Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2022, Volume 2, Page No: 178-187

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Analysis of Spontaneous Reports of Psychiatric Adverse Events Associated with GLP-1 Analogues

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Received: 23 May 2021; **Revised:** 12 September 2022; **Accepted:** 14 September 2022

ABSTRACT

Glucagon-like peptide 1 (GLP-1) analogues constitute a group of drugs that promote insulin secretion in a glucose-dependent manner and reduce the speed of gastric emptying. As prescriptions for these agents grow rapidly, the possibility of psychiatric side effects has not been thoroughly examined. The objective of this pharmacovigilance analysis was to assess the frequency of psychiatric adverse events (AEs) related to all marketed GLP-1 analogues using open-access national reporting systems from the United States (FAERS), Canada (CVAROD), and Australia (DAEN). All reports involving psychiatric AEs for approved GLP-1 analogues were collected from the three databases. Disproportionality measures were calculated, including reporting odds ratios (RORs) with corresponding 95% confidence intervals (CIs), for specific psychiatric events of concern. Strong signals were detected when increased RORs appeared in more than one database. Semaglutide displayed connections to depressive symptoms (FAERS, ROR = 6.24 CI 4.49–8.69), panic attacks (FAERS, ROR = 1.46 CI 1.16–1.82), and suicidal ideation (FAERS, ROR = 2.58 CI 2.31–2.88). Liraglutide demonstrated a link to depression (CVAROD, ROR = 1.68 CI 1.12–2.51), and dulaglutide exhibited signals for eating disorders (FAERS, ROR = 1.47 CI 1.26–1.71) as well as insomnia (FAERS, ROR = 2.93 CI 2.35–3.66). Certain GLP-1 analogues, notably semaglutide and liraglutide, show notable links to psychiatric adverse events, including depression and thoughts of suicide. More research is essential to clarify the underlying processes, especially among those with prior mental health issues.

Keywords: CVAROD, DAEN, FAERS, GLP-1 analogues, Pharmacovigilance, Psychiatric adverse events

How to Cite This Article: Kowalski P, Nowak M. Analysis of Spontaneous Reports of Psychiatric Adverse Events Associated with GLP-1 Analogues. Ann Pharm Pract Pharmacother. 2022;2:178-87. https://doi.org/10.51847/bl9XxFe3DD

Introduction

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs), frequently termed GLP-1 analogues, are manufactured compounds that mimic GLP-1 by triggering insulin release dependent on glucose levels and decelerating stomach emptying [1]. Their chief purpose is to enhance insulin output tied to glucose while curbing excess glucagon release for better blood sugar management [1]. In addition to controlling glycemia, these drugs offer advantages for heart health and facilitate body weight reduction [1, 2]. This has led to a sharp rise in their prescription rates over recent years. Data from the United States show that usage of GLP-1 analogues in patients with type 2 diabetes and established atherosclerotic cardiovascular disease rose substantially, from 5.2% in 2018 to 9.9% in 2022 [3]. Social media influence has also fueled considerable off-label prescribing for weight control, broadening the patient base considerably [4].

Extensive testing has established the safety and benefits of GLP-1 analogues, revealing a range of associated adverse events (AEs). The most frequent are digestive issues, such as nausea and diarrhea (seen in up to 50% of cases) along with abdominal discomfort and constipation (in up to 10% of cases) [5, 6]. Less common but serious reports include pancreatitis and certain cancers potentially tied to these medications [6, 7]. However, psychiatric side effects have received scant attention, which is worrisome for individuals with existing mental disorders who

could gain from this therapy. Recent publications on psychiatric outcomes have yielded mixed and unresolved results [8-10]. Certain reports noted improvements in depression and anxiety symptoms with GLP-1 analogues in animal models of corticosterone-induced depression or in people newly starting treatment for type 2 diabetes [8, 9]. Research by Wang *et al*. indicated that GLP-1 analogues, including semaglutide in particular, correlated with lower rates of suicidal actions versus alternative treatments for obesity (e.g., naltrexone, bupropion, etc.) or diabetes (e.g., metformin, insulin, etc.) [10]. On the other hand, some evidence pointed to greater risks of psychiatric issues like agitation, sleep disturbances, and disordered eating [11]. Work by Ruggiero *et al*. [12] revealed that semaglutide and liraglutide had 2- to 4-fold higher odds of reported suicidal incidents relative to exenatide and dulaglutide. A newer report from Guirguis *et al*. [13] also suggested ties between liraglutide, semaglutide, tirzepatide, and suicidal ideation or attempts, calling for deeper exploration.

Reviewing everyday clinical data can reveal novel side effects and guide further evaluation in diverse populations. Public databases including the US Food and Drug Administration Adverse Events Reporting System (FAERS), Health Canada's Vigilance Adverse Reaction Online Database (CVAROD), and the Australian Therapeutic Goods Administration's Database of Adverse Event Notifications (DAEN) allow medical professionals to submit suspected adverse reactions after market approval, aiding regulators and scientists in spotting potential risks [14-16]. Prior pharmacovigilance efforts have drawn on these resources to track real-life adverse event patterns [17, 18].

One recent study using the European Medicines Agency's EudraVigilance system to review psychiatric issues with semaglutide, liraglutide, and tirzepatide [19] found depression, anxiety, and suicidal thoughts to be leading complaints, with 20 of 372 cases resulting in death or severe threat to life. Without disproportionality testing, however, no firm link could be established between drug exposure and these events. That analysis also covered just three of the six available agents. A separate effort [11] using FAERS data through the first quarter of 2023 linked GLP-1 analogues to eight types of psychiatric problems. Given the swift worldwide increase in their application, cross-checking psychiatric signals in several major voluntary reporting systems is vital for a contemporary view of how GLP-1 analogue exposure relates to psychiatric adverse events.

Aim

Merging adverse event (AE) reports from various databases improves the robustness of the analysis by enlarging the dataset, broadening geographic and demographic coverage, and boosting the ability to identify meaningful signals. Accordingly, the goal of this study was to explore the frequency of psychiatric AEs tied to all presently marketed GLP-1 analogues using open national reporting systems from the United States (FAERS), Canada (CVAROD), and Australia (DAEN).

Ethics approval

This research did not require ethics approval because it involved no human or animal subjects and no gathering of identifiable personal information. The RMIT University ethics committee issued an exemption.

Materials and Methods

Data sources

Reports of adverse events for every approved GLP-1 analogue (exenatide, semaglutide, liraglutide, lixisenatide, dulaglutide, and tirzepatide) were retrieved from three publicly available online databases: FAERS, CVAROD, and DAEN. The timeframe for each agent spanned from its market introduction in the relevant country through to the most recent records accessible during data collection.

Search strategies

Each database was queried exhaustively for psychiatric AEs involving the GLP-1 analogues. For efficiency and consistency, the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy for psychiatric disorders was utilized, as all three systems organize reported AEs according to MedDRA terminology. Events falling outside this hierarchy were disregarded. Closely related events were consolidated into unified categories to improve readability (e.g., the insomnia group combined insomnia, initial insomnia, middle insomnia, and terminal insomnia).

Counts of psychiatric events were tallied, together with the number of affected individuals, their ages, and genders. Because information on co-medications and complete medical backgrounds was often missing or incomplete, these variables were omitted from the evaluation.

Data analysis

Disproportionality testing was conducted to uncover potential relationships between exposure to a GLP-1 analogue and a particular AE in comparison to all other medications documented in the database. To prevent over-reliance on isolated reports from one agent, psychiatric AEs were only highlighted if they fulfilled both of these requirements across the three databases:

1. At least 10 reports for one specific medication in one database, and
2. Reports involving at least two different medications in at least two databases.

Conventional ROR calculations often use a minimum of 3 cases [11]. However, because this investigation encompasses every GLP-1 analogue and incorporates data from three separate national sources, these more stringent thresholds were applied to lower the likelihood of spurious signals arising from sparse reports and to prioritize events with probable clinical importance.

For each psychiatric AE of interest, Reporting Odds Ratios (RORs) along with 95% confidence intervals (CIs) were determined individually for each drug within each of the three databases [20]. An ROR value above 1 signifies an elevated likelihood of the AE occurring with the drug. The study adhered to the Reporting of A Disproportionality analysis for drug Safety signal detection using individual case safety reports in Pharmacovigilance (READUS-PV) checklist when describing the disproportionality findings [21, 22].

The formula for calculating ROR is: $\frac{\left(\frac{a}{c}\right)}{\left(\frac{b}{d}\right)}$

where *a* represents the count of reports for a specific symptom linked to the drug under investigation; *b* denotes the count of all other symptoms reported for that same drug; *c* indicates the count of reports for the identical symptom linked to all remaining drugs; and d refers to the count of all other symptoms linked to all remaining drugs. An odds ratio exceeding 1 is interpreted as indicating that the drug in question has a higher likelihood of being associated with reports of that symptom compared to other drugs [20].

The 95% CI is calculated using the formula: $e^{\ln(R,O,R)\pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$

This equation produces two figures that mark the upper and lower limits of the confidence interval. When this interval excludes the value 1, the association is deemed statistically significant.

The largest dataset here comes from the United States, which supplies a much greater volume of cases for ROR computations and therefore delivers more dependable estimates. In comparison, the Canadian and Australian collections are far smaller, reducing the reliability of standalone conclusions from them. Sparse reporting can generate dramatically high ROR values paired with extremely broad confidence intervals, pointing to lower certainty. Accordingly, findings from the US source were employed to direct specific queries into the smaller collections.

Interpretations of signals from the smaller sources should remain conservative; however, when they match patterns in the larger US collection, credibility in the associations rises. Consistency between databases points toward potential generalizability across varied populations.

Results and Discussion

Overview of AE reports

In total, 16,678 psychiatric reports linked to the target GLP-1 analogues were collected from the three sources: exenatide (n = 5492, 32.9%), semaglutide (n = 4067, 24.4%), dulaglutide (n = 3024, 18.1%), tirzepatide (n = 1447, 8.7%), liraglutide (n = 2552, 15.3%), and lixisenatide (n = 96, 0.6%). Breakdown by source: FAERS (n = 16,090, 96.5%), CVAROD (n = 363, 2.2%), and DAEN (n = 225, 1.3%). Females accounted for the majority (n = 7990, 64.2%), and the median patient age was 60 years [interquartile range (IQR) = 54–68].

After processing, 14,510 psychiatric AEs qualified for inclusion across all sources **(Table 1)**. The leading five groupings were mood disorders (n = 7,147, 49.3%), sleep disturbances (n = 3,052, 21.0%), cognitive impairment

and confusion (n = 1,745, 12.0%), suicidal ideation and behavior (n = 955, 6.6%), and restlessness/agitation (n = 940, 6.5%).

Table 1. Comparative table of selected psychiatric AEs listed for each GLP-1 analogue in the three databases

Category / Event	Exenatide FAERS	Exenatide DAEN	Exenatide CVAROD	Semaglutide FAERS	Semaglutide DAEN	Semaglutide CVAROD	Tirzepatide FAERS	Tirzepatide DAEN	Dulaglutide FAERS	Dulaglutide DAEN	Dulaglutide CVAROD	Lixisenatide FAERS	Lixisenatide CVAROD	Liraglutide FAERS	Liraglutide DAEN	Liraglutide CVAROD
Agitation-related symptoms	394	1	–	151	3	11	70	1	152	2	–	6	–	141	2	6
Agitation	90	–	–	28	1	1	15	–	33	1	–	2	–	33	2	1
Anger	48	1	–	22	–	3	12	–	22	1	–	–	–	21	–	1
Irritability	217	–	–	78	2	7	32	–	82	–	–	3	–	61	–	3
Restlessness	39	–	–	23	–	–	11	1	15	–	–	1	–	26	–	1
Mood-related disorders	2549	6	2	1554	37	76	577	1	1250	9	–	37	1	955	24	69
Altered mood	44	–	–	35	1	5	16	–	29	–	–	–	–	26	1	4
Mood fluctuations	39	–	–	26	1	1	8	–	24	1	–	–	–	36	–	2
Depressive disorders (1)	520	4	–	609	14	34	174	–	290	2	–	9	–	354	10	31
Apathy	13	–	–	26	1	2	5	–	12	–	–	–	–	14	1	3
Emotional disturbance	23	–	–	18	2	–	6	–	17	1	–	–	–	13	–	1
Anxiety	574	1	1	434	11	19	217	1	327	2	–	8	–	291	9	21
Nervousness	695	–	–	113	–	3	33	–	163	1	–	10	–	90	–	2
Emotional distress	41	–	–	27	1	–	9	–	13	–	–	1	1	10	–	2
Panic episodes	54	–	–	77	3	2	53	–	37	–	–	1	–	33	2	1
Post-traumatic stress disorder	8	–	–	6	1	–	2	–	17	1	–	–	–	8	1	–
Stress	462	1	1	157	2	8	45	–	282	–	–	6	–	70	–	2
Fear	76	–	–	26	–	2	9	–	39	1	–	2	–	10	–	–
Confusional and cognitive effects	744	3	–	262	11	13	89	–	378	6	1	11	–	214	5	8
Confusional state	424	2	–	141	4	6	37	–	194	3	–	6	–	115	–	4
Disorientation	183	–	–	33	–	1	14	–	34	–	–	–	–	32	–	2
Mental disorder	45	1	–	41	5	2	19	–	71	2	–	2	–	25	4	1
Delirium	18	–	–	12	1	1	4	–	10	1	–	1	–	15	–	1
Abnormal thinking	48	–	–	16	–	1	9	–	53	–	–	1	–	18	1	–
Behavioral abnormalities	26	–	–	19	1	2	6	–	16	–	1	1	–	9	–	–
Eating-related disorders	83	1	–	44	–	5	36	–	172	1	–	2	–	33	–	2
Psychotic spectrum disorders	68	3	–	102	4	7	20	–	53	–	–	1	–	30	2	2
Hallucinations (2)	53	2	–	51	–	5	10	–	34	–	–	1	–	19	1	2
Paranoia	11	–	–	9	2	–	3	–	11	–	–	–	–	5	1	–

Psychotic disorder	4	1	–	42	2	2	7	–	8	–	–	–	–	6	–	–
Sleep-related conditions	820	5	–	684	4	45	408	–	565	3	1	20	–	456	9	32
Sleep disorders (3)	105	–	–	152	2	15	115	–	216	1	1	6	–	105	2	8
Insomnia (4)	608	3	–	423	1	21	241	–	284	1	–	12	–	293	5	18
Nightmares	32	1	–	49	–	4	12	–	16	1	–	1	–	22	1	–
Abnormal dreams	25	–	–	38	1	4	18	–	13	–	–	–	–	14	–	3
Poor sleep quality	50	1	–	22	–	1	22	–	36	–	–	1	–	22	1	3
Suicidal ideation and behaviors	95	3	–	422	25	30	80	–	73	1	–	1	–	176	27	22
Completed suicide	5	–	–	28	–	2	2	–	4	–	–	–	–	27	–	1
Suicidal depression	7	–	–	26	–	1	4	–	2	–	–	–	–	4	3	–
Suicidal ideation	65	3	–	325	23	26	72	–	47	1	–	–	–	98	23	19
Suicide attempt	**18**	**–**	**–**	**43**	**2**	**1**	**2**	**–**	**20**	**–**	**–**	**1**	**–**	**47**	**1**	**2**

Bolded rows are categories and these are not single AEs, with the numbers representing the total reports for the respective category. Eating disorder is the only report in its category so it is also bolded. (1)Depressive disorders include depressive mood; depression; depressive symptoms; major depression. (2)Hallucinations include hallucination; hallucination, auditory; hallucination, mixed; hallucination, synesthetic; hallucination, visual. (3)Sleep disorders include sleep disorder; sleep disorder due to a general medical condition; sleep disorder due to general medical condition, insomnia type; sleep disorder due to general medical condition, hypersomnia type. (4)Insomnia includes insomnia; initial insomnia; middle insomnia; terminal insomnia. (5)As of the search end dates, no data on the adverse effects of Tirzepatide has been submitted to the CVAROD, nor has any been submitted to the DEAN for Lixisenatide

The highest-frequency psychiatric events in each source were reviewed closely. Within FAERS, the most reported were depressive disorders (n = 1,956, 14%), insomnia (n = 1,861, 13.2%), and anxiety (n = 1,851, 13.2%). For CVAROD, the leaders were depressive disorders (n = 65, 19.5%), suicidal ideation (n = 45, 13.5%), and anxiety (n = 41, 12.3%). In DAEN, suicidal ideation topped the list (n = 50, 25.1%), followed by depressive disorders (n = 30, 15.1%) and anxiety (n = 24, 12.1%) **(Table 1)**. Among the final selected events, exenatide contributed the most reports (n = 4,777, 32.9%), then semaglutide (n = 3,490, 24.1%), dulaglutide (n = 2,667, 18.4%), liraglutide (n = 2,215, 15.3%), tirzepatide (n = 1,282, 8.8%), and lixisenatide (n = 79, 0.5%) **(Table 1)**.

Reporting odds ratio findings

ROR values and corresponding confidence intervals were derived for the psychiatric events of focus across all sources. Key significant outcomes appear in **Table 2**.

Table 2. Significant ROR and CI results from the FAERS database

Drug	Reported adverse event	Reporting Odds Ratio (ROR)	95% CI (Upper bound)	95% CI (Lower bound)
Exenatide	Spatial disorientation	1.32	1.52	1.14
	Nervous system hyperactivity	3.75	4.05	3.48
	Psychological stress	1.90	2.08	1.73
Semaglutide	Depressive mood state	1.48	1.76	1.25
	Clinical depression	1.35	1.48	1.22
	Depressive symptomatology	6.24	8.69	4.49
	Nervousness	1.59	1.91	1.32
	Panic episodes	1.46	1.82	1.16
	Stress-related symptoms	1.24	1.45	1.06
	Suicidal depression	4.35	6.40	2.95
	Suicidal ideation	2.58	2.88	2.31

Dulaglutide	Eating-related disorder	1.47	1.71	1.26
	Insomnia-type sleep disorder secondary to medical condition	2.93	3.66	2.35
Tirzepatide	Eating-related disorder	1.58	2.20	1.14
	Panic attack	1.79	2.35	1.37
	Insomnia-type sleep disorder secondary to medical condition	6.13	7.95	4.73

The data reveal meaningful statistical connections between particular drugs and assorted mental health issues, with especially prominent signals for certain combinations (e.g., depressive symptoms linked to semaglutide and sleep disorders linked to tirzepatide).

Patterns identified in the US FAERS collection informed targeted checks in the Australian DAEN and Canadian CVAROD sources for replication. Six overlapping significant associations were detected in DAEN, listed in **Table 3**.

Table 3. Significant ROR and CI results from DAEN which were also significant in FAERS

Drug	Reported adverse event	Reporting Odds Ratio (ROR)	95% CI (Upper bound)	95% CI (Lower bound)
Semaglutide	Depressed mood state	4.97	13.38	1.85
	Clinical depression	6.75	12.69	3.59
	Panic episode	3.56	11.12	1.14
	Stress-related condition	4.15	16.78	1.03
Dulaglutide	Eating-related disorder	17.66	127.37	2.45
	Insomnia-type sleep disturbance secondary to medical condition	259.13	2161.43	31.07

From CVAROD, a single overlap with FAERS emerged: semaglutide with suicidal ideation (ROR = 4.38 CI 2.97–6.47). Notably, both DAEN and CVAROD showed a clear association of liraglutide with depression (DAEN ROR = 2.51 CI 1.12–5.61; CVAROD ROR = 1.68 CI 1.12–2.51), absent from the US results. **Table 4** offers a consolidated summary of all significant signals, grouped by symptom.

Table 4. Summary table of significant ROR and CI results across the FAERS database and corresponding significant results from DAEN and CVAROD

Reported Event	Drug	Data Source	ROR	95% CI (Upper)	95% CI (Lower)
Depressed mood state	Semaglutide	FAERS	1.48	1.76	1.25
	Semaglutide	DAEN	4.97	13.38	1.85
Clinical depression	Semaglutide	FAERS	1.35	1.48	1.22
	Semaglutide	DAEN	6.75	12.69	3.59
	Liraglutide	DAEN	2.51	5.61	1.12
	Liraglutide	CVAROD	1.68	2.51	1.12
Panic episodes	Semaglutide	FAERS	1.46	1.82	1.16
	Semaglutide	DAEN	3.56	11.12	1.14
Stress-related symptoms	Semaglutide	FAERS	1.24	1.45	1.06
	Semaglutide	DAEN	4.15	16.78	1.03
Suicidal ideation	Semaglutide	FAERS	2.58	2.88	2.31
	Semaglutide	CVAROD	4.38	6.47	2.97
Eating-related disorder	Dulaglutide	FAERS	1.47	1.71	1.26
	Dulaglutide	DAEN	17.66	127.37	2.45
Insomnia-type sleep disorder secondary to medical condition	Dulaglutide	FAERS	2.93	3.66	2.35
	Dulaglutide	DAEN	259.13	2161.43	31.07

GLP-1 analogues have gained substantial popularity over recent decades due to their proven efficacy in enhancing blood sugar management, facilitating weight reduction, and delivering cardiovascular advantages [1-3]. Although

multiple investigations have explored possible psychiatric adverse events (AEs) linked to GLP-1 analogues, results across these studies continue to conflict [8-13]. The present research represents the first pharmacovigilance analysis to integrate data from three distinct international databases in order to assess potential psychiatric risks tied to GLP-1 receptor agonists (GLP-1RAs). Covering the specified search periods, we detected a combined total of 16,678 psychiatric AE reports for the targeted GLP-1 analogues across all three sources. Strikingly, psychiatric AE reports in FAERS alone reached 16,090—roughly double the figure (8,240) reported in an earlier pharmacovigilance analysis that reviewed psychiatric AEs for all GLP-1 analogues in FAERS from Q1 2004 through Q1 2023 [11]. This underscores a marked rise in psychiatric AEs related to GLP-1 analogues over the past 2 years.

Over 57% of reports involved individuals aged 18 or above (with 42% lacking age specification), and approximately 64% concerned females, suggesting greater utilization of GLP-1 analogues in adult women. Comparable patterns emerged in a prior analysis of the EudraVigilance database, where around 50% of reports originated from the 18–64 age bracket and 65% involved females [19].

Several notable associations surfaced between specific GLP-1 analogues and particular psychiatric AEs. Semaglutide treatment showed strong links to depressed mood, panic attacks, and stress in both FAERS and DAEN, while also demonstrating a clear connection to suicidal ideation in FAERS and CVAROD. Dulaglutide exhibited robust associations with eating disorders and sleep disorders due to general medical condition, insomnia type across FAERS and DAEN. Meanwhile, liraglutide revealed a pronounced relationship with depression in both DAEN and CVAROD.

These observations align with the work of Chen *et al*. [11], who similarly identified significant class-wide associations for GLP-1 analogues with stress, eating disorders, and sleep disorder due to general medical condition-insomnia type. That study, however, found no positive signals for depression, depressed mood, panic attacks, or suicidal ideation with the class. In contrast, a large-scale cohort analysis by Kornelius *et al*. [23] reported that GLP-1 analogues—especially liraglutide and semaglutide—carried a 195% elevated risk of depression and a 106% greater risk of suicidal ideation. Their results, together with ours, correspond to two additional pharmacovigilance reports that flagged heightened reporting odds for suicidal thoughts and behaviors, particularly with semaglutide [12, 13]. On the opposing side, one retrospective cohort investigation [10] documented reduced incidence and recurrence of suicidal ideation among patients receiving semaglutide. Moreover, a randomized trial with 3,377 participants and a cohort study encompassing 124,517 individuals concluded that GLP-1 analogues showed no ties to suicidal ideation, depression, or suicide-related mortality [24, 25]. Such discrepancies among studies highlight ongoing uncertainty about the psychiatric impact of GLP-1 analogues and reinforce the necessity for deeper research.

The observed frequency of psychiatric AEs during GLP-1 analogue therapy might stem from underlying psychiatric conditions in treated patients [11]. The databases analyzed here lacked details on any prior mental health diagnoses among those reporting AEs. Although the relationship between GLP-1 analogue exposure and psychiatric AEs remains unresolved, the grave potential outcomes of these events call for heightened caution in drug choice and vigilant monitoring of patients. Consistent with recommendations from prior work, continued pharmacovigilance efforts alongside clinical trials are essential to confirm causality and uncover mechanisms linking psychiatric AEs to GLP-1 analogue administration [10-13, 25].

Strengths

Incorporating three separate databases from three distinct nations yielded a more extensive dataset than previous investigations. This enhances statistical robustness, enabling more confident detection of AEs that might remain undetected in single-country analyses with limited cases. The selected countries feature varied demographic profiles that could affect drug responses, offering valuable perspective on whether AE patterns hold steady across populations and possibly revealing broader safety issues.

Furthermore, employing reporting odds ratios (RORs) to quantify drug-AE associations facilitates direct cross-database and cross-drug comparisons. Examining multiple agents within the same class helps pinpoint potential variations in psychiatric AE profiles among individual GLP-1 analogues, which could guide clinicians toward more personalized prescribing, especially for patients with established psychiatric histories.

Limitations

This study has several limitations that should be taken into account when interpreting its findings. The research depended on self-reported adverse events (AEs) from patients and prescribers, which may introduce bias resulting in over- or under-reporting. Furthermore, these reports were subjective, relying on the reporter's judgment, which complicates the identification of the precise cause of each event.

An additional limitation was the absence of detailed patient characteristics, including medical history, comorbidities, family history, and lifestyle factors. This lack of information hindered the ability to differentiate between medication-induced reactions and events linked to underlying health conditions. Consequently, establishing a causal relationship between medication use and AEs remains challenging. It should be noted that there are currently no clinically significant drug-drug interactions with any GLP-1 analogues, and therefore this aspect was not evaluated [26].

The total number of patients prescribed each medication in each country was not available, preventing the calculation of the true incidence of AEs. Under these circumstances, the reporting odds ratio (ROR) represents the most appropriate statistical tool accessible to the researchers. Newer drugs have accumulated fewer reports due to their shorter time on the market, which complicated direct comparisons with medications that have been available for longer periods.

Thus, while these reports generate signals of potential drug safety risks, they must be interpreted cautiously and complemented by clinical studies to verify any associations.

Conclusion

This study represents the first pharmacovigilance analysis to incorporate multiple databases from the US, Canada, and Australia in examining psychiatric adverse events associated with GLP-1 analogues. Several significant associations were identified between specific GLP-1 analogues and particular psychiatric AEs. Despite the presence of certain limitations, this preliminary investigation offers important insights to guide future research on psychiatric AEs linked to GLP-1 analogues and underscores the importance of continued monitoring and assessment of these drugs, particularly given the potentially severe implications of psychiatric AEs. Healthcare professionals are advised to prescribe these medications judiciously, carefully balancing their potential risks against their benefits.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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