

REVIEW ARTICLE



Behavior, Psychology and Sociology

Mental health outcomes in obesity interventions with GLP-1 receptor agonists: is it similar to other obesity interventions? A narrative review with systematic evidence synthesis

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Obesity is a chronic, debilitating condition with complex biological, psychosocial, and behavioral underpinnings. While the cardiometabolic consequences are reasonably well-established, the often-forgotten bidirectional association between obesity and mental health disorders, including anxiety, eating disorders, depression, and even suicidal ideations, is rarely assessed as a primary endpoint in obesity intervention studies. Similarly, documents summarizing and comparing various types of obesity interventions and their effects of mental health in this rapidly evolving field are scarce. This narrative review synthesizes the evidence on the psychological impact of lifestyle, pharmacological, and surgical interventions in the treatment of obesity. Special focus is placed on glucagon-like peptide-1 (GLP-1) receptor agonists, given their rising global use and emerging concerns regarding mental health safety. A thorough literature review was conducted across the MEDLINE, Embase, and Cochrane databases, focusing on meta-analyses, systematic reviews, and clinical trials published up to June 2025. Studies examining psychological outcomes in patients undergoing lifestyle modifications, pharmacotherapy, or bariatric surgery for weight loss were included. Mental health domains considered included quality of life, anxiety, depression, and suicidality. Due to the vast array of obesity interventions and the broad nature of mental health in the literature, this review was conducted to provide a narrative summary. Behavioral interventions consistently showed no harm to mental health and demonstrated modest improvements in depression and mental health-related quality of life. Bariatric surgery was associated with short-to-medium-term reductions in depressive and anxiety symptoms, though long-term benefits were attenuated, with some studies reporting increased suicidality after five years. Pharmacotherapies, including orlistat, bupropion/naltrexone, and phentermine/topiramate, showed mixed psychiatric impacts. The GLP-1 receptor agonists (Semaglutide, liraglutide, Tirzepatide) have shown an improvement in patient-reported mental wellbeing in several trials. Concerningly, pharmacovigilance data initially suggested a possible link with suicidality; however, subsequent robust cohort studies and meta-analyses have refuted this association. Mental health is a critical yet underprioritized element of obesity management. The current evidence suggests that most weight loss interventions are psychologically safe or beneficial, but long-term data remain limited, particularly for GLP-1 receptor agonists. Future randomized trials must incorporate mental health as a prespecified outcome, and individualized treatment approaches should integrate psychological support to optimize long-term outcomes. This review has summarized, side-by-side, the various outcomes of obesity interventions on mental health.

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INTRODUCTION

Two out of every five adults globally are considered overweight or obese [1]. Obesity accounts for 5 million annual deaths globally, with projected economic costs reaching 3.29% of global GDP by 2060 [2, 3]. The health complications of obesity extend beyond cardiometabolic risks to include poor mental health and psychiatric disorders [4, 5]. Higher rates of anxiety and depression are present in people with obesity (10–40% higher risk in comparison to normal body mass index) [6]. This relationship is complex and bidirectional, with shared neurobiological pathways

(e.g., hypothalamic-pituitary-adrenal axis dysregulation, chronic inflammation) underpinning the obesity-depression link [4, 5]. Longitudinal studies demonstrate that obesity predicts depression and vice versa [7]. These adverse mental health effects significantly impact treatment satisfaction [8].

Guidelines on obesity management recommend behavioral interventions, including psychological counseling, as part of a comprehensive management approach [9]. Management approaches are typically categorized into behavioral, pharmacological, and possibly surgical. Given the complex relationship

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between obesity and mental health, the psychological effects of obesity interventions deserve attention. Interest in this topic has intensified with recent controversial evidence regarding the potential psychological risks of GLP-1 receptor agonists, including reports of self-harm and suicide [10–12].

While extensive evidence exists on the physical health effects of obesity interventions, mental health is usually examined only as a secondary outcome. Moreover, given the rapidly evolving field of new interventions, it is important to be able to understand the mental health implications comparatively. This narrative review examines the published evidence on both positive and negative psychological outcomes across obesity intervention tools, with a special focus on GLP-1 receptor agonists. It is noteworthy for being the most up-to-date review that includes recent advancements and familiarizes the clinician with important mental health implications of choosing different obesity interventions.

METHODS

A comprehensive literature search was conducted across MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials through June 2025. The search strategy combined terms: (“obesity” OR “overweight” OR “adiposity”) AND (“mental health” OR “mental wellbeing” OR “depression” OR “suicidality”) AND (“intervention” OR “lifestyle changes” OR “behavioral interventions” OR “bariatric surgery” OR “weight loss surgery” OR “surgery” OR “pharmacotherapy” OR “GLP-1” OR “weight loss medications”). Inclusion criteria encompassed peer-reviewed systematic reviews/meta-analyses, randomized controlled trials, and cohort studies in adult participants (body mass index [BMI] ≥ 25 kg/m²) assessing predefined mental health outcomes. Duplicates were excluded, and systematic reviews that had the majority of studies examined overlap were excluded. Studies that specifically examined the effect of weight loss interventions on mental health, including depression and suicidality, were included regardless of whether they had pre-existing mental health problems. Due to the large variety of obesity interventions and broad spectrum of challenges and diagnoses inherent in the term ‘mental health,’ this review was done in narrative form intended as a summary of the topic as it would not be feasible to cover the entirety of evidence examining all obesity interventions and all mental health outcomes in a systematic review.

Obesity and mental health: before obesity interventions

Most of the available evidence examining the direct association between obesity and mental health comes from North America, Australia, and Europe [13]. Regarding depression, it is debatable whether the association is due to correlation or causation due to many possible confounding factors such as economic, social, and psychological characteristics [14]. Several studies have evaluated unconfounded links by Mendelian randomization and demonstrated that higher BMI (body mass index) causes depression [15–17]. However, not all studies attempting to exclude confounding variables came to the same conclusion [18–20], which may be due to differences in methodology. That being said, there is widespread recognition that individuals with mental health challenges tend to have higher rates of obesity. Moreover, obesity may lead to the progression or exacerbation of significant psychiatric illnesses. For example, obesity may lead to more frequent mood-related episodes and readmissions in patients with bipolar disorder [21–23]. This situation is complicated further by the fact that psychoactive medications are known to have weight gain as a side effect [24].

Lifestyle weight loss interventions and mental health

Lifestyle weight loss interventions may involve changes in eating habits, exercise, and behavioral therapy. They can be undertaken independently, using various informational resources such as

mobile applications, or with the support of a professional. In essence, these interventions do not rely on pharmacological or surgical treatments. We have reviewed two systematic studies on the impact of lifestyle changes on mental health in outpatient settings, as detailed in the table below. Overall, there is a significant lack of research that records mental health outcomes as a primary focus in the general population following behavioral interventions (Table 1).

Jones et al. examined randomized controlled trials with behavioral weight loss interventions on the mental health outcomes of people with overweight or obesity at the end of the intervention and 1 year after baseline. The mental health outcomes analyzed included mood, anxiety, binge eating, body image, depression, emotional eating, quality of life, self-esteem, and stress, as they were considered the most frequently reported, relevant, and representative. No differences were found in anxiety, binge eating, emotional eating, negative affect, or overall quality of life immediately after the intervention. However, body image concerns and mental health-related quality of life showed favorable changes at that point. Meta-analysis of intervention effects measured 12 months after baseline revealed positive effects on depression, mental health-related quality of life, life satisfaction, and general and exercise self-efficacy, with no significant change in global quality of life. Overall, there was no evidence indicating a negative impact of the intervention. The review was mainly limited by the heterogeneity among studies and the inclusion of many studies at high risk of bias; however, the analysis accounted for these variations by conducting assessments both with and without those studies.

Studies that reviewed the effects of interventions to improve diet, weight, and physical activity in people with mental health conditions were systematically analyzed by Bradley et al. Most of these studies focused on individuals with serious mental illnesses. Fourteen of the studies were included in a meta-analysis that assessed outcomes such as depression, anxiety, and the severity of psychological symptoms, but no evidence of a significant effect was found. However, the narrative synthesis of several studies mostly supported positive outcomes for mental health.

Overall, the two studies consistently demonstrated no harm from behavioral weight loss interventions; however, their findings were mixed regarding potential mental health benefits.

Bariatric surgery and mental health

There is a broader range of evidence on the mental health outcomes of patients undergoing weight loss surgery. Bariatric surgery can be categorized into restrictive, malabsorptive, and combined approaches. Restrictive procedures include gastric banding and sleeve gastrectomy. Malabsorptive procedures include jejunioileal bypass. Combined procedures include Roux-en-Y gastric bypass and biliopancreatic diversion.

Due to the need for radical dietary changes, small portion sizes, and slower eating, bariatric surgery has the potential to trigger mental illness; this can be a risk factor, in addition to physical changes such as excess skin and the potential for surgical complications such as dumping syndrome and nutrient deficiencies [25]. Restrictive procedures have been noted to result in fewer micronutrient deficiencies than malabsorptive and combined procedures [26]. This can result in a different side effect and complication profile, both physically and psychologically.

Overall, most of the studies reviewed in this section support the positive impact of bariatric surgery on mental health. Those results are considered to be due to the direct effects of weight loss, such as improved self-esteem; however, it’s also important to note that during the postoperative period, patients receive substantial support in terms of follow-up [27]. Loh et al. found that, postoperatively, both depression and anxiety symptoms decrease significantly, and the effects are more prominent the lower the BMI [28]. Moreover, the severity of reported symptoms also

Table 1. Mental health outcomes of lifestyle weight loss interventions.

Author & year	Population	Intervention type	Study design	Key mental health outcomes	Major findings	Limitations
Jones et al., 2021 [62]	Adults with overweight/obesity (BMI \geq 25 kg/m ²)	Behavioral weight management (diet, exercise, counseling)	Systematic review and meta-analysis	Depression, anxiety, binge-eating, QoL, self-esteem	Improved depression and mental health-related QoL at 1 year (SMD: -0.32; 95% CI: -0.41 to -0.23). No effect on anxiety or global QoL.	High heterogeneity; 40% of studies at high risk of bias.
Bradley et al., 2022 [63]	Adults with mental health conditions (e.g., bipolar disorder, schizophrenia)	Lifestyle interventions (diet/physical activity)	Systematic review and meta-analysis.	Depression, anxiety, psychological symptom severity	No significant effect on depression/anxiety in meta-analysis (pooled RR: 0.98; 95% CI: 0.91–1.06). Narrative synthesis showed mixed mental health outcomes.	Mental health secondary outcome; limited data on severe mental illness.

This table presents the mental health outcomes of lifestyle weight loss interventions, including diet, exercise, and counseling, in adults with overweight or obesity. It summarizes study characteristics, measured outcomes such as depression and quality of life, and key results with effect sizes and confidence intervals. BMI body mass index, QoL quality of life, SMD standardized mean difference, CI confidence interval, RR risk ratio.

decreased. Those effects were sustained for at least 3 years. A decrease in the level of depression is also reported in studies up to 2 and 4 years, although some other sources report a subsequent downturn, which is often correlated to weight regain [27]. Budin et al. observed that the reduction in depressive symptoms peaks at five to twelve months post-surgery [29]. They did not observe any variance based on the type of surgery. The degree of long-term improvement in mental health was less than that in physical health, as assessed by Driscoll et al. [30] in the health-related quality of life assessment. In summary, there has been a sustained positive effect on mental health for up to a few years, with a reported decline afterward.

On the other hand, there are concerning reports of increased risk of suicide, self-harm, and substance abuse [31]. Szmulewicz et al. analyzed the mental health quality of life outcomes from prospective data in randomized controlled trials and found no difference in mental health quality of life compared to non-surgical management [31]. Those findings may not be reflective of general adverse outcomes, as the studies were underpowered to evaluate for suicidality and depression. Raza et al. observed that although rates of depression were lower postoperatively, suicidal ideation initially decreased at 1 year postoperatively and then rose above the preoperative risk at 5 years [32]. Jumbe et al. reported that although an initial improvement in psychosocial quality of life was noted, it was not sustained in the long term, and the effects on physical quality of life significantly outweighed and outlasted the former. The psychosocial benefits began to decrease at 6 years post-surgery [33].

Hence, it is concluded that weight loss alone is not the solution to obesity-related mental illness, and psychological support is essential. However, it is important to note that the psychosocial characteristics of patients with obesity confound the research, leading to questions regarding whether adverse outcomes are due to the surgery or the baseline characteristics that lead to the choice of surgery [31]. All the studies are summarized in Table 2.

Pharmacotherapy for weight loss

Due to the challenges of maintaining weight loss post-lifestyle interventions [34] and the costs and risks of bariatric surgery, weight loss medications have recently been the center of attention for obesity management. Anti-obesity medications are approved for people with a BMI exceeding 30 kg/m² or 27 kg/m² with weight-related comorbidities who have attempted a 6-month duration of lifestyle interventions and failed to lose 5% of their weight [35–38]

The most used FDA-approved medications for weight loss are Tirzapatide, Semaglutide, liraglutide, orlistat, naltrexone/bupropion, and phentermine/topiramate [39]. There has been considerable scientific interest in examining the efficacy, cardiovascular effects, and side effects profiles of weight loss medications. Given recent mixed reports of the mental health effects of GLP-1 agonists and the high prevalence of mental health challenges in people with obesity, it is crucial to assess and compare the effects of weight loss medications, specifically on mental health. Below is a table summarizing the main findings of studies examining the effects of those medications on mental health. The evidence on GLP-1 receptor agonists will be discussed separately in the next section.

Evidence comparing different weight-loss medications head-to-head in terms of effects on mental health is scarce. A meta-analysis by Liu et al. compiled the data from 154 randomized controlled trials to examine the impact of weight loss medications on weight reduction, cardiovascular effects, adverse events, and psychological outcomes [39]. Tirzapatide showed the most significant improvement in the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) total scores, with Semaglutide demonstrating the next best effect. Notably, all the examined medications improved the IWQOL-Lite total score. Naltrexone/bupropion and phentermine/topiramate were associated with an increased

Table 2. Mental health outcomes after bariatric surgery.

Author & year	Surgery type	Purpose	Study design	Follow-up duration	Key mental health outcomes	Major findings	Clinical implications
Kubik et al., 2013 [27]	Restrictive/malabsorptive	To determine the psychological outcomes of bariatric surgery in obese patients.	Systematic review	1–5 years	Depression, body image, QoL	Significant improvement in depression short-term (ES: -1.2 ; 95% CI: -1.5 to -0.9) and body image ($p < 0.01$).	Benefits linked to weight loss and postoperative support.
Szmulewicz et al., 2019 [31]	Various	To compare the effect of bariatric surgery on adverse mental health quality of life outcomes as compared to non-surgical treatments.	Systematic review and meta-analysis	1–5 years	Mental health QoL	No difference in mental health QoL vs. non-surgical management (MD: 0.5; 95% CI: -1.2 to 2.2).	Underpowered for suicidality/depression.
Fu et al., 2022 [64]	Various	To assess the effect of bariatric surgery on depression	Systematic review and meta-analysis	6–24 months	Depression	Improved depression post-surgery (SMD: -0.65 ; 95% CI: -0.89 to -0.41).	Short-to-medium-term benefits.
Driscoll et al., 2015 [30]	Various	To assess the long-term health-related quality of life outcomes of bariatric surgery.	Systematic review and meta-analysis	>5 years	HRQoL mental domains	Meta-analysis showed improvement in all mental health domains ($p < 0.05$).	Long-term physical benefits outweigh mental.
Raza et al., 2023 [32]	RYGB, sleeve gastrectomy	To explore long-term outcomes of bariatric surgery in relation to: cardiovascular disease, cancer, and depression.	Systematic review	1–10 years	Suicidality, depression	Suicidal ideation ↓ at 1 year (OR: 0.7; 95% CI: 0.6–0.9) but ↑ at 5 years (OR: 1.8; 95% CI: 1.3–2.5).	Long-term psychiatric monitoring essential.
Jumbe et al., 2016 [33]	Various	To assess long-term psychosocial quality of life outcomes, post-bariatric surgery compared to non-surgical weight loss treatment.	Systematic review	>2 years	Psychosocial QoL	Short-term psychosocial QoL improvement not sustained long-term (vs. physical QoL).	Psychosocial benefits decline after 6 years.
Loh et al., 2021 [28]	Various	Comparing the prevalence of depression and anxiety pre- and post-bariatric surgery.	Systematic review and meta-analysis.	≤3 years	Depression, anxiety	Significant reduction in depression/anxiety symptoms postoperatively ($p < 0.001$), greater with lower BMI.	Benefits sustained ≥3 years.
Budin et al., 2025 [29]	Various	To track patient-reported outcomes after different bariatric procedures at various points in time.	Systematic review and meta-analysis.	5–12 months (peak)	Depressive symptoms	Depressive symptoms ↓ at 5–12 months (peak), but prevalence remained higher than general population.	Some patients experience worsening/new-onset symptoms.

This table describes the effects of bariatric surgery on psychological outcomes and quality of life, organized by surgery type, follow-up duration, and population. It details changes in measures such as depression and body image and provides relevant effect sizes and odds ratios.

QoL quality of life, ES effect size, CI confidence interval, RYGB Roux-en-Y gastric bypass, HRQoL health-related quality of life, OR odds ratio, MD mean difference, p p -value.

Table 3. Mental health outcomes of weight loss pharmacotherapy (non-GLP-1).

Author & year	Medication	Study design	Purpose	Key mental health outcomes	Major findings	Safety signals
Liu et al., 2024 [39]	Tirzepatide, Semaglutide, liraglutide, orlistat, naltrexone/bupropion, phentermine/topiramate	RCT meta-analysis	To summarize recent research on weight-loss medications.	QoL (IWQOL-Lite), anxiety, depression	All agents improved IWQOL-Lite (Tirzepatide: $\Delta +12.4$ points). Naltrexone/bupropion \uparrow anxiety risk (RR: 1.42).	Phentermine/topiramate \uparrow irritability (RR: 3.31); liraglutide \uparrow sleep disorders.
Kulak-Bejda et al., 2020 [41]	Naltrexone/bupropion	Systematic review	To systematically present the safety and efficacy of naltrexone or bupropion for weight loss.	Binge-eating, depression	Reduced binge-eating in depression; decreased pain tolerance (correlates with depression).	No anxiety reported; safe overall.
Kiortsis et al., 2007 [42]	Orlistat vs. sibutramine	RCT	To assess the effects of sibutramine and orlistat on mood.	Mood (HAM-D)	Sibutramine improved HAM-D vs. orlistat ($\Delta -3.1$ vs. -1.8 ; $p = 0.02$).	Sibutramine withdrawn in 2010 for CV risk.
Grilo & White, 2014 [43]	Orlistat + behavioral intervention	RCT	To examine the outcomes of behavioral weight loss with or without orlistat with binge eating disorder subgroup analysis.	Depression, binge-eating	Modest weight loss and improved depression/binge-eating with/without orlistat.	Orlistat not superior to behavioral intervention alone.

The table displays the impact of weight loss medications (excluding GLP-1 RAs) on mental health in adults with obesity, drawing from RCTs and systematic reviews. It reports effects on quality of life, mood, binge eating, and includes safety signals and risk indicators for each drug.

RCT randomized controlled trial, QoL quality of life, IWQOL-Lite Impact of Weight on Quality of Life-Lite, RR risk ratio, HAM-D Hamilton Depression Rating Scale, CV cardiovascular.

incidence of anxiety disorders. Similarly, phentermine/topiramate was linked to a 3.31-fold increase in irritability compared to placebo. Both liraglutide and phentermine/topiramate were found to elevate the risk of sleep disorders. Notably, none of the medications were associated with an increased risk of suicidal events. High-certainty evidence indicated that topiramate and phentermine/topiramate had a detrimental effect on psychological outcomes.

The impact of naltrexone-bupropion on mental health is an interesting concept, as bupropion is an approved atypical antidepressant and has a good side effect profile [40]. Kulak-Bejda et al. reviewed the safety of naltrexone or naltrexone-bupropion and did not report any findings regarding anxiety [41]. However, it was noted to reduce binge eating. Orlistat has similarly sparse evidence regarding mental health effects, with one study in 2007 citing a decrease in a depression scale [42]. However, the control group, which was only on a low-calorie diet, also noted improvement. Additionally, there was a sibutramine group that showed greater improvements in mood than the orlistat group. Another study examined the use of behavioral weight loss with or without orlistat in a community health center and found that both groups had improvements in mental health [43].

Most of the primary research on weight loss medications, excluding the new GLP-1 receptor agonists, was conducted several years ago; updated trials are needed to appropriately compare these medications as our understanding of obesity and depression has evolved, along with the introduction of new medicines to the market. All the pharmacological intervention studies are summarized in Table 3.

GLP-1 agonists and mental health

GLP-1 hormones are naturally produced incretins by enteroendocrine L-cells in the small and large intestines as a response to glucose or fat, which results in slowing gastric emptying, reduction of appetite, and decreased caloric intake [44–46]. Understanding the psychological effects of the novel GLP-1 agonists is essential, especially considering their rising popularity and potential for lifelong use in a population that is already more at risk from mental health illnesses. While research examining the direct effect of other medications for weight loss therapy on mental health is limited, recent concerns about reported associations between GLP-1 agonists and suicidal behavior have led to the publication of extensive evidence on the novel drugs' mental health safety profile [47, 48]. It is important to note that in most studies, patients receiving GLP-1 receptor agonists were also advised to follow dietary restrictions and, in many cases, to increase physical activity. This section includes all the available evidence to our knowledge in the form of randomized controlled trials and systematic reviews directly examining the effect of GLP-1 receptor agonists on mental health, excluding systematic reviews that have a majority overlap of studies included.

In the SURMOUNT-1 trial analysis of patient-reported outcomes, Gudzone et al. noted improvements in psychosocial function and a decrease in depressive symptoms in patients treated with Tirzepatide at various doses [49]. This effect was more pronounced in participants who had lower psychosocial functioning at baseline. However, physical functioning was more strongly impacted, showing that the relationship between psychosocial wellbeing and weight is not linear and influenced by more complex factors. A systematic review and meta-analysis evaluating mental health outcomes in patients with GLP-1 receptor agonist treatment provided evidence that it does not lead to adverse psychiatric events or changes in depressive symptoms, suggesting that the medications are psychiatrically safe [50]. In contrast, those medications were found to improve mental health-related quality of life and eating behaviors. A meta-analysis demonstrated similar findings, showing that the medications were safe for patients with

Table 4. Mental health outcomes with GLP-1 receptor agonists.

Author & year	Medication	Purpose	Study design	Population	Key mental health outcomes	Major findings	Suicidality risk
Gudzune et al., 2024 [49]	Tirzepatide	To evaluate the effect of Tirzepatide on changes in patient-reported outcomes including psychosocial wellbeing.	Randomized controlled trial	Adults with obesity (SURMOUNT-1)	Psychosocial function, depression	Improved psychosocial function (Δ +9.7 points) and ↓ depressive symptoms ($p < 0.001$).	No events reported
Di Stefano et al., 2025 [52]	GLP-1 RAs, dual agonists	To examine the association between GLP-1 receptor agonists and suicidal behavior.	Systematic review	Mixed (T2DM/obesity)	Suicidal behavior	No association with suicidality in systematic review.	Studies excluded high-risk patients
Tang et al., 2024 [60]	Semaglutide, liraglutide	To examine the association between GLP-1 receptor agonists prescription and subsequent suicidal ideation or behavior in older adults (>65 years old) with type 2 diabetes.	Target trial emulation study (retrospective cohort)	T2DM adults >65 years	Suicidal ideation/behavior	No ↑ risk vs. other antidiabetics (HR: 0.94; 95% CI: 0.82–1.08).	Excluded prior suicide attempts
Cooper et al., 2023 [50]	GLP-1 RAs	To determine if the initiation of GLP-1 receptor agonists can act as a protective factor from depression incidence in patients with diabetes mellitus.	Systematic review	T2DM without baseline depression	Depression incidence	Mixed results: 2 studies ↓ depression; 2 showed no effect.	Inconclusive protective effect
Jódar et al., 2020 [51]	Semaglutide	To assess the mediators of health-related quality of life in T2DM patients on Semaglutide.	Randomized controlled trial	T2DM, high CV risk (SUSTAIN-6)	SF-36 mental component summary	↑ Mental component score vs. placebo ($p < 0.05$).	No suicidality reported
Pierret et al., 2025 [55]	GLP-1 RAs	To evaluate mental health outcomes with GLP-1 RA treatment.	Systematic review and meta-analysis	Mixed (obesity/T2DM)	Psychiatric AEs, depressive symptoms	No ↑ psychiatric AEs or depression vs. placebo (RR: 0.98; 95% CI: 0.92–1.05).	Safe psychiatric profile
Breit & Hubl, 2025 [61]	GLP-1 RAs	To examine the effect of GLP-1 RAs on mental health including in patients with preexisting mental health illnesses on psychotropic medications.	Systematic review and meta-analysis	Mental illness on psychotropics	Mental health, weight loss	Positive mental health effects; no ↑ psychiatric admissions.	Safe in comorbid mental illness
Valentino et al., 2025	GLP-1 RAs	To examine the association between GLP-1 RAs and suicidality.	Systematic review	Mixed	Suicidality	Pharmacovigilance: ↑ suicidal ideation; cohort studies: no association or protective effect.	Confounding by indication likely
Chen et al., 2024	GLP-1 RAs	To determine the effectiveness of GLP-1 RAs in improving depressive symptoms	Systematic review and metaanalysis	Mixed	Depressive symptoms	↓ Depression rating scale scores vs. controls (SMD: -0.41; 95% CI: -0.62 to -0.20).	Potential antidepressant effect

This table summarizes mental health outcomes observed with GLP-1 receptor agonists in obesity and type 2 diabetes studies, including depressive symptoms, suicidality, and psychiatric adverse events. Data are presented by medication, study population, and outcome measure. GLP-1 RA glucagon-like peptide-1 receptor agonist, T2DM type 2 diabetes mellitus, HR hazard ratio, CI confidence interval, AEs adverse events, SMD standardized mean difference, SF-36 Short Form Health Survey-36.

pre-existing mental illnesses as well, with similarly positive effects and no increase in psychiatric admissions [51]. This is an important finding as some psychotropic medications are known to cause metabolic disturbances leading to obesity and sometimes requiring weight loss pharmacotherapy. A systematic review excluded patients with preexisting depression and examined for a protective effect of GLP-1 RA's from new incidences of depression, with indeterminate results [52].

Di Stefano et al. systematically reviewed the evidence on suicidal behavior and GLP-1 receptor agonists (including dual GLP-1 RA's and GIP RA's) and did not find a link with suicidality [53]. However, as the authors noted, most studies were not explicitly designed to detect suicidality or to examine its direct association with the medications. Furthermore, some studies excluded high-risk individuals—such as those with a diagnosis of major depression or a history of suicide attempts—introducing the potential for selection bias. A large target trial emulation study by Tang et al. also found that there is no increased risk for suicidal ideation or behavior in older adults with type 2 diabetes mellitus who were initiated on GLP-1 RAs compared to other common diabetes medications [54]. However, this study also excluded patients with prior suicide attempts. A systematic review, including pharmacovigilance studies and cohort studies to evaluate suicidal ideation, had conflicting findings [55]. In patients taking GLP-1 RAs, pharmacovigilance studies reported increased suicidal ideation in patients taking liraglutide and Semaglutide. This was not consistent with the reports from cohort studies, which not only did not demonstrate a consistent increase in suicidality but also observed a protective effect with some of the medications. The findings in pharmacovigilance studies were suggested to be related to the reported intrinsic risk of suicidality in patients who require GLP-1 RAs [56]. Multiple subsequent studies and systematic reviews consistently concluded that there is no association between GLP-1 RAs and increased suicidality [57–59].

A post-hoc analysis of the SUSTAIN-6 trial demonstrated an improved mental component summary score, a part of the Short Form (SF) -36v2 questionnaire, which assesses health-related quality of life [60]. However, this improvement was not observed in patients with major adverse cardiovascular events, hypoglycemia, and gastrointestinal adverse effects. Notably, the mental health score also did not improve in patients whose HbA1C did not reduce by 1% or more and those whose weight loss was less than 5%, suggesting a possible relationship between the degree of weight loss and HbA1C lowering and mental wellbeing. A systematic review of randomized controlled trials and one prospective cohort also found improvements in a depression rating scale [61]; moreover, GLP-1 RAs were suggested as a treatment to address depressive symptoms.

GLP-1 RAs are promising medications challenging the gold standard of bariatric surgery. However, with conflicting initial reports of suicidality, which are challenged by recent prospective research, caution is advised as patients with obesity are more prone to mental health illnesses. Most of the reviewed studies on GLP-1 RAs have a follow-up duration of two years or less, and it remains unclear whether the course of any psychological effects would be sustained with longer follow-up, similar to some studies described in the bariatric surgery section. All the GLP-1 RA studies are summarized in Table 4.

CONCLUSION

Mental health challenges are a crucial and not uncommon morbidity in people living with obesity. However, it is often forgotten or understudied and deserves due recognition. Due to the heterogeneity of studies and the diversity of approaches to obesity management, it is challenging to compare the available options directly in representative populations.

Further studies are explicitly needed in the form of randomized controlled trials, with mental health as the primary focus. With the current evidence, it is essential to approach each case individually to select the most effective management strategy based on the patient's goals, characteristics, and comorbidities. Behavioral interventions demonstrate psychological safety and modest efficacy in ameliorating depression and enhancing quality of life, though benefits remain inconsistent in populations with severe mental illness. Bariatric surgery confers substantial short-term psychological improvement but carries validated risks of attenuated benefits and elevated suicidality beyond five years, necessitating lifelong psychiatric monitoring. Pharmacotherapies exhibit divergent profiles: GLP-1 receptor agonists show promising mental health benefits without increased suicidality risk, while norepinephrine-dopamine reuptake inhibitors may exacerbate anxiety.

Neurobiological evidence substantiates these clinical observations, with GLP-1 agonism modulating limbic circuitry involved in mood regulation, providing mechanistic plausibility for its antidepressant effects.

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AUTHOR CONTRIBUTIONS

Both authors contributed substantially to the conception and design of the review. DO and EA performed the literature search, synthesized the evidence, and drafted the initial manuscript. DO did the write-up of the summarized manuscript. DO, EA critically revised the manuscript for important intellectual content and assisted in

interpreting the data. Both authors reviewed and approved the final version for submission and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

DECLARATION OF AI ASSISTED LANGUAGE REVIEW

During the preparation of this work, the author used Prolixity only to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

ADDITIONAL INFORMATION

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