an increased risk of suicidality. GLP-1 receptor agonists have become among the most widely used pharmacological agents for the treatment of obesity. At the same time, contradictory data have emerged regarding possible psychiatric effects of this therapy, particularly outside the setting of randomized controlled trials. For clinical practice, it is important to determine whether these signals reflect a real risk or are the result of methodological limitations of real-world data and pharmacovigilance.

NOVELTY

The novelty of the article lies not in the identification of a new effect, but in the systematic comparison of different types of evidence. The work consistently contrasts data from randomized controlled trials, observational cohorts, pharmacovigilance databases, and qualitative studies, with an emphasis on discrepancies between them. Unlike previous reviews, the article focuses on the sources of these inconsistencies and their methodological causes rather

than on a pooled effect estimate or a meta-analytic conclusion.

AIM

The aim of this narrative review is to critically evaluate the association between therapy with GLP-1 receptor agonists and depressive symptoms in adult patients with obesity, taking into account differences between available types of evidence.

RESEARCH OBJECTIVES

To analyze the results of randomized controlled trials with respect to depressive symptoms and suicidality during therapy with GLP-1 receptor agonists.

To compare these results with data from real-world clinical practice and observational cohort studies.

To assess the nature and limitations of signals related to depression and suicidality identified in pharmacovigilance databases.

To summarize evidence from qualitative and patient-reported studies on subjective mood changes.

To identify methodological limitations of existing studies and gaps that hinder causal interpretation of the available data.

2. METHODS

This narrative review was conducted in accordance with established principles for evidence synthesis in non-systematic academic reviews. The primary aim of the methodological approach was to ensure transparency, reproducibility, and consistency in identifying and selecting studies assessing the relationship between GLP-1 receptor agonists and depressive symptoms in adults with obesity. A structured search strategy was applied using PubMed as the sole database, reflecting its comprehensive coverage of biomedical literature and its suitability for focused clinical research topics. The search was performed for articles published between 1 January 2022 and 31 December 2025, a period selected to capture the most recent evidence following the approval and widespread adoption of modern GLP-1 receptor agonists for obesity management.

The search strategy combined controlled vocabulary and free-text terms related to GLP-1 receptor agonists, depression, and obesity. The final search query applied in PubMed was as follows: ("GLP-1 receptor agonist" OR semaglutide OR liraglutide OR tirzepatide) AND ("Depression" OR depressive OR "depressive symptoms" OR mood) AND ("obesity" OR obesity).

No filters were applied for study design to avoid prematurely excluding potentially relevant evidence, particularly real-world studies and pharmacovigilance reports that may provide unique safety signals which could remain undetected in randomized controlled trials due to their strict exclusion criteria. [16]

All retrieved records were screened for eligibility in a two-stage process. First, titles and abstracts were assessed to identify articles relevant to depressive symptoms, mood changes, suicidal ideation, or broader psychiatric outcomes in individuals with overweight or obesity treated with GLP-1 receptor agonists. In the second stage, full-text articles were reviewed to confirm eligibility. Studies were included if they met the following criteria: (1) original research articles; (2) human participants aged 18 years or older; (3) treatment with semaglutide, liraglutide, tirzepatide, or other GLP-1 receptor agonists; (4) outcomes related to depression, depressive symptoms, mood, or related psychiatric endpoints; (5) populations with overweight or obesity; and (6) full text available in English. Exclusion criteria encompassed non-original articles such as commentaries, editorials, and narrative reviews, studies not involving GLP-1 receptor agonists, studies focusing exclusively on diabetes without obesity context, non-human research, and papers lacking mental health outcomes.

Following the application of inclusion and exclusion criteria, 32 studies were selected for qualitative synthesis. These comprised randomized controlled trials, post-hoc analyses, cohort and case-control studies, pharmacovigilance reports, and qualitative or patient-reported evidence. Data extraction focused on study design, sample characteristics, GLP-1 agent used, duration of treatment, psychiatric outcomes assessed, measurement tools, and key findings. Given the heterogeneity of study designs, populations, and outcome measures, a narrative synthesis approach was employed. This allowed integration of evidence across multiple domains including controlled trials, observational datasets, and patient-reported experiences while highlighting convergent patterns, discrepancies, and methodological limitations across the literature.

Original studies involving adult patients with overweight or obesity treated with GLP-1 receptor agonists were included if they assessed depressive symptoms, mood changes, anxiety disorders, suicidal ideation, or other psychiatric outcomes. Eligible study designs comprised randomized clinical trials, post hoc analyses of clinical trial programs, cohort and case control studies, pharmacovigilance analyses, as well as qualitative and patient reported

studies, provided that data on mental health outcomes during GLP-1 therapy were available. Review articles, editorials, letters to the editor, and other non-original publications were excluded, as were animal studies and preclinical research. Studies focusing exclusively on diabetes without a separate analysis of populations with obesity or overweight were not included.

Publications lacking data on psychiatric or affective outcomes were excluded, as were articles for which the full text was unavailable or that were published in languages other than English.

Outcomes of interest included depressive symptoms, suicidal ideation, and anxiety related measures as reported in the included studies.

Findings from randomized controlled trials, observational studies, pharmacovigilance reports, and qualitative research were interpreted within their respective methodological contexts and were not treated as equivalent levels of evidence.

No causal inferences were drawn from observational or pharmacovigilance data.

In randomized controlled trials, psychiatric outcomes were considered secondary or exploratory endpoints rather than primary efficacy outcomes.

Pharmacovigilance studies were used to identify potential safety signals and were interpreted descriptively.

The use of a single bibliographic database may have limited the completeness of the retrieved literature.

3. RESULTS

PATHOPHYSIOLOGICAL BACKGROUND

Glucagon-like peptide-1 (GLP-1) is an incretin hormone with well-established metabolic roles, but growing evidence demonstrates its broad distribution and functional relevance within the central nervous system (CNS). GLP-1 receptors are expressed in multiple brain regions implicated in appetite regulation, stress responses, reward processing, and emotional control, including the hypothalamus, brainstem nuclei, hippocampus, ventral tegmental area (VTA), lateral septal nucleus, and nucleus accumbens (NAc) [17–20]. Systemically administered GLP-1 receptor agonists (GLP-1 RAs) can access these CNS sites, either directly or through vagal-mediated pathways, allowing them to influence neural circuits that overlap substantially with pathways involved in mood regulation. Notably, semaglutide and liraglutide show differences in brain penetrance and regional distribution, with semaglutide engaging broader hypothalamic and septal networks than liraglutide, suggesting agent-specific neurobiological effects [17].

A prominent mechanism through which GLP-1 RAs may influence emotional states relates to their actions on hypothalamic circuits regulating feeding behaviour. GLP-1R activation in the arcuate nucleus modulates proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons, which contribute to satiety signalling and energy homeostasis. Simultaneously, GLP-1 suppresses activity of neuropeptide-Y/agouti-related peptide (NPY/AgRP) neurons, reducing hunger and potentially altering stress-related eating patterns [17,19]. These effects, while metabolic in nature, intersect with mood pathways given the strong bidirectional links between stress, appetite, and emotional regulation, which provide a detailed description of the mechanisms linking metabolic syndrome with depressive disorders. [21]

Beyond homeostatic feeding circuits, GLP-1 influences the mesolimbic reward system. Several studies and mechanistic analyses indicate that GLP-1R agonism affects dopaminergic signalling in the VTA–NAc pathway, with some evidence suggesting attenuation of dopamine release or blunting of reward responsiveness [6,8,18]. This blunting effect is critical; as highlighted by Volkow (2025), while it underpins the therapeutic reduction of craving, it may biologically explain the emergence of dysphoric symptoms or anhedonia in patients without pre-existing substance use disorders [22]. Thus, this modulation may reduce reward-driven overeating, but it could also, in susceptible individuals, contribute to reduced motivation, anhedonia, or dysphoria core symptoms of depressive syndromes. Preclinical data reveal that GLP-1 agonists interact with GABAergic medium spiny neurons and glutamatergic terminals within the mesolimbic system, ultimately shaping the balance between inhibitory and excitatory neurotransmission that governs dopaminergic output [6]. These neurochemical effects offer a biologically plausible route through which GLP-1 RAs may exert either therapeutic or adverse psychiatric effects depending on baseline dopamine function.

Inflammatory and neuroendocrine pathways represent an additional mechanistic link between GLP-1 signalling and mood. Chronic inflammation and hypothalamic pituitary adrenal (HPA) axis dysregulation are well-recognized contributors to depression, particularly in metabolic disorders. GLP-1 receptor activation has demonstrated immunomodulatory effects in preclinical models, including reductions in pro-inflammatory cytokines and activation of intracellular pathways (e.g., cAMP–PKA, PI3K–Akt–CREB) that promote cellular resilience and neuroprotection [17,18,23]. Conversely, some studies show that acute GLP-1R stimulation can transiently increase stress-related

hormonal responses, such as corticosterone release, raising the possibility of dual and time-dependent emotional effects [17]. These bidirectional findings align with evidence that acute GLP-1 administration may provoke anxiogenic responses, while chronic exposure appears to exert antidepressant-like effects in animal models [18].

Taken together, GLP-1 receptor agonists interact with multiple neurobiological systems relevant to mood regulation hypothalamic appetite circuits, mesolimbic dopamine pathways, neuroinflammatory networks, and the HPA axis. Theoretical mechanisms linking GLP-1 RAs to depressive symptoms therefore encompass both protective and adverse possibilities. On one hand, improvements in neuroinflammation, metabolic stress, and neuroplasticity may confer antidepressant potential, consistent with preclinical findings showing normalization of hippocampal function and stress biomarkers [17,18]. On the other hand, blunting of dopaminergic reward signalling, acute HPA activation, or CNS penetration differences between specific agents may contribute to dysphoria, anhedonia, or depressive symptoms in vulnerable individuals [6,17]. These mechanistic complexities underscore the importance of examining clinical and real-world evidence to determine whether neurobiological plausibility translates into meaningful psychiatric outcomes in patients treated with GLP-1 receptor agonists.

EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

Randomized controlled trials (RCTs) represent the most rigorous source of evidence regarding the efficacy and safety of GLP-1 receptor agonists in obesity treatment. Across the major obesity-focused trials including the STEP program evaluating semaglutide 2.4 mg, as well as studies investigating liraglutide and other GLP-1 RAs psychiatric outcomes were generally secondary or exploratory, yet consistently reported. These trials enrolled tens of thousands of participants and followed them over extended periods ranging from 20 to 104 weeks, providing substantial opportunity to assess mood-related endpoints under controlled conditions [8,9,24,25].

Within the STEP trials, which constitute the most robust body of randomized evidence, participants treated with semaglutide typically demonstrated neutral or slightly improved depressive symptom scores compared with placebo. Measures such as the Patient Health Questionnaire-9 (PHQ-9) and other validated mood scales revealed small but statistically non-significant reductions in depressive symptoms over time, both in terms of absolute score and categorical thresholds for clinically relevant depression [6, 7]. Importantly, PHQ-9 scores at baseline in these trials were generally low, reflecting exclusion criteria that omitted individuals with major psychiatric disorders, recent suicidal ideation, or unstable mental health conditions. Consequently, observed changes in mood scores took place in a population with low initial psychiatric vulnerability.

Across multiple STEP trials including STEP 1, STEP 2, STEP 3, and STEP 5 psychiatric adverse events were uncommon, and the incidence of clinically significant depression or mood-related discontinuations did not differ meaningfully between the semaglutide and placebo groups. Post-hoc analyses further confirmed that semaglutide did not increase the risk of mood deterioration, even in participants who reported mild baseline emotional distress [8,24]. Improvements in weight, physical functioning, or metabolic health may have contributed to small favourable trends in mood scores, although causal inferences are limited by the secondary nature of these endpoints.

Safety data regarding suicidal ideation and behaviour were also reassuring. Throughout the STEP program, no increase in suicidal thoughts, self-harm behaviours, or psychiatric serious adverse events was observed in semaglutide-treated participants compared with controls [8,9]. Several trials reported no instances of suicidal behaviour, and when suicidal ideation was recorded, rates were low and balanced across treatment arms. Similar findings were noted in RCTs involving liraglutide and other GLP-1 RAs, which likewise detected no elevation in depressive symptoms or suicidal risk relative to placebo or active comparators [26–28].

Despite the consistency of these findings, important limitations must be acknowledged. Participants with significant psychiatric history, including active major depressive disorder, bipolar disorder, eating disorders, substance misuse, or recent suicidal behaviour, were systematically excluded from most RCTs [8,9]. As a result, the trial populations do not fully reflect routine clinical settings, where GLP-1 RAs are increasingly prescribed to individuals with complex psychiatric profiles. Furthermore, mood-related outcomes were typically secondary or exploratory, raising the risk of underpowered analyses and incomplete ascertainment of psychiatric events. Follow-up durations, although longer than many pharmacological trials, may still be insufficient to detect rare adverse effects or delayed-onset mood changes.

Taken together, evidence from randomized controlled trials suggests that GLP-1 receptor agonists do not increase the risk of depressive symptoms or suicidal ideation in adults with obesity under controlled conditions. If anything, minor improvements in mood have been observed, though these effects are modest and difficult to disentangle from weight loss and overall health improvements. However, the exclusion of high-risk psychiatric populations and the limited focus on mental health outcomes necessitate caution in extrapolating these findings to broader clinical practice. These limitations underscore the importance of integrating RCT findings with real-world observational data, pharmacovigilance reports, and qualitative evidence to obtain a more comprehensive understanding of the psychiatric safety profile of GLP-1 receptor agonists.

REAL-WORLD EVIDENCE (RWE) AND COHORT STUDIES

Real-world evidence provides an essential complement to randomized controlled trials by capturing outcomes in broader, more heterogeneous populations than those typically enrolled in clinical studies. Between 2022 and 2025, several large-scale cohort analyses and population-based studies evaluated the psychiatric safety of GLP-1 receptor agonists in adults with overweight or obesity. These investigations often relied on insurance databases, electronic health records, and national pharmacovigilance systems, allowing assessment of depressive symptoms, clinically diagnosed depression, anxiety-related disorders, and suicidal behaviours in routine clinical practice [11,28–32].

Across these observational datasets, associations between GLP-1 RA use and depression risk have been mixed. Some studies demonstrated a modestly increased incidence of newly diagnosed depression, mood instability, or prescription of antidepressant medications shortly after initiation of semaglutide or other GLP-1 agents, particularly in younger adults or those without prior psychiatric diagnoses [11,30]. Other analyses found no significant elevation in depression risk compared with non-users or with individuals treated with alternative anti-obesity medications, suggesting that observed mood disturbances may reflect underlying vulnerabilities rather than direct drug effects [13,28,33]. A subset of studies indicated potential mood improvements in individuals who achieved substantial weight loss, although these findings were inconsistent and appeared to vary according to baseline psychiatric status and degree of metabolic improvement [13,14].

Anxiety symptoms and suicidal behaviour were also examined in several real-world analyses. Although absolute event rates were low, certain datasets reported a relative increase in anxiety-related clinical encounters or self-reported anxiety symptoms among GLP-1 RA users, particularly during early treatment phases [13,30]. Reports of suicidal ideation were rare but did appear in pharmacovigilance-linked observational cohorts, warranting careful interpretation given the possibility of reporting bias and the inherent difficulty of establishing causality in spontaneous reporting systems [10,11,34]. Other large cohorts, however, found no significant differences in suicidal thoughts or behaviours between GLP-1 RA users and matched controls, and some suggested a potential reduction in psychiatric crisis events in individuals who experienced meaningful weight reduction [28,29,35].

While RWE studies offer valuable insights, their methodological limitations must be considered. Unlike RCTs, real-world cohorts typically include individuals with diverse psychiatric histories, varying adherence to treatment, and multiple concurrent medications, all of which can influence mental health outcomes. Residual confounding particularly related to baseline depression, socioeconomic stressors, binge-eating tendencies, or comorbid metabolic conditions may distort associations between GLP-1 RA exposure and psychiatric outcomes. Several studies acknowledged incomplete capture of symptom severity, reliance on diagnostic codes, and variability in follow-up durations as important constraints [29,30]. In addition, the temporal relationship between treatment initiation and mood changes may be difficult to establish in observational designs, making it challenging to distinguish transient adjustment reactions from genuine drug-related effects.

Confounding by indication is a critical consideration in interpreting real-world findings. Individuals prescribed GLP-1 RAs for obesity often present with long-standing weight-related distress, body image dissatisfaction, or emotional eating patterns, all of which increase their baseline risk for depression and anxiety independent of pharmacotherapy. The decision to initiate GLP-1 RA treatment may itself reflect clinical concerns about psychological burden or poor metabolic control, further complicating causal inference. Thus, some of the observed associations between GLP-1 RA use and psychiatric events may reflect pre-existing vulnerabilities rather than direct neuropsychological effects of the medication [10,28,30].

Taken together, real-world evidence suggests a more heterogeneous and complex psychiatric profile for GLP-1 receptor agonists than indicated by randomized trials. While certain studies have reported increased rates of depression or anxiety, others have demonstrated neutral or even favourable outcomes. Given the limitations of observational data and the high baseline risk of psychiatric symptoms in individuals with obesity, these findings highlight the need for cautious interpretation and underscore the importance of integrating multiple data sources when evaluating mental health effects of GLP-1 RA therapy.

PHARMACOVIGILANCE DATA

Pharmacovigilance systems such as VigiBase and EudraVigilance play a critical role in identifying potential psychiatric adverse effects of GLP-1 receptor agonists that may not be detected in randomized controlled trials. These large, passive reporting databases collect spontaneous adverse event notifications from healthcare professionals, patients, and regulatory bodies worldwide, enabling detection of safety signals that emerge during real-world use. Between 2022 and 2025, several analyses of global pharmacovigilance datasets examined the psychiatric profiles of GLP-1 RAs, with particular focus on semaglutide given its rapidly increasing clinical adoption [10,11].

Findings derived from VigiBase analyses indicated the presence of disproportionality signals for several psychiatric events, including depression, anxiety, and, less commonly, suicidal ideation. Although absolute numbers of reports remained low, the proportional reporting ratio (PRR) and related signal detection metrics suggested that these events

occurred more frequently than would be expected relative to background rates for comparable medications [10]. Notably, semaglutide demonstrated a stronger signal than some older GLP-1 RAs, such as liraglutide, a pattern possibly influenced by differences in prescribing patterns, dosing, or population characteristics. Some analyses also noted temporal clustering of reports within the first months after treatment initiation, which may reflect adjustment reactions, heightened vigilance following media attention, or early neuropsychiatric effects [11].

EudraVigilance reports showed similar trends. Submissions from European regulatory sources documented cases of depressive symptoms, mood changes, anxiety, and isolated instances of suicidal ideation associated with GLP-1 RA therapy [11,12]. As in VigiBase, semaglutide appeared to contribute disproportionately to psychiatric signal detection; however, this may partly reflect its dominant market share and widespread use for obesity, a condition inherently associated with high baseline psychological vulnerability. Reports frequently highlighted concomitant factors such as rapid weight loss, gastrointestinal side effects, or complex psychiatric histories, underscoring the difficulty of attributing causality within spontaneous notification systems [12].

Across datasets, the most consistently emerging pattern involved the reporting of depressive symptoms and anxiety, often described as mood lability, increased emotional distress, or reduced motivation. Suicidal ideation was reported less frequently, and completed suicides were exceedingly rare, but the presence of such cases nonetheless contributed to heightened regulatory scrutiny [10,11]. Several reports also described appetite dysregulation and symptoms suggestive of emerging or worsening eating disorders, such as restrictive behaviours or compulsive thoughts about food, which may reflect both pharmacological effects on appetite and psychological responses to rapid weight change [12,13].

Interpreting pharmacovigilance data requires caution. Spontaneous reporting is subject to substantial limitations, including reporting bias, underreporting, lack of denominator data, and inability to confirm causality. External influences such as media coverage of psychiatric risks associated with GLP-1 RAs may substantially increase the likelihood of reporting certain types of adverse events without indicating a true change in incidence. Many reports lack detailed clinical information, making it difficult to determine whether psychiatric symptoms preceded treatment, were triggered by comorbid conditions, or emerged as psychological reactions to weight loss, lifestyle changes, or expectations around treatment outcomes [11,12].

Despite these challenges, pharmacovigilance signal detection provides meaningful insight into potential safety concerns not captured in clinical trials. The signals observed for depression, anxiety, and eating disorder–related symptoms warrant continued monitoring, particularly given the rapid expansion of GLP-1 RA prescribing for obesity. While these findings do not establish a causal link between GLP-1 RAs and psychiatric adverse effects, they underscore the need for vigilant clinical assessment, careful patient selection, and integration of pharmacovigilance data with randomized and observational evidence to inform balanced risk–benefit evaluations.

QUALITATIVE AND PATIENT-REPORTED EVIDENCE

Qualitative research and patient-reported data provide unique insights into the lived experiences of individuals treated with GLP-1 receptor agonists, complementing the structured outcomes of randomized trials and the large-scale trends observed in real-world cohorts. Across qualitative interview studies, patient narratives often highlighted a complex interplay between metabolic improvements, psychological responses, and evolving self-perceptions during treatment. Participants commonly reported greater control over eating behaviour, reduced intrusive food-related thoughts, and improved energy levels, which many attributed to a sense of relief and emotional stabilization during therapy [13,14]. For some individuals, these perceived improvements translated into enhanced motivation, reduced feelings of hopelessness associated with long-standing weight challenges, and a more positive outlook on daily functioning.

At the same time, patient-reported outcomes revealed considerable variability in mood responses. While many described improvements, others reported emerging or fluctuating emotional difficulties during treatment. These included episodes of low mood, heightened anxiety, irritability, or diminished emotional reactivity, sometimes described as "emotional blunting." Such experiences were often reported during early treatment phases or at dose escalations. In several accounts, patients linked mood shifts to gastrointestinal side effects, reduced appetite, or challenges adapting to new eating patterns [13,14,36].

For individuals with pre-existing mental health vulnerabilities, restructuring eating behaviour and experiencing rapid reductions in hunger could provoke distress or exacerbate underlying tendencies toward restrictive eating.

Rapid weight loss, a hallmark of GLP-1 RA therapy, also contributed to a spectrum of emotional outcomes. Many individuals reported increased confidence, improved body image, and a revived sense of agency as weight decreased. However, a subset described feeling psychologically unprepared for the speed or magnitude of weight change, expressing concerns about identity, social reactions, or fears regarding long-term weight maintenance.

Some narratives suggested that profound alterations in appetite disrupted ingrained coping mechanisms tied to emotional eating, leading to transient emotional instability while new behavioural patterns were established [13,14].

These nuanced experiences illustrate that weight loss alone does not uniformly predict improved emotional well-being.

Analyses of social media content and online patient forums offered additional perspectives on mood-related effects of GLP-1 RAs, revealing both positive and negative sentiments from diverse patient populations [13]. Users frequently discussed changes in emotional regulation, energy, motivation, and social functioning during treatment, often in more candid and spontaneous language than that captured in clinical research settings. These platforms also highlighted experiences not commonly reported in formal studies, such as subjective feelings of detachment, reduced interest in pleasurable activities, or anxiety surrounding dose escalation. At the same time, many individuals conveyed strong satisfaction with treatment, emphasizing improved mental clarity, reduced food preoccupation, and a sense of "mental quieting" accompanying appetite suppression.

A consistent finding across qualitative and patient-reported evidence is the marked variability in individual experiences. While many patients report psychological benefits associated with improved metabolic health and decreased food-related distress, others describe mood fluctuations that may emerge in response to rapid physiological changes, side effects, personal expectations, or pre-existing mental health conditions. This heterogeneity underscores the importance of individualized assessment when considering the emotional impact of GLP-1 RA therapy. It also reinforces the need for integrated care approaches that recognize mental health as a dynamic part of obesity treatment rather than a secondary or peripheral concern [13,14].

4. DISCUSSION

INTEGRATED EVIDENCE SYNTHESIS

Synthesizing evidence across randomized controlled trials, real-world cohort studies, pharmacovigilance databases, and qualitative research reveals a complex and multifaceted picture of the relationship between GLP-1 receptor agonist therapy and depressive symptoms in individuals with obesity. While RCTs offer reassuring data with respect to mood stability and the absence of increased suicidal ideation under controlled conditions [8,9,29], findings from real-world observational studies and pharmacovigilance systems present a more heterogeneous profile, with signals that warrant careful interpretation [10–12,29]. Qualitative and patient-reported evidence adds an additional layer of nuance, highlighting emotional responses that may not be fully captured through structured clinical instruments [13,14].

Across data sources, several areas of convergence can be identified. First, most evidence indicates that GLP-1 RAs do not universally worsen mood and, for many patients, may be associated with psychological improvements linked to enhanced weight control, reduced food preoccupation, and improved daily functioning. These benefits may also stem from the direct neuroprotective and anti-inflammatory action of GLP-1 agonists in the central nervous system[37]. Second, serious psychiatric adverse events including suicidal behaviours appear rare relative to the scale of global GLP-1 RA use. Third, weight loss itself often plays a central role in shaping emotional experiences, acting as a mediator of both positive and negative psychological responses across patient populations. These consistent patterns emerge across RCTs, RWE, and qualitative work, suggesting a broadly favourable psychiatric profile for most individuals receiving these medications.

However, substantial discrepancies exist across evidence streams. RCTs consistently show stable or slightly improved mood scores, whereas several real-world cohorts report elevated rates of depressive symptoms, anxiety, or related psychiatric encounters shortly after treatment initiation [11,29,30,38]. Pharmacovigilance systems further amplify these concerns by detecting disproportionality signals for depression, anxiety, and, less commonly, suicidal ideation signals not observed in controlled trials [10–12]. This discrepancy is frequently attributed to 'stimulated reporting' driven by widespread media publicity regarding potential side effects [39]. Qualitative data reveal additional discrepancies, describing emotional blunting, transient dysphoria, or distress related to appetite suppression and rapid weight loss, phenomena rarely documented in clinical trial reports [13,14].

Several explanations may account for these conflicting findings. Methodological differences represent a primary contributor: RCTs systematically exclude individuals with significant psychiatric histories, thereby limiting the generalizability of their findings to real-world populations that frequently present with complex mental health backgrounds. In contrast, observational studies and pharmacovigilance systems capture a much broader spectrum of patients, including those at elevated baseline risk for depression and anxiety. Confounding by indication, differential prescribing to psychologically vulnerable individuals, incomplete adjustment for underlying mental health status, and the use of diagnostic codes rather than validated symptom measures may further distort associations observed in real-world data [11,29,30]. Additionally, media coverage and public awareness can increase spontaneous reporting of psychiatric adverse events, contributing to apparent safety signals that do not necessarily reflect true pharmacological effects.

Biological factors may also play a role in divergent results. GLP-1 RAs influence neural circuits involved in reward processing, appetite regulation, and emotional responses. These actions may yield beneficial effects such as reduced

emotional eating or improved metabolic health for some individuals, while provoking emotional discomfort or motivational blunting in others, particularly during early treatment or dose escalation phases [13,14]. Rapid weight loss and changes in eating patterns may further destabilize mood in susceptible individuals, providing a plausible physiological and psychological pathway for adverse outcomes outside trial settings.

Despite expanding research, several knowledge gaps remain. High-quality trials specifically designed to evaluate psychiatric outcomes in GLP-1 RA users are lacking, particularly among individuals with pre-existing depression, eating disorders, or other psychiatric comorbidities. The long-term emotional impact of profound and sustained weight loss remains insufficiently understood. Mechanistic studies that clarify agent-specific differences in central nervous system effects especially those comparing semaglutide with older GLP-1 RAs are similarly limited. Furthermore, current pharmacovigilance systems lack detailed clinical context, making it difficult to differentiate drug-related effects from underlying vulnerabilities, psychosocial stressors, or behavioural changes.

The observed heterogeneity between randomized controlled trials, real-world data, and pharmacovigilance findings is structured and summarized in Table 1, which highlights the inherent methodological limitations of each evidence source.

Table 1. Summary of discrepancies and limitations in psychiatric safety evidence across different study designs.

Data Source / Study Type	Key Findings: Depression & Mood	Key Findings: Suicidality	Methodological Limitations	Source
Randomized Controlled Trials (RCTs)	Neutral or slightly favourable mood scores (e.g., PHQ-9); no increased risk of depressive symptoms.	No increase in suicidal thoughts or self-harm behaviours compared with controls.	Exclusion of participants with significant psychiatric history; outcomes often secondary.	[8, 9]
Real-World Evidence (RWE)	Heterogeneous: some cohorts report increased incidence of depression/ anxiety; others find no association.	Reports of suicidal ideation are rare; some cohorts suggest reduction in crisis events after weight loss.	Residual confounding; confounding by indication; diagnostic codes used rather than validated scales.	[11, 28, 29, 30, 38]
Pharmacovigilance Databases	Disproportionality signals for depression and anxiety detected (e.g., in VigiBase).	Suicidal ideation reported less frequently than mood symptoms but signals exist.	Reporting bias; stimulated reporting due to media coverage; lack of denominator data.	[10–12]
Qualitative & Patient-Reported	Variable: ranges from "mental quieting" and relief to emotional blunting and dysphoria.	Not typically assessed as a primary outcome in qualitative interviews.	Subjective experiences influenced by rapid weight loss and changing eating patterns.	[13, 14]

Taken together, an integrated assessment of available evidence suggests that while GLP-1 receptor agonists appear psychiatrically safe for the majority of individuals in controlled settings, real-world data highlight a subset of patients who may experience mood-related challenges during therapy. This underscores the importance of personalized risk assessment, proactive monitoring, and continued research to better understand the emotional dimensions of GLP-1

RA treatment.

CLINICAL IMPLICATIONS

Incorporating the available evidence into clinical practice requires a balanced approach that recognizes both the reassuring findings from randomized trials and the more heterogeneous signals emerging from real-world and pharmacovigilance data. Given the elevated baseline prevalence of depression, anxiety, and disordered eating in individuals with obesity, careful psychiatric evaluation should be an integral component of initiating and managing GLP-1 receptor agonist therapy. Clinicians are encouraged to conduct structured screening for pre-existing psychiatric conditions, including major depressive disorder, anxiety disorders, eating disorders, and a history of suicidal ideation or behaviour. This approach aligns with the latest clinical guidelines, which recommend routine mental health assessment as an integral part of obesity management [40]. Such assessments not only help identify individuals who may benefit from additional monitoring but also provide a baseline against which any subsequent changes in emotional state can be evaluated [13,14,30].

Ongoing monitoring for mood changes and suicidal thoughts is essential, particularly during the early stages of treatment and during dose escalation periods, when reports of emotional fluctuations appear most frequent in patient-reported and observational data [11,13,14]. This vigilance aligns with regulatory updates stating that while a causal link to suicidal ideation has not been established, clinical monitoring remains prudent given the potential for rare adverse events [41]. Routine inquiries about emotional well-being integrated into standard follow-up visits can facilitate early detection of emerging symptoms. Clinicians may consider brief mood questionnaires, structured interviews, or collaborative communication with mental health providers for patients who demonstrate increased vulnerability. This collaborative framework aligns with the World Health Organization's most recent guidance, which explicitly promotes multidisciplinary care models to ensure comprehensive, person-centred support for individuals living with obesity[42]. Importantly, mood changes should not be assumed to be drug-related without a broader clinical assessment, as metabolic improvements, rapid weight loss, or disruptions in established coping mechanisms may also influence emotional stability.

Patient education plays a central role in mitigating distress and optimizing treatment outcomes. Clear communication about expected effects including appetite suppression, changes in eating behaviours, and potential emotional responses can help patients feel prepared and reduce anxiety associated with unfamiliar physiological sensations. Patients should be advised to report any new or worsening depressive symptoms, anxiety, or intrusive thoughts as early as possible. Providing reassurance that emotional changes may occur and are manageable within a supportive clinical framework may encourage transparency and adherence. Discussions should also address the psychological impact of rapid weight loss, including shifting body image, evolving social dynamics, and the need for behavioural adjustments to maintain long-term weight control [13,14,43].

Decisions regarding the continuation or discontinuation of GLP-1 RA therapy must balance the metabolic benefits of treatment with any emerging psychiatric concerns. In cases of mild or transient mood changes, ongoing monitoring and supportive interventions may be appropriate. However, clinicians should consider dose reduction, temporary interruption, or transition to alternative therapies if significant mood deterioration, persistent depressive symptoms, or suicidal ideation arises, particularly if these symptoms appear temporally linked to treatment initiation or intensification. Collaboration with mental health professionals is advisable when symptoms raise concern, and abrupt discontinuation should generally be avoided unless clinically necessary.

For prescribers treating obesity, these findings underscore the importance of adopting a holistic approach that integrates metabolic and psychiatric care. Obesity is a complex, biopsychosocial condition, and individuals seeking weight management often carry substantial emotional burdens that can influence treatment responses. GLP-1 RAs should be positioned within a comprehensive care model that includes psychological support, nutritional counselling, and regular follow-up. Recognizing the heterogeneity in patient experiences as documented across qualitative and real-world studies can help clinicians identify those who may require closer supervision or tailored interventions [11,12,30].

Overall, clinical practice should reflect an appreciation of both the therapeutic potential and the nuanced psychiatric landscape associated with GLP-1 receptor agonist therapy. Proactive screening, ongoing monitoring, patient-centred communication, and individualized decision-making offer the most effective means of ensuring that these medications are used safely and effectively in adults with obesity.

To bridge the gap between inconsistent findings and daily practice, we have proposed a set of practical considerations (Table 2). It is important to emphasize that these strategies represent a translation of our narrative review into clinical considerations rather than conclusions derived from a formal, high-level evidence base. The proposed actions reflect the authors' clinical perspective, based predominantly on observational data, pharmacovigilance reports, and qualitative patient experiences.

These suggestions are not supported by randomized controlled trials and do not constitute formal clinical guidelines. Instead, Table 2 should be viewed as an illustration of how clinicians might interpret heterogeneous evidence to

enhance patient safety.

Table 2. Authors' clinical perspective on potential psychiatric monitoring during GLP-1 RA therapy (based on observational and qualitative data).

Clinical Phase	Suggested considerations	Rationale / Details	Source
Screening	Consider assessing history of MDD, anxiety, eating disorders, and suicidal ideation.	May provide a baseline for evaluation; helps identify individuals requiring closer monitoring.	[13, 14, 30]
Observation	Routine inquiries about emotional well-being (mood questionnaires or interviews) could be considered.	Might be helpful during early treatment stages and dose escalations when fluctuations are most frequent.	[11, 13, 14]
Patient Education	Discussing expected effects (appetite suppression, weight loss speed, and potential emotional responses) may be useful.	Aims to reduces anxiety associated with unfamiliar physiological sensations; helps patients feel prepared.	[13, 14, 43]
Care integration	Potential collaboration with mental health professionals and nutritional counselling.	Recognizes heterogeneity in patient experiences; addresses the biopsychosocial nature of obesity.	[11, 12, 30]
Adjustment	Clinicians might consider dose reduction, interruption, or transition to alternative therapies if mood deterioration occurs.	A cautious approach to balances metabolic benefits with emerging psychiatric concerns.	

LIMITATIONS OF THIS REVIEW

This review has several limitations that should be acknowledged when interpreting its findings. As a narrative review, the synthesis is not based on a systematic search or formal meta-analytic procedures, which introduces a degree of subjectivity in study selection, interpretation, and weighting of evidence. Although efforts were made to identify relevant studies published between 2022 and 2025, the included literature remains heterogeneous with respect to study design, sample characteristics, psychiatric assessment tools, and treatment regimens. Such variability limits the comparability of findings and complicates the ability to draw definitive conclusions.

Observational and pharmacovigilance data, while valuable for detecting early safety signals, are inherently constrained by confounding, reporting bias, incomplete clinical information, and the inability to establish causality. These sources often include individuals with diverse psychiatric histories and socioeconomic backgrounds, making it difficult to disentangle drug-related effects from underlying vulnerabilities or external factors. At the same time, randomized controlled trials the most methodologically rigorous evidence systematically exclude individuals with significant psychiatric comorbidities, resulting in limited understanding of how GLP-1 receptor agonists affect high-risk psychiatric populations. Consequently, the applicability of RCT findings to real-world clinical settings, where such comorbidities are common, remains uncertain.

Taken together, these limitations highlight the need for more robust and targeted research, including prospective studies explicitly designed to evaluate psychiatric outcomes among diverse patient groups treated with GLP-1 receptor agonists.

5. CONCLUSIONS

This narrative review synthesizes recent evidence on the relationship between GLP-1 receptor agonist therapy and depressive symptoms in adults with obesity, drawing on randomized trials, real-world cohort studies, pharmacovigilance reports, and qualitative research. Across these diverse data sources, randomized controlled trials

consistently demonstrate that GLP-1 RAs do not increase the risk of depression or suicidal ideation in controlled settings, and often show slight improvements in mood among individuals without significant baseline psychiatric burden. In contrast, real-world evidence and pharmacovigilance analyses present a more heterogeneous profile, with some studies identifying signals of depressive symptoms, anxiety, or eating disorder–related concerns in subsets of patients. Qualitative accounts further highlight substantial variability in emotional experiences, underscoring the complex interaction between metabolic changes, psychological factors, and individual vulnerability.

Clinically, these findings suggest that GLP-1 receptor agonists remain a generally safe and effective treatment option for obesity, yet require thoughtful application when prescribed to individuals with pre-existing or emerging mental health concerns. Routine psychiatric screening, ongoing monitoring of mood and emotional well-being, and proactive patient education should be integrated into standard care. Awareness of the potential for variable emotional responses both positive and negative can support clinicians in tailoring treatment plans and facilitating early intervention when necessary.

Future research should prioritize prospective studies explicitly designed to evaluate psychiatric outcomes associated with GLP-1 RA therapy, especially in populations with elevated psychological risk. Comparative investigations of individual GLP-1 agents, mechanistic studies exploring central nervous system effects, and integration of patient-reported outcome measures will be essential to clarify the causal pathways underlying observed mood changes. Strengthening the methodological rigor of real-world analyses and enhancing the quality of pharmacovigilance data may further refine understanding of the psychiatric safety profile of these medications.

Overall, while current evidence does not support a generalizable association between GLP-1 receptor agonist use and clinically significant depression, the heterogeneity of reported experiences highlights the importance of individualized assessment and vigilant clinical oversight. A nuanced, patient-centred approach remains essential to ensuring the safe and effective use of GLP-1 RAs in obesity management.

Taken together, the findings of this review address the predefined research objectives by demonstrating that the apparent discrepancies between randomized trials, real world studies, pharmacovigilance data, and qualitative evidence are largely attributable to differences in study design, population selection, outcome assessment, and analytical limitations. Randomized controlled trials primarily capture short to medium term effects in selected populations without significant psychiatric comorbidity, whereas observational and pharmacovigilance sources reflect broader and more vulnerable patient groups and are inherently limited in causal interpretation. These methodological differences explain much of the observed heterogeneity and underscore that current evidence does not support a direct causal link between GLP 1 receptor agonist therapy and clinically significant depression, while highlighting areas where existing data remain insufficient for definitive conclusions.

DISCLOSURE

AUTHOR'S CONTRIBUTIONS

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All authors have read and agreed with the published version of the manuscript.

USE OF AI

The authors declare that no artificial intelligence tools were used for data analysis, interpretation of results, or manuscript writing.

REFERENCES

1. Phelps NH, Singleton RK, Zhou B, Heap RA, Mishra A, Bennett JE, et al. Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. The Lancet. 2024;403:1027–50. https://doi.org/10.1016/

S0140-6736(23)02750-2

2. Liu L, Li Z, Ye W, Peng P, Wang Y, Wan L, et al. Safety and effects of anti-obesity medications on weight loss, cardiometabolic, and psychological outcomes in people living with overweight or obesity: a systematic review and meta-analysis. eClinicalMedicine. 2025;79:103020. https://doi.org/10.1016/j.eclinm.2024.103020
3. Stojkovska A, Rus Prelog P, Kokalj Palandacic A. Association of semaglutide use with depressive symptoms and suicidal behavior in a patient with type 2 diabetes: A case report. J Int Med Res. 2025;53:03000605251349393. https://doi.org/10.1177/03000605251349393
4. Følling IS, Reigstad SL, Hyldmo ÅA, Helvik A-S. Patient experiences with liraglutide for obesity and binge eating disorder–A qualitative study. Ahmed S, editor. PLOS One. 2025;20:e0335806. https://doi.org/10.1371/journal.pone.0335806
5. Thomsen RW, Mailhac A, Løhde JB, Pottegård A. Real-world evidence on the utilization, clinical and comparative effectiveness, and adverse effects of newer GLP - 1RA -based weight-loss therapies. Diabetes Obes Metab. 2025;27:66–88. https://doi.org/10.1111/dom.16364
6. Sharafshah A, Lewandrowski K-U, Gold MS, Fuehrlein B, Ashford JW, Thanos PK, et al. *In Silico* Pharmacogenomic Assessment of Glucagon-like Peptide-1 (GLP1) Agonists and the Genetic Addiction Risk Score (GARS) Related Pathways: Implications for Suicidal Ideation and Substance Use Disorder. Curr Neuropharmacol. 2025;23:974–95. https://doi.org/10.2174/011570159X349579241231080602
7. Puhl RM. Weight Stigma and Barriers to Effective Obesity Care. Gastroenterol Clin North Am. 2023;52:417–28. https://doi.org/10.1016/j.gtc.2023.02.002
8. Wadden TA, Brown GK, Egebjerg C, Frenkel O, Goldman B, Kushner RF, 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;184:1290. https://doi.org/10.1001/jamainternmed.2024.4346
9. Al-Najim W, Dehestani B, Al-Humadi AW, Bodicoat DH, Papamargaritis D, Lean M, et al. Outcomes of Different Lifestyle Approaches in a Multicentre, Open-Label, Parallel-Group, Randomised Controlled Trial of the Effectiveness of Integrating a Pragmatic Pathway for Prescribing Liraglutide 3.0 mg in Weight Management Services (STRIVE Study). Metabolites. 2025;15:398. https://doi.org/10.3390/metabo15060398
10. Nishida K, Chrétien B, Dolladille C, Ebina T, Aleksic B, Cabé N, et al. Psychiatric and psychological adverse effects associated with dulaglutide, semaglutide, and liraglutide: A vigibase study. Clin Nutr. 2025;51:252–65. https://doi.org/10.1016/j.clnu.2025.06.011
11. Tobaiqy M, Elkout H. Psychiatric adverse events associated with semaglutide, liraglutide and tirzepatide: a pharmacovigilance analysis of individual case safety reports submitted to the EudraVigilance database. Int J Clin Pharm. 2024;46:488–95. https://doi.org/10.1007/s11096-023-01694-7
12. Witaszek T, Kłoda K, Mastalerz-Migas A, Babicki M. Association between Symptoms of Depression and Generalised Anxiety Disorder Evaluated through PHQ-9 and GAD-7 and Anti-Obesity Treatment in Polish Adult Women. Nutrients. 2024;16:2438. https://doi.org/10.3390/nu16152438
13. Arillotta D, Floresta G, Guirguis A, Corkery JM, Catalani V, Martinotti G, et al. GLP-1 Receptor Agonists and Related Mental Health Issues; Insights from a Range of Social Media Platforms Using a Mixed-Methods Approach. Brain Sci. 2023;13:1503. https://doi.org/10.3390/brainsci13111503
14. Pierret ACS, Benton M, Sen Gupta P, Ismail K. A qualitative study of the mental health outcomes in people being treated for obesity and type 2 diabetes with glucagon-like peptide-1 receptor agonists. Acta Diabetol. 2024;62:731–42. https://doi.org/10.1007/s00592-024-02392-0
15. Valentino K, Teopiz KM, Cheung W, Wong S, Le GH, Rosenblat JD, et al. The effect of glucagon-like Peptide-1 receptor agonists on measures of suicidality: A systematic review. J Psychiatr Res. 2025;183:112–26. https://doi.org/10.1016/j.jpsychires.2025.02.008
16. He L, Li Q, Yang Y, Li J, Luo W, Huang Y, et al. Pharmacovigilance study of GLP-1 receptor agonists for metabolic and nutritional adverse events. Front Pharmacol. 2024;15:1416985. https://doi.org/10.3389/fphar.2024.1416985
17. Herman RJ, Schmidt HD. Targeting GLP-1 receptors to reduce nicotine use disorder: Preclinical and clinical evidence. Physiol Behav. 2024;281:114565. https://doi.org/10.1016/j.physbeh.2024.114565
18. Chen J, Zhang Q, Wu Q, Zhang X, Xiang Z, Zhu S, et al. Impact of GLP -1 Receptor Agonists on Suicide Behavior: A Meta-Analysis Based on Randomized Controlled Trials. J Diabetes. 2025;17:e70151. https://doi.org/10.1111/1753-0407.70151
19. Popoviciu M-S, Păduraru L, Yahya G, Metwally K, Cavalu S. Emerging Role of GLP-1 Agonists in Obesity: A Comprehensive Review of Randomised Controlled Trials. Int J Mol Sci. 2023;24:10449. https://doi.org/10.3390/ijms241310449
20. O'Keefe JH, Franco WG, O'Keefe EL. Anti-consumption agents: Tirzepatide and semaglutide for treating obesity-related diseases and addictions, and improving life expectancy. Prog Cardiovasc Dis. 2025;89:102–12.

https://doi.org/10.1016/j.pcad.2024.12.010

21. Detka J, Głombik K. Insights into a possible role of glucagon-like peptide-1 receptor agonists in the treatment of depression. Pharmacol Rep. 2021;73:1020–32. https://doi.org/10.1007/s43440-021-00274-8
22. Volkow ND, Xu R. GLP-1R agonist medications for addiction treatment. Addiction. 2025;120:198–200. https://doi.org/10.1111/add.16626
23. Wang M, Chen X, Liu Z, Li Z, Zhu Z, Liu S, et al. Exploring potential associations between GLP-1RAs and depressive disorders: a pharmacovigilance study based on FAERS and VigiBase data. eClinicalMedicine 2025;86:103385. https://doi.org/10.1016/j.eclinm.2025.103385
24. Mok J, Adeleke MO, Brown A, Magee CG, Firman C, Makahamadze C, et al. Safety and Efficacy of Liraglutide, 3.0 mg, Once Daily vs Placebo in Patients With Poor Weight Loss Following Metabolic Surgery: The BARI-OPTIMISE Randomized Clinical Trial. JAMA Surg 2023;158:1003. https://doi.org/10.1001/jamasurg.2023.2930
25. Nagy N, Kleinová P, Péč MJ, Samoš M, Dedinská I. Improving the Quality of Two Lives by Treating Obesity. Y Rep 2025;8:85. https://doi.org/10.3390/reports8020085
26. Avignon A, Bonnet J, Anitcheou J, Tournayre S, Attalin V, Boegner C, et al. Clustering of intuitive eating and psychological health identifies subgroups associated with weight loss following semaglutide. Obesity 2025;33:892–902. https://doi.org/10.1002/oby.24262
27. Hurtado I, Robles C, Peiró S, García-Sempere A, Sanfélix-Gimeno G. Association of glucagon-like peptide-1 receptor agonists with suicidal ideation and self-injury in individuals with diabetes and obesity: a propensity-weighted, population-based cohort study. Diabetologia 2024;67:2471–80. https://doi.org/10.1007/s00125-024-06243-z
28. Lee S, Li M, Le GH, Teopiz KM, Vinberg M, Ho R, et al. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) as treatment for nicotine cessation in psychiatric populations: a systematic review. Ann Gen Psychiatry 2024;23:45. https://doi.org/10.1186/s12991-024-00527-9
29. West J, Li M, Wong S, Le GH, Teopiz KM, Valentino K, et al. Are Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists Central Nervous System (CNS) Penetrant: A Narrative Review. Neurol Ther 2025;14:1157–66. https://doi.org/10.1007/s40120-025-00724-y
30. Kornelius E, Huang J-Y, Lo S-C, Huang C-N, Yang Y-S. The risk of depression, anxiety, and suicidal behavior in patients with obesity on glucagon like peptide-1 receptor agonist therapy. Sci Rep 2024;14:24433. https://doi.org/10.1038/s41598-024-75965-2
31. McIntyre RS, Mansur RB, Rosenblat JD, Rhee TG, Cao B, Teopiz KM, et al. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: A replication study using reports to the World Health Organization pharmacovigilance database (VigiBase®). J Affect Disord 2025;369:922–7. https://doi.org/10.1016/j.jad.2024.10.062
32. Börchers S, Skibicka KP. GLP-1 and Its Analogs: Does Sex Matter? Endocrinology 2025;166:bqae165. https://doi.org/10.1210/endocr/bqae165
33. Gundapaneni SRC, Burri RG, Kaku R, Mamytova A, Kondadasula P, Tagaev T. Semaglutide in Obesity and Type 2 Diabetes Management: A Systematic Review of Clinical Outcomes. Cureus 2025; https://doi.org/10.7759/cureus.78555
34. Tsankof A, Neokosmidis G, Koureta E, Veneti S, Cholongitas E, Tziomalos K. Which is the optimal antiobesity agent for patients with nonalcoholic fatty liver disease? Front Endocrinol 2022;13:984041. https://doi.org/10.3389/fendo.2022.984041
35. 35. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with risk of suicidal ideation in a real-world cohort. Nat Med 2024;30:168–76. https://doi.org/10.1038/s41591-023-02672-2
36. Alhowiti A, Mirghani H, Abdulrahman Qrmli A, Albalawi AA, Abdulrahman Aljohani R. Barriers to glucagon-like peptide-1 agonists used for obesity management among the general population in Tabuk City, Saudi Arabia, and their relation to smoking cessation and antidepressants. Front Pharmacol 2025;16:1510554. https://doi.org/10.3389/fphar.2025.1510554
37. Kong F, Wu T, Dai J, Zhai Z, Cai J, Zhu Z, et al. Glucagon-like peptide 1 (GLP-1) receptor agonists in experimental Alzheimer's disease models: a systematic review and meta-analysis of preclinical studies. Front Pharmacol 2023;14:1205207. https://doi.org/10.3389/fphar.2023.1205207
38. O'Neil PM, Rubino DM. Exploring the wider benefits of semaglutide treatment in obesity: insight from the STEP program. Postgrad Med 2022;134:28–36. https://doi.org/10.1080/00325481.2022.2150006
39. 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. https://doi.org/10.3389/fendo.2024.1330936

40. Pedersen SD, Manjoo P, Dash S, Jain A, Pearce N, Poddar M. Pharmacotherapy for obesity management in adults: 2025 clinical practice guideline update. Can Med Assoc J 2025;197:E797–809. https://doi.org/10.1503/cmaj.250502
41. FDA. Update on FDA's ongoing evaluation of reports of suicidal thoughts or actions in patients taking a certain type of medicines approved for type 2 diabetes and obesity U.S. Food and Drug Administration; 2024 Jan. https://www.fda.gov/drugs/drug-safety-and-availability/update-fdas-ongoing-evaluation-reports-suicidal-thoughts-or-actions-patients-taking-certain-type
42. World Health Organization. Guideline on the use of glucagon-like peptide-1 (GLP-1) therapies for the treatment of obesity in adults. World Health Organization; 2025. https://www.who.int/news/item/01-12-2025-who-issues-global-guideline-on-the-use-of-glp-1-medicines-in-treating-obesity
43. Sabbagh M, Boschini C, Cohen S, Fugger M, Jessen F, Dandanell S, et al. Safety considerations of semaglutide in the potential treatment of Alzheimer's disease: A pooled analysis of semaglutide in adults aged ≥ 65 years. Alzheimers Dement Transl Res Clin Interv. 2025;11:e70076. https://doi.org/10.1002/trc2.70076

back