DSX 19 (2025) 103238

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Glucagon-Like Peptide-1 receptor agonists, dual GIP/GLP-1 receptor agonist tirzepatide and suicidal ideation and behavior: A systematic review of clinical studies and pharmacovigilance reports

Ramona Di Stefano [a,b,*], Lorenzo V. Rindi [c], Valentina Baldini [d,e], Rodolfo Rossi [c], Francesca Pacitti [a], Emmanuele A. Jannini [b], Alessandro Rossi [a]

[a] Department of Biotechnological and Applied Clinical Sciences, University of l'Aquila, L'Aquila, Italy
[b] Endocrinology and Medical Sexology (ENDOSEX), Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy
[c] Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[d] Department of Biomedical and Neuromotor Sciences (DIBINEM), Alma Mater Studiorum, University of Bologna, Bologna, Italy
[e] Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

ARTICLE INFO

Keywords:
GLP-1 receptor agonist
Suicide risk
Suicidal ideation and self-injury
Obesity
Diabetes

ABSTRACT

Aims: Suicide is a global public health concern, accounting for nearly 700,000 deaths annually. Although well-established risk factors, including mental health disorders, are widely recognized, emerging concerns have surfaced regarding a potential association between glucagon-like peptide-1 receptor agonists (GLP-1 RAs), the dual Gastric Inhibitory Polypeptide (GIP)/GLP-1 Receptor Agonist tirzepatide and suicidal behavior. This systematic review aims to synthesize the available evidence on the potential association between these drugs and suicidal behavior.

Methods: This review was conducted following PRISMA guidelines. A systematic search was performed in MEDLINE, Embase, and APA PsycInfo up to September 24, 2024, using terms related to GLP-1 RAs/GIP/GLP-1 RAs and suicidal behavior.Three independent reviewers conducted article screening and data extraction. Risk of bias was evaluated using the Newcastle-Ottawa Scale for cohort studies and ROB2 for RCTs.

Results: The review identified 16 studies published between 2017 and 2024, consisting of 5 observational studies, 2 randomized controlled trials, 8 pharmacovigilance analyses, and 1 post-hoc analysis of RCTs. No consistent evidence indicated an increased suicide risk among GLP-1 RA users. Pharmacovigilance analyses produced mixed findings; while some disproportionality analyses reported higher rates relative to other antihyperglycemic drugs, no causal link was confirmed. Cohort studies involving diabetic and obese populations generally did not demonstrate a significant increase in suicidal behavior.

Conclusions: Although current data do not warrant changes in prescribing practices, further research is needed before definitive conclusions can be drawn. Moreover, the generalizability and reliability of these findings should be interpreted in light of the methodological limitations of the included studies.

1. Introduction

Suicide is a significant public health concern with an impact on global mortality. According to the World Health Organization (WHO), nearly 700,000 people die by suicide each year [1]. Several risk factors, including mental health disorders and socio-economic stressors, have been well-documented [2–4]. Recently, however, growing concerns have emerged regarding a potential link between certain Glucagon-Like Peptide-1 receptor agonists (GLP-1 RAs), the dual Gastric Inhibitory Polypeptide (GIP)/GLP-1 Receptor Agonist tirzepatide and an elevated risk of suicidal ideation and behavior [5,6].

GLP-1 RAs are a class of medications that mimic the action of the endogenous incretin hormone GLP-1. They work by stimulating insulin release, inhibiting glucagon secretion, and delaying gastric emptying [7]. These drugs, including liraglutide and semaglutide, are widely used because of their efficacy in improving glycemic control and promoting weight loss. Moreover, they showed cardiovascular and renal beneficial effects. These aspects solidified their role as a cornerstone in the

* Corresponding author. Department of Biotechnological and Applied Clinical Sciences, University of l'Aquila, L'Aquila, Italy.
E-mail address: ramonadist@gmail.com (R. Di Stefano).

https://doi.org/10.1016/j.dsx.2025.103238
Received 24 November 2024; Received in revised form 9 May 2025; Accepted 12 May 2025
Available online 13 May 2025

management of Type 2 Diabetes (T2D) and obesity [8].

GIP/GLP-1 RA tirzepatide is an acylated peptide designed to activate both GIP and GLP-1 receptors, which play a crucial role in insulin secretion and are also found in brain regions involved in regulating appetite [9]. GIP/GLP-1 RA not only exerts antiobesity effects by targeting peripheral and central pathways that increase insulin and inhibit glucagon secretion, but additionally acts on peripheral tissues and islets, improving pancreatic beta cell function and augmenting energy expenditure. As for GLP-1 RAs, tirzepatide reduces cardiovascular-risk and mortality in T2D and obesity [10,11].

Due to their efficacy in promoting weight loss, GLP-1 RAs have received significant attention, including via non-scientific channels, social media and non-academic outlets, endorsing their effect on weight control [12,13]. As a result, drugs like Ozempic® (Semaglutide) and other GLP-1 RAs have become the subject of widespread attention in turn leading to difficulties in distribution and drug availability [14–16].

However, despite their success, reports were issued potentially linking these drugs to adverse psychiatric outcomes, including suicidal ideation and behavior. This potential association has led to increased scrutiny by regulatory authorities, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), who are currently investigating the issue [5,6].

A careful monitoring for signs of depression and a recommendation about evaluating suicidal thoughts is already advised in the prescribing information available in the U.S. for liraglutide 3.0 mg [17]. Likewise, a similar warning is included in the U.S. prescribing information for the semaglutide formulation Wegovy®, which is prescribed at higher doses for weight management than for the treatment of T2D [18].

Understanding the potential link between GLP-1 receptor agonists, GIP/GLP-1 RAs and suicidal behavior is critical for informing both prescribers and patients about the risks and benefits of these treatment options, which became rapidly popular since their expanded use for the treatment of obesity [19,20]. In this systematic review, our aim is to summarize the existing literature on the relationship between these drugs and suicidal ideation and behavior. This is the first comprehensive systematic review integrating clinical trial data and pharmacovigilance reports to critically assess the potential association between GLP-1 receptor agonists—including the dual GIP/GLP-1 RA tirzepatide—and suicidal ideation or behavior.

2. Methods

This systematic review of the literature was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. Articles were identified via the electronic databases “MEDLINE” (National Library of Medicine–Bethesda USA), Embase and APA PsycInfo, by an *ad hoc* all-term search for each of the selected databases. Search strategies included the terms “exenatide”, “liraglutide”, “dulaglutide”, “semaglutide”, “albiglutide”, “tirzepatide”, “lixisenatide”, “suicid*”, “suicidal behavior”, “nssi”, “non suicidal self injury”, “non-suicidal self injury”, “non suicidal self-injury”, “complete suicide” and “suicid* attempt” joined by the Boolean operator “AND”. Search period was from inception to September 24, 2024. The complete search strategy is available as Supplementary Material 1. The protocol for the systematic review was registered on PROSPERO (CRD420251027131).

2.1. Inclusion criteria

To be included, articles had to be identifiable by searching the aforementioned databases and be fully published on scientific journals after being peer-reviewed. The search was not restricted to any language or country. Studies analyzing or reporting suicidal ideation, non-suicidal self-injury (NSSI), complete suicide, or any suicidal behavior during the administration of any of the included GLP-1 RA (i.e. exenatide, liraglutide, dulaglutide, semaglutide, albiglutide, lixisenatide) or GIP/GLP-1 RA (i.e. tirzepatide) were considered relevant to our search and therefore included, unless they had at least one exclusion criterion. Included population was aged 12 and above.

2.2. Exclusion criteria

Animal studies were excluded from this analysis. Additionally, records with designs such as "abstract," "letter," "commentary," "short communication," "feature article," "personal view," "case report," "case series," and reviews were also excluded.

2.3. Article selection and data extraction

The database search was conducted by RDS across the selected databases, and the resulting list of records was merged in the computerized tool Rayyan for deduplication and the subsequent selection process [22]. Three authors (RDS, LVR and VB) independently screened the records by reviewing titles and abstracts. The following phase of selection involved a blinded review of the study full texts. Any conflicts that arose during the process were resolved through consultation with the study coordinator, AR. For studies that met the inclusion criteria, relevant information was extracted. The abstracted data included publication title, first author, journal name, year of publication, study design, primary study objective (if applicable), population characteristics (including treatment details and indication, if relevant), scales and measures used to assess outcomes, number and type of suicide events, and key findings.

2.4. Risk of bias analysis

Included studies were assessed for potential risk of bias according to their study design. Cohort studies were evaluated by means of the Newcastle-Ottawa Scale [23]. Randomized studies were analyzed via the Risk Of Bias tool (ROB) 2.0 [24].

3. Results

The database search identified 211 records. After the removal of 37 duplicates, 174 studies were screened for title and abstract. The screening process led to 152 studies being excluded. The full text of the remaining 22 studies was assessed. Finally, 16 studies were included into the database of the present review following the aforementioned inclusion criteria. The study selection process is depicted in Fig. 1 (PRISMA Flowchart). A list of excluded studies is available as Supplementary Material 2.

Included records were published between 2017 and 2024. Among the included records, 5 were observational studies, 2 were Randomized Controlled Trials (RCTs), 8 records discussing pharmacovigilance data and 1 post-hoc analysis of RCTs were included. The indication for use for any of the included drugs was either T2D or obesity.

The main characteristics of the included studies are summarized in Table 1.

A pharmacovigilance analysis by Chen and colleagues investigated the potential association between GLP-1RAs and suicide/self-injury reports by analyzing the FDA Adverse Event Reporting System (FAERS). Between 2005 and 2023, 534 cases of suicide/self-injury linked to GLP-1RA were identified. However, no overall safety signal of increased risk for suicide or self-injury was detected in GLP-1 RAs (Reported Odds Ratio-ROR: 0.16, 95 % CI 0.15–0.18, $p < 0.001$). In children, a slight elevation in risk was observed (ROR: 2.50, 95 % CI 1.02–6.13, $p = 0.05$), but this was not confirmed by other analysis metrics [26].

Guirguis et al. conducted a pharmacovigilance disproportionality analysis of FAERS reports, studying the association between suicidal ideation and self-injury (SIS) and GLP-1 RAs/dual GIP/GLP-1 RA comparing ROR with those of metformin and orlistat. They subsequently implemented an “unmasking” procedure, excluding any potential

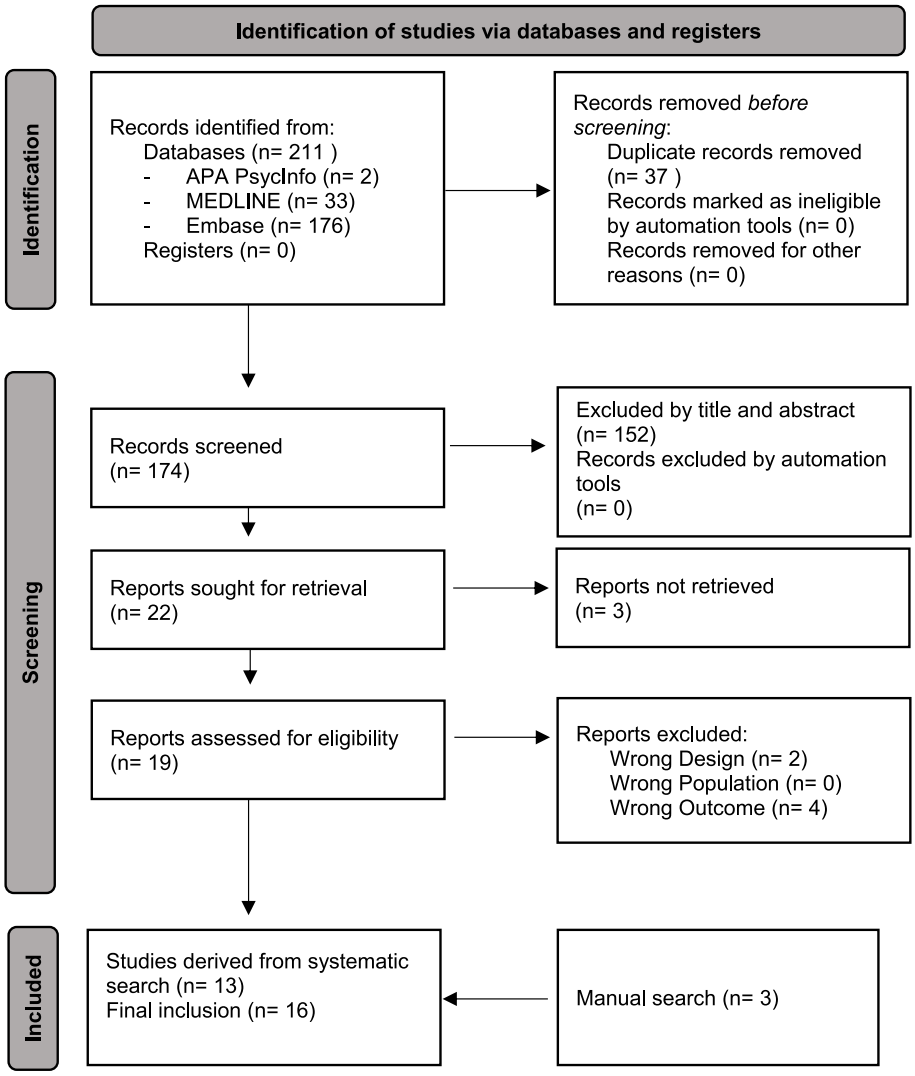

Fig. 1. PRISMA 2020 flow diagram of included studies.

confounding effect due to concomitant drugs. SIS reports regarding semaglutide, tirzepatide, and liraglutide were well represented, although lower than metformin. After unmasking, pharmacovigilance disproportionality analyses using ROR showed that GLP-1 RA/dual GIP/GLP-1 RA were associated with SIS in the following descending order: semaglutide, tirzepatide and liraglutide, all with ROR values > 1.0 [28].

A pharmacovigilance analysis highlighted a disproportionate reporting of suicidal ideation and "depression/suicidal" in semaglutide and liraglutide when compared to metformin and insulin as separate controls. Nevertheless, no disproportionate reporting of suicidal behavior, suicide attempts, and completed suicide was observed for any of the FDA-approved GLP-1 RAs [32].

In a disproportionality analysis conducted by Zhou and colleagues using post-marketing information from FAERS, 204 SIS were reported in association with GLP-1 RAs, without showing an increase in association between this class of drugs and SIS when compared to orlistat or empagliflozin [40].

Ruggiero et al. compiled an analysis of real-world data from the European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC), focusing on the possible link between suicidal event reports and GLP-1 RAs. Specifically, their disproportionality analysis found higher reporting probability of suicidal events in semaglutide and liraglutide, which were also associated with significantly higher reporting probabilities when compared to other GLP-1 RAs (semaglutide vs dulaglutide ROR 2.05, 95 % CI 1.4–3.01, p = 0.0002; liraglutide vs dulaglutide ROR 3.98, 95 % CI 2.73–5.82, p < 0.0001) [34].

A disproportionality analysis of the WHO global Individual Case Safety Reports (ICSR) database found a significant disproportionality for semaglutide-associated suicidal ideation compared with other GLP-1 RAs only. Researchers performed sensitivity analyses focusing on co-reported administration of antidepressants and benzodiazepines, suggesting people with anxiety/depressive disorders might be subject to an increased probability of reporting suicidal ideation if exposed to semaglutide. When repeating the analysis after excluding cases in which antidepressants were coreported, the disproportionality signal was no longer detected [35].

In their pharmacovigilance analysis of Eudra Vigilance database, Tobaiqy and Elkout investigated psychiatric adverse events (PAE) linked to GLP-1 RAs use. Among psychiatric events, they found 4 completed suicide in liraglutide users (on a total of 147 PAE with liraglutide), 40 suicidal ideation in semaglutide users (on a total of 210 PAE with semaglutide) [36].

In a real world study including 13846 individuals, equally split between tirzepatide and semaglutide users, no difference in risk of suicide attempt or ideation was found in either group (HR 0.55, 95 % CI, 0.22–1.37, p = 0.192) [25].

In a cohort study by Hurtado and colleagues on 3040 patients initiating treatment with GLP-1 RAs and 11,627 with sodium-glucose

Table 1
Characteristics and findings of the included studies

First author	Study Design	GLP-1 and GIP/GLP-1 Receptor Agonist	Indication	Suicide/Self-Injury Evaluation	Relevant Findings
Anson et al., 2024 [25]	Cohort Study	Tirzepatide and Semaglutide	T2D, Obesity	Suicidal ideation and/or attempt (ICD-10 R45.851 & T14.91) from TriNetX (TriNetX LLC, Cambridge, MA, USA) platform.	No significant statistical difference in suicidal attempt or ideation between subjects treated with tirzepatide or semaglutide
Chen et al., 2023 [26]	Pharmacovigilance Analysis	Liraglutide, Lixisenatide, Exenatide, Albiglutide, Semaglutide and Dulaglutide	T2D, Obesity	534 reports in FAERS	The cases of suicide or self-injury reported to FAERS do not indicate any overall safety signal attributable to GLP-1RA.
Gamble et al., 2018 [27]	Cohort Study	Any GLP-1 RAs	T2D, Obesity	Reports in UK Clinical Practice Research Datalink	GLP-1 RAs users did not have an increased risk of new diagnosis of depression or episode of self-harm (composite outcome including suicide and suicidal ideation) when compared with sulfonylureas in a 9-year observation span.
Guirguis et al., 2024 [28]	Pharmacovigilance Analysis	Liraglutide, Exenatide, Semaglutide, Dulaglutide, Tirzepatide and Albiglutide	T2D, Obesity	236 suicidal ideation reports in FAERS	Pharmacovigilance disproportionality analyses using ROR showed that GLP-1 RA were associated with ad increase in suicidal and self-injurious ideation in the following descending order: semaglutide, tirzepatide and liraglutide, all with ROR values > 1.0. No causality link between suicidal ideation and use of any GLP-1 RA can be inferred.
Hurtado et al., 2024 [29]	Cohort Study	Any GLP-1 RAs	T2D, Obesity	Suicidal ideation or Self Injury (ICD9 E95.x,V62.84, 300.9) from Valencia Health System Integrated Database	Results do not support an increased risk of SSIB when taking GLP-1RA in individuals with T2D or obesity. However, caution is due to the rarity of SSIB events and the wide uncertainty of the effect size.
Kelly et al., 2020 [30]	Randomized Controlled Trial	Liraglutide vs placebo	Obesity	C-SSRS	1 completed suicide (previous ADHD diagnosis) and 1 suicide attempt (previous depression diagnosis) in the Liraglutide arm.
Le Roux et al., 2017(31)	Randomized Double Blind Trial	Liraglutide vs placebo	Obesity	C-SSRS	No observed between-group differences for psychiatric disorders, or questionnaire-based depression, or suicidal behavior scores. However, seven individuals treated with liraglutide (vs none treated with placebo) reported eight suicidal ideation events and one individual in the placebo group (vs none in the liraglutide group) reported suicidal depression. One suicide attempt occurred in each group.
McIntyre et al., 2024 [32]	Pharmacovigilance Analysis	Semaglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, and Tirzepatide	T2D, Obesity	Reports in FAERS	Disproportionate reporting of suicidal ideation and "depression/suicidal" was observed with semaglutide and liraglutide. Disproportionate reporting of suicidal behavior, suicide attempts, and completed suicide was not observed for any of the FDA-approved GLP-1 RAs. Taking into consideration confounders, no causal link between GLP-1 RAs and suicidality exists.
Nassar et al., 2024 [33]	Cohort Study	Any GLP-1 RAs	T2D	Reports in TriNetX Analytics platform based on the Research US Collaborative Network	GLP-1RAs were associated with a lower risk of suicide in individuals with T2D. Additionally, the use of GLP-1RA was linked to a particularly reduced suicide risk when compared to dipeptidyl peptidase-4 inhibitors (DPP-4i) use in T2D patients with a history of depression or previous suicide attempts
Ruggiero et al., 2024 [34]	Pharmacovigilance Analysis	Semaglutide, Dulaglutide, Liraglutide, Exanatide	T2D, Obesity	European pharmacovigilance database reports	Suicidal events were mostly reported with semaglutide and liraglutide, which were also associated with significantly higher reporting probabilities compared to other GLP1 RAs.
Schoretsanitis et al., 2024 (35)	Case-control Study (Disproportionality Analysis)	Semaglutide, Liraglutide	T2D, Obesity	Suicidal or Self-Injurious suspected adverse drug reactions events within the WHO global Individual Case Safety Reports (ICSR) database	Significant disproportionality in reporting was detected only for semaglutide-associated suicidal ideation, which remained significant in patients with co-reported use of antidepressants and benzodiazepines, when compared with dapagliflozin, metformin or orlistat.
Tobaiqy and Elkout, 2023 (36)	Pharmacovigilance Analysis	Semaglutide, Liraglutide, Tirzepatide	T2D, Obesity	EudraVigilance database-C-SSRS	Suicidal ideation was the third reported psychiatric adverse event (19.6 %). The fatal outcomes occurred primarily among men (8 out of 9) resulting from completed suicidal attempts and depression.

(*continued on next page*)

Table 1 (*continued*)

First author	Study Design	GLP-1 and GIP/GLP-1 Receptor Agonist	Indication	Suicide/Self-Injury Evaluation	Relevant Findings
Ueda et al., 2024 (37)	Cohort Study	Any GLP-1 RAs- Liraglutide (50 %), Semaglutide (41 %)	T2D	Suicide death and nonfatal self-harm recorded in register data from Sweden and Denmark	No signaled association between use of GLP-1 RAs and an increased risk of suicide death, self-harm, incident depression or anxiety-related disorders.
Wadden et al., 2024 [38]	Post Hoc Analysis of Trials	Semaglutide vs placebo	Obesity	C-SSRS	The proportion of participants reporting suicidal ideation/behavior was also similar between semaglutide, 2.4 mg, and placebo. The results suggest that the risk of developing symptoms of depression or suicidal ideation/ behavior was similar between groups.
Wang et al., 2024 [39]	Cohort Study	Semaglutide	T2D, Obesity	Reports in TriNetX Analytics platform based on the Research US Collaborative Network	In patients with overweight or obesity semaglutide compared with non-GLP-1RAs was associated with lower risk for incident and recurrent suicidal ideation, consistent across sex, age and ethnicity stratification. Similar findings were replicated in patients with T2D. Findings do not support higher risks of suicidal ideation with semaglutide compared with non-GLP-1RAs.
Zhou et al., 2024 [40]	Pharmacovigilance Analysis	Semaglutide, Liraglutide, Dulaglutide, Exenatide, and Albiglutide	T2D, Obesity	Self-reported (204 Suicidal and Self-injury reports) in FAERS	No signal of disproportionate reporting of an association between GLP-1RA use and SSIBs was found.

cotransporter 2 inhibitors (SGLT-2i), no increased risk of SIS was found when taking GLP-1RA in individuals with T2D and obesity [29].

Another cohort study compared 124,517 adults who initiated treatment with GLP-1 RAs and 174,036 with SGLT2 inhibitors, the latter with no known link to increased suicide behavior. The hazard ratio (HR) for suicide and nonfatal self-harm was 0.83 (95 % CI, 0.70–0.97), and for depression and anxiety-related disorders was 1.01 (95 % CI, 0.97–1.06). This cohort study, primarily involving people with T2D, did not find any significant association between GLP-1 receptor agonist use and an increased risk of suicide, self-harm, or mood disorders. Upper confidence limit for suicide indicates a maximum risk increase of 0.16 events per 1000 person-years [37].

A cohort study of electronic health records from the TriNetX Analytics Network investigated incident and recurrent suicidal ideation in 240,618 patients with overweight or obesity and 1,589,855 patients with T2D who were prescribed semaglutide or non-GLP-1 RAs. In patients with overweight and obesity, semaglutide compared with non GLP-1 RAs medications was associated with lower risk for incident (HR = 0.27, 95 % CI 0.2–0.6) and recurrent (HR = 0.44, 95 % CI 0.32–0.6) suicidal ideation. Similar findings were replicated in patients with T2D [39].

A similar study collecting data from the TriNetX global database compared incidence of suicide attempts among people with T2D treated with GLP-1 RAs (373,041 individuals) with those treated with dipeptidyl peptidase-4 inhibitors (DPP-4i) (372,944 individuals). Findings showed that people with T2D treated with GLP-1RA presented a lower risk of suicide attempts, compared to those treated with DPP-4i (OR 0.461, 95 % CI 0.366–0.58, $p < 0.001$). The calculated risk per 100,000 was 28.41 for GLP-1 RAs versus 61.67 for DPP-4i. The effect resulted even higher when limiting the analysis to a subset of people with history of depression or previous suicide attempts (OR 0.377, 95 % CI 0.285–0.499, $p < 0.001$) [33].

In a cohort study including 488 GLP-1 RAs propensity score matched patients with 488 sulfonylureas users, no increased risk of new diagnosis of depression or episode of self-harm including suicide was found (adjusted HR 1.07, 95 % CI 0.39–2.94) [27].

A randomized study comparing liraglutide to placebo in an adolescent sample (12–18 years of age) observed 1 completed suicide (with a previous Attention-deficit/hyperactivity disorder – ADHD - diagnosis) and 1 suicide attempt (with a previous depression diagnosis) in the liraglutide arm. Authors did not describe any relationship between liraglutide and the reported suicidal events [30].

In a randomized double-blind trial comparing liraglutide 3.0 mg and placebo, no significant difference was reported in depression severity or suicidal ideation, based on Patient Health Questionnaire- 9 (PHQ-9) and Columbia-Suicide Severity Rating Scale (C-SSRS), respectively. However, there was a numerical imbalance, with seven individuals in the liraglutide group reporting suicidal ideation events, versus none in the placebo group. One suicide attempt occurred in each treatment group. Most individuals who experienced suicidal ideation or behavior had a history of psychiatric disorders or life stressors. Only one liraglutide-treated individual reported suicidal ideation at baseline, and none reported suicidal behavior at baseline in either group [31].

In a post-hoc analysis of four randomized trials investigating depressive symptoms and suicidal ideation/behavior by PHQ-9 and C-SSRS during semaglutide treatment compared with placebo, participants treated with semaglutide were less likely to shift (from baseline to week 68) to a more severe category of PHQ-9 depression (OR 0.63; $p < 0.001$; 95 % CI 0.5–0.79) and less than 1 % of participants reported suicidal ideation/behavior during treatment with no differences between semaglutide and placebo. Overall psychiatric adverse events were found to be balanced between groups [38].

ROR data from pharmacovigilance studies are reported in Supplementary Material 3.

3.1. *Quality appraisal of included studies*

Overall quality of the included observational studies was appraised via NOS, resulting in a mean score of 7.8, indicating an overall low risk of bias. Randomized studies assessed via ROB2 tool achieved an overall average score of “Low” risk of bias. The complete risk of bias assessment is available as Supplementary Material 4.

4. Discussion and conclusions

The present review aims at summarizing the evidence coming from the latest literature on SIS risk during the administration of GLP-1 RA/dual GIP/GLP-1 RA for the treatment of T2D or obesity.

In developing our analysis, we intended to provide a comprehensive and balanced assessment by integrating data from pharmacovigilance databases and clinical trials. This strategy was intentionally chosen to capture a broader range of evidence, particularly given the rarity of the reported side effect, which may not be detectable in individual studies alone. Our findings complement those of a recent review [41].

Examined literature, including data from pharmacovigilance analysis, cohort and randomized studies failed to support the current claim that the use of GLP-1 RA/dual GIP/GLP-1 RA could be linked to an excess risk/reporting of any suicide behavior; nevertheless, several key issues need to be specified.

First, most of the included studies were not designed to investigate directly, nor geared to detect with sufficient accuracy, a potential signal over the background risk of suicide in the general obese/diabetic population. Several studies present in the literature reporting GLP-1RA/dual GIP/GLP-1 RA use did not gather such data at all, and were therefore excluded, resulting in a possible limitation of the present study. Furthermore, when discussing cohort or randomized studies, some included studies excluded higher-risk individuals at enrollment (e.g. those with major depression disorder and/or a previous suicidal attempt). We think this could have led to a potentially substantial selection bias with a consequent underestimation of the actual potential SIS risk.

Another key issue in interpreting the findings presented here is the heavy reliance on disproportionality analyses in our dataset, a study design that presents several methodological limitations. This is primarily due to the spontaneous nature of adverse event reporting systems, which may not capture all adverse events, may overreport certain events, and face challenges with the varied coding systems used to report suicidality. Additionally, the recent approval of GLP-1RA for broader indications, such as obesity, along with increased media attention and social media promotion for off-label uses, may contribute to the temporary spurious overreporting of drug-related adverse events—a phenomenon commonly known as the Weber effect [42]. Moreover, the analyses do not account for the total prescription volume, nor check for adherence to the drug regimen limiting a detailed assessment. Furthermore, physicians, especially during the first phase of prescription of a new drug, may artifactually increase their evaluations, in turn increasing trust in the prescriber and consequently decrease suicide behavior (or at the very least its reporting) in the patients. Last but not least, no causality link could be inferred between GLP-1 RAs/dual GIP/GLP-1 RA and suicidality by this study design.

Included drugs may be used for the treatment of both obesity and diabetes, our review collectively gathered data from studies including patients for both indications. Nevertheless, even if these populations may often overlap, it might be inappropriate to consider the two populations alike as for their baseline risk of suicide. To further complicate the interpretation of the results, the diabetic population inherently faces a higher baseline risk of depression and of suicide behavior with respect to the general population [43]. Similarly, obese individuals have higher odds of having high suicide risk (odds ratios: overweight, 3.02; 95 % CI, 0.98–9.34, p -value of 0.028) and severe depression compared to lean individuals (odds ratios: overweight or obese, 2.36; 95 % CI, 1.05–5.29, $p = 0.019$) [44]. This could represent a potential confounding factor when dealing with analyzing a side effect of a drug.

As for the quality appraisal of the included studies, even though the overall ROB score describes a good quality, it might be important to specify a potential selection bias in some of the observational and randomized studies which excluded *a priori* the more at-risk population (e.g. by excluding those with major depression disorder or a previous suicide attempt), resulting in a possible underestimation of the effect of the drug in a more fragile population.

From a neurophysiological standpoint, the evidence regarding GLP-1 role in the nervous system is mixed. Some authors highlight the GLP-1 RAs effects on the hypothalamus, as hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis has been linked to suicidal behavior [45,46]. On the contrary, some studies suggest that GLP-1 may help reducing neuroinflammation, shielding neurons and glial cells from oxidative stress, and enhancing neurotransmitter balance [47]. GLP-1 RAs may be neuroprotective by supporting survival and encouraging growth, which in turn preserves the structural and functional integrity of synapses. For example, exenatide exerts a neuroprotective effect, through activation of the GLP-1 signaling pathway, safeguarding dopaminergic neurons [48]. Furthermore, research has explored how GLP-1 may interact with serotonin pathways. Serotonin turnover and expression of 5-hydroxytryptamine (5-HT) 2A (5-HT2A) and 5-HT2C serotonin receptors in the hypothalamus were altered by GLP-1R activation [49]. Moreover, GLP-1 RAs increase the activity of the dorsal raphe serotonin neurons [49], an interaction which could potentially influence the development of depression and suicidal ideation, although this remains speculative. In rodents, it has been found that administration of semaglutide induces deficits in social interaction in group-housed mice and rescues social deficits in isolated mice, suggesting a non-univocal action on mood of GLP-1 RAs [50]. As such, establishing a clear cause-effect relationship of its action is complex. It is likely that a combination of psychosocial and biological factors contributes to the emergence of suicidal behaviors in patients treated with GLP-1 RAs. Interestingly, a recent metanalysis failed to show that this class of drug may reduce the risk of incident depression in patients with T2D [51]. Additionally, it would be worthwhile to investigate the potential effects or interactions of GLP-1 RAs on the glymphatic system, and subsequently, their psychiatric effects [52].

The unclear role, if any, in suicidal risk of GLP-1 RAs/dual GIP/GLP-1 RA should not limit a more careful evaluation of mood and suicide risk in all patients with obesity, metabolic syndrome, and diabetes, regardless of the treatment for their condition. A stronger collaboration between endocrinologists and psychiatrists should be encouraged as a strategy to decrease possible treatment-related risks and increase the therapeutical adherence. A routine monitoring via psychometric assessment for depression and suicidal thoughts is suggested in all clinical settings managing *diabesity*.

In conclusion, the present systematic review found no specific evidence to support a causal link between the use of GLP-1RAs/dual GIP/GLP-1 RA and an increase in risk of suicidal behavior. Nevertheless, well-designed studies specifically geared at detecting this signal are necessary to reach a definitive conclusion. In the meantime, physicians prescribing GLP-1 RAs/dual GIP/GLP-1 RA should closely monitor for any sign of mental status changes in treated patients.

5. Limitations

This systematic review has several limitations. Many of the included studies were not specifically designed to assess suicidal ideation or behavior, limiting their power to detect rare psychiatric adverse events. Additionally, several clinical trials and cohort studies excluded individuals with pre-existing psychiatric disorders or prior suicide attempts, introducing selection bias that may underestimate risk in vulnerable populations. A substantial portion of the evidence derives from pharmacovigilance databases and disproportionality analyses, which, while valuable for hypothesis generation, have significant methodological constraints. These include underreporting, reporting bias, lack of standardized diagnostic criteria, and inability to determine causality. Media influence and the so-called Weber effect may also distort reporting patterns, particularly for newer or high-profile drugs. Furthermore, the review included studies conducted in populations with varying baseline risks—such as patients with obesity *versus* T2D—without consistently adjusting for psychiatric comorbidities. This heterogeneity may obscure subgroup-specific risks. Most studies also lacked detailed information on dosage, treatment duration, and adherence, which are relevant factors in assessing neuropsychiatric safety.

6. Clinical relevance

This review provides reassurance for clinicians prescribing GLP-1 RAs and tirzepatide in the treatment of diabetes and obesity by showing no consistent evidence of a causal link with suicidal ideation or behavior. While psychiatric monitoring remains important, particularly in high-risk individuals, these findings suggest that concerns over

suicidality should not deter appropriate use of these effective therapies. The review also highlights gaps in existing data, guiding clinicians to adopt a more structured approach to mental health screening in *diabesity* care. Ultimately, this work informs safer, more confident prescribing and encourages integration of psychiatric vigilance into metabolic disease management.

Acknowledgments and contributions

RDS designed the study. RDS, LVR and VB performed all phases of screening and study selection. AR, FP, RR and EAJ equally participated to the manuscript editing, critically reviewed and approved its current form.

The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, tables, or their captions.

No third-party contributions were involved in the preparation of this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2025.103238.

References

[1] WHO Mental Health, Brain Health and Substance Use Suicide Data. [cited 2024 Sep 24]; Available from: https://www.who.int/teams/mental-health-and-substance-use/data-research/suicide-data.
[2] Favril L, Yu R, Uyar A, Sharpe M, Fazel S. Risk factors for suicide in adults: systematic review and meta-analysis of psychological autopsy studies. Evid Base Ment Health 2022 Nov;25(4):148–55.
[3] Richardson C, Robb KA, O'Connor RC. A systematic review of suicidal behaviour in men: A narrative synthesis of risk factors. Soc Sci Med 2021 May;276:113831.
[4] Baldini V, Stefano RD, Rindi LV, Ahmed AO, Koola MM, Solmi M, et al. Association between adverse childhood experiences and suicidal behavior in schizophrenia spectrum disorders: a systematic review and meta-analysis. Psychiatry Res 2023 Nov;329:115488.
[5] EMA statement on ongoing review of GLP-1 receptor agonists. [cited 2024 Sep 24]; Available from: https://www.ema.europa.eu/en/news/ema-statement-ongoing-review-glp-1-receptor-agonists.
[6] 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. [cited 2024 Sep 24]; Available from: https://www.fda.gov/drugs/drug-safety-and-availability/update-fdas-ongoing-evaluation-reports-suicidal-thoughts-or-actions-patients-taking-certain-type.
[7] Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metab 2022 Mar;57:101351.
[8] Nachawi N, Rao PP, Makin V. The role of GLP-1 receptor agonists in managing type 2 diabetes. Cleve Clin J Med 2022 Aug;89(8):457–64.
[9] Nauck MA, Tirzepatide D'Alessio DA. A dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction. Cardiovasc Diabetol 2022 Sep 1;21(1):169.
[10] Stefanou MI, Palaiodimou L, Theodorou A, Safouris A, Fischer U, Kelly PJ, et al. Risk of major adverse cardiovascular events and all-cause mortality under treatment with GLP-1 RAs or the dual GIP/GLP-1 receptor agonist tirzepatide in overweight or obese adults without diabetes: a systematic review and meta-analysis. Ther Adv Neurol Disord 2024 Jan;17:17562864241281903.
[11] Stefanou MI, Theodorou A, Malhotra K, Aguiar De Sousa D, Katan M, Palaiodimou L, et al. Risk of major adverse cardiovascular events and stroke associated with treatment with GLP-1 or the dual GIP/GLP-1 receptor agonist tirzepatide for type 2 diabetes: a systematic review and meta-analysis. Eur Stroke J 2024 Sep;9(3):530–9.
[12] Basch CH, Narayanan S, Tang H, Fera J, Basch CE. Descriptive analysis of TikTok videos posted under the hashtag #Ozempic. J Med Surg Public Health 2023;1:100013.
[13] National Geographic The unexpected health benefits of Ozempic and Mounjaro. [cited 2024 Sep 24]; Available from: https://www.nationalgeographic.com/premium/article/weight-loss-drugs-glp1-benefits-addiction-heart-kidney-failure-infertility.
[14] WHO issues warning on falsified medicines used for diabetes treatment and weight loss. [cited 2024 Sep 24]; Available from: https://www.who.int/news/item/20-06-2024-who-issues-warning-on-falsified-medicines-used-for-diabetes-treatment-and-weight-loss.
[15] EU actions to tackle shortages of GLP-1 receptor agonists. [cited 2024 Sep 24]; Available from: https://www.ema.europa.eu/en/news/eu-actions-tackle-shortages-glp-1-receptor-agonists.
[16] Mahase E. GLP-1 agonist shortage will last until end of 2024, government warns. BMJ 2024 Jan 5:q28.
[17] Food and Drug Admistration (FDA). Saxenda—Highlights of Prescribing Information. [Internet]. [cited 2024 Sep 28]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/206321s016lbl.pdf.
[18] Food and Drug Administration. Wegovy—Highlights of Prescribing Information. [Internet]. [cited 2024 Sep 28]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215256s011lbl.pdf.
[19] 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 Oct 24;13(11):1503.
[20] Silverii GA, Marinelli C, Mannucci E, Rotella F. Glucagon-like peptide-1 receptor agonists and mental health: a meta-analysis of randomized controlled trials. Diabetes Obes Metab 2024 Jun;26(6):2505–8.
[21] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021 Mar 29;n71.
[22] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev 2016 Dec;5(1):210.
[23] Lo CKL, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol 2014 Dec;14(1):45.
[24] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019 Aug;28:l4898.
[25] Anson M, Henney AE, Broadwell N, Zhao SS, Ibarburu GH, Lip GYH, et al. Incidence of new onset type 2 diabetes in adults living with obesity treated with tirzepatide or semaglutide: real world evidence from an international retrospective cohort study. eClinicalMedicine 2024 Sep;75:102777.
[26] Chen C, Zhou R, Fu F, Xiao J. Postmarket safety profile of suicide/self-injury for GLP-1 receptor agonist: a real-world pharmacovigilance analysis. Eur Psychiatry 2023;66(1):e99.
[27] Gamble JM, Chibrikov E, Midodzi WK, Twells LK, Majumdar SR. Examining the risk of depression or self-harm associated with incretin-based therapies used to manage hyperglycaemia in patients with type 2 diabetes: a cohort study using the UK Clinical Practice Research Datalink. BMJ Open 2018 Oct;8(10):e023830.
[28] Guirguis A, Chiappini S, Papanti PG, Vickers-Smith R, Harris D, Corkery J, et al. Exploring the association between suicidal thoughts, self-injury, and GLP-1 receptor agonists in weight loss treatments: insights from pharmacovigilance measures and unmasking analysis. Eur Neuropsychopharmacol 2024 May;82:82–91.
[29] 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 Aug 6;67(11):2471–80 [Internet] [cited 2024 Sep 28]; Available from: https://link.springer.com/10.1007/s00125-024-06243-z.
[30] Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, et al. A randomized, controlled trial of liraglutide for adolescents with obesity. N Engl J Med 2020 May 28;382(22):2117–28.
[31] Le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017 Apr;389(10077):1399–409.
[32] McIntyre RS, Mansur RB, Rosenblat JD, Kwan ATH. The association between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: reports to the Food and Drug Administration Adverse Event Reporting System (FAERS). Expert Opin Drug Saf 2024 Jan 2;23(1):47–55.
[33] Nassar M, Misra A, Bloomgarden Z. Impact of treatment with GLP-1RAs on suicide attempts in adults persons with type 2 diabetes: a retrospective comparative effectiveness study based on a global TriNetX health research database. J Diabetes 2024 Mar;16(3):e13547.
[34] Ruggiero R, Mascolo A, Spezzaferri A, Carpentieri C, Torella D, Sportiello L, et al. Glucagon-like peptide-1 receptor agonists and suicidal ideation: analysis of real-word data collected in the European pharmacovigilance database. Pharmaceuticals 2024 Jan 23;17(2):147.
[35] Schoretsanitis G, Weiler S, Barbui C, Raschi E, Gastaldon C. Disproportionality analysis from world health organization data on semaglutide, liraglutide, and suicidality. JAMA Netw Open 2024 Aug 20;7(8):e2423385.
[36] 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 Apr;46(2):488–95.
[37] Ueda P, Söderling J, Wintzell V, Svanström H, Pazzagli L, Eliasson B, et al. GLP-1 receptor agonist use and risk of suicide death. JAMA Intern Med 2024 Sep 3;184(11):1301–12 [Internet] [cited 2024 Sep 28]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2823083.
[38] 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 Sep 3;184(11):1290–300 [Internet] [cited 2024 Sep 29];

Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2823084.
[39] 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 Jan;30(1):168–76.
[40] Zhou J, Zheng Y, Xu B, Long S, Zhu L e, Liu Y, et al. Exploration of the potential association between GLP-1 receptor agonists and suicidal or self-injurious behaviors: a pharmacovigilance study based on the FDA Adverse Event Reporting System database. BMC Med 2024 Feb 14;22(1):65.
[41] Bushi G, Khatib MN, Rohilla S, Singh MP, Uniyal N, Ballal S, et al. Association of GLP-1 receptor agonists with risk of suicidal ideation and behaviour: a systematic review and meta-analysis. Diabetes Metab Res Rev 2025 Feb;41(2):e70037.
[42] Hoffman KB, Dimbil M, Erdman CB, Tatonetti NP, Overstreet BM. The weber effect and the United States food and drug administration's adverse event reporting system (FAERS): analysis of sixty-two drugs approved from 2006 to 2010. Drug Saf 2014 Apr;37(4):283–94.
[43] Kim YC, Um YH, Kim SM, Kim TW, Seo HJ, Hong SC, et al. Suicide risk in patients with diabetes varies by the duration of diabetes: the Korea National health and nutrition examination survey (2019). Psychiatry Investig 2022 Apr 25;19(4):326–32.
[44] Ninla-aesong P, Puangsri P, Kietdumrongwong P, Jongkrijak H, Noipha K. Being overweight and obese increases suicide risk, the severity of depression, and the inflammatory response in adolescents with major depressive disorders. Front Immunol 2023 Nov 1;14:1197775.
[45] Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metab 2022 Mar;57:101351.
[46] Wisłowska-Stanek A, Kołosowska K, Maciejak P. Neurobiological basis of increased risk for suicidal behaviour. Cells 2021 Sep 23;10(10):2519.
[47] Kim YK, Kim OY, Song J. Alleviation of depression by glucagon-like peptide 1 through the regulation of neuroinflammation, neurotransmitters, Neurogenesis, and Synaptic function. Front Pharmacol 2020 Aug 14;11:1270.
[48] Zhao X, Wang M, Wen Z, Lu Z, Cui L, Fu C, et al. GLP-1 receptor agonists: beyond their pancreatic effects. Front Endocrinol 2021 Aug 23;12:721135.
[49] Anderberg RH, Richard JE, Eerola K, López-Ferreras L, Banke E, Hansson C, et al. Glucagon-like peptide 1 and its Analogs act in the dorsal raphe and modulate central serotonin to reduce appetite and body weight. Diabetes 2017 Apr 1;66(4):1062–73.
[50] Kolling LJ, Khan K, Wang R, Pierson SR, Hartman BD, Balasubramanian N, et al. Interaction of serotonin/GLP-1 circuitry in a dual preclinical model for psychiatric disorders and metabolic dysfunction. Psychiatry Res 2024 Jul;337:115951.
[51] Cooper DH, Ramachandra R, Ceban F, Di Vincenzo JD, Rhee TG, Mansur RB, et al. Glucagon-like peptide 1 (GLP-1) receptor agonists as a protective factor for incident depression in patients with diabetes mellitus: a systematic review. J Psychiatr Res 2023 Aug;164:80–9.
[52] Voumvourakis KI, Sideri E, Papadimitropoulos GN, Tsantzali I, Hewlett P, Kitsos D, et al. The dynamic relationship between the glymphatic system, aging, memory, and sleep. Biomedicines 2023 Jul 25;11(8):2092.