

Exploring potential associations between GLP-1RAs and depressive disorders: a pharmacovigilance study based on FAERS and Vigibase data



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Summary

Background GLP-1 receptor agonists (GLP-1RAs) are increasingly prescribed for diabetes and obesity management. Recent pharmacovigilance reports have raised concerns about potential neuropsychiatric adverse events, yet comprehensive safety assessments focusing on depressive disorders remain limited. This study investigated associations between specific GLP-1RAs and depressive disorders using real-world post-marketing surveillance data.

Methods We analyzed individual case safety reports (ICSRs) for liraglutide, semaglutide, and tirzepatide from the FDA Adverse Event Reporting System (FAERS) and WHO Vigibase databases through December 2024. Disproportionality analysis using reporting odds ratio (ROR) and information component (IC) identified signals of disproportionate reporting (SDRs) for depressive disorders. Time-to-onset analysis, stratified analyses, active comparator assessments, and co-medication evaluations were conducted to characterize these associations.

Findings Only semaglutide demonstrated statistically significant SDRs for depressive disorders in both databases (FAERS: ROR 1.26, 95% confidence interval (CI) 1.15–1.37; IC 0.33, 95% CI 0.20–0.45; Vigibase: ROR 1.38, 95% CI 1.27–1.49; IC 0.46, 95% CI 0.34–0.57), while liraglutide and tirzepatide showed no SDRs. Stratified analyses revealed increased disproportionality in females and healthcare professional reports. WSP analysis showed semaglutide-associated depression followed an early failure pattern, with no significant drug interactions identified with psychotropic medications.

Interpretation This pharmacovigilance investigation identified a semaglutide-specific SDR for depressive disorders across both databases, while liraglutide and tirzepatide showed no SDRs. Although inconsistent with reported protective effects in existing studies of GLP-1RAs, these findings suggest drug-specific rather than class-wide safety monitoring is warranted.

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Research in context

Evidence before this study

We searched PubMed, Embase, and Cochrane Library databases through December 2024, using keywords “GLP-1 receptor agonists,” “semaglutide,” “liraglutide,” “tirzepatide” combined with “depression,” “psychiatric adverse events,” and “neuropsychiatric safety.” Previous research on the neuropsychiatric effects of GLP-1RAs has been limited and contradictory. Recent systematic reviews and meta-analyses have demonstrated that GLP-1RAs may actually exert protective effects against depression, with a comprehensive meta-analysis of 2071 participants showing that GLP-1RAs significantly decreased depression rating scale scores compared to control treatments. However, some pharmacovigilance reports suggest a link between GLP-1RAs and psychiatric adverse events like depression and suicidal ideation, with regulatory agencies highlighting such risks. This conflict in the literature indicates a need for further investigation into the psychiatric safety of these medications. Notably, traditional clinical trials typically exclude patients with preexisting psychiatric conditions—the very population most vulnerable to adverse mental health effects—and comprehensive pharmacovigilance studies focusing specifically on depression-related adverse events remain lacking.

Added value of this study

This study represents the first comprehensive pharmacovigilance investigation conducted according to

READUS-PV guidelines, analyzing large-scale pharmacovigilance data from the FAERS and VigiBase databases. It identifies a semaglutide-specific association with depressive disorders while liraglutide and tirzepatide showed no such signals, establishing this as a drug-specific rather than class-wide effect. Using disproportionality and time-to-onset analysis, the study highlights semaglutide’s potential psychiatric risks, particularly for female patients. These findings present a striking contrast to established protective effects of GLP-1RAs, revealing important differences between controlled clinical trial populations and real-world patient experiences.

Implications of all the available evidence

Given the apparent contradiction between our pharmacovigilance signals and established protective effects of GLP-1RAs, clinicians should carefully monitor patients, especially those with a psychiatric history. Our findings suggest the need for drug-specific rather than class-wide monitoring protocols, particularly for patients with psychiatric risk factors. Stratified analyses revealing increased disproportionality in females and healthcare professional reports provide guidance for targeted surveillance strategies. While this study provides important insights, larger-scale prospective studies with active psychiatric assessment are necessary to validate these findings and explore the underlying mechanisms of these psychiatric effect.

Introduction

An alarming global health crisis is unfolding as 537 million adults battle diabetes and over 650 million face obesity,¹ conditions often intertwined with a significant and frequently overlooked comorbidity: depression.^{2,3} Studies indicate that individuals with diabetes and obesity are at twice the risk of developing depression, creating a vicious cycle where metabolic dysfunction exacerbates mood disorders,^{4,5} while depression itself hinders adherence to treatment regimens and lifestyle changes.⁶ This dual epidemic has profound implications for both patient well-being and treatment efficacy, demanding urgent attention from clinicians and researchers alike.

The burden of this dual crisis is set to worsen in the coming decades. Global projections predict that the number of people with diabetes will increase to 783 million by 2045,⁷ exacerbating the ongoing challenge of managing both metabolic and mood disorders. Against this backdrop, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a transformative class of drugs, offering a promising solution to multiple facets of metabolic dysfunction. Semaglutide, for example, was approved by the FDA in 2017 for the treatment of diabetes and in 2021 for obesity, triggering

unprecedented global demand.⁸ In March 2024, semaglutide made another significant leap by becoming the first anti-obesity medication approved for cardiovascular risk reduction in patients with established heart disease.⁹ Similarly, tirzepatide, a novel dual GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, received FDA approval for type 2 diabetes in 2022 and for weight management in 2023, further expanding the clinical potential of GLP-1RAs.¹⁰

Despite their remarkable benefits, the safety profile of GLP-1RAs has raised increasing concerns, particularly regarding their potential neuropsychiatric effects. While gastrointestinal side effects are well-characterized and generally manageable,^{11,12} there have been troubling reports of more serious psychiatric events, including suicidal ideation and self-harm. Notably, the Icelandic Medicines Agency recently alerted European regulators to 150 cases of GLP-1RA-related suicidal or self-injurious behaviors, underscoring the urgency of addressing these safety concerns.¹³ Other signals of disproportionate reporting (SDRs), including alopecia and aspiration, have also been identified, while the current product labeling only mentions mild neurological side effects such as dizziness and taste disturbances.^{14,15} This creates a

concerning gap in our understanding of the full mental health implications of these medications.¹⁶

The relationship between GLP-1RAs and depression is particularly concerning, given that GLP-1 receptors are widely expressed in regions of the central nervous system involved in mood regulation.¹⁷ The complex interactions between metabolic changes, rapid weight loss, and psychological well-being may create multiple pathways through which these medications could impact mood states. Despite these potential concerns, comprehensive studies on the risk of depression associated with GLP-1RAs remain strikingly scarce.¹⁸ This gap in the literature has critical clinical implications, as millions of patients are prescribed these medications without sufficient understanding of their neuropsychiatric safety.

Traditional clinical trials evaluating GLP-1RAs are often limited in their ability to assess neuropsychiatric outcomes. They typically exclude patients with pre-existing psychiatric conditions—the very population most vulnerable to adverse mental health effects.^{19,20} Additionally, the short duration of follow-up in these trials may fail to capture delayed-onset psychiatric events. Moreover, these trials primarily focus on metabolic endpoints, leaving important safety concerns unaddressed. Real-world data, however, offer a complementary approach by capturing longer-term outcomes across a broader, more diverse patient population. Databases such as the FDA Adverse Event Reporting System (FAERS) and the World Health Organization's global Individual Case Safety Report database (VigiBase) contain extensive post-marketing data that can provide valuable insights into the real-world safety profile of these medications.^{21,22}

This study aims to fill this critical gap by analyzing real-world adverse event reporting data to assess the potential relationship between GLP-1RAs and depression. However, it is important to note that recent systematic reviews and meta-analyses have demonstrated that GLP-1RAs may actually exert protective effects against depression. A comprehensive meta-analysis of 2071 participants showed that GLP-1RAs significantly decreased depression rating scale scores compared to control treatments.²³ Additionally, systematic reviews examining GLP-1RAs as protective factors for incident depression have shown mixed but generally favorable results, with some studies demonstrating significant risk reduction.²⁴ These findings create an apparent paradox with emerging pharmacovigilance signals that requires careful interpretation and may reflect the complex interplay between metabolic interventions, weight loss, and mood regulation.²⁵ Through comprehensive disproportionality analysis, detailed time-to-onset characterization, and evaluation of potential drug interactions, this investigation will offer crucial insights into the neuropsychiatric safety profile of GLP-

1RAs while acknowledging the broader context of contradictory evidence in the literature.

Methods

Data sources and study design

This pharmacovigilance study was conducted following the READUS-PV (REporting of studies Aimed at evaluating Disproportionality in pharmacovigilance Using real-world healthcare Data) guidelines to ensure transparency and reproducibility in disproportionality analysis. Individual case safety reports (ICSRs) for this study were obtained from two major pharmacovigilance databases: the FDA Adverse Event Reporting System (FAERS) and the WHO VigiBase database accessed through VigiAccess. For the FAERS database, we accessed quarterly data extraction files from the official U.S. FDA website, covering ASCII data packages from Q1 2004 through Q4 2024. Full individual case safety reports with complete demographic and clinical data were available for comprehensive analysis. For the VigiBase database, data were retrieved through the VigiAccess public interface (<https://vigiaccess.org/>) using Python 3.10, encompassing all publicly available drug data up until December 2024. Notably, VigiAccess provides only aggregated reporting data rather than individual case reports, which prevents detailed demographic analyses but enables disproportionality assessment.

Both data sources contain information related to post-marketing safety surveillance reports in the form of ICSR submitted by healthcare professionals, consumers, and other sources.²⁶ To address potential biases from duplicate or implausible reports, we implemented comprehensive data cleaning and normalization procedures following established pharmacovigilance standards. For the FAERS database, duplicate ICSR were identified and removed using the FDA-recommended deduplication algorithm based on CASE ID, FDA_DT (FDA receipt date), and MFRID (manufacturer report ID). When multiple versions of the same case existed, we retained the most recent version with the highest CASE ID. Data validation procedures excluded reports with missing or invalid temporal information, including cases where EVENT_DT preceded START_DT, contained future dates, or had non-existent dates from time-to-onset analyses. The VigiAccess platform returned data in JSON format, which was subsequently processed and analyzed using the Pandas package for data manipulation and quality assessment. Standardization procedures encompassed MedDRA terminology harmonization (version 27.1) for adverse event coding, drug name mapping to WHO Drug Dictionary BASENAME entries, and date format standardization across both databases. The flow of data processing is detailed in Fig. 1.

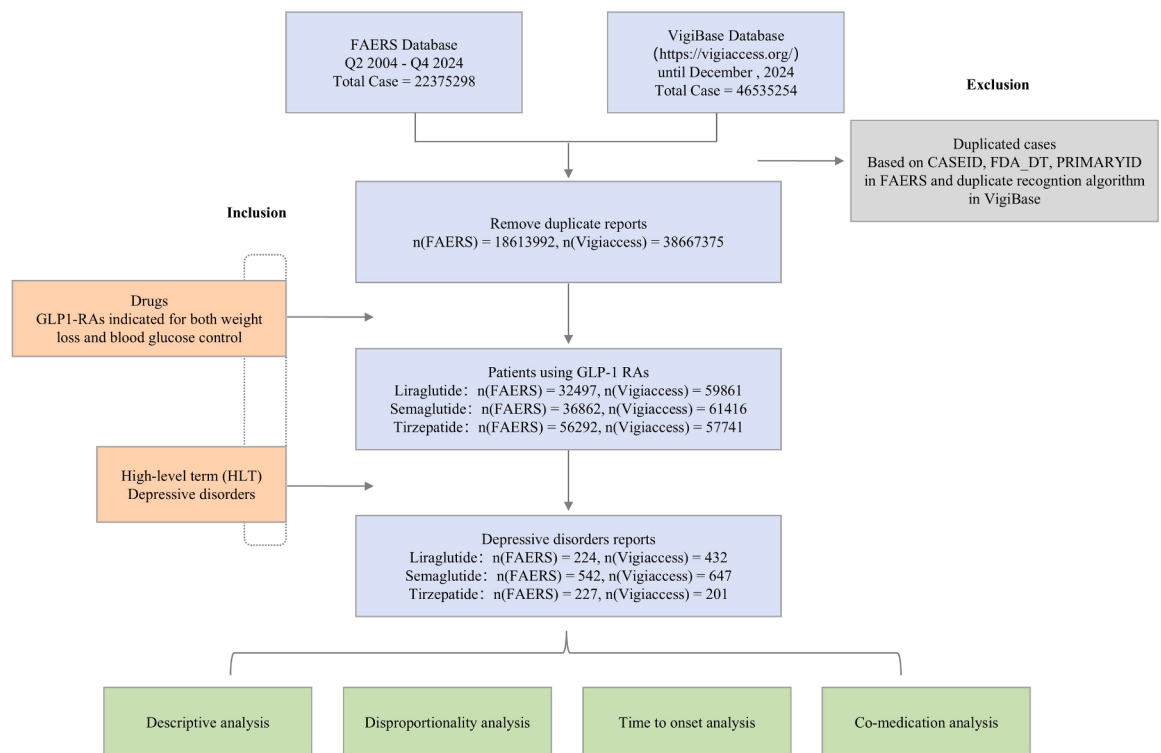


Fig. 1: Flow chart showing the analysis process of the study. The flowchart illustrates the complete process of data extraction and processing from the FAERS and VigiBase databases, including data screening, deduplication, application of exclusion criteria, and the final number of cases included in the analysis. Abbreviations: FAERS, FDA Adverse Event Reporting System.

Adverse events and drug identification

In both databases, ADRs are classified according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology in terms of signs and symptoms, which are called preferred terms (PTs).²⁷ The ADRs of interest include Depression, Major depression, and Depression suicidal (Supplementary file: [Supplementary Table S1](#)), which are homogeneously attributed to a high-level term (HLT) named depressive disorders by MedDRA (version 27.1). To ensure comprehensive capture of depression-related adverse events, we pre-planned complementary analyses using different MedDRA classification approaches. While our primary analysis focused on HLT-level “depressive disorders,” we recognized that certain depression-related PTs (e.g., “Depressed mood,” “Discouragement”) are excluded from this HLT category but included in the Standardized MedDRA Query (SMQ) “Depression (excluding suicide and self-injury).” Therefore, we pre-specified a supplementary SMQ-level analysis to capture these additional depression-related events. Standardized drug terminologies (i.e., generic non-proprietary drug name, liraglutide, semaglutide and tirzepatide) were utilized to ensure consistency in data representation. For the analysis of depressive disorders following GLP-1RAs

treatment, we only considered cases where liraglutide, semaglutide and tirzepatide were identified as the “primary suspect (PS)” drug in FAERS or a “suspect” drug in VigiAccess.

Disproportionality analysis

We employed a case/non-case approach akin to a case-control study design. Cases were defined as reports involving depressive disorders, while non-cases included all other adverse event reports in FAERS or VigiBase. Within this cohort, we assessed disproportionality: if the proportion of GLP1-RA exposure is higher in reports with depressive disorders (cases) compared to reports without depressive disorders (non-cases), an association between the medication and the event can be hypothesized, indicating a signal of disproportionate reporting (SDR). Additionally, we conducted stratified analyses by gender, age groups, and reporter type in the FAERS database. To address potential confounding by indication given the known association between diabetes/obesity and depression, we also performed sensitivity analyses using active therapeutic comparators, including antidiabetic medications (metformin), SGLT-2 inhibitors (empagliflozin), and anti-obesity drugs (orlistat). Additionally, to

evaluate the potential impact of notoriety bias on reporting patterns, we conducted temporal stratified disproportionality analysis using July 2023 as the index date to assess changes in signal detection before and after increased public attention to neuropsychiatric safety concerns.

There is currently no gold standard methodology for detecting SDRs. In this study, we utilized reporting odds ratio (ROR) and Bayesian information component (IC) to examine the likelihood of an AE of interest for a suspected drug as reported previously.^{28,29} The ROR method generated SDRs when the number of reports (n) was greater than or equal to 3 and the lower bound of the 95% confidence interval (CI) exceeded 1, with higher ROR values indicating stronger signal intensity. While the IC was deemed significant if the 95% CI Lower (IC₀₂₅) was above 0. To ensure robust signal detection, AEs were considered significant only when identified by both methodological approaches. All analyses were conducted using the 2 × 2 contingency table for disproportionality assessment, with detailed mathematical formulae for both ROR and IC calculations provided in Supplementary file: [Supplementary Table S2](#).

Time-to-onset analysis

The interval between AE occurrence (EVENT_DT, DEMO file) and GLP-1RAs use (START_DT, THER file) is used to estimate time-to-onset (TTO). We used cumulative distribution curves to present the event-to-onset characteristics of depressive disorders following treatment with different GLP-1RAs, based on data from FAERS. For semaglutide-associated depressive disorders, a Weibull Shape Parameter (WSP) analysis was conducted at the PT level to assess whether the reporting pattern varied over time.³⁰

While integrating the median, quartiles, minimum, maximum, and WSP evaluation for TTO, data issues such as EVENT_DT preceding START_DT, erroneous dates, and nonexistent data are excluded to assure study precision.

Co-medication analysis

We used the Ω shrinkage to measure drug-drug interactions because a previous study showed that it is the most conservative method among multiple algorithms.³¹ The detection criterion is the lower limit of the 95% CI of the Ω (Ω_{025}) > 0. The calculation process of Ω and the list of drugs were described in Supplementary file: [Supplementary Table S3](#). When at least one neuropsychiatric drug (such as antipsychotics, antidepressants, and anxiolytics) was recorded in the report, the patient was defined to have a medication history.

Statistics

Statistical analyses were performed using SAS 9.4 software, with all procedures conducted in accordance

with the FDA guidance documents for signal detection methodologies and Uppsala Monitoring Centre (UMC) standards for disproportionality analysis. Kaplan-Meier plots show cumulative proportion of reported events, and Kruskal-Wallis Test compare groups. The WSP analysis characterizes the temporal distribution of reported events using the scale (α) and shape (β) parameters, which determine the distribution function's characteristics. The scale parameter α represents the time at which 63.2% of reported events have occurred within the distribution. The shape parameter β describes the temporal reporting pattern: $\beta < 1$ indicates a decreasing reporting rate over time (early-failure type), $\beta > 1$ indicates an increasing reporting rate over time (wear-out failure type), and $\beta = 1$ suggests a constant reporting rate throughout the observation period (random failure type).

All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant. Confidence intervals were calculated at the 95% level for all estimates.

Global assessment of the evidence

Causality was assessed using the adjusted Bradford Hill criteria used in epidemiology to assess the causality of the entire evidence, including multiple dimensions such as biological plausibility, strength, consistency, specificity, coherence, and analogy.³² With these approaches, we hope to assess evidence for the potential association between GLP-1RAs and depressive disorders.

Ethics

The FAERS and VigiAccess database are publicly accessible. Both databases anonymize and de-identify patient records. Consequently, ethical clearance and informed consent are exempted for this study.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Data overview of adverse events reported in the FAERS and VigiAccess

As of December 31, 2024, ICSRs for the three drugs were collected from the FAERS and VigiAccess databases: liraglutide had 74,308 (involving 32,497 patients) and 138,852 (involving 59,861 patients) reports, respectively; semaglutide had 107,600 (involving 36,862 patients) and 159,255 (involving 61,416 patients) reports; and tirzepatide had 115,325 (involving 56,292 patients) and 114,421 (involving 57,741 patients)

Characteristic	Reports of depressive disorders (FAERS)		
	Liraglutide n = 224, (%)	Semaglutide n = 535, (%)	Tirzepatide n = 227, (%)
Sex			
Male	159 (70.98)	371 (69.35)	52 (22.91)
Female	58 (25.89)	124 (23.18)	146 (64.32)
Unknown or missing	7 (3.13)	40 (7.48)	29 (12.78)
Age (year)			
<18	3 (1.34)	NA	NA
18–44	18 (8.04)	115 (21.50)	53 (23.35)
45–64	76 (33.93)	174 (32.52)	69 (30.83)
≥65	28 (12.50)	78 (14.58)	29 (12.78)
Unknown or missing	99 (44.20)	168 (31.40)	76 (33.48)
Weight (kg)			
≤80	11 (4.91)	64 (11.96)	20 (8.93)
80–100	13 (5.80)	75 (14.02)	30 (13.39)
≥100	29 (12.95)	83 (15.51)	24 (10.57)
Unknown or missing	171 (76.34)	313 (58.50)	153 (67.40)
Reporter ^a			
Healthcare professional	71 (31.70)	179 (29.73)	24 (10.71)
Non-healthcare professional	148 (66.07)	414 (68.77)	202 (90.18)
Unknown or missing	5 (2.23)	9 (1.50)	1 (0.45)
Reporter country			
United States of America	164 (73.21)	397 (71.43)	193 (85.02)
United Kingdom	11 (4.91)	34 (7.97)	20 (8.93)
Canada	8 (3.57)	24 (4.49)	NA
Germany	NA	NA	3 (1.34)
Serious report ^b			
Serious	105 (46.88)	370 (69.16)	101 (45.09)
Non-serious	119 (53.12)	172 (32.15)	126 (56.25)
Indication			
Type 2 diabetes mellitus	74 (33.03)	167 (31.21)	70 (30.84)
Weight loss	34 (15.18)	158 (29.53)	64 (28.19)
Others	2 (0.90)	7 (1.31)	3 (1.32)
Unknown or missing	114 (50.89)	203 (37.94)	90 (39.65)
Outcome ^b			
Death	2 (0.90)	8 (1.50)	3 (1.32)
Life-threatening	7 (3.13)	55 (10.28)	8 (3.52)
Hospitalization	26 (11.61)	58 (10.84)	26 (11.45)
Disability	9 (4.02)	49 (9.16)	6 (2.64)
Required intervention to prevent permanent impairment/damage	2 (0.90)	43 (8.04)	6 (2.64)
Other serious illness	82 (36.61)	282 (52.71)	77 (34.07)
Unknown or missing	119 (53.13)	172 (32.15)	126 (55.51)

FAERS, FDA Adverse Event Reporting System; NA, not applicable. ^aHealthcare professionals including reporters such as physicians and pharmacists; non-healthcare professionals including reporters such as consumer and lawyer. ^bSince a case may experience different clinical outcomes during drug therapy, it is reasonable that the sum percentage of the outcome under this item may exceed 100%.

Table 1: Clinical and demographic characteristics of adverse events associated with Liraglutide, Semaglutide, and Tirzepatide.

reports. Detailed demographic information for all adverse reactions can be found in Supplementary file: [Supplementary Table S4](#). When SDRs for AEs associated with the three drugs were categorized according to System Organ Class (SOC), gastrointestinal disorders and general disorders and administration site conditions were the most numerous SOC categories for all three drugs in both the FAERS and VigAccess

databases, as detailed in Supplementary file: [Supplementary Table S5](#). Next, all SDRs at the PT level were analyzed, focusing on the top 50 most frequent and highest signal strength detections appearing in both the VigAccess and FAERS databases, see Supplementary file: [Supplementary Fig. S1](#).

Descriptive analysis

Due to VigAccess data accessibility limitations that provide only aggregated reporting data rather than individual case safety reports, detailed demographic characteristic analysis was only conducted for FAERS data during the study period. In the FAERS database, 224, 535, and 227 reports of depressive disorders related to liraglutide, semaglutide, and tirzepatide were found ([Table 1](#)). Despite some missing or unknown data, the proportion of reports for females was significantly higher than for males (male-to-female ratio approximately 1:3), with the 45–64 age group having the highest percentage (32.4%). Type 2 diabetes and weight reduction were the main indications, and patients were generally overweight, with the proportion of patients ≥100 kg being 12.95%, 15.51%, and 10.57% for liraglutide, semaglutide, and tirzepatide, respectively. As depicted in [Fig. 2](#), the distribution of reporting years for semaglutide and tirzepatide-related depressive disorders adverse reactions showed a year-by-year increasing pattern, with a noticeable upward trend observed in 2024; the number of annual reports for liraglutide remained relatively stable. Geographic analysis revealed that the United States contributed 164 reports (73.21%), 397 reports (71.43%), and 193 reports (85.02%) of depression-related adverse events for liraglutide, semaglutide, and tirzepatide, respectively. Among the remaining reports, European countries and other developed healthcare systems contributed the majority, while developing regions showed lower reporting frequencies.

Disproportionality analysis

Comparing GLP-1RAs with other drugs in the FAERS database, the disproportionality analysis results for depressive disorders-related adverse reactions indicated that semaglutide (ROR, 1.26, 95% CI, 1.15–1.37; IC, 0.33, 95% CI, 0.20–0.45) showed a statistically significant SDR, while liraglutide (ROR, 0.75, 95% CI, 0.66–0.85; IC, −0.41, 95% CI, −0.61 to −0.22) and tirzepatide (ROR, 0.49, 95% CI, 0.43–0.56; IC, −1.03, 95% CI, −1.22 to −0.83) showed significantly lower reporting rates for depressive disorders compared to other drugs in the database, indicating no SDR. The VigAccess data almost confirmed these results: liraglutide (ROR, 1.05, 95% CI, 0.96–1.16; IC, 0.08, 95% CI, −0.06 to 0.21), semaglutide (ROR, 1.38, 95% CI, 1.27–1.49; IC, 0.46, 95% CI, 0.34–0.57), tirzepatide (ROR, 0.59, 95% CI, 0.51–0.68; IC, −0.75, 95% CI, −0.95 to −0.54), as shown in [Fig. 3](#). In both databases, we further calculated the

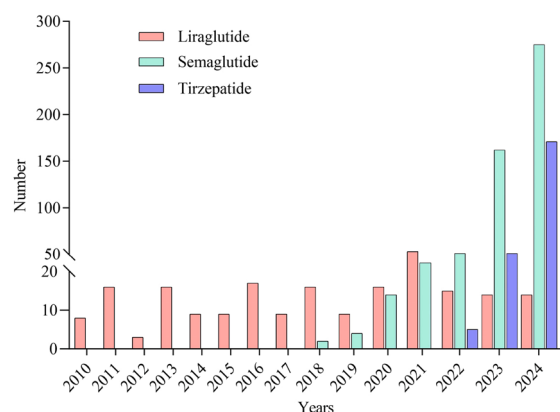


Fig. 2: Annual reporting numbers of depressive disorders adverse events associated with GLP-1RAs in FAERS database. The figure shows the annual trends of depressive disorders adverse events reports for liraglutide, semaglutide, and tirzepatide from 2004 to 2024. A year-by-year increasing trend can be observed for semaglutide and tirzepatide, with a notable upward trend in 2024.

pattern of PT level disproportion corresponding to depressive disorders. Again, only a positive SDR was present for semaglutide; raw data for the above analysis are shown in Supplementary file: [Supplementary Table S6](#).

As pre-planned, we conducted supplementary SMQ-level analysis for 'Depression (excluding suicide and self-injury)' to capture additional depression-related PTs not included in our primary HLT analysis. Consequently, we conducted disproportionality analysis at the SMQ level for Depression (excluding suicide and self-injury) across both databases. These results aligned with our HLT level findings, with only semaglutide showing positive SDRs: FAERS database (ROR, 1.12,

95% CI, 1.04–1.21; IC, 0.17, 95% CI, 0.06–0.28) and VigAccess database (ROR, 1.59, 95% CI, 1.50–1.69; IC, 0.67, 95% CI, 0.58–0.75). Complete data for these analyses are available in the Supplementary file: [Supplementary Table S7](#).

In the comparative disproportionality analysis of GLP-1RAs versus three reference drugs (orlistat, metformin, and empagliflozin), we found that semaglutide demonstrated disproportionate reporting signals compared to all three reference medications. Tirzepatide showed no disproportionate reporting signals when compared to any of the three reference drugs. Liraglutide exhibited disproportionate reporting signals compared to metformin and empagliflozin, but showed no disproportionate reporting signal when compared to orlistat. Complete data for these analyses are available in the [Table 2](#).

To assess individual characteristics and potential risk factors for semaglutide-induced depressive disorders adverse reactions, stratified analyses were conducted based on gender, age, and reporter in FAERS ([Fig. 4](#)). Stratified analysis by gender showed that the ROR and IC were slightly elevated in females (ROR, 1.25, 95% CI, 1.13–1.38; IC, 0.32, 95% CI, 0.17–0.47). When stratified by age, SDRs were observed across all age groups. In the stratified analysis by reporter, we found positive SDRs in Healthcare Professional reports (ROR, 1.78, 95% CI, 1.52–2.08; IC, 0.82, 95% CI, 0.58–1.08). Additionally, to evaluate the potential impact of notoriety bias on our findings, we conducted temporal stratified analysis using July 2023 as the index date, coinciding with the European Medicines Agency's initiation of safety review for GLP-1RA-associated neuropsychiatric events. In Q2 2023 and earlier, semaglutide showed no disproportionate reporting signal for depressive disorders (ROR, 0.66, 95% CI, 0.56–0.77;

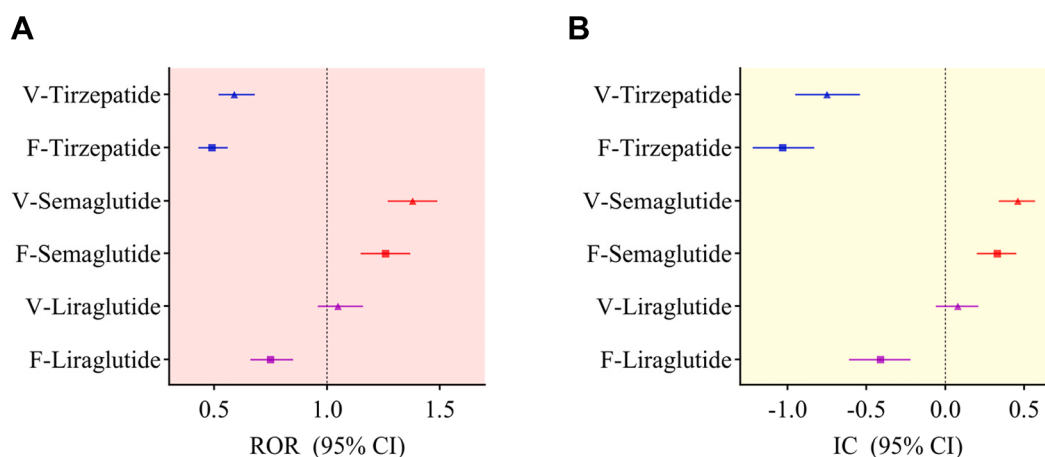


Fig. 3: Results of overall disproportionality analysis for GLP-1RAs-associated depressive disorders adverse in two database. (A) and (B) show forest plots for ROR and IC, respectively. Abbreviations: The "V" in front of the drug stands for VigAccess, and the "F" stands for FAERS; ROR, Reporting Odds Ratio; CI, Confidence Interval; IC, Bayesian Information Component.

Drug 1 (case)		Drug 2 (non-case)		ROR	95% CI	IC	95% CI
Liraglutide	224	Orlistat	116	1.38	1.11–1.73	0.17	–0.075 to 0.42
Liraglutide	224	Metformin	368	1.94	1.64–2.29	0.66	0.43–0.88
Liraglutide	224	Empagliflozin	67	2.88	2.19–3.78	0.51	0.25–0.77
Semaglutide	542	Orlistat	116	2.32	1.90–2.83	0.30	0.13–0.46
Semaglutide	542	Metformin	368	3.25	2.85–3.71	0.93	0.77–1.08
Semaglutide	542	Empagliflozin	67	4.82	3.74–6.22	0.50	0.33–0.67
Tirzepatide	227	Orlistat	116	0.90	0.72–1.13	–0.052	–0.30 to 0.19
Tirzepatide	227	Metformin	368	1.06	1.07–1.49	0.22	–0.087 to 0.44
Tirzepatide	227	Empagliflozin	67	1.58	1.19–2.10	0.26	–0.024 to 0.51

Note: ROR, reporting odds ratio; CI, confidence interval; IC, Bayesian information component.

Table 2: Disproportionality analysis of GLP-1RAs-associated depressive disorders versus reference non-GLP-1RA drugs in the FAERS database.

IC, –0.61, 95% CI, –0.85 to 0.36), while in Q3 2023 onwards, semaglutide demonstrated significant disproportionate reporting signals for depressive disorders (ROR, 2.52, 95% CI, 2.28–2.78; IC, 1.31, 95% CI, 1.16–1.45).

Time-to-onset analyses

We analyzed the time-to-onset in the FAERS database. Among the ICSRs reporting depressive disorders associated with liraglutide, semaglutide and tirzepatide, time-to-onset data were available for 38, 180 and 67 reports, respectively. The median times to onset for depressive disorders associated with liraglutide, semaglutide and tirzepatide were 28.0 (3.5–40.0), 23.0 (1.0–69.0) and 31.0 (5.5–84.0) days, respectively. The Kaplan–Meier analysis of time-to-onset patterns for depressive disorders is presented in Fig. 5. The cumulative occurrence of these psychiatric adverse events showed no statistically significant differences among the three GLP-1RAs (Kruskal–Wallis test, $p > 0.05$).

To assess whether the likelihood of semaglutide-related depressive disorders changes over time, we conducted WSP analysis on PTs with SDRs at the high-level term (Table 3). Depression was classified as early failure type, depression suicidal as a random failure type.

Co-medication analysis

In the FAERS database, we conducted a co-medication analysis of the neuropsychiatric medications with the highest reported frequency of use for liraglutide, semaglutide and tirzepatide-associated depressive disorders. Multiple neuropsychiatric drugs, including fluoxetine, bupropion, escitalopram, venlafaxine and aripiprazole, were identified, and disproportionality analysis with depressive disorders yielded a reporting signal. Subsequent Ω shrinkage results indicated no potential for drug-drug interactions between GLP-1RAs and neuropsychiatric drugs (all $\Omega_{025} < 0$; refer to Table 4 for the medications' ROR, IC_{025} , and Ω_{025}).

Global assessment of the evidence

By evaluating adopted Bradford Hill criteria, the associations between semaglutide and depressive disorders failed to meet the majority of criteria for causality assessment. The assessment revealed contradictions in biological plausibility and coherence due to established neuroprotective mechanisms of GLP-1RAs, compromised consistency due to contradictory clinical evidence, weak association strength, and contradicted analogy with other GLP-1RAs showing protective effects. Only temporal relationship was partially met. Overall, while a pharmacovigilance SDR exists, the Bradford Hill criteria assessment indicated insufficient evidence for establishing causal inference. More details are shown in Table 5.

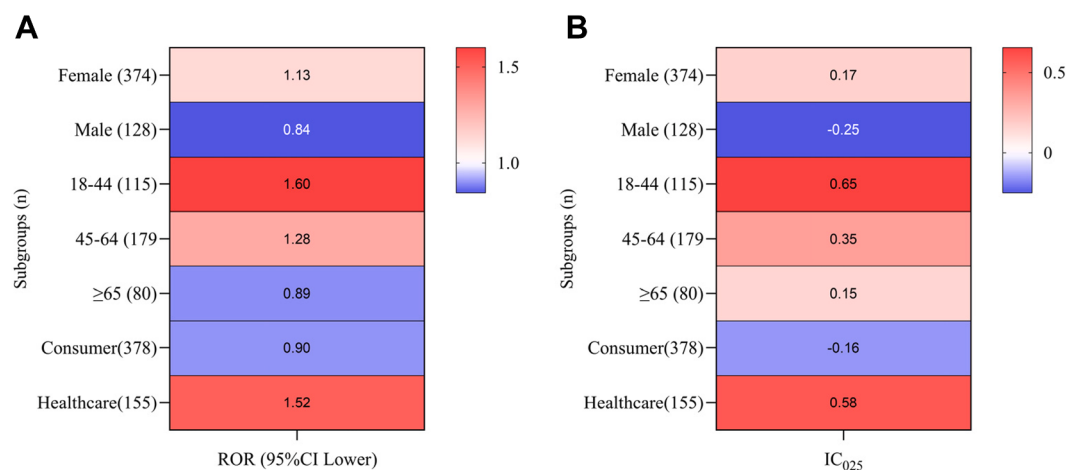


Fig. 4: Results of subgroup disproportionality analysis of GLP-1RAs-associated depressive disorders adverse events stratified by sex, age and reporter type in FAERS database. (A) and (B) show ROR and IC values stratified by different subgroups, respectively. Abbreviations: ROR, Reporting Odds Ratio; CI, Confidence Interval; IC_{025} , 95% Confidence Interval Lower of Bayesian Information Component.

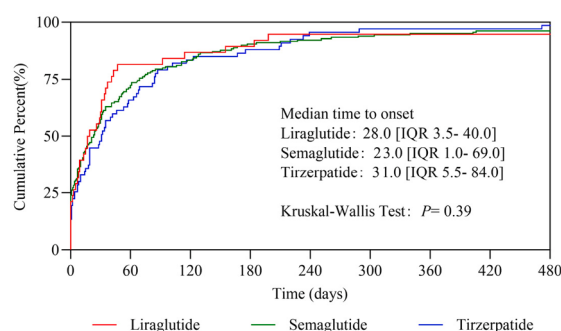


Fig. 5: Cumulative distribution functions of time-to-onset for depressive disorders associated with different GLP-1RAs in FAERS database. The figure shows the time-to-onset distribution patterns for depression-related adverse events associated with liraglutide, semaglutide, and tirzepatide. The median times to onset were 28.0 days (IQR: 3.5–40.0), 23.0 days (IQR: 1.0–69.0), and 31.0 days (IQR: 5.5–84.0) for liraglutide, semaglutide, and tirzepatide, respectively. Kruskal-Wallis test showed no statistically significant differences in cumulative occurrence among the three GLP-1RAs ($p > 0.05$). Abbreviations: IQR, Interquartile Range.

Discussion

This pharmacovigilance study examining depression-related adverse events across multiple GLP-1RAs, conducted according to READUS-PV guidelines, identified a novel semaglutide-specific SDR that was consistently observed across both FAERS and Vigibase databases. Notably, liraglutide and tirzepatide showed no disproportionality signals, suggesting a potential drug-specific rather than class-wide effect. The validity of this finding was strengthened through multiple complementary analyses, including HLT and SMQ-level assessments, active comparator evaluations against metformin, empagliflozin, and orlistat, and stratified analyses by demographics and reporter type.

Our findings present an apparent paradox when considered against established clinical evidence. Recent systematic reviews and meta-analyses have demonstrated protective effects of GLP-1RAs against depression, with a comprehensive meta-analysis of 2071 participants showing significant decreases in depression rating scales compared to controls.²³ Several clinical studies have reported mood improvements

following GLP-1RA treatment, particularly in diabetic populations.^{24,25} This contradiction between our pharmacovigilance signals and controlled clinical trial evidence highlights important differences between controlled study populations and real-world patient experiences.

The discrepancy may reflect several factors unique to post-marketing surveillance. Clinical trials typically exclude patients with psychiatric comorbidities—precisely the population most vulnerable to mood-related adverse events.³³ Additionally, the short follow-up periods in controlled trials may fail to capture delayed-onset psychiatric effects, while our analysis encompasses longer-term real-world outcomes. The protective effects observed in clinical studies may be confounded by intensive medical supervision, careful patient selection, and concurrent lifestyle interventions that are absent in routine clinical practice.

The geographic distribution of depression-related adverse event reports provides valuable insights into pharmacovigilance patterns and healthcare system characteristics. The predominance of reports from the United States (73.21%, 71.43%, and 85.02% for liraglutide, semaglutide, and tirzepatide, respectively) and other developed healthcare systems reflects established pharmacovigilance infrastructure capabilities and market penetration patterns, corresponding to regions with robust adverse event reporting mechanisms, trained healthcare professional networks, and widespread GLP-1RA clinical adoption. The higher reporting frequencies from developed healthcare systems may reflect greater awareness of neuropsychiatric adverse events and more systematic monitoring practices, potentially facilitating earlier detection of emerging safety signals, while standardized diagnostic criteria and consistent psychiatric evaluation practices may reduce heterogeneity in signal interpretation compared to more diverse international datasets.

The temporal stratified analysis reveals important considerations for pharmacovigilance signal interpretation. The transition from no disproportionate reporting signal (Q2 2023 and earlier) to significant disproportionate reporting (Q3 2023 onwards) illustrates the temporal variability inherent in spontaneous reporting systems. While this pattern may reflect

PT	Time-to-onset (days)			Weibull distribution				Failure type
				Scale parameter		Shape parameter		
	N	Median (IQR)	Min-Max	α	95% CI	β	95% CI	
Depression	492	21.0 (2.0, 69.0)	0–1116	74.67	57.70–96.62	0.71	0.62–0.80	Early failure
Depression suicidal	29	0.0 (0.0, 15.5)	0–111	46.85	13.75–159.65	0.98	0.40–2.39	Random failure
Note: Text in bold signifies that the signal is categorized as an important medical events (IMEs). IMEs are developed and updated by European Medicines Agency (EMA). IQR, Interquartile Range.								
Table 3: Time-to-onset analysis of semaglutide-related depressive disorders signals using the Weibull distribution test in the FAERS database.								

Drug 2	Disproportion analysis					Drug 1					
	N	ROR	95% CI	IC	95% CI	Liraglutide		Semaglutide		Tirzepatide	
						Ω	$\Omega_{0.25}-\Omega_{0.95}$	Ω	$\Omega_{0.25}-\Omega_{0.95}$	Ω	$\Omega_{0.25}-\Omega_{0.95}$
Duloxetine	3177	3.09	2.99–3.21	1.60	1.55–1.65	0.51	–2.32 to 3.34	1.84	–0.16 to 3.84	NA	NA
Venlafaxine	2236	3.31	3.17–3.45	1.70	1.64–1.76	NA	NA	–0.24	–2.24 to 1.76	NA	NA
Sertraline	2150	2.88	2.76–3.01	1.51	1.44–1.57	NA	NA	0.45	–0.96 to 1.87	–0.75	–3.57 to 2.08
Aripiprazole	1892	2.18	2.08–2.28	1.11	1.04–1.18	NA	NA	1.66	–0.34 to 3.66	NA	NA
Fluoxetine	1275	3.28	3.10–3.47	1.70	1.61–1.77	–0.55	–2.55 to 1.45	0.81	–0.82 to 2.44	NA	NA
Escitalopram	1082	3.11	2.93–3.30	1.62	1.53–1.71	0.64	–2.19 to 3.46	0.54	–1.46 to 2.54	NA	NA
Citalopram	926	2.36	2.22–2.52	1.23	1.13–1.32	NA	NA	NA	NA	0.73	–2.09 to 3.56
Mirtazapine	621	2.26	2.09–2.45	1.17	1.05–1.28	NA	NA	NA	NA	NA	NA
Diazepam	222	0.97	0.85–1.10	–0.05	–0.24 to 0.15	1.19	–1.64 to 4.02	NA	NA	NA	NA
Trazodone	116	1.75	1.16–2.10	0.80	0.52–1.06	NA	NA	NA	NA	1.53	–1.29 to 4.36

Note: ROR, reporting odds ratio; CI, confidence interval; IC, Bayesian information component; NA, not applicable.

Table 4: Disproportionality analysis of neuropsychiatric medications and drug-drug interaction assessment with GLP-1RAs in the FAERS database.

changes in reporting behavior following increased regulatory and media attention, it may also indicate genuine signal emergence as prescribing patterns expanded to broader patient populations beyond initial clinical trial cohorts. The observed temporal difference demonstrates the importance of incorporating temporal analysis in pharmacovigilance assessments, particularly for recently approved medications where reporting patterns may evolve as clinical experience accumulates and prescribing contexts changed.

The mechanism underlying the semaglutide-specific association remains unclear and contrasts with established neuroprotective pathways of GLP-1RAs. GLP-1 receptors are widely distributed throughout brain regions involved in mood regulation, and preclinical evidence suggests beneficial effects through neurotransmitter modulation, anti-inflammatory pathways, and enhanced neuroplasticity.^{34–36} However, the drug-specific nature of our findings suggests that semaglutide may possess unique pharmacokinetic

Criteria	Assessment	Description	Source/method
Strength of the association	Weak	Although ROR and ICs show a modest positive signal in pharmacovigilance databases, this contradicts clinical study evidence showing protective effects of GLP-1RAs against depression.	Disproportionality analysis, Clinical literature
Consistency	Inconsistent	While pharmacovigilance results are consistent across FAERS and VigAccess databases, they are fundamentally inconsistent with systematic reviews and meta-analyses demonstrating antidepressant effects of GLP-1RAs in clinical studies.	Disproportionality analysis, Literature review
Analogy	Contradicted	While isolated case reports exist, the majority of evidence for other GLP-1RAs (liraglutide, exenatide, dulaglutide) demonstrates neuroprotective and antidepressant effects. Our study found no depressive signals for liraglutide or tirzepatide, contradicting a class effect.	Literature, Current study findings
Biological plausibility/ empirical evidence	Contradicted	Established biological mechanisms contradict our observed association. GLP-1RAs demonstrate neuroprotective effects through: (1) anti-neuroinflammatory pathways, (2) beneficial modulation of neurotransmitter systems (serotonin, dopamine, GABA), (3) enhanced neuroplasticity and neurogenesis, (4) improved brain insulin signaling. These mechanisms theoretically support mood improvement rather than depression.	Preclinical and mechanistic studies
Exclusion of biases/ confounders	Not Met	Multiple potential confounders cannot be excluded: (1) indication bias (patients with obesity have higher baseline depression risk), (2) detection bias (increased media attention leading to enhanced reporting), (3) rapid weight loss psychological effects, (4) gastrointestinal side effects impacting mood. Pharmacovigilance databases cannot adequately control for these factors.	Disproportionality analysis, Methodological limitations
Specificity	Inconsistent	While only semaglutide showed signals in our pharmacovigilance analysis, this contradicts clinical literature where multiple GLP-1RAs demonstrate protective effects. The apparent specificity may reflect differential reporting patterns rather than true drug-specific effects.	Literature, Disproportionality analysis
Temporal relationship	Partially Met	Temporal relationship exists in pharmacovigilance data, but this alone is insufficient given the contradictory evidence from controlled clinical studies showing mood improvement with GLP-1RAs.	Time-to-onset analysis, Literature
Reversibility	Not Applicable	This criterion is of limited value here as there is no data on discontinuation and de-challenge in the FAERS and VigAccess database.	Not applicable
Coherence	Not Met	Our findings lack coherence with established scientific knowledge. The observed association conflicts with: (1) systematic reviews showing antidepressant effects, (2) established neuroprotective mechanisms, (3) clinical trial evidence of mood improvement, creating fundamental incoherence in the causal assessment.	Literature, Systematic reviews

Table 5: Global assessment through adapted Bradford Hill Criteria about Semaglutide.

properties, differential blood-brain barrier penetration, or specific receptor binding characteristics that distinguish it from other GLP-1RAs.³⁷ Importantly, tirzepatide, despite causing more severe gastrointestinal effects and greater weight loss, showed lower depression reporting rates. This pattern argues against common class-related factors such as gastrointestinal discomfort or rapid weight loss as primary explanatory mechanisms for the semaglutide association, further supporting semaglutide-specific rather than class-wide mechanisms.

The drug-specific nature of our findings has important implications for clinical practice and safety monitoring strategies. Rather than assuming uniform safety profiles across the GLP-1RA class, our results suggest the need for drug-specific monitoring protocols, particularly for patients with psychiatric risk factors.³⁸ The stratified analyses revealing increased disproportionality in females and healthcare professional reports provide guidance for targeted surveillance strategies. The early failure pattern identified through WSP analysis indicates that enhanced psychiatric monitoring during initial treatment phases may facilitate early detection and intervention.

These findings also emphasize the value of post-marketing surveillance in complementing clinical trial data. Our study demonstrates that pharmacovigilance databases can identify unexpected signals even for well-established drug classes with favorable trial safety profiles. The consistency of the semaglutide-specific SDR across independent databases, different analytical approaches, and active comparator assessments strengthens the validity of this signal and supports its clinical relevance despite not meeting traditional Bradford Hill causality criteria.

Several important limitations require acknowledgment when interpreting our results. Pharmacovigilance databases are subject to inherent reporting bias, incomplete data, and lack of appropriate denominators for incidence calculation.^{39,40} The substantial differences in market exposure times among the three GLP-1RAs—liraglutide (>15 years), semaglutide (7–8 years), and tirzepatide (2–3 years)—create potential temporal confounding through the Weber effect and differential baseline reporting patterns. Notoriety bias represents a particularly critical limitation, as increased media attention to GLP-1RA neuropsychiatric safety may have disproportionately affected semaglutide reporting during 2023–2024. Additionally, our Bradford Hill criteria assessment revealed insufficient evidence for causal inference, with contradictions in biological plausibility and weak association strength. These findings should therefore be interpreted as potential SDRs requiring further investigation rather than definitive evidence of causal relationships.

Future investigations should focus on prospective validation studies to definitively establish whether our

findings represent true safety signals or methodological artifacts. Mechanistic studies are needed to understand potential semaglutide-specific effects that distinguish it from other GLP-1RAs. The development of evidence-based risk stratification tools incorporating patient demographics, psychiatric history, and concurrent medications would enhance clinical decision-making. Long-term prospective cohort studies with active psychiatric assessment are particularly valuable given the limited neuropsychiatric safety data from controlled trials that typically exclude patients with psychiatric comorbidities.¹⁶

In conclusion, while our pharmacovigilance findings appear inconsistent with established protective effects of GLP-1RAs, they provide important complementary safety surveillance data that warrant continued clinical attention and investigation. The semaglutide-specific signal challenges class-wide safety assumptions and underscores the continued importance of robust post-marketing surveillance in complementing clinical trial evidence for comprehensive drug safety assessment.

This pharmacovigilance study examining depression-related adverse events across multiple GLP-1RAs identified a consistent semaglutide-specific signal in both FAERS and Vigibase databases, while liraglutide and tirzepatide showed no disproportionate reporting. This drug-specific finding challenges class-wide safety assumptions and reveals important heterogeneity within the GLP-1RA therapeutic class.

These findings demonstrate the value of post-marketing surveillance in identifying unexpected signals that may not emerge in controlled clinical trials. While our results contradict established evidence of GLP-1RA protective effects against depression, the consistency across independent databases and analytical approaches supports the validity of this signal. Important limitations include potential temporal confounding and notoriety bias, and disproportionality analysis cannot establish causality. Future prospective studies with active psychiatric assessment are needed to validate these findings and develop evidence-based monitoring protocols for clinical practice.

Contributors

Conceptualization, Min Wang, Sa Xiao, and Shao Liu; Formal analysis, Xiao-Hong Chen, Zai-Qiang Liu, and Zi-Yi Li; Resources, Min Wang, and Sa Xiao; Software, Xiao-Hong Chen, Zai-Qiang Liu, Zhi-Hong Zhu, and Zi-Yi Li; Supervision, Shao Liu, and Sa Xiao; Visualization, Zhi-Hong Zhu, Min Wang, and Zai-Qiang Liu; Writing—original draft, Min Wang, and Xiao-Hong Chen; Writing—review & editing, Sa Xiao, and Shao Liu had primary responsibility for final content. All authors read and approved the final version of the manuscript. Sa Xiao and Shao Liu have verified the underlying data.

Data sharing statement

This study utilizes data from the FAERS and Vigibase databases, both of which are publicly accessible. Further information is available from the corresponding author upon request.

Declaration of interests

All authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2025.103385>.

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