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Exploring the association between suicidal thoughts, self-injury, and GLP-1 receptor agonists in weight loss treatments: Insights from pharmacovigilance measures and unmasking analysis

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ABSTRACT

Introduction: The study addresses concerns about potential psychiatric side effects of Glucagon-like peptide-1 receptor agonists (GLP-1 RA).
Aim: The aim of this work was to analyse adverse drug reports (ADRs) from the Food and Drug Administration Adverse Events Reporting System (FAERS) using metformin and orlistat as comparators.
Methods: Descriptive and pharmacovigilance disproportionality analyses was performed.
Results: A total of 209,354 ADRs were reported, including 59,300 serious cases. Of those, a total of 5378 psychiatric disorder cases, including 383 'serious' cases related to selected ADRs were registered during 2005–2023. After unmasking, 271 cases where *individual* GLP-1 RA were implicated showing liraglutide ($n = 90$; Reported Odds Ratio (ROR) = 1.64), exenatide ($n = 67$; ROR = 0.80), semaglutide ($n = 61$; ROR = 2.03), dulaglutide ($n = 45$; ROR = 0.84), tirzepatide ($n = 5$; ROR = 1.76) and albiglutide ($n = 2$; ROR = 0.04). A greater association between these ADRs with metformin was observed, but not orlistat. With regards to selected preferred terms (PTs), 42 deaths including 13 completed suicides were recorded. Suicidal ideation was recorded in $n = 236$ cases for 6/7 GLP-1 RA (excluding lixisenatide).
Discussion: Suicide/self-injury reports pertaining to semaglutide; tirzepatide; and liraglutide were characterised, although lower than metformin. It is postulated that rapid weight loss achieved with GLP-1 RA can trigger significant emotional, biological, and psychological responses, hence possibly impacting on suicidal and self-injurious ideations.
Conclusions: With the current pharmacovigilance approach, no causality link between suicidal ideation and use of any GLP-1 RA can be inferred. There is a need for further research and vigilance in GLP-1 RA prescribing, particularly in patients with co-existing psychiatric disorders.

1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have been prescribed as therapeutic options for individuals with type 2 diabetes mellitus (T2DM) (NICE, 2023a). These medications stimulate the release of insulin, suppress glucagon secretion, slow down gastric emptying, and promote satiety (EMC, 2022). Both GLP-1 RA products, Wegovy® (containing semaglutide) and Saxenda® (containing liraglutide)

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subcutaneous injections, have been recommended by the National Institute for Health and Care Excellence (NICE) as treatment options for weight loss and weight management (NICE, 2023b; NICE, 2020). Both Wegovy® and Saxenda® are licensed for weight loss in addition to low-calorie diet and exercise in individuals with raised body mass index (BMI) (NICE, 2023b; NICE, 2020). For Saxenda®, the recommended BMI is at least 35 kg/m^2 or at least 32.5 kg/m^2 for members of minority ethnic groups at equivalent risk of obesity-related consequences at a lower BMI than the Caucasian population. Similarly, for Wegovy®, the BMI criterion is at least 35.0 kg/m^2 or 30.0–34.9 kg/m^2. Lower BMI thresholds apply for specific ethnic backgrounds (NICE, 2023b; NICE, 2020). The GLP-1 RA Ozempic (containing low strength semaglutide) is not licensed for weight loss or weight management currently in the United Kingdom (UK).

In general, the desire to achieve an ideal body image is prevalent in society, and individuals with obesity or diabetes may face additional challenges in this regard. It is believed that GLP-1 RA, with their weight-reducing effects, can lead to body image enhancement and improved self-esteem, positively impacting mental wellbeing for many individuals.

While GLP-1 RA have proven efficacy in glycaemic control and weight management, a growing concern has emerged regarding their potential impact on mental health, with multiple reports being documented on the development of suicidal ideation by users (MHRA, 2023a; MHRA, 2023b). GLP-1 RA are broadly well-tolerated but have some well-documented effects. One of the most commonly reported adverse effects of GLP-1 RA is gastrointestinal disturbances (EMC, 2022). These include nausea, vomiting, diarrhoea, and abdominal discomfort. Such symptoms typically occur during the initial weeks of treatment but tend to subside over time. Nevertheless, these side effects can be bothersome and may lead to treatment discontinuation in some patients. Pancreatitis, although rare, has been reported in some patients using GLP-1 RA (Storgaard et al., 2017). In addition, in preclinical studies, GLP-1 RA have been shown to cause an increased incidence of thyroid C-cell tumours in rodents (Butler et al., 2013). GLP-1 receptor agonists have a low risk of inducing hypoglycaemia unless combined with other anti-diabetic agents, particularly insulin or sulfonylureas (Ahrén, 2011), and have demonstrated favourable cardiovascular outcomes in large clinical trials, including a reduction in major adverse cardiovascular events (Gilbert and Pratley, 2020). However, certain concerns have been raised regarding potential increased heart rates (EMC, 2022; EMC, 2023). The relationship between GLP-1 receptor agonists and these adverse events requires further investigations to establish a definitive causal association. The summary of product characteristics for both semaglutide and liraglutide state that the use of both agents is not recommended in patients classified as New York Heart Association (NYHA) class IV with congestive heart failure due to a lack of clinical experience (EMC, 2022; EMC, 2023).

Surprisingly, a phase III clinical trial of liraglutide (Saxenda®) showed some evidence of suicidal thoughts, as well as renal impairment, gallbladder disease and pancreatitis (Johnson, 2023). Despite that the manufacturer reportedly denied any causal association between the drugs (Wegovy® and Saxenda®) and suicidal thoughts, the manufacturer's prescribing information for both drugs advised on monitoring patients, and possibly discontinuing treatment if patients reported suicidal thoughts (Novo Nordisk, 2023). In addition, allegedly, it is claimed that during the clinical trials investigating both semaglutide and liraglutide (marketed as Wegovy® and Saxenda®, respectively), participants with the following criteria were excluded from the trials: a prior history of suicidal attempts, any suicidal behaviour within 30 days prior to the screening, a history of depression within two years before the screening, and a diagnosis of any severe mental health disorder, such as schizophrenia or bipolar disorder (Johnson, 2023).

In response to a range of reports relating to individuals experiencing suicidal thoughts and self-injury while using liraglutide and semaglutide, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has undertaken a comprehensive review, as initiated by the Icelandic Medicines Agency and announced by the European Union (EU) watchdog (EMA, 2023). Following this initial assessment, the EMA has requested additional data from the Marketing Authorisation Holders (MAH), with the anticipated release of results in mid-2024 (Patchen, 2023). Notably, Saxenda carries a warning for 'suicidal behaviour and ideation' (Patchen, 2023).

The current GLP-1 RA product literature does not include any mental health effects associated with the use of these therapy agents for weight loss (EMC, 2022). Emerging reports have hinted at a plausible connection between GLP-1 RA and psychiatric disorders, particularly depression and suicidal ideation (EMA, 2023). Yet, the current body of evidence remains restricted and inconclusive, posing a significant challenge in definitively establishing a causal relationship. As of January 2024, the United States Food and Drug Administration (FDA) has stated that no robust link has been identified between GLP-1 RA and 'suicidal thoughts or actions' (Food and Drug Administration (FDA), 2024). Nevertheless, ongoing vigilance will be maintained through a meta-analysis of clinical trials and the gathering of post-marketing data related to these drugs. Consequently, the prescribing information for these agents used in weight management has been revised to incorporate details about the potential risks associated with suicidal thoughts or actions (Food and Drug Administration (FDA), 2024). The FDA has advised prescribers to continue monitoring these potential adverse drug reactions (ADRs) (Food and Drug Administration (FDA), 2024). Consistent with this, the current pharmacovigilance study aimed at providing valuable insights into the potential association between GLP-1 RA and certain psychiatric issues. Conversely, it is also important to consider confounding factors such as the underlying medical conditions, lifestyle changes, and psychosocial aspects when evaluating the mental health impact of GLP-1 RA. Hence, comprehensive studies, including longer-term follow-up and rigorous assessment of mental health outcomes, are needed to clarify the potential risks and benefits. Despite the inherent constraints of disproportionality analysis, this study aimed at shedding further light on the claimed GLP-1 RA-related suicidal adverse effects.

2. Methods

For the purpose of this study, the Food and Drug Administration Adverse Events Reporting System (FAERS) was queried in July 2023 for adverse drug reports (ADRs) related to seven non-combination GLP-1 RA products (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide and tirzepatide) and selected preferred terms (PTs) related to psychiatric disorders (system organ class as defined by the MedDRA hierarchy (MedDRA (Medical Dictionary for Regulatory Activities), 2023) or 'reaction group' as described on the FAERS database): 'Suicidal ideation', 'Suicidal attempt', 'Suicidal depression', 'assisted suicide', 'Columbia Suicide Severity Rating Scale abnormality', 'completed suicide', 'suicidal behaviour', 'suicide threat', 'suspected suicide', and 'suspected suicide attempt'. Due to increasing reports associating suicide and self-injury with GLP-1 RA, these PTs (or 'reactions' as described on the FAERS database) were selected from the PTs described within psychiatric disorders on the FAERS database as they include the terms "suicide, suicidal, self-injury or self-injurious". Lowest Level Terms (LLT) such as 'self-injurious ideation' and 'intentional self-injury' were considered in the analysis where they were identified. Standardised drug terminologies (i.e. generic non-proprietary drug name) were utilised to ensure consistency in data representation. Drug salts were not included in the search to ensure the results encompass as many drug salts as possible. Text mining and natural language processing (NLP) techniques were implemented to automatically extract and identify drug names from free-text fields in FAERS reports. Drug data were normalised by applying data cleaning and standardisation techniques. This includes correcting misspellings, abbreviations, and variations in drug names (including brand names) to ensure consistency across the dataset. In our

analysis of FAERS data, drug codification was performed using role codes assigned by the FAERS database. Each drug entry in FAERS is assigned a role code to indicate its role in the reported adverse event. The role codes used here were PS (Primary Suspect). This role code is assigned to the drug considered most likely to be responsible for the reported adverse event. It is important to note that the current analysis included as well information on drugs administered simultaneously with the primary suspect drug but not implicated as a direct cause of the adverse event (assigned the concomitant role code). The role codes provide insights into the perceived relationship between the drug and the adverse event within individual case reports. Our use of these role codes allows for a nuanced analysis of the drugs associated with reported adverse events in the FAERS database, considering their varying degrees of suspected involvement. In this respect, supplementary analyses, termed 'unmasking,' were conducted in alignment with Capogrosso Sansone et al. (Capogrosso Sansone et al., 2017). However, the process of identifying potential masking drug products potentially remains dependent on a pragmatic methodology (Maignen et al., 2014). To adopt a more cautious approach, unmasking was achieved by re-executing the primary analysis. This involved excluding concomitant suspect drugs (Baldini et al., 2023).

The FAERS data were available through the FAERS Public Dashboard on their publicly-available website (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard; accessed on July 22nd, 2023). Descriptive and pharmacovigilance disproportionality analyses of the registered psychiatric disorder-related ADRs, with a focus on 'serious' ADRs related to suicidal and self-injurious ideations was performed. Descriptive analyses included anagraphic characteristics, country of origin, most common diagnoses, concomitant licit/illicit drugs, reporter of the ADR(s), number of cases per year and per reaction, and the outcomes (e.g. patient died, was hospitalised, developed a disability) were performed for the seven drugs. The frequentist reporting odds ratio (ROR) pharmacovigilance measure of the EudraVigilance data analysis system (EVDAS) was employed (Table 1) (Bihan et al., 2020).

$$ROR = \frac{a/b}{c/d}$$

The values employed in the calculation of the Reporting Odds Ratio (ROR)

	Number of reports with event of interest	Number of reports without event of interest
GLP-1 RA of interest	a	b
Remaining GLP-1 RA agents	c	d

Both ROR and 'the proportional reporting ratio (PRR)' frequentist pharmacovigilance measures provide similar outcomes to the analysis (Montastruc et al., 2011). The ROR of suicidal and self-injurious ideations related to GLP-1 RA were compared to the ROR of the same events related to both metformin and orlistat, which have been employed here as comparators and controls (McIntyre et al., 2024). The Samaritans media guidelines for reporting 'suicide' were followed (Samaritan's Media Advice Team, 2020). Adherence to these guidelines contributes to ethical reporting whilst ensuring the use of non-sensational and non-stigmatising language when discussing suicide; minimises harm from drugs; and promotes public health. Data analyses were performed using Microsoft Excel (version 97–2003). Data were reported anonymously, and hence ethical approval was not required.

3. Results

A total of 209,354 ADRs were reported, including 59,300 serious cases (see Table 1). Of those, a total of 5378 psychiatric disorder cases, including 383 'serious' cases related to suicidal and self-injurious ideations were registered during 2005–2023 for the seven GLP-1 RA. The Reported Odds Ratio (ROR) were as follows for the seven GLP-1 RA:

Table 1
Suicide and self-injury adverse effects being reported to the Food and Drug Administration Adverse Events Reporting System (FDA FAERS) in association with Glucagon-Like Peptide receptor agonists (GLP-1 RA).

Drug Name	Total ADR* Cases	Serious cases (including deaths) (% of total ADR cases)	Psychiatric Disorders Cases (%of serious cases)	Suicide and self-injury-related Cases	Breakdown of Suicide and self-injury-related Cases	Timeline of ADR Reporting
Albiglutide	9610	8636 (90 %)	154 (0.02 %)	3 (0.02 %)	Suicidal ideation (3 cases)	2010–2022
Dulaglutide	58,207	11,377 (20 %)	2124 (19 %)	59 (3 %)	Suicidal ideation (34 cases) Suicidal attempts (20 cases) Completed suicide (3 cases) Suicidal behaviour (2 cases) Suicidal depression (2 cases)	2016–2023
Exenatide	77,019	17,243 (22 %)	4259 (25 %)	96 (2 %)	Suicidal ideation (62 cases) Suicidal attempts (18 cases) Suicidal behaviour (2 cases) Self-injurious ideation (2 cases)	2010–2023
Liraglutide	35,774	13,816 (39 %)	1519 (11 %)	143 (9 %)	Suicidal ideation (71 cases) Suicidal attempts (28 cases) Completed suicide (25 cases) Suspected suicide (5 cases) Suicidal behaviour (3 cases) Suicidal depression (2) Self-injurious ideation (4 cases) Intentional self-injury (5 cases)	20,052,023
Lixisenatide	166	144 (87 %)	10 (7 %)	0 (0 %)	N/A	2013–2023
Semaglutide	18,923	7455 (39 %)	1221 (16 %)	76 (6 %)	Suicidal ideation (60 cases) Suicidal attempts (7 cases) Suicidal depression (7) Self-injurious ideation (1 case) Intentional self-injury (1 case)	2018–2023
Tirzepatide	9655	629 (65 %)	269 (43 %)	6 (2 %)	Suicidal ideation (6 cases)	2022–2023

* *Abbreviations:* ADR: adverse drug reactions.

liraglutide ($n = 143$; ROR = **1.97**; 95 % CI = 0.89, 0.47), exenatide ($n = 96$; ROR = 0.81; 95 % CI = 0.03, −0.44), semaglutide ($n = 76$; ROR = **1.73**; 95 % CI = 0.80, 0.30), dulaglutide ($n = 59$; ROR = 0.77; 95 % CI = 0.01, −0.54), tirzepatide ($n = 6$; ROR = **1.49**; 95 % CI = 1.21, −0.41), albiglutide ($n = 3$; ROR = 0.05; 95 % CI = −1.94, −4.22), and lixisenatide ($n = 0$; ROR = 0) (see Table 2 and Fig. 1).

Most cases were reported by healthcare professionals for individuals aged 18–64 YO, and from the United States of America. With regards to selected PTs, 42 deaths including 13 completed suicides were recorded. Suicidal ideation was recorded in $n = 233$ cases for 6/7 GLP-1 receptor agonists (excluding lixisenatide). Pharmacovigilance disproportionality analyses using ROR showed that GLP-1 RA were associated with suicidal and self-injurious ideations in the following descending order: liraglutide, semaglutide, tirzepatide. Evaluation of both comparators metformin ($n = 3401$; ROR = **13.08**; 95 % CI = 2.68, 2.46) and orlistat ($n = 79$; ROR = 0.91; 95 % CI = 0.15, −0.34) showed greater levels of association between these ADRs with metformin as compared to GLP-1 RA (see forest plot in Fig. 2).

Considering the high frequency of reported concomitant medications (e.g. benzodiazepines, antidepressants, antipsychotics, opioids, sedatives, GABAergic drugs and other psychoactive substances), an unmasking analysis (e.g. all cases in which concomitant medicines were identified were excluded here) was also conducted. After unmasking, 271 cases where the *individual drugs were implicated as the sole drug* in the selected ADRs were identified; results were as follows: liraglutide ($n = 90$; Reported Odds Ratio (ROR) = **1.64**; 95 % CI = 0.75, 0.24), exenatide ($n = 67$; ROR = 0.80; 95 % CI = 0.05, −0.50), semaglutide ($n = 61$; ROR = **2.03**; 95 % CI = 0.99, 0.42), dulaglutide ($n = 45$; ROR = 0.84; 95 % CI = 0.14, −0.50), tirzepatide ($n = 5$; ROR = **1.76**; 95 % CI = 1.45, −0.32), albiglutide ($n = 2$; ROR = 0.04; 95 % CI = −1.75, −4.53) and lixisenatide ($n = 0$; ROR = 0). Using the unmasking analysis, pharmacovigilance disproportionality analyses using ROR showed that GLP-1 RA were associated with suicidal and self-injurious ideations in the following descending order: semaglutide, tirzepatide and liraglutide, all with ROR values > 1.0. Using the unmasking analysis, evaluation of both the comparators metformin ($n = 1955$; ROR = **10.63**; 95 % CI = 2.50, 2.24) and orlistat ($n = 48$; ROR = 0.81; 95 % CI = 0.09, −0.52) confirmed a greater association between these ADRs with metformin as compared to GLP-1 RA (see forest plot in Fig. 3).

4. Discussion and conclusions

This article examined the FDA ADRs related to psychiatric reactions, specifically, those related to suicidal and self-injurious reactions associated with GLP-1 RA in response to the review undertaken by the Icelandic Medicines Agency and the announcement made by the EU watchdog (EMA, 2023). This study findings showed a potential increased association between liraglutide, semaglutide and tirzepatide and suicidal thoughts/actions. Research undertaken by Ruggiero et al. (2024) showed similar findings and uncovered a notable prevalence of suicidal events linked to semaglutide and liraglutide, with markedly higher reporting probabilities compared to other GLP-1 RA. Their research hinted at a potential correlation between the risk of suicidal events and the utilisation of higher doses of GLP-1 RA for weight management (Ruggiero et al., 2024). Similarly, in the research conducted by McIntyre et al. (2024), an uneven reporting pattern emerged regarding suicidal ideation and 'depression/suicidal' events associated with both semaglutide and liraglutide in comparison to metformin and insulin. Conversely, consistent with current data, dulaglutide, exenatide, and lixisenatide did not manifest disproportionate reporting of the assessed psychiatric events.

Notably, the U.S. prescribing information for liraglutide 3.0 mg already recommends vigilant monitoring for depression or suicidal thoughts, emphasising discontinuation if these symptoms manifest (Food and Drug Admistration (FDA), 2024). Similarly, a parallel cautionary note is present in the U.S. prescribing information for the semaglutide formulation Wegovy®, being administered at higher dosages for weight control than for T2DM (Food and Drug Administration, 2022). One could wonder if the putative suicidal risk associated with GLP-1 RA may be tied to their impact on the hypothalamus (Drucker, 2022), considering the established association between the hyperactivity of the hypothalamic–pituitary–adrenal axis and the occurrence of suicidal behaviours (Drucker, 2022; Wisłowska-Stanek et al., 2021). Acknowledging the well-established correlation between T2DM/obesity and depressive disorders, the current study suggests that factors associated with these conditions may contribute to the observed, pharmacovigilance-related, instances of suicidality thoughts and actions. Additionally, one could wonder about the existence of a cohort bias, e.g. related to the hypothesis that semaglutide and liraglutide are being preferentially prescribed to individuals with depressive disorders, possibly owing to their suggested antidepressant and pro-cognitive effects (Cooper et al., 2023; Mansur et al., 2018; Seo et al., 2023; Hanna et al., 2015; Sharma et al., 2015; Weina et al., 2018; Ma et al., 2023; Nazeem et al., 2021; Çiçekli et al., 2022). Furthermore, the study posits that the considerable attention garnered by GLP-1 RA, especially semaglutide and liraglutide, in mainstream and social media may have contributed to an elevated reporting rate relative to other medications. This hypothesis underscores the potential impact of media coverage on the perception and reporting of psychiatric events associated with these drugs (McIntyre et al., 2024).

To better assess the above findings, Chen et al. (2023) conducted a subgroup analysis specific to each of six GLP-1 RA (liraglutide, lixisenatide, exenatide, albiglutide, semaglutide and dulaglutide; tirzepatide was not included). Although some 199; 134; and 106 suicide/self-injury reports were found to be respectively associated with liraglutide; exenatide; and semaglutide, they found that the overall class of GLP-1 RA, per se, did not demonstrate an increased risk of suicidal/self-injurious events. However, in the subgroup analysis of children, the reporting pattern for suicide or self-injury relating to the whole GLP-1 RA class showed ROR values greater than 1.0 (Chen et al., 2023). Furthermore, Wang et al. (2024) conducted a retrospective cohort study in the United States utilising electronic health records (EHR) extracted from the TriNetX Analytics Network (https://trinetx.com/). Their aim was to investigate the potential association between semaglutide and suicidal ideation. Their study revealed a lower risk for both occurrence and recurrence of suicidal ideation in patients prescribed semaglutide when compared to those using non-GLP1 RA for either obesity (which included naltrexone and bupropion, among others) or diabetes, which included metformin as well. One could argue that naltrexone and bupropion are being prescribed in either depressive disorders or in specific addiction-related conditions, e.g. in populations where high rates of depression and suicide, are indeed a reason of concern; this may pose a challenge to adequately interpret Wang et al. (2024) results. Conversely, consistent with their observations, in our study, even after unmasking, the current suicide/self-injury data pertaining to semaglutide (e.g. ROR = 2.03) were clearly lower than those relating to metformin (e.g. ROR = 10.63). Additionally, Wang et al. (2024) highlighted the higher prevalence of mental health disorders, particularly depression and suicidal ideation, in individuals with T2DM.

In general, the desire to achieve an ideal body image is prevalent in society, and individuals with obesity or diabetes may face additional challenges in this regard. Anti-obesity medications, with their weight-reducing effects, can lead to body image enhancement and improved self-esteem, positively impacting mental well-being for many individuals. However, it is important to recognise that body image perception is multifaceted and can be influenced by various psychological and societal factors. While GLP-1 RA may contribute to body image improvement, it is crucial to consider the broader mental health implications. It is important to note that the association between GLP-1 RA and mental health problems, such as depression and suicidal ideation, is still being investigated and the underlying mechanisms are not fully understood. However, several hypotheses have been proposed to

Table 2
Glucagon-Like Peptide (GLP-1) receptor agonist cases involving psychiatric disorder* cases specifically focussing on self-injury and suicidal issues** recorded by the Food and Drug Administration Adverse Events Reporting System (FAERS) over the period 2005 – 2023.

Parameters	Albiglutide ($n = 3$) during 2010–2022	Dulaglutide cases ($n = 59$) during 2016–2023	Exenatide cases ($n = 96$) during 2010–2023	Liraglutide cases ($n = 143$) during 2005–2022	Semaglutide cases ($n = 76$) during 2018–2023 (including 1 unspecified case and 1 death)	Tirzepatide cases ($n = 6$) during 2022–2023
F/M	2/1	27/29 (unspecified $n = 3$)	60/35 (unspecified $n = 1$)	77/51 (unspecified $n = 9$)	44/23 (unspecified $n = 7$)	2F 4M
Age			12–17yy ($n = 3$)			
	18–64yy ($n = 2$)	18–64yy ($n = 27$) 65–85yy ($n = 10$)	18–64yy ($n = 47$) 65–85yy ($n = 11$)	18–64yy ($n = 81$) 65–85yy ($n = 16$)	18–64yy ($n = 39$) 65–85yy ($n = 1$)	18–64yy ($n = 5$) 65–85yy ($n = 1$)
	Not specified ($n = 1$)	Not specified ($n = 22$)	Not specified ($n = 35$)	Not specified ($n = 40$)	Not specified ($n = 34$)	
Indications	Diabetes Mellitus ($n = 2$)	Diabetes Mellitus ($n = 25$) Product use for unknow indication ($n = 30$)	Diabetes Mellitus ($n = 57$) Product use for unknow indication ($n = 3$)	Diabetes Mellitus ($n = 51$) Product use for unknow indication ($n = 69$)	Diabetes Mellitus ($n = 19$) Product use for unknow indication ($n = 44$)	Diabetes Mellitus ($n = 5$) Obesity ($n = 1$)
	Not specified ($n = 1$)	Not specified ($n = 4$)	Overweight/obesity/ weight control/weight decreased ($n = 2$) Not specified ($n = 1$)	Overweight/obesity/ weight control/ weight decreased ($n = 21$)	Overweight/obesity/ weight control/weight decreased ($n = 12$) Not specified ($n = 1$)	
Concomitant drugs	Benzodiazepines: Alprazolam; Opioids: Hydrocodone; Antidepressants: Venlafaxine; Cyclobenzaprine; Other: Dapagliflozin; Glimepiride, Lantus; Metformin; Toujeo; Clonidine; Valsartan; Hydrochlorothiazide; Trilipix; Simvastatin; Aspirin; Omeprazole; Omega-3 Fatty Acids; Iron; Folic Acid	Benzodiazepines: alprazolam; Bromazepam; flunitrazepam; Antidepressants: citalopram; Fluoxetine; Trazodone; Antipsychotics: quetiapine; Psychoactive drugs: Cannabis Sativa Seed Oil\Herbals; Other: Fenofibrate; pramipexole; lansoprazole; Luseogliflozin; Pioglitazone; Metformin Hydrochloride; Omeprazole; Naproxen; Losartan; Iron; Prilosec; Vitamin C; Humulin Nos; Tamoxifen; Zyrtec; Montelukast; Dapagliflozin; Lantus; Lisinopril; Synthroid; Cholecalciferol; Dietary Supplement; Folic Acid; Fish Oil; Biotin; Beta Carotene; Aspirin; Flaxseed; Magnesium; Toujeo; Tamsulosin; Duloxetine; Captopril; Ludiomil; Glyburide; Aldactone; Singulair; Oxybutynin; Ranitidine; Lexapro; Tegretol; Synthroid; Bentyl	Benzodiazepines: Lorazepam; Xanax; Antidepressants: Fluoxetine; Prozac; Escitalopram; Sertraline; Bupropion; Antipsychotics: Aripiprazole; Opioids: Acetaminophen\ Oxycodone; Morphine; Hydrocodone; Sedatives: Acetaminophen \Diphenhydramine; Pseudoephedrine: Sudafed; GABAergic drugs: Gabapentin; Neurontin; Psychoactive drugs: Adderall; Other: Claritin; Zyrtec; Dilantin; Zocor; Carvedilol; Nitrostat; Mucinex Dm; Lisinopril; Advair Hfa; Glipizide; Lisinopril; Diltiazem Hydrochloride; Alogliptin; Vicks Dayquil; Carvedilol; Lisinopril; Vancomycin; Ciprofloxacin; Hydrochloride; Hydralazine; Docusate Sodium; Ezetimibe; Benazepril; Narcan; Cefazolin; Naloxone; Imitrex; Vitamin B12; Wellbutrin; Valtrex; Glimepiride; Metformin; Zetia; Zenpep; Iron; Synthroid; Metoprolol Succinate; Lipitor; Protonix; Glimepiride; Lexapro; Tricor; Metformin; Pioglitazone; Lantus; Avapro; Aciphex; Simvastatin;	Benzodiazepines/ Z-drugs: Flunitrazepam; Etizolam; Valium; Lorazepam; Alprazolam; Prozac; Zolpidem Tartrate; Brotizolam; Alprazolam; Antidepressants: Fluoxetine; Trazodone; Prozac; Citalopram; Paroxetine Hydrochloride; Amoxapine; Escitalopram; Antipsychotics: Risperidone; Olanzapine; Abilify; GABAergic drugs: Lyrica; Neurontin; Pregabalin; Opioids: Codeine Phosphate; Norco; Psychoactive drugs: Modafinil; Other: Herbals; Lexapro; Estradiol; Perindopril; Metformin; Apixaban; Amlodipine; Torsemide; Atorvastatin; Modafinil; Prasterone; Prilosec; Pravachol; Xalatan; Flexeril; Coumadin; Cholecalciferol; Enalapril; Atorvastatin Calcium; Synthroid; Telmisartan; Toprol Xl; Repaglinide; Crestor; Insulin Glargine; Magnesium Oxide; Eldecalcitol; Temocapril Hydrochloride; Acyclovir;	Benzodiazepines/ Z-drugs: Zolpidem Tartrate; alprazolam; Mexazolam; Clonazepam; Antidepressants: Fluoxetine; Citalopram; Escitalopram; Bupropion; Mirtazapine; Venlafaxine; sertraline; Reboxetine; Sedatives: Promethazine; Pseudoephedrine: Cetirizine Hydrochloride \Pseudoephedrine Hydrochloride; Other: tamsulosin; metformin; Omeprazole; Atorvastatin; Glipizide; Simvastatin; Losartan; empagoflozin; Diclofenac; paracetamol; Lisinopril; Fenofibrate; Hydrochlorothiazide; Fish Oil; Yasmin; Mebeverine Embonate; Glyburide; gliclazide; exenatide; lantus; Perindopril Arginine; Aspirin; iron; Isosorbide Mononitrate; diltiazem; Finasteride; Famotidine; Levothyroxine	Antidepressants: Sertraline; GABAergic drugs: Pregabalin; Gabapentin; Sedatives: Promethazine; Other: Famotidine; Hydrochlorothiazide; Duloxetine; Atorvastatin; Humalog; Ibuprofen; Lisinopril; Amlodipine; Metformin; Sildenafil; Insulin Glargine; Fish Oil; Lexapro; Hydrochlorothiazide \Valsartan; Pioglitazone; Nystatin; Novolog; Tylenol; Tadalafil; Amlodipine; Pravastatin; Metformin; Farxiga; Lantus

(*continued on next page*)

Table 2 (*continued*)

Parameters	Albiglutide ($n = 3$) during 2010–2022	Dulaglutide cases ($n = 59$) during 2016–2023	Exenatide cases ($n = 96$) during 2010–2023	Liraglutide cases ($n = 143$) during 2005–2022	Semaglutide cases ($n = 76$) during 2018–2023 (including 1 unspecified case and 1 death)	Tirzepatide cases ($n = 6$) during 2022–2023
			Allopurinol; Detrol; Fluconazole; Bydureon Bcise; Simvastatin; Aciphex; Cefdinir; Pristiq Extended-Release; Glimepiride; Meloxicam; Pravastatin Sodium; Aspirin; Combigan; Remicade; Cetirizine; Pantoprazole; Ranitidine; Klonopin; Atorvastatin; Potassium; Torsemide; Warfarin	Atorvastatin; Glumetza; Atenolol; Simvastatin; Fenofibrate; Vitamins; Vitamin B12; Citalopram; Losartan; Ferrous Sulfate; Glipizide; Vitamin D3; Levothyroxine; Naproxen Sodium; Novolog; Lamictal; Klonopin; Seroquel; Actos; Aspirin; Fenofibrate; Esidrex		
Country of origin (Most recorded)	United States of America ($n = 3$)	United States of America ($n = 31$) Japan ($n = 7$) United Kingdom ($n = 5$) Not specified ($n = 4$) France ($n = 4$)	United States of America ($n = 32$) Canada ($n = 9$) Not specified ($n = 7$) France ($n = 5$) Australia ($n = 4$) United Kingdom ($n = 3$)	United States of America ($n = 72$) Japan ($n = 14$) Canada ($n = 12$) Not specified ($n = 6$) France ($n = 6$) United Kingdom ($n = 6$)	United States of America ($n = 32$) Canada ($n = 9$) Not specified ($n = 7$) France ($n = 5$) Australia ($n = 4$) United Kingdom ($n = 3$)	United States of America ($n = 2$) Not specified ($n = 4$)
Case count be received year	2016 ($n = 1$) 2017 ($n = 1$) 2018 ($n = 1$)	2016 ($n = 10$) 2017 ($n = 5$) 2018 ($n = 11$) 2019 ($n = 8$) 2020 ($n = 11$) 2021 ($n = 10$) 2022 ($n = 15$) 2023 ($n = 2$)	2016 ($n = 13$) 2017 ($n = 3$) 2018 ($n = 3$) 2019 ($n = 9$) 2020 ($n = 8$) 2021 ($n = 3$) 2022 ($n = 4$)	2016 ($n = 13$) 2017 ($n = 9$) 2018 ($n = 18$) 2019 ($n = 9$) 2020 ($n = 31$) 2021 ($n = 10$) 2022 ($n = 15$) 2023 ($n = 15$)	2018 ($n = 2$) 2019 ($n = 4$) 2020 ($n = 9$) 2021 ($n = 22$) 2022 ($n = 31$) 2023 ($n = 17$)	2022 ($n = 1$) 2023 ($n = 5$)
Reporter	Healthcare professional ($n = 2$)	Healthcare professional ($n = 26$)	Healthcare professional ($n = 48$)	Healthcare professional ($n = 112$)	Healthcare professional ($n = 43$)	Healthcare professional ($n = 1$)
	Consumer ($n = 1$)	Consumer ($n = 33$)	Consumer ($n = 47$) Unspecified ($n = 1$)	Consumer ($n = 23$) Unspecified ($n = 2$)	Consumer ($n = 31$)	Consumer ($n = 5$)
Outcome		Died ($n = 3$) Disabled ($n = 4$) Hospitalised ($n = 23$) Life threatening ($n = 25$)	Died ($n = 8$) Disabled ($n = 12$) Hospitalised ($n = 44$) Life threatening ($n = 54$)	Died ($n = 30$) Disabled ($n = 2$) Hospitalised ($n = 43$) Life threatening ($n = 12$)	Died ($n = 1$) Disabled ($n = 3$) Hospitalised ($n = 11$) Life threatening ($n = 16$)	Hospitalised ($n = 1$) Life threatening ($n = 1$)
	Other outcomes ($n = 3$)	Other outcomes ($n = 55$) Required intervention ($n = 59$)	Other outcomes ($n = 86$)	Other outcomes ($n = 92$) Required intervention ($n = 1$)	Other outcomes ($n = 67$) Required intervention ($n = 1$)	Other outcomes ($n = 4$) Required intervention ($n = 1$)
No. of cases by reaction	Suicidal ideation ($n = 3$)	Suicidal ideation ($n = 34$) Suicide attempt ($n = 20$) Completed suicide ($n = 3$) Suicidal behaviour ($n = 2$) Depression suicidal ($n = 2$)	Suicidal ideation ($n = 71$) Suicide attempt ($n = 28$) Depression suicidal ($n = 2$) Intentional self-injury ($n = 5$) Completed suicide ($n = 5$) Suicidal behaviour ($n = 3$) Suspected suicide ($n = 5$) Self-injurious ideation ($n = 4$)	Suicidal ideation ($n = 62$) Suicide attempt ($n = 18$) Depression suicidal ($n = 7$) Intentional self-injury ($n = 5$) Completed suicide ($n = 5$) Suicidal behaviour ($n = 2$) Self-injurious ideation ($n = 2$)	Suicidal ideation ($n = 60$) Suicide attempt ($n = 7$) Depression suicidal ($n = 7$) Intentional self-injury ($n = 1$) Self-injurious ideation ($n = 1$)	Suicidal ideation ($n = 6$)

Abbreviations: F: female, M: male.

[*] Psychiatric disorders include: Insomnia, depression, anxiety, confusional state, nervousness, suicidal ideation, irritability, depressed mood, mood swings, disorientation, sleep disorder due to a general medical condition.

[**] Self-injury and suicidal issues include: depression suicidal, suicidal ideation, suicidal attempt, assisted suicide, Columbia Suicide Severity Rating Scale abnormality, completed suicide, suicidal behaviour, suicide threat, suspected suicide, suspected suicide attempt.

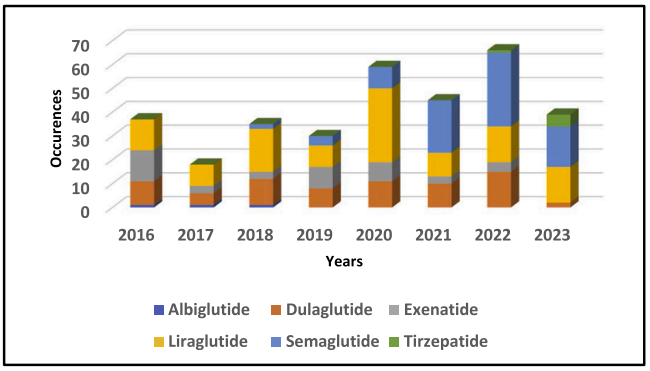

Fig. 1. Incidence of occurrence of GLP-1 RA over 2016 – 2023.

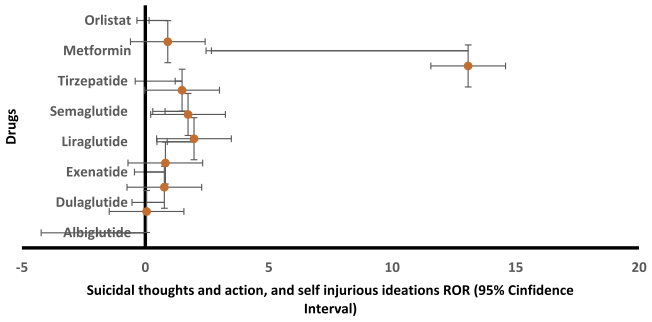

Fig. 2. Forest plot showing the reporting odds ratio (ROR) (95 % Confidence Interval) for suicidal thoughts and actions, and self-injurious ideations with GLP-1 RA versus reference non- GLP-1 RA drugs.

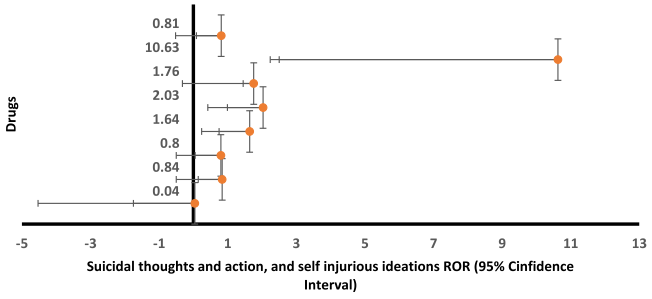

Fig. 3. Forest plot showing the reporting odds ratio (ROR) (95 % Confidence Interval) for suicidal thoughts and actions, and self-injurious ideations with GLP-1 RA versus reference non- GLP-1 RA drugs after conducting the unmasking analysis.

explain the potential link between GLP-1 RA and mental health issues (Arillotta et al., 24). One of the psychological conditions in those considering taking GLP-1 RA, particularly semaglutide (Chiappini et al., 2023), is body dysmorphic disorder (BDD). This is a condition characterised by obsessive thoughts and preoccupations with perceived flaws or defects in one's appearance. Individuals with BDD often experience significant psychological distress, impaired functioning, and a negative impact on their overall quality of life. They can be consumed by negative thoughts and obsessive concerns about their appearance, often spending excessive time engaging in repetitive behaviours (e.g., mirror checking, seeking reassurance) or avoiding situations that trigger distress (Veale and Riley, 2001). This preoccupation with appearance can lead to feelings of anxiety, depression, shame, and social isolation. In addition, BDD frequently coexists with other mental health disorders. Common comorbidities include anxiety disorders (e.g., social anxiety disorder or generalised anxiety disorder (GAD)), depression, obsessive-compulsive disorder (OCD), eating disorders (e.g., anorexia nervosa, bulimia nervosa), and exercise addiction (Corazza et al., 2019). The presence of these additional mental health conditions can exacerbate the distress experienced by individuals with BDD. The burden of BDD can be severe, leading to increased risk of suicidal ideation and behaviour. Research has shown that individuals with BDD may be at a higher risk of suicide attempts and completed suicides compared to the general population (Crerand et al., 2005; Phillips, 2007). The distress caused by BDD, coupled with the impairment in social functioning and self-esteem, can contribute to feelings of hopelessness and a desire to escape the individual's perceived flaws. While body image dissatisfaction is common in society, individuals with BDD experience a distorted perception of their appearance, even when there may be little or no observable physical abnormality. This distorted perception fuels their distress and the obsessive thoughts surrounding their appearance.

Another mental health issue of interest here is emotional eating, which is the tendency to use food as a coping mechanism for emotional distress. The condition is prevalent among individuals with obesity and can be associated with increased levels of stress, anxiety, and depression. Additionally, some research suggests that certain foods, particularly those high in sugar and fat, can have addictive properties, leading to compulsive overeating and contributing to obesity and mental health issues (Yau and Potenza, 2013). Obesity can also be influenced by a combination of biological, psychological, and social factors. Genetic predisposition, hormonal imbalances, and certain medications can contribute to weight gain. Additionally, psychological factors like unhealthy coping mechanisms may play a role in the development and maintenance of obesity whilst also possibly impacting on mental health (Milaneschi et al., 2019; Lopresti and Drummond, 2013). Indeed, both conditions involve dysregulation of neurotransmitters (e.g., serotonin, dopamine), hormones (e.g., leptin, cortisol), and inflammatory markers (Ouakinin et al., 2018). These imbalances are postulated to affect mood, appetite regulation, and cognitive function, contributing to the development of both obesity and mental health disorders. It is of interest that evidence suggests an elevated risk of suicide after undergoing bariatric surgeries, specifically Roux-en-Y gastric bypass surgery (RYGBP) (Pories et al., 1995). RYGBP is known to bring about substantial changes in gastrointestinal peptides, contributing to reduced appetite and enhanced satiation, thereby promoting weight loss (Berthoud, 2008). These peripherally released peptides, e.g. GLP-1, also affect the central nervous system, potentially influencing mood, anxiety, and cognition (Gunstad et al., 2011). Obesity has been associated with diminished cognitive function, and improvements in memory have been documented as early as 12 weeks post-RYGBP (Isacson et al., 2011). It is suggested that this could be due to the consistent and rapid increase of GLP-1 peptides following RYGBP. More evidence is required to explore both the connection between post-RYGBP cognitive enhancement and GLP-1, and whether the post-surgery increase in GLP-1 may influence suicidality (Mitchell et al., 2013).

Conversely, Verovnik and Vovk (2024) found no significant change in resting-state functional connectivity (RSFC) after a semaglutide intervention in participants with polycystic ovary syndrome and obesity compared to a placebo group, as investigated in specific brain regions of interest (ROIs). However, upon closer examination, significant changes in RSFC were observed in ROIs associated with suicidal ideation and behaviour. The semaglutide group exhibited higher connectivity, while the placebo group showed lower RSFC in certain regions. This change in connectivity was opposite to what previous studies on suicidal ideation in patients with major depressive disorder (MDD) had found (Verovnik and Vovk, 2024).

The link between obesity; weight loss; anti-obesity medications; and suicidal ideation is a complex and evolving topic that requires careful consideration by health professionals, especially prescribers. While some studies have reported associations between certain anti-obesity medications and an increased risk of suicidal ideation or behaviour, it is essential to interpret these findings within the broader context of their use.

In fact, several anti-obesity medications, such as selective serotonin reuptake inhibitors (SSRIs) and the naltrexone/bupropion combination have been associated with potential psychological side-effects, including changes in mood and the occurrence of suicidal ideation (Shettar et al., 2017). Rimonabant, which is a selective cannabinoid type 1 (CB1) receptor antagonist that was initially developed as an anti-obesity medication, is another example. It was designed to reduce appetite and food intake by blocking the CB1 receptors in the brain, which are involved in the regulation of appetite and energy balance. However, rimonabant was withdrawn from the market due to safety concerns related to its potential psychiatric side-effects including increased risks of depression, suicidal ideations (Van Gaal et al., 2008; Robertson and Allison, 2009), and completed suicide (Mitchell and Morris, 2007; Boekholdt and Peters, 2010). This led to its withdrawal from the market in several countries (Christensen et al., 2007). The exact mechanisms underlying these psychiatric side-effects are not fully understood (Drugs.com 2008), but they are believed to be related to the drug's antagonistic action on the endocannabinoid system in the brain, thus impacting on dopamine, decreasing both its levels and the associated activation of the reward pathways (Hughes, 2008; Melis et al., 2007), resulting in anhedonia, depression and suicidal feelings.

It is here relevant to emphasise that GLP-1 receptors are not only present in the pancreas but also in various regions of the brain, including areas associated with mood regulation (Chiappini et al., 2023). GLP-1 receptors in the hypothalamus, hippocampus, and amygdala, among others, play a role in modulating emotions and behaviour. It is theorised that GLP-1 RA may directly affect these brain regions, potentially influencing mood and mental well-being. Using pharmacovigilance approaches, our research group identified a potential for misuse and the development of withdrawal symptoms with semaglutide (Chiappini et al., 2023), with this potential of misuse possibly being associated with the presence of GLP-1 receptors in the reward pathway areas including the nucleus accumbens, ventral tegmental area and the amygdala (Anderberg et al., 2014). Hence, one would assume that if an individual is affected by BDD and/or emotional eating, as well as misusing with a GLP-1 RA, they will be at higher risk of depression and suicide (cohort bias).

Additionally, GLP-1 receptors interact with various neurotransmitter systems, including serotonin, dopamine, and glutamate (Athauda et al., 2017). These neurotransmitters play critical roles in mood regulation and can be involved in the development of depression and other mental health conditions. GLP-1 RA may modulate these neurotransmitter systems, potentially impacting on mood and emotional states. Furthermore, semaglutide and similar drugs promote satiety (van Bloemendaal et al., 2014), possibly because GLP-1 RA show pro-dopaminergic efficacy (van Bloemendaal et al., 2014) and can modulate reward (Chiappini et al., 2023). However, it is not clear whether suicidal thoughts occur when the individual is taking the drug regularly or when it is withdrawn. From this point of view, one can hypothesise that in withdrawal cases, as for other acute appetite suppressant and pro-dopaminergic substances, depressive and suicidal feelings can develop (Gawin, 1991a; 1991b).

Furthermore, rapid weight loss or adjustment to a new body image may trigger both biological and psychological responses that could influence suicidal ideation. Indeed, it is well-known that serum lipid levels, and specifically low levels of cholesterol, could have an impact on the development of both suicidality (Engelberg, 1992) and impulsivity (Tomson-Johanson et al., 2020). Since the early 1990s, there has been a growing interest in exploring cholesterol as a potential biomarker for suicide (Muldoon et al., 1990). According to the cholesterol-serotonin hypothesis, decreased cholesterol levels have a negative impact on serotonergic activity, particularly by inducing alterations in the structure and function of cell membranes within the central nervous system. These changes directly influence the affinity and configuration of serotonin receptors and transporters (Engelberg, 1992). The resulting decrease in serotoninergic activity is believed to be associated with a decreased ability to regulate impulsivity. A mechanism similar to that hypothesised for cholesterol may apply to the use of GLP-1 agonists, which can alter overall glucose and lipid metabolism (Patel et al., 2014).

5. Limitations

While the current findings are of interest, their interpretation demands caution due to the inherent limitations in utilising the FDA FAERS for pharmacovigilance (Chen et al., 2023). The indispensable role of FAERS is acknowledged, yet its application faces significant constraints. The disproportionality analysis employed to quantify signs of drug-related adverse reactions, whilst a suitable tool, has limitations in distinguishing between different types or reasons for reactions, such as underlying medical conditions, lifestyle changes, and psychosocial aspects. This analysis also struggles to account for confounding factors like comorbidities and dosages/routes of administration. Conversely, the possible bias related to the concurrent use of other drugs was possibly mitigated here by the current study's unmasking analysis. These limitations arise from the nature of the primary sources—reports submitted to the FDA—which only provide information from reporters and often lack evidence establishing a clear causal link between reported Adverse Event Reports (AERs) and drug exposure.

The observed associations between GLP-1 RA and mental health issues discussed here may also be influenced by various confounding factors, including the underlying medical conditions being treated, individual patient characteristics, and other concurrent medications. Ultimately, a comprehensive understanding of the potential psychiatric effects of GLP-1 RA necessitates more research, including large-scale clinical trials, longitudinal studies, and further exploration of the neurobiological pathways involved. Such studies will help clarify the exact mechanisms through which GLP-1 RA may impact on mental health and guide clinical decision-making regarding the use of these medications.

Whilst our analysis revealed an association between the intake of albiglutide, dulaglutide, exenatide and lixisenatide, and a decreased occurrence of suicidal ideation events, it is essential to note that disproportionalities are interdependent, and safety endorsement cannot be inferred. Furthermore, it is crucial to emphasise that our findings do not imply a protective effect (reduced occurrence) but rather highlight a statistical association within the limitations of disproportionality analyses. It is important to clarify that the observed association does not imply causation or safety endorsement. It explicitly addresses the interdependence of disproportionalities and underscores the importance of avoiding claims of a protective effect.

The underreporting of adverse drug reactions poses a foundational hurdle in interpreting studies on pharmacovigilance databases. Factors contributing to underreporting include reporter experience, drug characteristics, reaction severity, and unexpectedness relative to the drug's safety profile. These biases and limitations introduced by underreporting add intricacy to disproportionality studies, underscoring the necessity for meticulous consideration and the incorporation of additional methods to address these challenges. Compounding these complexities are biases in pharmacovigilance disproportionality analyses, such as the Weber effect, e.g., a time-dependent surge in reporting post-drug launch due to incomplete safety profiles and heightened exposure. The impact of the Weber effect varies based on its intensity for the specific adverse reaction compared to others. Disproportionality analyses encounter difficulties in detecting long-term effects as they distance themselves from the marketing period. The notoriety effect amplifies reports after media coverage of an adverse drug reaction. Additionally, patient-related biases, including indication bias, severity bias, channelling bias, or the healthy user effect, may influence comparisons in these analyses. These challenges, coupled with underreporting complexities, underscore the importance of cautious interpretation and the integration of alternative methodologies in pharmacovigilance studies (Faillie, 2019).

It is also to be acknowledged here the difficulties in assessing the correlation between GLP-1RA dosage, indication, and suicidal actions/ideations, along with the incapacity to thoroughly evaluate other potential risk factors or comorbidities. Relying solely on AERs is rarely sufficient to definitively attribute a particular effect in a patient to a specific drug, as the effect may be linked to the treated disease, a new disease in the patient, or another medicine they are taking. Caution must be exercised in drawing direct conclusions from AERs alone.

6. Conclusions

Despite these limitations and inherent biases in pharmacovigilance studies based on spontaneous reporting, it is essential to consider the identified ROR and other statistical values as valid signals of disproportionality. These signals can help raise awareness of potential issues but should be further investigated using complementary methods to establish causality conclusively. Future research employing additional approaches, such as prospective clinical trials, to both overcome pharmacovigilance data limitations and achieve a more complete understanding of the causality of AERs, should be promoted in this field. There is the need for further research and vigilance in GLP-1 RA prescribing, particularly in patients with co-existing history of psychiatric disorders including but not limited to body dysmorphia and emotional eating, as well as history of substance misuse and/or diversion of prescription medicines.

7. Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to check the rephrasing in some sections. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Author contributions

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CRediT authorship contribution statement

A Guirguis: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **S Chiappini:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **GD Papanti P:** Writing – review & editing. **R. Vickers-Smith:** Writing – review & editing. **D Harris:** . **JM Corkery:** . **D Arillotta:** . **G. Floresta:** . **G Martinotti:** Writing – review & editing. **F Schifano:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

F.S. was a member of both the UK Advisory Council on the Misuse of Drugs (ACMD; 2011–2019) and of the EMA Advisory Board (2011–2023; Psychiatry). J.M.C. is a member of the ACMD's Novel Psychoactive Substances and Technical Committees. G.M. has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, and Recordati. A.G., S.C., R.V.-S., D.H.: declare no conflict of interest.

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