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Psychiatric Adverse Events Associated with GLP-1 Receptor Agonists: Evidence of Intraclass Heterogeneity in the WHO VigiBase Global Database

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Abstract

Background/Objectives: Concerns regarding the psychiatric safety profile of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have increased since the 2023 European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) reviews. However, it remains unclear whether this signal is uniform across the drug class or concentrated in specific compounds. This study aimed to characterize and compare, in a systematic manner, the global reporting patterns of psychiatric adverse drug reactions (ADRs) associated with the main GLP-1 RAs using the World Health Organization (WHO) VigiBase global pharmacovigilance database. **Methods:** A descriptive, cross-sectional pharmacovigilance study was conducted on individual case safety reports (ICSRs) retrieved from VigiAccess (January 2000–2026) for semaglutide, liraglutide, dulaglutide, exenatide, tirzepatide, and lixisenatide. A disproportionality analysis was performed within the MedDRA "Psychiatric disorders" System Organ Class (SOC) using the Reporting Odds Ratio (ROR) with 95% confidence intervals (CIs). This study adhered to the STROBE and READUS-PV guidelines. **Results:** A total of 537,519 ADR reports were analyzed across the five drugs with sufficient reporting volume (lixisenatide was excluded owing to n = 22 psychiatric events). Psychiatric disorders accounted for 24,899 reports, with marked intraclass heterogeneity in both the proportion of psychiatric reports (6.73% for semaglutide versus 3.12% for tirzepatide) and in disproportionality estimates. Signals of disproportionate reporting were identified exclusively for semaglutide (ROR 1.55; 95% CI 1.50–1.59) and liraglutide (ROR 1.19; 95% CI 1.15–1.23), whereas tirzepatide, dulaglutide, and exenatide showed point estimates below unity. **Conclusions:** The psychiatric safety profile of GLP-1 RAs is not homogeneous within the therapeutic class. The disproportionality signal is concentrated on semaglutide and, to a lesser extent, liraglutide. These findings extend previous WHO-based analyses limited to suicidality and support active clinical surveillance of psychiatric symptoms in patients treated with these specific agents.

Keywords: GLP-1 receptor agonists; pharmacovigilance; disproportionality analysis; VigiBase; psychiatric adverse events; semaglutide; liraglutide; intraclass heterogeneity

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1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide, and the dual GIP/GLP-1 agonist tirzepatide, have transformed the pharmacological management of type 2 diabetes mellitus (T2DM) and obesity. Beyond glycemic control, these agents have demonstrated sustained weight reduction and cardiovascular protection, and their prescription has grown exponentially worldwide over the past decade, driven by both approved indications and increasing off-label use for weight management [1,2].

These therapies exert their metabolic effects through coordinated pancreatic, gastrointestinal, peripheral, and central mechanisms. Activation of GLP-1 receptors enhances glucose-dependent insulin secretion from pancreatic β-cells while suppressing inappropriate glucagon release from α-cells, thereby reducing both postprandial and fasting glucose concentrations with a relatively low intrinsic risk of hypoglycemia. GLP-1 receptor activation also delays gastric emptying, particularly during the initial phases of treatment, which attenuates postprandial glucose excursions and contributes to early satiety. In parallel, signaling through hypothalamic and brainstem pathways involved in energy homeostasis reduces appetite, hunger, and caloric intake, representing a major mechanism underlying the weight loss observed with these agents. Additional peripheral effects, including improvements in insulin sensitivity, lipid metabolism, adipose tissue function, and cardiovascular physiology, may further contribute to their overall cardiometabolic benefits [3].

Tirzepatide additionally activates the GIP receptor, which may enhance its effects on glycemic regulation and body-weight reduction compared with selective GLP-1 receptor agonism [4]. Despite their shared incretin-based classification, these therapies are pharmacologically heterogeneous. Liraglutide and semaglutide are acylated human GLP-1 analogues with high sequence similarity to native GLP-1, whereas dulaglutide consists of a modified GLP-1 analogue linked to an immunoglobulin G4 Fc fragment. In contrast, exenatide and lixisenatide are derived from exendin-4 and therefore have lower sequence similarity to native human GLP-1 [3]. Tirzepatide is a 39-amino-acid peptide based predominantly on the GIP sequence and acts as a dual agonist at the GIP and GLP-1 receptors. These structural modifications confer resistance to enzymatic degradation and produce substantially different pharmacokinetic profiles. The approximate elimination half-lives range from 2–3 h for immediate-release exenatide and lixisenatide to approximately 13 h for liraglutide, approximately 5 days for dulaglutide and tirzepatide, and approximately 1 week for semaglutide; extended-release exenatide enables once-weekly administration. Bioavailability and absorption also vary according to the molecule and formulation, with most agents administered subcutaneously, while semaglutide is additionally available as an oral formulation with substantially lower bioavailability [3]. Anti-drug antibodies have been reported at variable frequencies across the class and tend to occur more frequently with exendin-4-derived compounds than with human GLP-1 analogues, although their clinical relevance has generally been limited. These pharmacological differences may influence patterns of exposure and clinical use but cannot be evaluated as mechanistic determinants of the reporting heterogeneity observed in the present study [4].

As exposure has expanded from the tightly controlled populations of phase III trials to broader real-world populations, concerns have emerged regarding less frequent but potentially serious adverse events. Among these, psychiatric reactions have attracted considerable regulatory and media attention. In July 2023, following reports submitted by the Icelandic medicines agency, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) initiated a class-wide review after identifying approximately 150 individual case safety reports of suicidal thoughts and self-

injury in users of liraglutide and semaglutide [5]. In parallel, the United States Food and Drug Administration (FDA) launched its own evaluation through the FDA Adverse Event Reporting System (FAERS). Although both agencies concluded in 2024 that the available evidence did not support a causal association, this signal prompted a sustained wave of pharmacoepidemiologic research into the psychiatric safety profile of this drug class [6].

Subsequent evidence has been inconsistent. Systematic reviews and meta-analyses of randomized clinical trials have not confirmed an increased risk of suicidal ideation or self-harm with GLP-1 RAs [7], and large cohort studies have even suggested a lower risk of incident suicidality in patients with obesity treated with these agents compared with other antihyperglycemic or anti-obesity therapies [8]. In contrast, disproportionality analyses of spontaneous reporting databases have detected statistically significant signals for semaglutide and liraglutide, both in FAERS [9,10] and in the WHO VigiBase database that underlies the present study [9,10]. More broadly, a recent systematic review synthesizing real-world and observational evidence reported increased risks of anxiety, depressive disorders, and suicidal behavior among GLP-1 RA users, while other analyses have described beneficial psychotropic effects in depression, anxiety, and substance use disorders [11]. This apparent contradiction reflects the methodological heterogeneity of available studies and the systematic exclusion of patients with psychiatric comorbidities from pivotal trials, which limits the generalizability of clinical trial safety data to the populations increasingly exposed in real clinical practice [12,13].

Within this context, post-marketing pharmacovigilance databases represent an essential complementary source of evidence, as they capture adverse events that phase III trials, constrained by strict exclusion criteria and limited sample sizes, are unable to detect. VigiBase, the WHO global database of individual case safety reports (ICSRs), is maintained by the Uppsala Monitoring Centre and aggregates spontaneous reports from more than 150 national pharmacovigilance programs, making it the largest pharmacovigilance repository worldwide. Its publicly accessible interface, VigiAccess, allows for large-scale signal detection across diverse geographic, demographic, and clinical settings [14]. To date, most pharmacovigilance analyses of the psychiatric safety of GLP-1 RAs have relied on FAERS [9], which predominantly reflects the reporting patterns of a single jurisdiction, and existing WHO-based analyses have focused exclusively on suicidality and have limited their scope to semaglutide and liraglutide [11]. A systematic and comparative characterization of the broader psychiatric adverse event profile across individual GLP-1 RAs using a truly global data source remains lacking.

The present study aimed to characterize and compare, in a systematic manner, the global reporting patterns of psychiatric adverse drug reactions associated with GLP-1 RAs, using the WHO VigiAccess database, to provide evidence that may help inform clinical practice and patient safety.

2. Materials and Methods

2.1. Study Design

A descriptive, cross-sectional pharmacovigilance study was conducted, based on spontaneous individual case safety reports (ICSRs) of adverse drug reactions (ADRs) associated with GLP-1 RAs, using the WHO global pharmacovigilance database through its public interface, VigiAccess. A disproportionality analysis was subsequently performed within the "Psychiatric disorders" System Organ Class (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA) to identify potential safety signals. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and to the Reporting of A Disproportionality analysis for Drug Safety signal detection using ICSRs in Pharmacovigilance (READUS-PV) guideline for pharmacovigi-

lance studies based on spontaneous reporting systems. The study period extended from 1 January 2000 to the data extraction date in 2026, encompassing the full post-marketing surveillance history of each product included in the analysis [15,16].

2.2. Data Source

Data were retrieved from VigiAccess, the public interface of VigiBase, the WHO global database of ICSRs, maintained by the Uppsala Monitoring Centre (UMC) on behalf of the WHO Program for International Drug Monitoring. VigiBase contains spontaneous safety reports submitted by national pharmacovigilance centers of more than 150 member countries since 1968, and currently holds more than 35 million ICSRs, making it the largest repository of suspected ADRs worldwide [14]. Reports are submitted by healthcare professionals, marketing authorization holders, and patients, and are standardized according to the ICH E2B format of the International Council for Harmonization. Adverse events are coded using MedDRA, which organizes ADRs in a hierarchical structure that includes 27 SOCs at the highest level and Preferred Terms (PTs) at the most granular clinical level. VigiAccess provides aggregated, de-identified data at the active substance level, regardless of brand name or manufacturer [17].

The following GLP-1 RAs were selected a priori based on their current global clinical relevance: semaglutide, liraglutide, dulaglutide, exenatide, tirzepatide, and lixisenatide. Reports were identified using the international non-proprietary name (INN) of each active substance. Lixisenatide was initially retrieved but subsequently excluded from comparative and disproportionality analyses owing to an insufficient number of reports (n = 22 psychiatric ADRs), which precluded statistically robust inferences. Consequently, the final comparative analyses included five active substances: semaglutide, liraglutide, dulaglutide, exenatide, and tirzepatide.

2.3. Variables and Outcomes

For each drug, the following variables were extracted: total number of ADR reports; distribution by sex (female, male, unknown); age group (<18, 18–44, 45–64, 65–74, >75 years, and unknown); geographic region (Africa, Americas, Asia, Europe, Oceania); year of notification; distribution of reports across the 27 MedDRA SOCs; and frequency of individual PTs within the "Psychiatric disorders" SOC. The primary outcome of interest was the reporting pattern of psychiatric ADRs, operationalized through the seven most frequently reported PTs within the "Psychiatric disorders" SOC for each drug. The reporting rate for each event was calculated as the ratio of reports of the specific PT to the total number of ADR reports for the corresponding drug.

2.4. Disproportionality Analysis Methods

To evaluate signals of disproportionate reporting of psychiatric ADRs, the Reporting Odds Ratio (ROR) was computed within the "Psychiatric disorders" SOC using a standard 2 × 2 contingency table. In pharmacovigilance, "disproportionate reporting" refers to a situation in which a specific drug–event combination is reported more frequently than would be statistically expected relative to all other drugs and events in the database; it is a signal-detection concept and does not, by itself, imply causality. The ROR was selected as the primary measure of disproportionality because its case–non-case design allows for direct epidemiological interpretation analogous to the odds ratio used in observational studies, and because it is the most widely used measure in contemporary VigiBase-based analyses [18].

For the SOC-level analysis, a denoted the number of psychiatric disorder reports for the drug of interest; b denoted all other reports for the drug of interest; c denoted psychiatric disorder reports for all other drugs in VigiBase; and d denoted all other reports for all other

drugs. The ROR was computed as (a × d)/(b × c). Ninety-five percent confidence intervals were estimated using the standard logarithmic approximation.

Following established pharmacovigilance criteria, a signal of disproportionate reporting was defined as the simultaneous fulfilment of two conditions: (i) at least three cases (a ≥ 3) for the drug–event combination; and (ii) ROR > 1 with the lower bound of the 95% CI > 1. This threshold identifies statistically significant disproportionate reporting relative to the overall database background, while minimizing the risk of spurious signals driven by small numbers of reports [18].

2.5. Statistical Analysis

Descriptive statistics were used to characterize the demographic and geographic distributions of ADR reports, the distribution of reports across the 27 MedDRA SOCs, and the frequency of the most frequently reported psychiatric PTs for each drug. Categorical variables were expressed as absolute frequencies and percentages. Data extraction, management, descriptive analyses, disproportionality calculations, and graphical presentation were performed using Microsoft Excel 2021 and R version 4.5.0. Reporting Odds Ratios were calculated using standard 2 × 2 case–non-case contingency tables, and 95% confidence intervals were estimated using the logarithmic approximation. A signal of disproportionate reporting was considered present when at least three reports were available, the ROR was greater than 1, and the lower bound of the 95% confidence interval exceeded 1.

Because VigiAccess provides aggregated data without individual-level treatment indications or population exposure denominators, calendar-time effects and changes in prescribing indications could not be adjusted using patient-level methods. These potential sources of bias were addressed descriptively through the evaluation of annual reporting patterns and were considered when interpreting differences in approval dates, time on the market, market uptake, expansion of weight-management indications, and regulatory attention.

3. Results

3.1. General Characteristics of Adverse Drug Reaction Reports

Between 1 January 2000 and the date of data extraction in 2026, a total of 537,519 ADR reports associated with the five analyzed GLP-1 RAs were retrieved from VigiAccess: 118,539 for semaglutide, 73,449 for liraglutide, 178,833 for tirzepatide, 85,139 for dulaglutide, and 81,559 for exenatide. Reports for lixisenatide (n = 1124) were excluded from comparative and disproportionality analyses owing to the insufficient number of psychiatric events (n = 22). Collectively, these reports yielded 959,622 drug–event pairs distributed across the 27 MedDRA SOCs, reflecting the fact that a single ICSR may contain multiple Preferred Terms (PTs).

A marked heterogeneity in reporting volume was observed among compounds, largely consistent with differences in time on the market and global uptake. Tirzepatide, despite being the most recently approved agent, concentrated the highest number of drugs–event pairs, with a pronounced acceleration in reporting from 2023 onward, including 95,617 reports in 2025 alone (53.5% of its total volume). Semaglutide followed a similar trajectory, with 45,377 reports in 2025 (38.3% of its total). In contrast, exenatide—approved substantially earlier—showed a progressively declining reporting trend, with 45.2% of its total volume accumulated prior to 2010. Table 1 summarizes the demographic and geographic characteristics of reports across the five analyzed drugs.

Table 1. Demographic and geographic characteristics of individual case safety reports associated with GLP-1 receptor agonists in VigiBase (2000–2026). For each drug, the highest value within sex, age, and region groups is shown in bold.

Category	Semaglutide	Liraglutide	Tirzepatide	Dulaglutide	Exenatide
Total ADR reports, n	118,539	73,449	178,833	85,139	81,559
Female, n (%)	**75,989 (64.1)**	**51,857 (70.6)**	**120,742 (67.5)**	**44,106 (51.8)**	**48,153 (59.0)**
Male, n (%)	34,870 (29.4)	18,711 (25.5)	33,396 (18.7)	32,697 (38.4)	30,832 (37.8)
Unknown sex, n (%)	7680 (6.5)	2881 (3.9)	24,695 (13.8)	8336 (9.8)	2574 (3.2)
<18 years, n (%)	324 (0.3)	891 (1.2)	70 (0.04)	83 (0.1)	94 (0.1)
18–44 years, n (%)	12,732 (10.7)	14,283 (19.5)	25,047 (14.0)	3526 (4.1)	4873 (6.0)
45–64 years, n (%)	**28,295 (23.9)**	**24,400 (33.2)**	**44,579 (24.9)**	**18,130 (21.3)**	**30,101 (36.9)**
65–74 years, n (%)	13,608 (11.5)	8216 (11.2)	14,975 (8.4)	11,146 (13.1)	15,398 (18.9)
>75 years, n (%)	5982 (5.1)	2203 (3.0)	5060 (2.8)	5341 (6.3)	4838 (5.9)
Unknown age, n (%)	57,598 (48.6)	23,456 (31.9)	89,102 (49.8)	46,913 (55.1)	26,255 (32.2)
Africa, n (%)	359 (0.3)	945 (1.3)	349 (0.2)	246 (0.3)	117 (0.1)
Americas, n (%)	**62,290 (52.6)**	**50,062 (68.2)**	**105,017 (58.7)**	**69,443 (81.6)**	**73,550 (90.2)**
Asia, n (%)	7635 (6.4)	8555 (11.7)	2837 (1.6)	3958 (4.7)	3558 (4.4)
Europe, n (%)	46,998 (39.7)	13,218 (18.0)	70,199 (39.3)	11,235 (13.2)	3942 (4.8)
Oceania, n (%)	1257 (1.1)	669 (0.9)	431 (0.2)	257 (0.3)	392 (0.5)

Percentages may not sum to 100 due to rounding and missing data. GLP-1: glucagon-like peptide-1; ADR: adverse drug reaction.

Demographic characteristics were broadly consistent across drugs. After exclusion of reports with unknown sex, female predominance was observed for all compounds, ranging from 51.8% for dulaglutide to 70.6% for liraglutide. This pattern was particularly marked for semaglutide (64.1% female) and tirzepatide (67.5% female) and aligns with the documented sex distribution in spontaneous reporting systems, in which women are consistently over-represented. Among reports with known age, the 45–64 year stratum accounted for the largest proportion for every drug (range, 21.3% dulaglutide to 36.9% exenatide), followed by the 18–44 year stratum, with a smaller but clinically relevant contribution from patients aged ≥65 years. A substantial proportion of reports (31.9–55.1%) lacked age information, consistent with the known limitations of spontaneous reporting data.

The geographic origin of reports varied substantially across compounds, reflecting differences in prescribing patterns and national pharmacovigilance activity. Reports from the Americas predominated for dulaglutide (81.6%) and exenatide (90.2%), whereas a more balanced distribution between the Americas and Europe was observed for semaglutide (52.6% vs. 39.6%) and tirzepatide (58.7% vs. 39.3%). Reporting from Asia, Africa, and Oceania remained comparatively limited across all drugs.

3.2. Distribution of Adverse Events Across System Organ Classes

As a supporting observation, gastrointestinal disorders consistently represented the most frequently reported SOC across all five compounds (range of 13.2–28.3% of all drug–event pairs), consistent with the well-established tolerability profile of this drug class. Because the focus of the present study is the psychiatric safety profile of GLP-1 RAs, the full distribution across the 27 SOCs is provided in the Supplementary Materials (Table S1), and the analysis below concentrates on the "Psychiatric disorders" SOC.

Psychiatric disorders accounted for 24,899 drug–event pairs across the five drugs analyzed. Semaglutide concentrated the largest absolute number of psychiatric reports (n = 7975), followed by tirzepatide (n = 5588), exenatide (n = 4399), liraglutide (n = 3876), and dulaglutide (n = 3061). More informatively, the proportion of psychiatric reports over the total number of reports for each drug revealed a pronounced gradient within the therapeutic class: semaglutide concentrated the highest relative psychiatric burden (6.73%

of its total reports), followed by exenatide (5.39%), liraglutide (5.28%), dulaglutide (3.60%), and tirzepatide (3.12%).

This gradient, which differs from the pattern observed when distribution is calculated exclusively within the psychiatric SOC, reinforces the existence of a differential reporting pattern within the therapeutic class and anticipates the findings of the disproportionality analysis presented in Section 3.4. Table 2 summarizes the psychiatric reporting burden for each drug.

Table 2. Psychiatric disorders reporting burden for each GLP-1 receptor agonist in VigiBase (2000–2026). The highest value in each row is shown in bold.

Parameter	Semaglutide	Liraglutide	Tirzepatide	Dulaglutide	Exenatide
Total ADR reports, n	118,539	73,449	**178,833**	85,139	81,559
Psychiatric reports, n	**7975**	3876	5588	3061	4399
Psychiatric reports, % of drug total	**6.73**	5.28	3.12	3.60	5.39

The complete distribution across all 27 MedDRA System Organ Classes is provided as Supplementary Material (Table S1). GLP-1: glucagon-like peptide-1; ADR: adverse drug reaction.

3.3. Distribution of Psychiatric Adverse Events by Preferred Term

Within the psychiatric disorder SOC, the most frequently reported PTs for each drug consistently clustered around four broad symptom domains: anxiety-spectrum symptoms (anxiety, panic attack, nervousness, stress), affective symptoms (depression, depressed mood, mood altered), sleep-related disturbances (insomnia, sleep disorder, nightmares), and suicidality-related events (suicidal ideation, suicide attempt, completed suicide).

For semaglutide, the most frequent psychiatric PTs were anxiety (n = 1446; 18.1% of psychiatric reports), depression (n = 1240; 15.6%), insomnia (n = 928; 11.6%), depressed mood (n = 808; 10.1%), and suicidal ideation (n = 586; 7.3%). Completed suicide (n = 40) and suicide attempt (n = 63) were also reported. The pattern for liraglutide was broadly similar, with insomnia as the leading PT (n = 806; 20.8%), followed by anxiety (n = 729; 18.8%), depression (n = 591; 15.2%), and suicidal ideation (n = 169; 4.4%).

Tirzepatide showed a distinctive profile characterized by a comparatively higher proportion of panic attack (n = 313; 5.6% of psychiatric reports)—substantially higher than observed with the other agents—alongside the expected predominance of anxiety (n = 1167; 20.9%), depressed mood (n = 872; 15.6%), insomnia (n = 820; 14.7%), and suicidal ideation (n = 299; 5.4%). Dulaglutide displayed a pattern dominated by anxiety (n = 470; 15.4%), insomnia (n = 330; 10.8%), and depression (n = 324; 10.6%), with a lower absolute number of suicidality-related events. For exenatide, the leading PTs were nervousness (n = 702; 16.0%), insomnia (n = 596; 13.5%), anxiety (n = 586; 13.3%), stress (n = 452; 10.3%), and depression (n = 380; 8.6%), with a lower reporting frequency of suicidality-related terms (suicidal ideation n = 54).

The seven most frequently reported PTs within the psychiatric disorder SOC for each drug are shown in Table 3.

Table 3. Seven most frequently reported Preferred Terms within the psychiatric disorder SOC for each GLP-1 receptor agonist in VigiBase (2000–2026). The most frequently reported term for each drug (rank 1) is shown in bold.

Rank	Semaglutide (n = 7975)	Liraglutide (n = 3876)	Tirzepatide (n = 5588)	Dulaglutide (n = 3061)	Exenatide (n = 4399)
1	**Anxiety—1446**	**Insomnia—806**	**Anxiety—1167**	**Anxiety—470**	**Nervousness—702**
2	Depression—1240	Anxiety—729	Depressed mood—872	Insomnia—330	Insomnia—596
3	Insomnia—928	Depression—591	Insomnia—820	Depression—324	Anxiety—586
4	Depressed mood—808	Depressed mood—219	Depression—638	Stress—295	Stress—452
5	Suicidal ideation—586	Suicidal ideation—169	Panic attack—313	Nervousness—188	Depression—380
6	Stress—277	Stress—156	Suicidal ideation—299	Depressed mood—113	Depressed mood—129
7	Nervousness—270	Nervousness—140	Nervousness—100	Suicidal ideation—47	Suicidal ideation—54

Values are number of reports. SOC: System Organ Class; GLP-1: glucagon-like peptide-1.

3.4. Disproportionality Analysis

Disproportionality measures for the overall psychiatric disorder SOC are summarized in Figure 1 (forest plot). Using the pre-specified signal criteria (ROR > 1 with the lower bound of the 95% CI > 1, and a $\geq$ 3), two of the five GLP-1 RAs analyzed met the threshold for a signal of disproportionate reporting for psychiatric disorders as a whole.

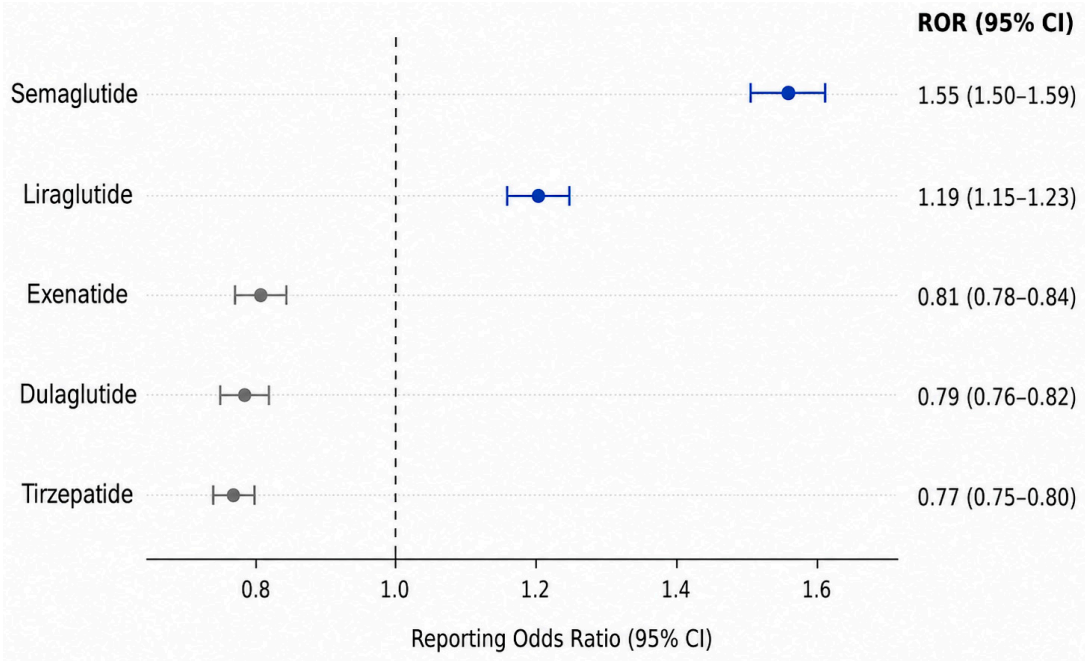


Figure 1. Forest plot of Reporting Odds Ratios (ROR) with 95% confidence intervals for the psychiatric disorder SOC across GLP-1 receptor agonists in VigiBase (2000–2026). Each marker represents the point estimate of the ROR for one drug and the horizontal line its 95% confidence interval. The vertical dashed line at ROR = 1 represents the null value (no disproportionate reporting). A signal was defined as a ROR > 1 with the lower bound of the 95% CI > 1. Signals of disproportionate reporting were identified for semaglutide and liraglutide, whereas tirzepatide, dulaglutide, and exenatide showed point estimates below unity. Blue markers indicate drugs that met the predefined criteria for a signal of disproportionate reporting, whereas grey markers indicate drugs that did not meet these criteria.

Semaglutide exhibited the most robust signal, with a ROR of 1.55 (95% CI 1.50–1.59), consistent with moderately increased reporting of psychiatric events relative to all other drugs in VigiBase. Liraglutide showed a positive signal of smaller magnitude but equally statistically significant (ROR 1.19, 95% CI 1.15–1.23). In both cases, the entire 95% confidence

interval was greater than 1, indicating a statistically consistent pattern of disproportionate reporting of psychiatric adverse events.

In contrast, tirzepatide (ROR 0.77, 95% CI 0.75–0.80), dulaglutide (ROR 0.79, 95% CI 0.76–0.82), and exenatide (ROR 0.81, 95% CI 0.78–0.84) showed point estimates below 1, with upper confidence bounds below unity. This indicates proportionally fewer psychiatric reports relative to the overall VigiBase background for these three compounds, and therefore no disproportionality signal was detected for any of them.

The forest plot (Figure 1) visually summarises this heterogeneity in disproportionality across the drug class: the reporting pattern for psychiatric events is not uniform among GLP-1 RAs, with the signal concentrated exclusively on semaglutide and liraglutide.

4. Discussion

The present study constitutes, to our knowledge, the first comparative pharmacovigilance analysis in the WHO VigiBase global database that characterizes the complete profile of psychiatric adverse drug reactions associated with the five most clinically relevant GLP-1 RAs: semaglutide, liraglutide, dulaglutide, exenatide, and tirzepatide. Our findings extend the previous work of Schoretsanitis et al., which was limited to suicidality and to semaglutide and liraglutide, by expanding the analysis to the full "Psychiatric disorders" SOC and to the entire therapeutic class [11].

The disproportionality signals identified for semaglutide (ROR 1.55; 95% CI 1.50–1.59) and liraglutide (ROR 1.19; 95% CI 1.15–1.23), together with the absence of signals for tirzepatide, dulaglutide, and exenatide, indicate heterogeneity in psychiatric reporting patterns across the analyzed therapies. However, this heterogeneity may reflect differences in treatment indications, exposed populations, baseline clinical characteristics, reporting behavior, time on the market, regulatory attention, and pharmacological properties. Therefore, these findings should not be interpreted as evidence of causal differences in psychiatric risk between compounds.

4.1. General Adverse Event Profile and External Validity

The 537,519 ADR reports analyzed reveal marked heterogeneity in reporting volumes across compounds, consistent with differences in marketing trajectories and global uptake of each agent. The accelerated accumulation of reports for semaglutide and tirzepatide from 2023 onwards reflects the rapid expansion of weight-management indications and off-label use in increasingly broad populations, a phenomenon previously documented in recent reviews [1,2].

As a brief supporting observation, the predominance of gastrointestinal disorders in our SOC distribution is consistent with the classic tolerability profile described in the pivotal clinical trials of this drug class, including the STEP program and the SELECT cardiovascular outcomes trial, where gastrointestinal events were the most common adverse reactions and the leading cause of treatment discontinuation. This concordance between VigiBase and pivotal trial data reinforces the external validity of our descriptive findings, although the focus of this study remains the psychiatric domain [19,20].

Regarding demographic profiles, the female predominance observed in reports (range 51.8–70.6%) is consistent with three converging and well-documented factors: the higher prevalence of obesity and of GLP-1 RA prescription for weight management in women, the greater propensity to report adverse events in this group, and the systematic over-representation of women in spontaneous reporting systems. The geographic predominance of the Americas and Europe is consistent with prescribing patterns described in US cohorts and highlights a structural limitation of VigiBase: the under-representation of Asia, Africa, and Oceania, where national pharmacovigilance activity is uneven [8].

4.2. Psychiatric Profile and Consistency with the Regulatory Signal

Our central finding—a signal of disproportionate reporting for psychiatric disorders with semaglutide and liraglutide, but not with tirzepatide, dulaglutide, or exenatide—is directionally consistent with previous pharmacovigilance evidence and with the regulatory context that motivated the EMA and FDA reviews in 2023–2024 [5,6]. The signal identified by the EMA in 2023, based on approximately 150 reports of suicidal thoughts and self-injury predominantly with liraglutide and semaglutide, is reflected in our analysis approximately three years later, using a substantially larger volume of reports and an assessment extended to the full spectrum of the psychiatric SOC. Nevertheless, the presence of a disproportionality signal indicates an unusual reporting pattern and should not be interpreted as evidence of a causal association or an increased absolute clinical risk.

Our results are consistent with Schoretsanitis et al., who, using the same data source but limited to suicidal ideation, reported a ROR of 1.45 (95% CI 1.18–1.77) for semaglutide that remained significant among patients with co-reported use of antidepressants and benzodiazepines [11]. In contrast, meta-analyses of randomized clinical trials have not confirmed an increase in the risk of suicidality or self-harm with GLP-1 RAs. Ebrahimi et al., in a meta-analysis of 34 trials including more than 56,000 participants, did not find a significant increase in the risk of suicidal or self-harm events in adults with diabetes or obesity treated with these agents [7]. Broader randomized evidence has similarly not demonstrated an overall increase in either serious psychiatric events or non-serious outcomes such as anxiety and insomnia compared with placebo [21].

This apparent discrepancy between clinical trial findings and post-marketing pharmacovigilance data illustrates the complementary—rather than contradictory—roles of these evidence sources. Randomized trials provide controlled comparative estimates but frequently exclude individuals with active psychiatric disorders, major psychopathology, or a history of suicidality. They may therefore have limited capacity to identify rare events or effects occurring predominantly in vulnerable subgroups. Spontaneous reporting systems capture events arising during broader real-world exposure but are highly susceptible to confounding, reporting biases, missing clinical information, and the absence of an exposure denominator [12,13].

The patterns by PT also provide clinically relevant information. The dominant psychiatric profile across all five compounds clustered into four symptom domains—anxiety, affective symptoms, sleep disturbances, and suicidality-related events—with qualitative differences between drugs. Tirzepatide showed a comparatively higher proportion of panic attacks (5.6%) than the remaining agents, while exenatide concentrated a higher proportion of nervousness and stress. However, these qualitative differences should be interpreted cautiously. They may reflect variation in pharmacological properties, treatment indications, patient characteristics, reporting practices, time on the market, or other unmeasured factors rather than intrinsic differences in psychiatric toxicity.

4.3. Clinical Population Heterogeneity, Channeling Bias, and Biological Context

An important contextual factor for interpreting the observed between-drug heterogeneity is confounding by indication and channeling bias. Individual GLP-1-based therapies are not prescribed uniformly across indications or clinical populations. In a large U.S. cohort of 41,222 adults initiating semaglutide or tirzepatide for weight management, 52.0% had type 2 diabetes, indicating that approximately 48% were treated in an obesity context without diabetes. Obesity-focused cohorts of semaglutide and tirzepatide users have also included approximately 70–75% women, whereas diabetes-only populations tend to show a more balanced sex distribution [22]. Furthermore, patients initiating tirzepatide had a higher baseline body weight than semaglutide users (126.5 vs. 115.2 kg) and a higher mean body

mass index (44.1 vs. 40.1 kg/m^2), suggesting differences in the populations receiving these therapies [23].

Differences are also apparent in diabetes-focused populations. In real-world comparisons, semaglutide users had a higher prevalence of obesity than dulaglutide users (38.2% vs. 30.5%) and more frequently received concomitant sodium–glucose cotransporter-2 inhibitors (29.2% vs. 22.7%), suggesting differences in cardiometabolic complexity and treatment intensity [24]. Medication persistence and healthcare engagement may also vary across agents; reported discontinuation rates were 9.2% for semaglutide, 28.5% for dulaglutide, and 41.7% for exenatide in one real-world analysis [25]. Comparative information regarding baseline psychiatric vulnerability across individual GLP-1-based therapies, however, remains limited.

Consequently, differences in spontaneous reporting patterns may partly reflect variation in patient characteristics, treatment indications, disease severity, healthcare utilization, and reporting behavior rather than intrinsic differences in psychiatric safety between compounds. This concern is particularly relevant when comparing agents with different approval dates, prescribing trajectories, durations of post-marketing exposure, and levels of public or regulatory attention. Therefore, between-drug ROR estimates should be interpreted as descriptive evidence of reporting heterogeneity and not as direct comparative estimates of psychiatric risk.

Central GLP-1 signaling participates in neural pathways involved in stress, emotional regulation, motivation, appetite, and reward [26,27]. Preclinical and neuroimaging studies suggest that GLP-1 receptor activation may influence hypothalamic, limbic, salience, and reward-related circuits, while individual agents may differ in their ability to access or influence the central nervous system [28,29]. However, these findings are primarily mechanistic or exploratory and do not establish that the psychiatric reporting patterns observed in the present study result from direct central effects of individual GLP-1-based therapies [30]. These mechanisms should therefore be regarded only as biological context and not as demonstrated explanations for the observed reporting heterogeneity [31].

The consistency of our findings with analyses conducted in other pharmacovigilance databases supports the presence of heterogeneity in psychiatric reporting patterns, although it does not establish causation. Chen et al., analyzing 181,238 FAERS reports from 2004 to 2023, found that psychiatric events represented 4.55% of GLP-1 RA-associated reports, a proportion similar to that observed in the present study, with a greater relative contribution from semaglutide and a lower contribution from tirzepatide [8]. Nishida et al. also identified heterogeneity in psychiatric reporting involving semaglutide in an adjusted VigiBase analysis [32]. Similarly, the multi-database analysis by Katranski et al. reported signals involving semaglutide and depressive symptoms or suicidal ideation, as well as liraglutide and depression in the Canadian database [33].

Nevertheless, differences in indications, exposed populations, database structures, reporting practices, market uptake, and regulatory attention limit direct comparisons among these estimates. Furthermore, the post hoc analysis of the STEP 1, 2, 3, and 5 trials by Wadden et al. confirmed that these pivotal studies excluded patients with known major psychopathology, limiting their ability to evaluate outcomes in patients with substantial baseline psychiatric vulnerability [34].

4.4. Underreporting and Differential Reporting

Spontaneous pharmacovigilance systems are affected by underreporting and differential reporting. Factors associated with underreporting include limited awareness of pharmacovigilance systems, uncertainty regarding causal attribution, lack of time, and professional attitudes toward reporting [35]. These limitations may be particularly

relevant for psychiatric symptoms such as anxiety, depression, and sleep disturbances, which frequently overlap with underlying conditions and may be difficult to attribute to a specific medication.

Conversely, media coverage and regulatory attention may increase the reporting of particular drug–event combinations. In the present study, public communication surrounding the EMA and FDA reviews in 2023–2024 may have influenced the reporting of psychiatric events, particularly for semaglutide and liraglutide. Because underreporting and stimulated reporting may operate simultaneously, the direction and magnitude of their influence on the observed disproportionality estimates cannot be determined from the available aggregated data.

4.5. Study Limitations and Methodological Adaptations

This study presents limitations inherent to its design and data source. First, VigiAccess provides aggregated and de-identified information at the active-substance level, without access to individual patient-level data, comorbidities, doses, duration of exposure, treatment indications, or co-prescriptions. This prevents adjustment for clinically relevant confounding factors and precludes establishing direct causality between the drug and the reported event.

Confounding by indication and channeling bias could not be statistically adjusted because reports arising from patients treated for obesity could not be distinguished from those arising from patients treated for type 2 diabetes. Adjustment was also not possible for age, sex, baseline psychiatric disorders, eating disorders, body-image concerns, severity of obesity or diabetes, previous treatments, concomitant medications, treatment persistence, or healthcare utilization. In addition, the analyzed therapies differ in approval dates, indications, prescribing trajectories, market uptake, and duration of post-marketing exposure. Calendar-time effects and changes in prescribing indications were therefore addressed descriptively through the evaluation of annual reporting patterns and were considered in the interpretation of the findings. Consequently, between-drug ROR estimates should not be interpreted as head-to-head comparisons of psychiatric risk.

Second, as discussed above, spontaneous reporting is susceptible to underreporting, differential reporting, notoriety bias, and the Weber effect. Regulatory and media attention surrounding psychiatric events may have influenced reporting patterns over time, but the magnitude and direction of these effects cannot be determined using aggregated VigiAccess data.

Third, the absence of a population exposure denominator prevents the calculation of true incidence rates. Disproportionality measures must therefore be interpreted as relative reporting measures within the database rather than as estimates of absolute clinical risk. Fourth, the exclusion of lixisenatide owing to the limited number of psychiatric reports (n = 22) restricts the generalizability of the findings to the entire therapeutic class, although this drug represents a comparatively small proportion of global GLP-1 RA use.

To strengthen methodological transparency, this study followed the STROBE and READUS-PV guidelines [15,16]. The use of the ROR with pre-specified signal criteria, consistent with the methodological framework described by Cutroneo et al. [18], provided a standardized approach for identifying patterns of disproportionate reporting. The findings were interpreted as signals for hypothesis generation rather than as confirmation of causality. Finally, the use of VigiBase allowed for the evaluation of reporting patterns across multiple geographic regions and pharmacovigilance systems, reducing reliance on data derived exclusively from a single jurisdiction such as FAERS.

5. Conclusions

This pharmacovigilance analysis, based on the WHO VigiBase global database, provides a comparative characterization of psychiatric adverse-event reporting across five clinically relevant GLP-1-based therapies. Signals of disproportionate reporting for the overall psychiatric disorder SOC were identified for semaglutide (ROR 1.55; 95% CI 1.50–1.59) and liraglutide (ROR 1.19; 95% CI 1.15–1.23), whereas tirzepatide, dulaglutide, and exenatide did not meet the pre-specified signal criteria. These findings indicate that psychiatric reporting patterns were not homogeneous across the analyzed therapies.

The predominant psychiatric profile clustered into four broad symptom domains: anxiety-spectrum symptoms, affective symptoms, sleep-related disturbances, and suicidality-related events. Qualitative differences were observed between agents; however, these differences may reflect a combination of treatment indications, patient characteristics, baseline psychiatric vulnerability, reporting behavior, time on the market, regulatory attention, and pharmacological properties. Their relative contributions cannot be determined using aggregated VigiAccess data.

These findings extend previous WHO-based analyses focused primarily on suicidality and on semaglutide and liraglutide by examining the broader psychiatric disorder SOC across additional GLP-1-based therapies. The apparent divergence between spontaneous reporting signals and the generally neutral findings of randomized clinical trial meta-analyses illustrates the complementary roles of pharmacovigilance and controlled clinical evidence. Nevertheless, disproportionality signals identify unusual reporting patterns and do not establish causality, incidence, or comparative clinical risk.

The results support continued pharmacovigilance, careful assessment of relevant psychiatric history when clinically indicated, and timely reporting of suspected adverse events. Further analytical studies using individual-level data, clearly defined treatment indications, appropriate active comparators, and adjustment for baseline psychiatric conditions, concomitant medications, channeling bias, and confounding by indication are required to determine whether the observed reporting heterogeneity reflects causal drug effects or differences between the populations receiving each therapy.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/endocrines7030044/s1, Table S1: Distribution of adverse drug reaction reports across MedDRA System Organ Classes by individual drug.

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Abbreviations

The following abbreviations are used in this manuscript:

ADR	Adverse Drug Reaction
CI	Confidence Interval
CVAROD	Canadian Vigilance Adverse Reaction Online Database
DAEN	Database of Adverse Event Notifications
EMA	European Medicines Agency
FAERS	FDA Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonist
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
INN	International Non-proprietary Name
MedDRA	Medical Dictionary for Regulatory Activities
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
READUS-PV	Reporting of A Disproportionality analysis for drug Safety signal detection using ICSRs in PharmacoVigilance
ROR	Reporting Odds Ratio
SOC	System Organ Class
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T2DM	Type 2 Diabetes Mellitus
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

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