

Real-World Pharmacovigilance Analysis of Suicidal Ideation and Self-Injurious Behavior Associated with GLP-1 Receptor Agonists: Disproportionality and Mechanistic Insights

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Abstract

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Pharmacological therapies for T2DM and obesity have undergone a revolution with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as semaglutide, liraglutide, dulaglutide, exenatide and tirzepatide. A number of spontaneous reports of adverse events, including suicidal ideation and self-injurious behaviour, were reported to the European Medicines Agency (EMA) and the Icelandic Medicines Agency, which were formally reviewed by the EMA, the United States Food and Drug Administration (FDA) and the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), beginning in 2023. This paper reviews the existing evidence on the actual link between exceptionally high blood pressure and certain events, based on the available cohort and case-control studies, as well as the proposed neurobiological pathways to this potential association. The results of disproportionality analyses from the FDA Adverse Event Reporting System (FAERS) and the World Health Organization's Vigibase database are inconsistent:

Some large analyses have found no disproportionality signal, but individual-agent analyses have identified weak, albeit statistically significant disproportionality signals in certain subgroups, notably for semaglutide and liraglutide. Large cohort studies, matched by propensity score on electronic health records, have however, mainly reported a reduced risk of incident and recurrent suicidal ideation in GLP-1 RA users vs other anti-obesity or anti-diabetic drugs. In a French nationwide case-time-control

study, no consistent elevated risk for suicide or suicide attempt was observed after accounting for psychiatric history and obesity severity in patients exposed to GLP-1 RA. On a mechanistic level, GLP-1 receptors are found in central circuits important for appetite, reward, mood, and stress reactivity, lending biological plausibility to both the beneficial (anti-inflammatory, neurotrophic) and detrimental (dysphoric, anhedonic) neuropsychiatric effects that have been observed in susceptible individuals. The evidence as it stands to date (2026) is not sufficient to support a strong causal link between GLP-1 RA use and increased suicidality at the population level; however, a group of patients with a certain risk profile may benefit from increased monitoring – those with a pre-existing psychiatric illness, rapid titration, and significant caloric restriction. Recommendations for pharmacovigilance methodology, clinical screening and future prospective research are provided.

1. Introduction

An incretin hormone, glucagon-like peptide-1 (GLP-1), is synthesized in the intestine's L-cells after food intake. Synthetic GLP-1 receptor agonists (GLP-1 RAs) bind to GLP-1 receptors, increasing glucose-dependent insulin secretion, reducing glucagon secretion, slowing gastric emptying and increasing satiety. Exenatide was approved in 2005 and has since been expanded to liraglutide, dulaglutide, and semaglutide, the latter also having a dual GLP-1/GIP receptor activation mechanism, as well as tirzepatide. Remarkable efficacy for weight reduction has been shown in trials like STEP and SURMOUNT, and this has led to unprecedented numbers of prescriptions written for T2DM and obesity outside the traditional endocrinology sphere and into primary care, cardiology and increasingly, cosmetic and lifestyle medicine.

The rapid expansion in use has been paralleled by an increased focus on the safety profile of the drug class. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has put liraglutide and semaglutide under review in July 2023, after receiving formal reports of suicidal ideation and/or self-injury in patients taking the drugs, including some from the Icelandic Medicines Agency. The FDA then began to review the data from FAERS and the MHRA in the UK undertook a parallel investigation. These regulatory decisions attracted significant press coverage and public concerns, given the number of tens of millions of patients who had been prescribed these agents in the world to date.

The implications for science and medicine to settle this issue are substantial. However, obesity and type 2 diabetes are also independently linked with increased rates of depression and suicidal ideation, and the epidemiological association found in prescription databases may just be due to confounding by indication. However, GLP-1 receptors are plentiful in brain areas involved in mood, motivation, and stress reactivity, offering a potential mechanism by which these medications may, at least in some sensitive individuals, trigger or exacerbate psychiatric disturbances. The distinction of these options relies on triangulation using multiple lines of evidence: passive pharmacovigilance databases, active-comparator cohort studies, randomized controlled trial safety data and mechanistic neuroscience.

In this paper, a comprehensive narrative synthesis of that body of evidence is performed as it existed in 2026. The biological plausibility of GLP-1 receptors in the CNS is first established by reviewing the pharmacology and CNS distribution of GLP-1 receptors. We then follow the regulatory history of the suicidality signal and outline the methodology of disproportionality analysis used for databases like FAERS and VigiBase. We combine the results of the main pharmacovigilance studies, the existing cohort studies and the one nationwide case-time-control study, and present them in tables and forest graphics so that they can be directly compared. Next, we explore candidate neurobiological mechanisms that might underlie either a protective or deleterious influence on mood, and critically review the methodological challenges—

channelling bias, indication bias, notoriety bias, and confounding by underlying psychiatric illness—that are inherent in observational pharmacovigilance data and impede causal inference. Finally, clinical recommendations for risk stratification and monitoring, a frank discussion on the state of the evidence base and priorities for future research.

2. Pharmacology and Central Mechanisms of GLP-1 Receptor Agonists

GLP-1 receptors (GLP-1Rs) are G-protein coupled receptors found in pancreatic islets and in the gastrointestinal tract, but also expressed all over the central nervous system, such as in the hypothalamic arcuate and paraventricular nuclei, the nucleus tractus solitarius and area postrema of the brainstem, the mesolimbic dopaminergic reward system (which connects the ventral tegmental area to the nucleus accumbens), in the hippocampus, and in the amygdala. Peripherally administered GLP-1 RAs may act directly on these central sites by penetrating the blood–brain barrier at circumventricular organs, which have a permeable barrier, or indirectly through the vagal afferent pathway, which emanates from the gut wall.

The main peripheral and central pathways of GLP-1 RA actions are summarized in Figure 1. At the periphery, an increase in GLP-1 receptor activation stimulates glucose-dependent insulin secretion and vagal afferent stimulation inhibits gastric emptying and induces early satiety. In the center, the hypothalamic arcuate nucleus regulates the balance of orexigenic and anorexigenic neuropeptides; which favors appetite suppression. At the same time, the activation of GLP-1 receptors in the mesolimbic dopamine pathway reduces hedonic and reward-driven eating, which has led to the consideration of GLP-1 RAs for the treatment of substance use disorders and behavioral addictions. Preliminary data also indicate that GLP-1 receptor activation stimulates the generation of new neurons in the hippocampus, increases synaptic plasticity, and decreases microglial activation and the production of inflammatory cytokines across a wide range of animal models of stress and metabolic dysfunction, which is broadly antidepressant and neuroprotective properties.

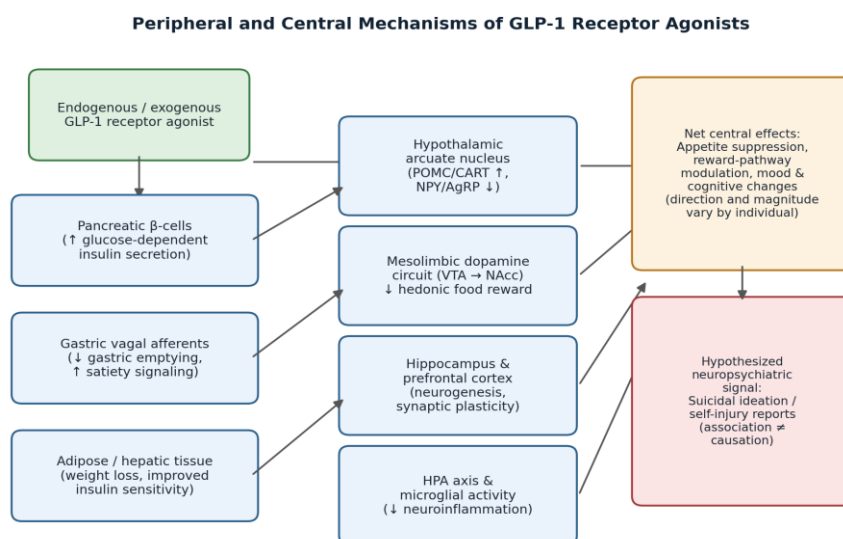


Figure 1. Peripheral and central mechanisms of GLP-1 receptor agonists, illustrating pathways from metabolic action to hypothesized neuropsychiatric effects.

This dualism in pharmacology is what is currently the subject of scientific debate. These same core circuits would, under some circumstances, give rise to dysphoric and anhedonic responses or increased distress, which are all hallmarks of an antidepressant. Hedonic reward is thought to be abnormally suppressed, resulting in an anhedonic state in susceptible individuals; metabolic and psychological stress from fast weight loss and caloric restriction; gastrointestinal stress (nausea, vomiting) leading to poor quality of life and sleep difficulties; and rapid withdrawal of concurrent

psychotropic medications as weight loss and dosing changes. The following mechanisms have not been proven to induce suicidal ideation in humans but each offers a testable hypothesis that is consistent with the distribution of the receptors.

3. Regulatory Background and Emergence of the Safety Signal

A case study of the GLP-1 RA spontaneous pharmacovigilance reporting is presented to show how a spontaneous reporting can lead to a formal, multi-agency safety evaluation. Figure 2 shows the key steps of the approval process, from the initial approval of exenatide in 2005 to the regulatory decisions made in 2024 and the updated analyses of subgroups in 2025 and 2026.

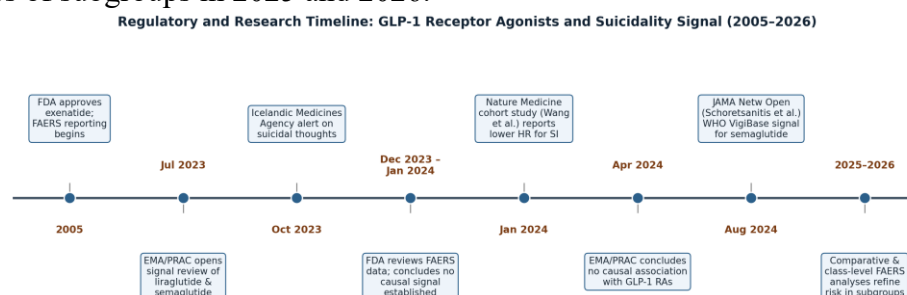


Figure 2. Regulatory and research timeline of the GLP-1 receptor agonist suicidality signal, 2005–2026.

Following a small number of individual case reports, the Icelandic Medicines Agency (ISA) issued an alert in July 2023 which led to the EMA's PRAC opening a formal Article 20 referral procedure for both liraglutide and semaglutide. The FDA followed suit, conducting its own review of FAERS data from 2005 through Oct 2023 for reports of suicidal ideation, depression/suicidal, suicidal behavior, suicide attempts, and completed suicide for all approved GLP-1 RAs, compared to other glucose-lowering medications. In January 2024, the FDA issued a public communication that it "did not see a clear causal relationship" between the use of GLP-1 RAs and suicidal thoughts or behaviors based on the data it had reviewed in FAERS, and a meta-analysis of clinical trial data, although a small residual risk could not be ruled out. In April 2024, the EMA's PRAC made the same finding, saying that there was no causal evidence that GLP-1 RAs cause suicidal or self-destructive ideas or behaviour.

The academic body expanded as well, providing important inputs to these regulatory decisions. The rest of this paper summarizes that literature in great detail, first into passive pharmacovigilance database studies and then to active-comparator cohort and case-time-control studies, and then addresses the underlying neurobiology and the methodological issues of causal inference in this field.

4. Methodology of Real-World Pharmacovigilance Research

Pharmacovigilance databases like FAERS and Vigibase gather spontaneous adverse-event reporting from clinicians, patients and pharmaceutical companies. Since these are not randomly sampled or systematically collected data, they cannot be used to estimate the incidence of an adverse event, instead researchers use disproportionality analysis to determine whether there are more reports for a particular adverse event occurring with a particular drug than would be anticipated based on the overall reporting rate of that adverse event across all other drugs in the database. Figure 3 provides a description of the standard analytic workflow.

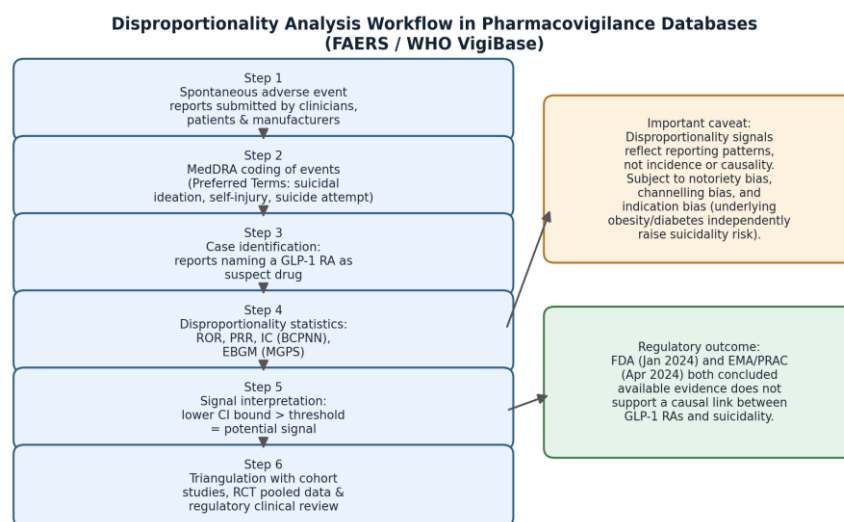


Figure 3. Disproportionality analysis workflow applied to FAERS and WHO VigiBase pharmacovigilance data.

There are a number of statistical measures that quantify disproportionality, each based on the construction of a two-by-two contingency table that compares the event of interest reported for the drug of interest to the counts of all other drug–event combinations. A simple frequentist measure is the reporting odds ratio (ROR) and proportional reporting ratio (PRR), which do stabilize estimates of rare events via a Bayesian shrinkage. Derived from the Bayesian Confidence Propagation Neural Network (BCPNN), the information component (IC) and derived from the Multi-Item Gamma Poisson Shrinker (MGPS), the Empirical Bayes Geometric Mean (EBGM) also constructs a Bayesian shrinkage of the estimates on rare events. If the lower limit of the 95% confidence interval for the ROR or PRR is >1.0 , or the lower limit of the 95% confidence interval for the IC is >0.0 , then the signal is considered present.

Most importantly, as noted in nearly all of the studies reported here, the positive disproportionality signal is not a causal or prevalence claim but rather only confirms that an adverse event is reported more frequently for a drug than is reported for the reporting database in general. Reporting rates are affected by drug notoriety, media coverage, product labelling changes, regulatory alerts (which also may be associated with increased reporting, a process referred to as 'Weber effect'), and channelling bias, where a new drug is more likely to be prescribed to patients who are systematically different from those prescribed comparator drugs. These constraints have been the motivation for the complementary use of both active-comparator cohort studies and case-time-control designs that are also discussed below.

Table 1 summarizes the design characteristics of the principal pharmacovigilance and epidemiological studies synthesized in this paper.

Study	Database / Data Source	Design	Populatio n	Primary Outcome(s)
Chen et al. (2023)	FAERS (2005 Q2–2023 Q2)	Disproportionali ty (ROR, EBGM)	All FAERS reports; GLP-1 RA vs. all other drugs	Suicide/self- injury composite
McIntyre et al. (2024)	FAERS (2005– Oct 2023)	Disproportionali ty (ROR)	GLP-1 RA vs. other glucose- lowering agents	Suicidal ideation, behavior,

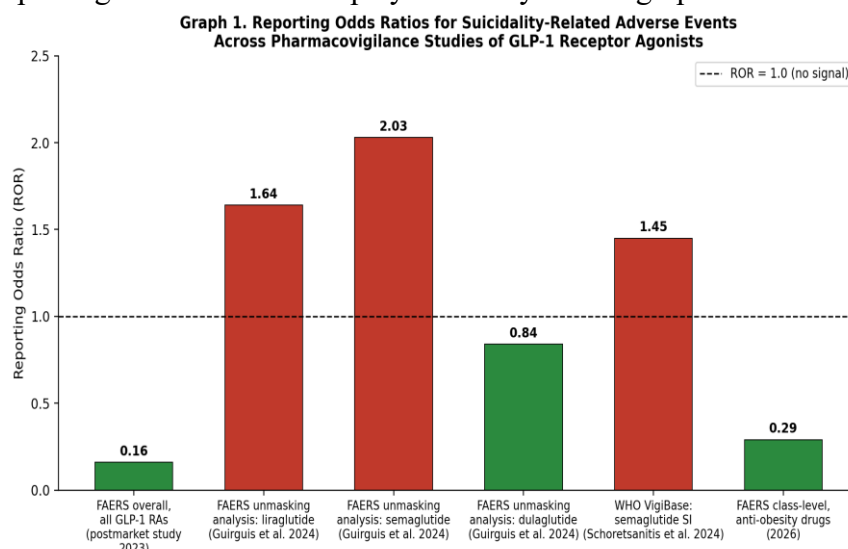
Study	Database / Data Source	Design	Population	Primary Outcome(s)
				attempt, completed suicide
Guirguis et al. (2024)	FAERS (2005–2023), unmasking analysis	Disproportionality with metformin/orlistat comparators	271 GLP-1 RA–implicated psychiatric ADR cases	Suicidal ideation, self-injury by individual agent
Schoretsanitis et al. (2024)	WHO Vigibase (inception–Aug 2023)	Case–control disproportionality (ROR, IC)	107 semaglutide and 162 liraglutide cases	Suicidal/self-injurious ADRs
Kim et al. (2024)	WHO Vigibase	Disproportionality, stratified by indication	GLP-1 RA reports, diabetes vs. obesity indication	Suicide/self-injury
Wang et al. (2024)	TriNetX electronic health records	Propensity-matched retrospective cohort	240,618 (obesity) + 1,589,855 (T2DM) patients	Incident and recurrent suicidal ideation (HR)
Bezin et al. (2025)	French National Health Data System (SNDS)	Nationwide case-time-control	Suicide deaths and hospitalized suicide attempts, 2013–2021	Suicide / suicide attempt
Ebrahimi et al. (2025)	Multiple databases (systematic review)	Systematic review & meta-analysis	Pooled cohort and pharmacovigilance studies	Suicide and self-harm events

Table 1. Design characteristics of principal studies examining GLP-1 receptor agonists and suicidality.

5. Findings From Pharmacovigilance Databases

Results of disproportionality analyses have been quite variable, depending on the database used, the period of analysis, the comparator, and the analysis level (drug class or single agent). When looking at all FAERS reports between Q2 2005 and Q2 2023, Chen et al. identified 534 cases of suicide/self-injury that were reported in relation to GLP-1 RAs as a class, and reported a lower than expected signal (ROR = 0.16, 95% CI [0.15, 0.18]) that was marginally elevated but was not statistically significant, with a higher than expected signal (ROR = 0.26, 95% CI [0.12, 0.53]) that was present for only a small number of reports in the pediatric population. McIntyre et al. (2024) analyzed data from FAERS up to October 2023, comparing it with other glucose-lowering medications, and found that there was disproportionate reporting of suicidal ideation and “depression/suicidal” terms specifically for semaglutide and liraglutide, but not for suicide attempts or completed suicide at the class level. After

applying an unmasking analysis, using the reporting odds ratio as a comparator, Guirguis et al. (2024) found reporting odds ratios were higher for agent-specific drugs, such as liraglutide ($n = 90$, $ROR = 1.64$) and semaglutide ($n = 61$, $ROR = 2.03$), than for dulaglutide ($ROR = 0.84$) and exenatide ($ROR = 0.80$). Schoretsanitis et al. (2024), found a significant disproportionality signal for semaglutide-associated suicidal ideation ($ROR = 1.45$, 95% CI [1.18, 1.77]) that was greatly magnified when sensitivity comparators were both antidepressant use ($ROR = 4.45$) and benzodiazepine use ($ROR = 4.07$) — both measures of which are proxies for pre-existing affective or anxiety disorders, and the authors interpreted as most consistent with confounding by indication. Importantly, there was no significant signal of liraglutide in this analysis. These reporting odds ratios are displayed side by side in graph 1.



Graph 1. Reporting odds ratios for suicidality-related adverse events across major pharmacovigilance studies of GLP-1 receptor agonists.

The small number of completed-suicide reports in the databases, and the very wide 95% confidence intervals for the estimates in this class-level comparative FAERS analysis (which range from below to well above unity), preclude any firm conclusion. Overall, the pharmacovigilance literature indicates that any disproportionality signal (DPS), if found, is found exclusively for semaglutide and liraglutide, is strongest for patients who report co-use of psychotropic medications, and is not consistently observed at the drug-class level or for the most severe outcome of completed suicide.

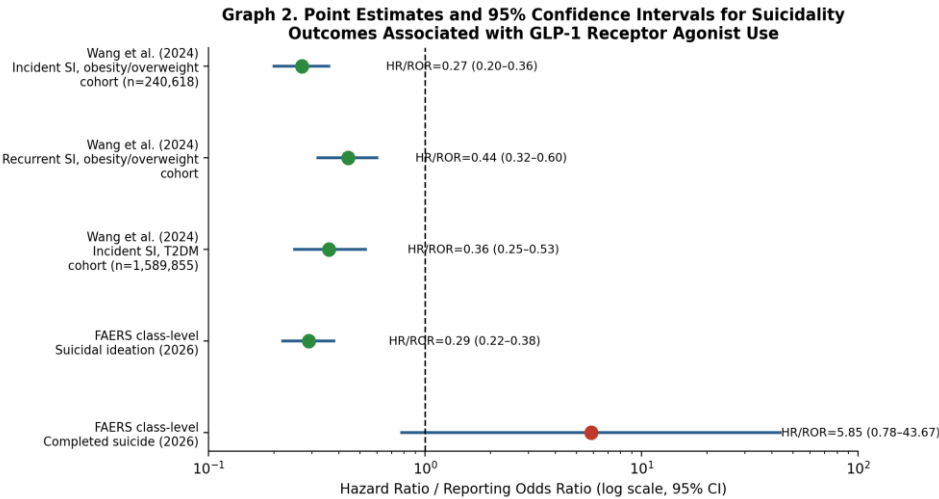
6. Findings From Cohort and Case-Time-Control Studies

Active-comparator cohort and case-time-control studies are valuable complementary data sources as they are more suitable for estimating absolute risk and controlling for confounding. Released by Wang et al. (2024) in *Nature Medicine* and led by the U.S. National Institute on Drug Abuse, this is the most influential study of this type, which compared semaglutide consumers to non-GLP-1 receptor agonist anti-obesity or anti-diabetic medication consumers using propensity-score matching in the TriNetX electronic health record network. The hazard of incident suicidal ideation and recurrent SI were substantially lower with semaglutide than with comparator medications, as was consistently seen across sex, age, and ethnicity strata in both cohorts (240,618 patients with overweight or obesity; 1,589,855 patients with type 2 diabetes).

Bezin, Bénard-Larivière, Hucteau, Tournier, Montastruc, Pariente and Faillie (2025) conducted a methodologically distinct nationwide case-time-control study in France, using data from the French National Health Data System, of people who died by suicide or were hospitalized for a suicide attempt between 2013 and 2021 and compared GLP-1 RA dispensing patterns in the 12-months before the index event with

reference periods before the index event. This within-person design provides natural confounder control for stable confounders like psychiatric history and chronic disease severity. After controlling for psychiatric history and obesity severity, no consistent increased risk of suicide or a suicide attempt was found after GLP-1 RA dispensing, a finding that supports the conclusion that much of the signal identified in spontaneous reporting systems is likely due to underlying vulnerability of the treated population and not due to the direct effects of the drugs.

Ebrahimi and colleagues conducted a pooled analysis of pharmacovigilance and cohort studies and found no evidence that GLP-1 RAs increase the risk of suicide or self-harm, and suggested that, for patients with obesity and an elevated baseline risk of suicide or self-harm owing to psychiatric history or psychosocial factors, GLP-1 RAs may be a better treatment choice than bariatric surgery, which is known to carry a higher risk of suicide following the procedure. The forest plots in Graph 2 show the direction and precision of the point estimates and confidence intervals for the principal cohort comparisons and disproportionality analyses presented in Sections 5 and 6, highlighting the large variation among study designs in terms of direction and precision of the effects estimates.



Graph 2. Point estimates and 95% confidence intervals for suicidality-related outcomes associated with GLP-1 receptor agonist use, comparing cohort hazard ratios and pharmacovigilance reporting odds ratios.

Table 2 consolidates the quantitative findings from the studies reviewed in Sections 5 and 6, permitting direct comparison of effect direction, magnitude, and precision.

Study (Year)	Comparator	Effect Measure	Estimate (95% CI)	Interpretati on
Chen et al. (2023)	All other FAERS drugs	ROR	0.16 (0.15–0.18)	No class-level signal
Guirguis et al. (2024) – semaglutide	Metformin/orlistat (unmasked)	ROR	2.03	Elevated signal
Guirguis et al. (2024) – liraglutide	Metformin/orlistat (unmasked)	ROR	1.64	Elevated signal

Study (Year)	Comparator	Effect Measure	Estimate (95% CI)	Interpretation
Schoresanitis et al. (2024) – semaglutide SI	All other WHO VigiBase drugs	ROR	1.45 (1.18–1.77)	Significant signal, amplified with antidepressant co-use
Schoresanitis et al. (2024) – liraglutide	All other WHO VigiBase drugs	ROR	Not significant	No signal detected
Wang et al. (2024) – incident SI, obesity cohort	Non-GLP-1 anti-obesity drugs	HR	0.27 (0.20–0.36)	Lower risk with semaglutide
Wang et al. (2024) – recurrent SI	Non-GLP-1 anti-obesity drugs	HR	0.44 (0.32–0.60)	Lower risk with semaglutide
FAERS class-level (2026)	Non-GLP-1 anti-obesity drugs	ROR	0.29 (0.22–0.38)	Lower reporting for GLP-1 class
Bezin et al. (2025)	Within-person reference periods	Case-time-control OR	No consistent excess risk	No causal signal after adjustment

Table 2. Comparative summary of quantitative effect estimates for GLP-1 receptor agonists and suicidality across study designs.

7. Mechanistic Insights: Central Neurocircuitry and Mood Regulation

To understand the differences in pharmacoepidemiological findings between drugs, databases and comparators, one must pay attention to the underlying neurobiology. The GLP-1 receptors are distributed among a cross-connected network of regions of the brain that work together to control energy balance, reward, threat appraisal, and mood, as suggested in Figure 4.

Candidate Central Neurocircuitry Linking GLP-1 Signaling to Mood and Suicidality Risk

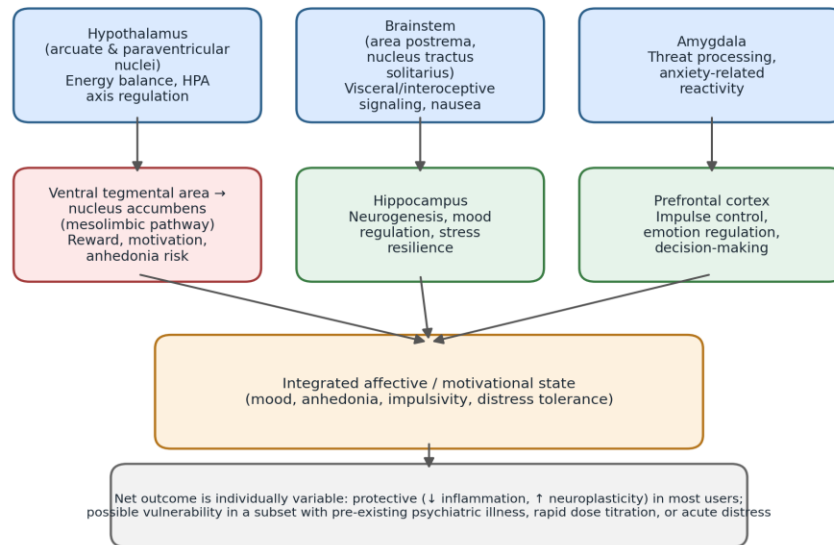


Figure 4. Candidate central neurocircuitry linking GLP-1 receptor signaling to mood and suicidality risk.

Acute, high dose central GLP-1 receptor stimulation has been shown to produce anxiogenic and aversive behavioural responses, presumably through the amygdala and the hindbrain nuclei involved in nausea/visceral malaise, while chronic and moderate dose stimulation more often has anxiolytic and antidepressant-like effects, likely via hippocampal neurogenesis and reduced responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis. This dose- and duration-dependent disconnect, reported by Anderberg et al. (2016) and later seen in other rodent models, could help account for the fact that clinical signals are not seen consistently, but rather in certain agents (e.g., semaglutide) and certain time periods (early treatment, dose escalation).

Complementary human neuroimaging and endocrine studies showed that GLP-1 receptor activation in the mesolimbic dopamine pathway dampened neural response to palatable food cues in the ventral striatum and orbitofrontal cortex, a therapeutic effect of GLP-1 receptor activation that can be desirable for weight management but might, if it extends to other aspects of reward processing, also reduce the broader hedonic capacity of the brain and thus increase the likelihood of developing anhedonia in susceptible individuals. At the same time, GLP-1 RAs have well-established anti-inflammatory properties that include the reduction of pro-inflammatory cytokines in the blood (including IL-6 and TNF- α), and attenuation of microglial activation, a biological pathway that has been strongly implicated in the pathophysiology of MDD; this provides a coherent mechanistic basis for the reported anti-inflammatory signal seen in several observational cohorts and small clinical trials conducted in patients with comorbid depression and metabolic disease.

The best current model is to recognize that GLP-1 RAs are neuropsychiatrically protective for the vast majority of patients (consistent with the cohort-level data that show a reduction in risk for suicidal ideation)—but that a small minority of patients (likely those with preexisting mood or anxiety disorders, patients who have rapid dose titration, and patients who experience severe GI adverse effects and profound caloric restriction) may have a net dysphoric or destabilizing effect. This variation among individuals is more reflective of individual harm rather than a consistent class-wide harm, which is what the pattern of disproportionality signals.

8. Confounding, Bias, and Challenges to Causal Inference

A thorough consideration of the benefits and drawbacks that can lead to a false drug–event association in observational data is inescapable in any discussion of this

literature. Figure 5 illustrates a biopsychosocial framework that incorporates the major sources of confounding that are pertinent to the GLP-1 RA – suicidality literature.

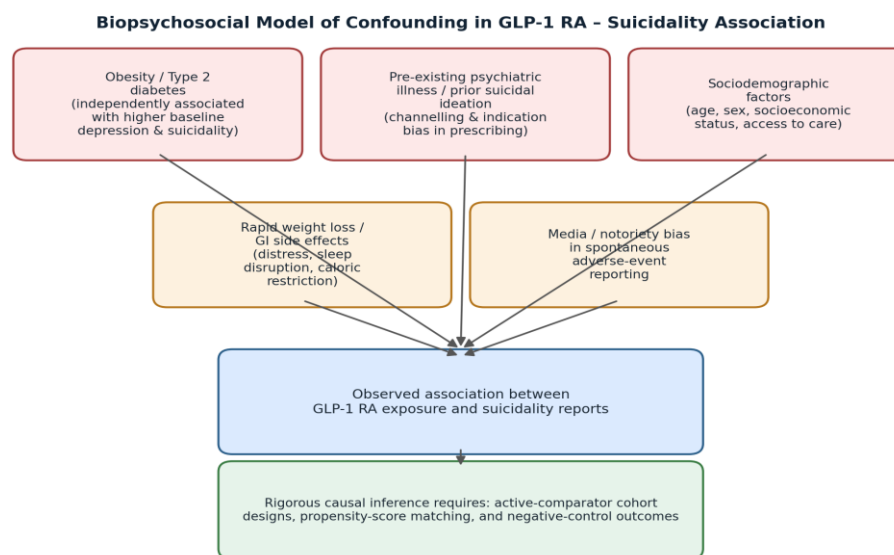


Figure 5. Biopsychosocial model of confounding in the observed association between GLP-1 receptor agonist exposure and suicidality reports.

First, confounding by indication is significant: obesity and type 2 diabetes independently carry approximately a two-fold higher psychiatric risk profile than the general population, and thus, a population of GLP-1 RA users will have an increased psychiatric risk profile prior to drug exposure. Second, channelling bias could occur when newer medications like semaglutide are preferentially offered to patients who did not respond to other treatment options, including those with the most severe or treatment-refractory obesity and psychological distress. Third, notoriety bias, or the Weber effect, refers to the phenomenon that reporting rates of an adverse event rise precipitously after an event becomes prominent through media coverage or a regulatory alert, separate from any actual increases in reports; the reporting surge that followed a review of the EMA is in keeping with this effect. Fourth, "unmeasured co-medication" – the use of antidepressants and benzodiazepines – both indicate underlying psychiatric disease and have an inherent potential for suicidality that can be mistaken for that of the GLP-1 RA.

Much of the seeming inconsistencies in the literature are due to these biases which are asymmetric across study design. Disproportionality analysis of spontaneous reports is most susceptible to notoriety and channelling bias because it does not have a denominator of unexposed or comparator patients, but instead is dependent on differential reporting behavior. Active-comparator cohort studies have attempted to be partially mitigated by propensity-score matching for measured psychiatric baseline variables, but unmeasured factors (such as symptom severity within a psychiatric diagnosis) could still contribute to residual confounding. The case-time control design used in Bezin et al. (2025) may provide the strongest control for unmeasured and stable confounding; when there is no consistent signal in this design, this is a particularly informative sign, albeit a transient effect focused within a broad window of time around the treatment start time cannot be ruled out entirely.

9. Clinical Risk Stratification and Monitoring Recommendations

Until further prospective studies are completed, a pragmatic, risk-stratified approach to clinical monitoring is warranted, with the substantial demonstrated metabolic and cardiovascular advantages of GLP-1 RAs outweighed by the potential though not proven risk of neuropsychiatric destabilisation in a subset of patients. A proposed monitoring framework, broken down by baseline risk category, is listed in

Table 3.

Risk Category	Defining Features	Suggested Monitoring Approach
Low risk	No personal or family history of depression, anxiety, or suicidal ideation; stable social circumstances	Routine clinical follow-up at standard intervals; brief mood check-in at each visit
Moderate risk	Past (resolved) depressive or anxiety disorder; obesity with significant psychosocial stressors; currently on stable antidepressant therapy	Structured mood/suicidality screening (e.g., PHQ-9 item 9) at baseline and at each dose-titration step; counsel patient and family on warning signs
High risk	Active depressive or anxiety disorder; recent suicidal ideation or attempt; concurrent benzodiazepine or antidepressant initiation/change; rapid or severe weight loss with reduced caloric intake	Joint management with mental health specialist before initiation; more frequent (e.g., biweekly to monthly) structured screening; slower dose titration; low threshold for temporary discontinuation and reassessment
Pediatric / adolescent patients	Any adolescent prescribed GLP-1 RA for obesity	Given the modestly elevated pediatric ROR signal in FAERS data, apply enhanced screening and family involvement regardless of baseline psychiatric history

Table 3. Proposed risk-stratified clinical monitoring framework for patients initiating GLP-1 receptor agonist therapy.

The content of this framework is provided as a reasonable, evidence-informed synthesis and should not be viewed as a formal clinical practice guideline, and individual clinicians and health systems should adapt it based on their locally endorsed guidelines from organisations such as the American Diabetes Association, the Endocrine Society, national psychiatric associations, which may change as additional data emerges. More importantly, no regulatory agency has recommended that patients with stable psychiatric disorder be excluded from GLP-1 RA therapy, but rather, a gradual consensus is emerging to favour informed, collaborative decision making, and structured monitoring, over categorical exclusions.

10. Regulatory and Public Health Implications

This signal is a good illustrative example for current pharmacovigilance practice. Within a period of about 6-9 months, both FDA and EMA have shifted from being alerted by a signal to communicating a signal and formally reviewing it, without acting too quickly to safety, but following the precautionary principle to a drug class with an extremely large and growing patient population. As of 2026, neither agency has required a boxed warning indicating suicidality for the GLP-1 RA class, though a similar pattern of historical signals resulted in indication-specific language about new or worsening depression and suicidal ideation being included in product labelling for other medication classes, such as anticonvulsants and smoking-cessation drugs.

Given the number of patients now taking GLP-1 RAs around the world (tens of millions) and the fact that a small absolute risk of developing suicidality in a susceptible population can result in a substantial number of patients affected, from a public health standpoint there is a need for continued pharmacovigilance surveillance and prospective registry-based studies. In contrast, hasty or overly strict regulatory decisions, in the absence of solid cause-and-effect data, could ultimately deny patients significant, well-established metabolic, cardiovascular, and perhaps antidepressant effects, such as the cardiovascular benefit seen in the SELECT trial and the potential antidepressant benefits mentioned in Section 7. The current regulatory stance (one of monitoring and informed consent, not restriction) seems proportionate given current evidence.

11. Limitations of the Current Evidence Base

The conclusions drawn from the literature collated in this paper are limited by a number of factors. First, there is a possibility of publication and reporting bias, as studies showing a null or protective association—especially if they are sponsored by a pharmaceutical company—may be more likely to be published in high-impact journals, and smaller signal detection studies from national medicines agencies may receive comparatively less attention. Second, outcome definitions vary widely across studies, from very specific completed suicide to very general composite outcomes of suicidal ideation or self-injury. Secondly, the outcome measured varies from one study to another, from very specific (completed suicide) to very general (suicidal ideation or self-injury). Third, most of the cohort studies conducted thus far have depended on the diagnosis coding in electronic health records to determine if the patient had suicidal ideation, which has the potential for under-ascertainment (when a patient does not report ideation to his or her treating clinician) and misclassification. Finally, the relatively short follow-up periods used in most cohort studies (usually six months), may not be adequate to detect delayed onset effects that may occur after one year or more of continuous treatment and significant weight loss. Lastly, virtually all evidence comes from adults in high-income countries in which pharmacovigilance systems are fully developed, with uncertainties about generalizability to adolescent populations, lower-income countries, and greater psychiatric comorbidity profiles.

12. Future Research Directions

This synthesis suggests a number of research priorities. Randomized controlled trials with systematic and validated psychiatric outcome assessment (e.g., Columbia-Suicide Severity Rating Scale at regular intervals) would greatly boost causal inference, in addition to providing very large samples or a pooled analysis of multiple trials, but given the low absolute rates of suicidality, this would be difficult to obtain with an observational design. Mechanical imaging studies (in vivo) performed before and after GLP-1 RA administration, comparing reward-circuit and limbic activation, and tailored to baseline psychiatric characteristics, might be able to identify individual-specific vulnerability markers. Extended duration cohort studies with follow-up periods greater than 12 months and studies specifically examining the period around dose escalation would help determine if risks, if any, are found within a specific period of treatment. Finally, other national health data systems with similarly complete longitudinal prescribing and mortality information (such as the Scandinavian countries, South Korea and Taiwan) would be of great value in the replication of the French case-time-control design, which is particularly resistant to confounding from stable patient characteristics.

13. Conclusion

The association of GLP-1 receptor agonist use with suicidal thoughts is illustrative of the overall issue of how to interpret a spontaneous pharmacovigilance signal in the presence of significant confounding due to underlying disease. These

disproportionality analyses of FAERS and WHO VigiBase data yielded inconsistent signals across the broad spectrum of evidence reviewed in this paper, with signals of suicidal ideation being stronger in the semaglutide data and weaker in the liraglutide data and these signals being strongest among patients with co-reported use of psychotropic medication, but no consistent disproportionality reporting was observed with the class-wide analyses or with the most severe outcome—completed suicide. In fact, large propensity-matched cohort studies and a comprehensive nationwide case-time-control study have indicated that GLP-1 RA users may be at a lower risk for suicidal ideation than anti-obesity or anti-diabetic medications in the comparator groups, and both the FDA and EMA arrived at the conclusion that available evidence does not support a causal association in 2024. A model consistent with the present data is that neuropsychiatric protective and harmful effects are plausible central neurobiological mechanisms, with the drug being protective and/or harmful in a meaningful number of a clearly identifiable group of individuals who have psychiatric vulnerability. Clinically, this evidence suggests that individuals can continue to use GLP-1 RAs safely and effectively, coupled with risk-stratified psychiatric screening and monitoring, without restriction, and that continued pharmacovigilance and prospective study are required, especially because the number of people exposed to GLP-1 RAs is huge and continues to increase.

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