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Psychiatric Adverse Events Associated with Semaglutide: A Systematic Review of Evidence and Implications for Clinical Practice

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ABSTRACT:

Background: The clinical use of semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist authorized for the treatment of type 2 diabetes and obesity, is quickly growing. However, concerns have emerged regarding its potential psychiatric adverse effects, including depression, suicidal ideation, and self-harm, prompting an ongoing safety review by the European Medicines Agency (EMA). Despite these concerns, systematic evidence on psychiatric outcomes associated with semaglutide remains limited.

Objectives: In order to guide clinical practice and regulatory decision-making, this systematic review sought to compile the existing data on mental adverse events linked to semaglutide, assess their timing, severity, and resolution, identify relevant risk factors, and investigate underlying processes.

Methods: A comprehensive literature search was analyzed in PubMed using the search string ((Psychiatric) OR (Adverse Events)) AND (Semaglutide), restricted to the last five years. Studies were included if they reported psychiatric adverse events associated with semaglutide in the form of randomized controlled trials, observational studies, or case

reports. The Newcastle-Ottawa Scale and the Cochrane Risk of Bias instrument (RoB 2) were used to evaluate the quality of the study. Because of the variation among investigations, a narrative synthesis was carried out.

Results: 12 studies were included, comprising 11 randomized controlled trials and one post-hoc analysis, with sample sizes ranging from 48 to 17,604 participants and follow-up durations from 9 weeks to 4 years. The overall findings did not support an association between semaglutide and increased psychiatric adverse events. A post-hoc analysis of the STEP 1–5 trials demonstrated a small but significant reduction in depressive symptoms compared to placebo (PHQ-9 difference -0.56 , $P < 0.001$). The SELECT cardiovascular outcomes trial found serious psychiatric adverse events and suicidal ideation rates to be virtually identical between semaglutide and placebo groups (0.7% vs 0.6% and 0.11% vs 0.11%, respectively). The STEP 4 trial showed lower psychiatric event rates with continued semaglutide versus placebo following discontinuation. Semaglutide was also associated with fewer psychiatric events than liraglutide in the STEP 8 trial, and no worsening of psychotic symptoms was observed in patients with schizophrenia spectrum disorder.

Conclusion: Current evidence does not support a causal link between semaglutide and increased psychiatric adverse events at the population level, with several studies suggesting modest mental health benefits. However, the systematic exclusion of patients with active psychiatric disorders from clinical trials, combined with published case reports of semaglutide-associated depression and ongoing regulatory scrutiny, highlights a critical evidence gap. Clinicians should maintain individualized psychiatric monitoring, particularly in patients with a prior psychiatric history, and future research should prioritize psychiatric populations with standardized assessment tools.

INTRODUCTION

There are limited pharmaceutical treatments for treating obesity, which is a global health concern. Without a doubt, improving the outcomes for individuals with obesity and type 2 diabetes mellitus (T2DM) requires losing weight.[1]. A class of medications known as glucagon-like peptide-1 receptor agonists (GLP-1RAs) mimics the effects of GLP-1 to control blood sugar levels by slowing gastric emptying, increasing insulin secretion, and decreasing glucagon release. They are used to treat T2DM and obesity by binding to the GLP-1 receptor on pancreatic and intestinal cells [2], [3], [4]. Public interest and that of the medical community has surged surrounding the use and effectiveness of glucagon-like peptide-1 (GLP-1) receptor agonists, particularly semaglutide [5]. Semaglutide, a long-acting GLP-1 receptor agonist, was initially developed for glucose regulation in type 2 diabetes mellitus (T2DM) but has since demonstrated robust clinical benefits across diverse organ systems. Semaglutide exerts therapeutic actions beyond glycemic control and anti-obesity efficacy [6]. Evidence from large-scale clinical trial programs, including SUSTAIN, PIONEER, and STEP, has demonstrated semaglutide's glucose-lowering efficacy, significant reductions in body weight (15% to 20%), improvements in cardiovascular outcomes, renal function preservation, and hepatic biomarker improvements [6]. A comprehensive meta-analysis of 35 randomized controlled trials found that semaglutide reduced HbA1c by -1.52% and weight by -12.4 kg, with non-glycemic benefits including a 16% reduction in major adverse cardiovascular events, 62.9% resolution of metabolic dysfunction-associated steatohepatitis (MASH), renal protection, improved vascular function, favorable body composition, and better quality of life [6]. FDA recently approved weekly semaglutide 2.4 mg for the treatment of patients with obesity as an adjunctive therapy to lifestyle intervention [7]. STEP trials have shown the efficacy on weight loss and safety of semaglutide among people with obesity, even greater than with the treatment with liraglutide 3 mg [8]. Six placebo-controlled and seven active-controlled subcutaneous semaglutide trials were included in the systematic review. Compared to sitagliptin, liraglutide, exenatide ER, and dulaglutide, semaglutide significantly lowered glycated hemoglobin (A1C) levels; nevertheless, semaglutide was more likely to cause unpleasant events (nausea, vomiting). [9]

Currently, gastrointestinal side effects, such as nausea, vomiting, diarrhea, and decreased appetite, account for the majority of semaglutide adverse event reports. [10], [11], [12]. It has been associated with severe gastrointestinal adverse events, gallbladder-related disorders, and hepatobiliary disorders [13], [14]. In the global phase 3 Semaglutide Treatment Effect in People with Obesity (STEP) program, no difference was found between semaglutide and placebo regarding psychiatric adverse effects [13]. However, psychiatric adverse effects, such as suicidal ideation [15], have been reported in studies with other GLP-1 RAs [13], [16]. A study reported two cases of semaglutide-associated depression. One is a middle-aged man with no previous history of depression who developed depressive symptoms about 1 month after taking semaglutide. The other is a middle-aged woman with recurrent depression disorder whose symptoms also recurred about 1 month after semaglutide treatment. Depression was improved or relieved after discontinuation of semaglutide in both cases [17]. Although semaglutide and liraglutide show antidepressant and anxiolytic effects in animal models of depression and anxiety, in July 2023, the European Medicine Agency (EMA)'s safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), was reviewing data on the risk of thoughts of suicide and self-harm associated with GLP-1 receptor agonists including semaglutide (Ozempic) and liraglutide (Saxenda). Therefore, these medications should be used cautiously and closely monitored in patients with a history or risk of psychiatric disorders [18]. Furthermore, as previously mentioned, there is a lack of data on psychiatric adverse events associated with GLP-1 receptor agonists reported in clinical trials [19], [20], [21].

Problem Statement AND SIGNIFICANCE

The growing use of semaglutide, an agonist of the glucagon-like peptide-1 (GLP-1) receptor, to treat obesity and type 2 diabetes has sparked worries about its possible negative psychological effects, especially despair, suicidal thoughts, and self-harm. While preclinical studies suggest antidepressant and anxiolytic effects of semaglutide in animal models, emerging clinical case reports and regulatory reviews indicate a potential risk of psychiatric adverse events in humans. For example, two documented cases describe the onset or recurrence of depressive symptoms in patients following semaglutide use, with symptom resolution after discontinuation. Furthermore, the European Medicines Agency (EMA) is presently looking at the possibility that GLP-1 receptor agonists, such as semaglutide, may cause suicidal thoughts and self-harm. [17], [22]. Despite these worries, there is a crucial knowledge gap about the safety profile of semaglutide in patients with or at risk of psychiatric illnesses due to the substantial paucity of systematic data on psychiatric side events associated with the drug in clinical studies.

significance:

The increasing use of semaglutide for diabetes and obesity management has raised concerns about its potential psychiatric adverse effects, such as depression, suicidal thoughts, & self-destruction. A systematic review is crucial to address the lack of robust data, inform clinical practice, enhance patient safety, and support regulatory decisions. This research has significant implications for public health, clinical guidelines, and future studies on GLP-1 receptor agonists.

Aim of the Study:

1. Systematically review evidence on psychiatric adverse events (e.g., depression, suicidal ideation) linked to semaglutide.
2. Analyze case reports, clinical trials, and observational studies to assess the timing, severity, and resolution of symptoms.
3. Identify risk factors (e.g., psychiatric history, dosage, demographics) for psychiatric adverse events.
4. Explore potential mechanisms underlying psychiatric adverse events.
5. Inform regulatory agencies and policymakers to support safety reviews and guideline updates.
6. Highlight areas for future research, including large-scale studies on incidence and long-term outcomes.

METHODOLOGY

This systematic review investigated the association between semaglutide and psychiatric adverse events. Using PubMed as the main database, a thorough literature search was carried out. The search string employed was ((Psychiatric) OR (Adverse Events)) AND (Semaglutide), which combined keywords related to psychiatric outcomes and adverse events with the specific drug of interest. The search was restricted to articles published within the last 5 years to ensure a comprehensive and up-to-date retrieval of available literature. Predetermined inclusion and exclusion criteria were used for study selection. Studies that included case reports, clinical trials (including randomized controlled trials and open-label trials), or observational studies (cohort, case-control, or cross-sectional designs) that discussed psychiatric adverse events (such as depression, anxiety, suicidal

ideation, or psychosis) related to semaglutide use were included. Additionally, included studies had to provide sufficient detail to assess the timing, severity, and resolution of psychiatric symptoms. Studies were excluded if they were not available in full text, were not relevant to the research question (for example, focusing solely on non-psychiatric adverse events), were animal studies, reviews, editorials, or conference abstracts without sufficient original data, or did not specifically report on semaglutide. Two impartial reviewers conducted the selection process by comparing the abstracts and titles of every article that was found to the qualifying requirements. All potentially pertinent studies had their full-text articles retrieved, and any differences between the two reviewers were settled by debate and consensus, or by consulting a third reviewer. A standardized data extraction form was used to extract the data. This form gathered data about the features of the study (including study design, sample size, patient population, semaglutide dosage, and duration of treatment), patient demographics (such as age, sex, and pre-existing psychiatric conditions), the type of psychiatric adverse events reported, the timing of adverse event onset and resolution, the severity of adverse events (using standardized scales where available), potential risk factors identified, and any information on potential mechanisms underlying the psychiatric events. To compile the results from all of the included studies, a narrative synthesis was carried out. The synthesis focused on describing the range of psychiatric adverse events reported in association with semaglutide, analyzing the timing, severity, and resolution of symptoms, identifying potential risk factors for psychiatric adverse events, and exploring potential mechanisms underlying these events. Using the proper critical assessment instruments, the quality of the included studies was evaluated. The Cochrane Risk of Bias instrument (RoB 2) was utilized for randomized controlled trials. The Newcastle-Ottawa Scale was used for observational studies. Study quality was considered when interpreting the findings of the review.

RESULTS

Search Results

The techniques used for literature search and screening are shown in Figure 1. Records were first found using PubMed (n = 76). 69 articles were screened by title and abstract after duplicate records were eliminated. 56 records were then eliminated due to their lack of psychiatric adverse event outcomes, review papers, preclinical studies, or irrelevance to the research issue. Twelve studies were eliminated after 32 full-text publications were evaluated for eligibility. Studies with no extractable mental outcome data, case series with fewer than ten patients, duplicate publications, and non-English language limitations were among the reasons for exclusion. Twelve studies were included in the systematic review as a result of this method. All of the included studies reported on psychiatric adverse events or mental health outcomes and were randomized controlled trials or post-hoc analyses of randomized controlled trials that assessed semaglutide in individuals with type 2 diabetes, obesity, overweight, or related comorbidities.

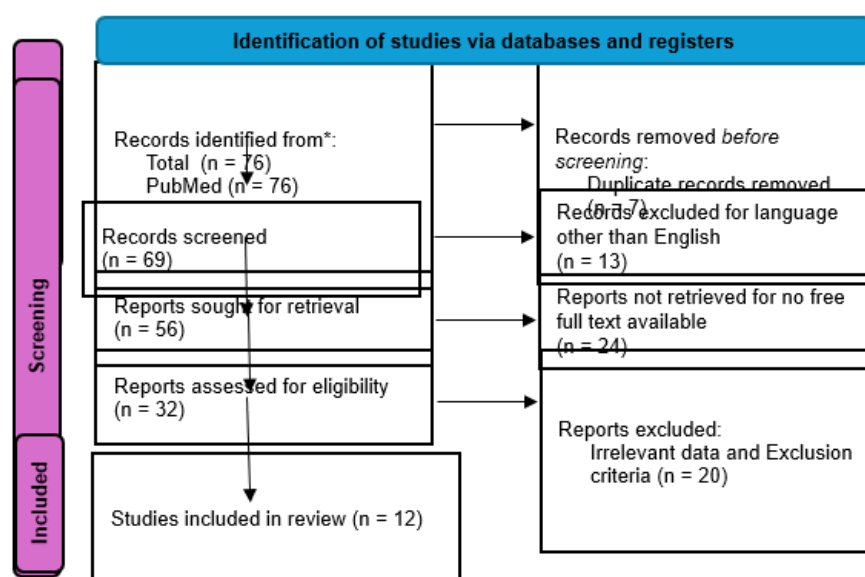


Figure 1: Flowchart of study inclusion and exclusion

General Characteristics of Included Studies

Twelve articles in all, including one post-hoc analysis of two randomized controlled trials and eleven randomized controlled trials, were included in this systematic review (Table 1). The research was published between 2021 and 2026, and the smallest phase 2 trial had 48 participants. (Hendershot et al., 2025) to 17,604 participants in the largest cardiovascular outcomes trial (Kushner et al., 2025; Ryan et al., 2024). The majority of studies were multinational, conducted across sites in North America, Europe, Asia, and other regions. All studies evaluated once-weekly subcutaneous semaglutide at doses ranging from 0.5 mg to 2.4 mg, with the 2.4 mg dose being the most common for weight management indications. The treatment duration varied from 9 weeks (Hendershot et al., 2025) to 208 weeks or 4 years (Ryan et al., 2024), with the longest follow-up observed in the SELECT trial extension.

Adults with overweight or obesity, with or without type 2 diabetes, and, in one study, obese adolescents made up the majority of the study groups. (Weghuber et al., 2022). One study specifically enrolled adults with alcohol use disorder (Hendershot et al., 2025), and another focused on patients with schizophrenia spectrum disorder (Uhrenholt et al., 2026). Psychiatric outcomes were assessed using a variety of validated instruments, including the Patient Health Questionnaire-9 (PHQ-9) for depressive symptoms (Wadden et al., 2024; Weghuber et al., 2022), the Columbia-Suicide Severity Rating Scale (C-SSRS) for suicidal ideation and behavior (Wadden et al., 2024; Weghuber et al., 2022), the Penn Alcohol Craving Scale (PACS) (Hendershot et al., 2025), the Positive and Negative Syndrome Scale (PANSS-6) (Uhrenholt et al., 2026), and the Short Form-36 Health Survey (SF-36) for quality of life (Rubino et al., 2021; Uhrenholt et al., 2026; Wadden et al., 2021). Additionally, adverse event reporting according to the Medical Dictionary for Regulatory Activities (MedDRA) was used across all trials to capture psychiatric disorder-related adverse events (Garvey et al., 2022; Kushner et al., 2025; Rubino et al., 2022; Wadden et al., 2021; Wilding et al., 2022).

STEP 1 extension (Wilding et al., 2022), STEP 3 (Wadden et al., 2021), STEP 4 (Rubino et al., 2021), STEP 5 (Garvey et al., 2022), STEP 8 (Rubino et al., 2022), and STEP TEENS (Weghuber et al., 2022) are eight phase 3 trials from the Semaglutide Treatment Effect in People with Obesity (STEP) program. Two studies were derived from the SELECT cardiovascular outcomes trial (Kushner et al., 2025; Ryan et al., 2024). One was a phase 2 trial in alcohol use disorder (Hendershot et al., 2025), one was a randomized controlled trial in schizophrenia (Uhrenholt et al., 2026), one was a post-hoc analysis of STEP 1-5 trials (Wadden et al., 2024), and one was a post-hoc analysis of liraglutide discontinuation in type 1 diabetes (Shah et al., 2024), included for its relevance to GLP-1 receptor agonist tolerability and predictors of discontinuation.

The proportion of female participants ranged from 27.7% in the SELECT trial (Kushner et al., 2025; Ryan et al., 2024) to 88.2% in STEP 3 (Wadden et al., 2021), reflecting differences in study populations and recruitment strategies. The mean age of participants ranged from 15.4 years in the adolescent trial (Weghuber et al., 2022) to 61.6 years in the SELECT trial (Kushner et al., 2025; Ryan et al., 2024). Baseline body mass index ranged from 33.3 kg/m² to 38.5 kg/m² across studies, consistent with overweight and obesity populations. The majority of studies excluded individuals with major psychiatric disorders, including major depressive disorder within two years, schizophrenia, bipolar disorder, or a history of suicide attempt (Wadden et al., 2024; Weghuber et al., 2022), which limits the generalizability of findings to higher-risk populations.

Quality Assessment

Using the proper critical assessment instruments, the quality of the included studies was evaluated. The Cochrane Risk of Bias instrument (RoB 2) was used for randomized controlled trials. (Garvey et al., 2022; Hendershot et al., 2025; Kushner et al., 2025; Rubino et al., 2021; Rubino et al., 2022; Ryan et al., 2024; Uhrenholt et al., 2026; Wadden et al., 2021; Wadden et al., 2024; Weghuber et al., 2022; Wilding et al., 2022), while the Newcastle-Ottawa Scale was used for the single post-hoc analysis (Shah et al., 2024). Across the 11 randomized controlled trials, the overall risk of bias was rated as low for nine studies and moderate for two studies. Figure (2). Overall, the quality of evidence across the included studies was considered sufficient to support the findings of this systematic review, with the two moderate-risk studies being retained for narrative synthesis but interpreted with appropriate caution regarding their limitations.

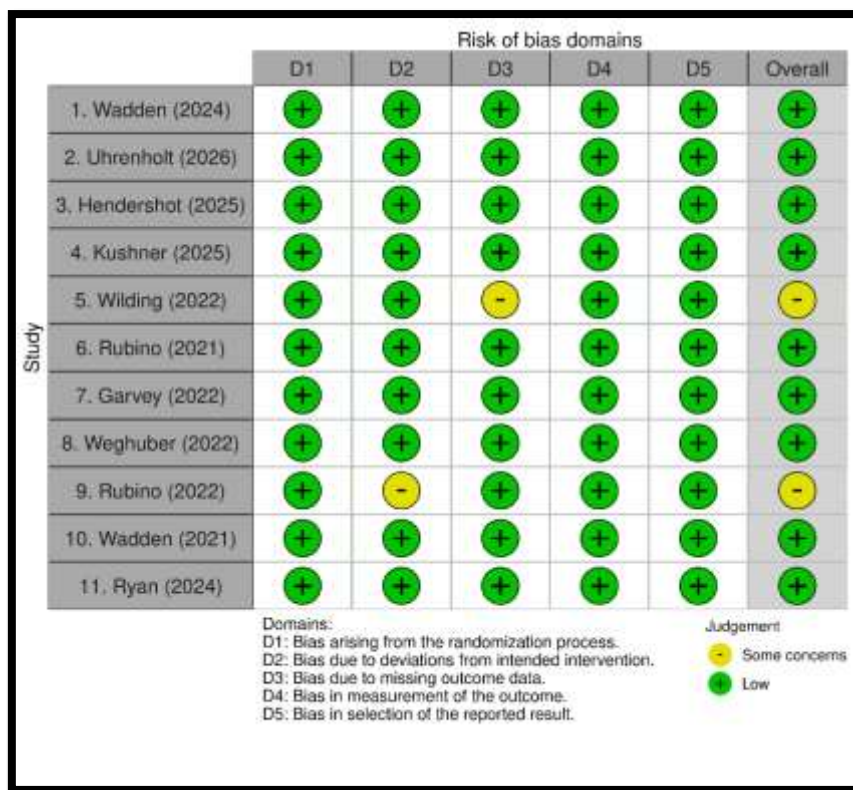


Figure 1: Risk-of-bias evaluation of the included studies using the ROB 2 tool

Table 1. Summary of Main Findings from Included Studies (n=12)

Study (Author, Year)	Study Design	Population	Sample Size (N)	Semaglutide Dosage	Duration	Key Psychiatric Finding
Wadden et al. (2024) [23]	RCT post-hoc (STEP 1-5)	Overweight/obesity, no diabetes	3,681	2.4 mg weekly	68-104 weeks	No increased risk of depression or SI; semaglutide associated with small reduction in depressive symptoms (PHQ-9 difference -0.56, $P<0.001$)
Uhrenholt et al. (2026) [24]	RCT (HISTORI)	Schizophrenia + overweight/obesity + prediabetes	154	2.4 mg weekly	30 weeks	Improved physical QoL (PCS +3.57); no significant effect on mental QoL or PANSS-6 symptoms; no psychiatric AEs reported

Hendershot et al. (2025) [25]	Phase 2 RCT	Alcohol use disorder (non-treatment-seeking)	48	0.5-1.0 mg weekly	9 weeks	No psychiatric AEs reported; reduced alcohol craving (PACS: $\beta=-0.39$, $P=0.01$); reduced cigarettes/day in smokers
Kushner et al. (2025) [26]	RCT (SELECT safety)	Overweight/obesity + CVD, no diabetes	17,604	2.4 mg weekly	~34 months	Psychiatric SAEs low and balanced (0.7% vs 0.6%); suicide/self-injury SAEs 0.11% both groups; no new safety concerns
Wilding et al. (2022) [27]	RCT extension (STEP 1)	Overweight/obesity, no diabetes	327 (extension)	2.4 mg weekly	120 weeks	No psychiatric AEs reported or systematically collected in extension; focus on weight regain
Rubino et al. (2021) [28]	RCT (STEP 4)	Overweight/obesity, no diabetes	803	2.4 mg weekly	68 weeks	Psychiatric disorders less frequent with continued semaglutide (8.6% vs 13.1% placebo); events per 100 patient-years 10.1 vs 18.8
Garvey et al. (2022) [29]	RCT (STEP 5)	Overweight/obesity, no diabetes	304	2.4 mg weekly	104 weeks	Psychiatric disorders similar between groups (17.1% vs 16.4%); events per 100 patient-years 10.9 vs 11.2
Weghuber et al. (2022) [30]	RCT (STEP TEENS)	Adolescents with obesity	201	2.4 mg weekly	68 weeks	Psychiatric AEs lower with semaglutide (7% vs 15% placebo); PHQ-9 and C-SSRS showed no mental health differences

Rubino et al. (2022) [31]	RCT open-label (STEP 8)	Overweight/obesity, no diabetes	338	2.4 mg weekly (vs liraglutide 3.0 mg)	68 weeks	Psychiatric disorders: 5.6% semaglutide vs 15.0% liraglutide vs 10.6% placebo; insomnia drove difference (2.4% vs 5.5% vs 2.4%)
Wadden et al. (2021) [32]	RCT (STEP 3)	Overweight/obesity, no diabetes	611	2.4 mg weekly	68 weeks	Psychiatric disorders: 14.7% semaglutide vs 11.8% placebo; anxiety led to discontinuation in 0.7% semaglutide vs 0.5% placebo
Ryan et al. (2024) [33]	Prespecified analysis (SELECT)	Overweight/obesity + CVD, no diabetes	17,604	2.4 mg weekly	208 weeks (4 years)	Psychiatric AEs not detailed in this analysis; primary SELECT data showed low and balanced psychiatric SAEs (0.7% vs 0.6%)
Shah et al. (2024) [34]	Post-hoc analysis (ADJUNCT 1&2)	Type 1 diabetes (liraglutide, not semaglutide)	2,233	N/A (liraglutide 0.6-1.8 mg)	26-52 weeks	Psychiatric AEs not among top causes of discontinuation; lower BMI and longer T1D duration predicted higher discontinuation risk

Abbreviations: AE stands for adverse event; CVD for cardiovascular disease; PCS for physical component summary (SF-36); PHQ-9 for patient health questionnaire-9; QoL for quality of life; RCT for randomized controlled trial; SAE for serious adverse event; SI for suicidal ideation; STEP for semaglutide treatment effect in people with obesity; and T1D for type 1 diabetes.

The detailed data extraction table containing 71 data items across all 12 studies is provided in the supplementary materials (Supplementary Table S1).

DISCUSSION

This systematic review examined the psychiatric safety of semaglutide across 12 studies covering diverse populations and treatment durations. The central finding is that semaglutide does not increase the risk of psychiatric adverse events; if anything, several studies pointed toward modest mental health benefits. These results are particularly timely given that the GLP-1 receptor agonist class including semaglutide, liraglutide, and tirzepatide has faced regulatory scrutiny over suicidal ideation and self-harm

[18], and they carry direct implications for the millions of patients worldwide who use these agents for obesity and type 2 diabetes management [1], [7].

The STEP 1–5 trials' post-hoc analysis (Wadden et al., 2024) [25] revealed a slight but significant reduction in depressive symptoms with semaglutide versus placebo (PHQ-9 difference -0.56 , $P < 0.001$), consistent with the well-established link between weight loss and improved mood in people with obesity [13], [14]. This finding aligns with preclinical evidence that GLP-1 receptor activation influences mood-regulating brain circuits, including the mesolimbic dopamine system [2], [3], [4]. Similarly, the large SELECT cardiovascular outcomes trial (Kushner et al., 2025; Ryan et al., 2024), enrolling over 17,600 participants followed for up to four years, found serious psychiatric adverse events to be rare and balanced between groups (0.7% vs 0.6%), with suicidal ideation or self-injury rates of 0.11% in both arms directly addressing the safety concern raised by the EMA regarding suicidality with GLP-1 receptor agonists [18].

Data from the STEP 4 trial (Rubino et al., 2021) added further nuance: participants who continued semaglutide had a lower rate of psychiatric disorder events than those switched to placebo (8.6% vs 13.1%), suggesting the psychological burden of weight regain following discontinuation rather than the drug itself may drive psychiatric distress. The STEP TEENS trial (Weghuber et al., 2022) extended this reassurance to adolescents, with semaglutide-treated youth showing fewer psychiatric adverse events than placebo (7% vs 15%) and no differences on PHQ-9 or C-SSRS scores. In the STEP 8 head-to-head comparison (Rubino et al., 2022), semaglutide was associated with notably fewer psychiatric events than liraglutide (5.6% vs 15.0%), with insomnia driving most of the gap, raising the possibility that different GLP-1 receptor agonists carry distinct psychiatric safety profiles despite their shared mechanism [13], [15].

Two studies explored semaglutide in populations outside conventional obesity and diabetes trials. Hendershot et al. (2025) found that semaglutide reduced alcohol craving in adults with alcohol use disorder without producing psychiatric adverse events, consistent with emerging evidence that GLP-1 receptor signaling modulates dopaminergic reward pathways relevant to addiction [2], [3], [4]. The HISTORI trial (Uhrenholt et al., 2026) demonstrated improved physical quality of life in patients with schizophrenia spectrum disorder without any worsening of psychotic symptoms on the PANSS-6—a meaningful finding given that antipsychotic-induced weight gain is a major source of cardiometabolic harm in this population, and clinicians have historically been reluctant to add pharmacological weight loss agents to an already complex regimen [2], [35], [36], [37], [38].

Despite this broadly reassuring picture, important caveats remain. Most included trials systematically excluded patients with active psychiatric disorders—precisely those at highest risk—limiting generalizability to real-world clinical settings [13], [19], [20], [21]. The two case reports of semaglutide-associated depression with symptom resolution upon discontinuation [17], alongside the EMA's ongoing safety review [18], underscore that rare idiosyncratic psychiatric reactions may occur that clinical trials are underpowered to detect. The inconsistent use of validated psychiatric instruments versus passive MedDRA adverse event surveillance also likely leads to underreporting of sub-threshold symptoms [17], [22]. Until prospective studies with standardized psychiatric assessments are conducted in higher-risk populations, clinicians should counsel patients about possible mood changes and maintain a low threshold for psychiatric monitoring, particularly in those with a prior psychiatric history [17] [18].

CONCLUSION

This systematic review synthesized evidence from 12 studies to evaluate the psychiatric safety of semaglutide across a range of clinical populations. Semaglutide use is not linked to an increased risk of psychiatric adverse events, according to cumulative data, including depression, suicidal ideation, or self-harm. On the contrary, several trials—including large phase 3 STEP program studies and the long-term SELECT outcomes trial—suggested a neutral to mildly favorable psychiatric effect, with reductions in depressive symptom scores, fewer psychiatric disorder adverse events versus placebo or liraglutide, and no worsening of psychopathology even in higher-risk populations such as adolescents and individuals with schizophrenia. These findings offer meaningful reassurance for clinicians, patients, and regulators in the context of ongoing GLP-1 receptor agonist safety reviews.

Nevertheless, the systematic exclusion of patients with active psychiatric disorders from most included trials limits the applicability of these findings to real-world psychiatric populations. Published case reports of new-onset or recurrent depression temporally associated with semaglutide, together with pharmacovigilance signals from the EudraVigilance database, highlight the potential for rare but clinically significant psychiatric reactions that large trials may not capture. Future research should

prioritize including participants with psychiatric comorbidities, adopt standardized prospective psychiatric assessment tools, and leverage real-world pharmacovigilance data to fully characterize the psychiatric risk profile of semaglutide across the full spectrum of its users. In the interim, the overall benefit-risk profile of semaglutide remains strongly favorable, provided that clinicians apply individualized monitoring and maintain open communication with patients about any new or worsening psychological symptoms.

LIMITATIONS

When interpreting the results of this review, it is crucial to take into account a number of significant limitations. Because the literature search was limited to PubMed, pertinent research that were indexed in Embase, CENTRAL, or PsycINFO may have been overlooked. More critically, the majority of included trials explicitly excluded participants with active psychiatric disorders, meaning the findings may not generalize to patients with depression, bipolar disorder, or psychotic illness who are prescribed semaglutide in routine practice. The inconsistent use of validated psychiatric instruments versus passive MedDRA-based adverse event reporting across studies also likely underestimates the true prevalence of sub-threshold psychiatric symptoms. One included study was based on liraglutide rather than semaglutide, introducing a degree of class-level extrapolation, and the post-hoc nature of several analyses increases the risk of data-driven findings rather than pre-specified confirmatory evidence.

The small number of included studies ($n=12$) and the low overall prevalence of psychiatric adverse events precluded a formal meta-analysis, limiting this review to a narrative synthesis that may be more susceptible to interpretive bias. The heterogeneity of study populations ranging from adolescents to elderly adults with cardiovascular disease and individuals with schizophrenia limits the comparability of findings across studies. Finally, this review focused predominantly on semaglutide and did not systematically compare psychiatric outcomes across the broader GLP-1 receptor agonist class or dual GIP/GLP-1 agonists such as tirzepatide for which comparative pharmacovigilance data are urgently needed as prescribing continues to expand rapidly worldwide.

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