Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

# Class-Wide Disproportionate Reporting of Impaired Gastric Emptying Across Nine Glucagon-Like Peptide-1 Receptor Agonist Products: A Signal-Detection Analysis of the FDA Adverse Event Reporting System

**Igor Eduardo**

igorcnnbd@gmail.com

Independent Researcher https://orcid.org/0009-0005-6288-1135

**Research Article**

**Keywords:** GLP-1 receptor agonists, pharmacovigilance, FAERS, disproportionality analysis, impaired gastric emptying, signal detection

**Posted Date:** August 26th, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-9818062/v3

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

**Additional Declarations:** The authors declare no competing interests.

# Class-Wide Disproportionate Reporting of Impaired Gastric Emptying Across Nine Glucagon-Like Peptide-1 Receptor Agonist Products: A Signal-Detection Analysis of the FDA Adverse Event Reporting System

**Igor Eduardo**
*Independent Researcher, Austin, Texas, USA*
ORCID: 0009-0005-6288-1135
Correspondence: igorcnnbd@gmail.com

## Abstract

**Background.** Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) delay gastric emptying as an on-target pharmacological effect. Independent pharmacovigilance analyses have reported that GLP-1 RAs account for a large share of impaired-gastric-emptying (IGE) reports in spontaneous databases (Huang et al., 2025; Tu et al., 2026). We sought to reproduce these observations across marketed products using a fully transparent, reproducible pipeline, without asserting causation.

**Methods.** We queried the public openFDA interface to the FDA Adverse Event Reporting System (FAERS) for nine GLP-1 RA products. The outcome was the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term "Impaired gastric emptying" (10021518). For each product we computed the proportional reporting ratio (PRR), reporting odds ratio (ROR), 95% confidence intervals, and the Yates-corrected chi-square against all other drugs in the database. Counts reflect the full database snapshot at the extraction date; all reported figures are reproducible from the public openFDA source using the analysis script.

**Results.** All nine products met conventional signal criteria (PRR $\geq 2$, $\chi^2 \geq 4$, $N \geq 3$). Semaglutide-based products showed the strongest disproportionality (Ozempic PRR 109.1; Rybelsus 66.4), followed by dulaglutide (Trulicity 38.5), semaglutide for obesity (Wegovy 31.5), tirzepatide for diabetes (Mounjaro 29.5), liraglutide (Victoza 22.3; Saxenda 19.3), and the lowest signals for tirzepatide-obesity (Zepbound 4.5) and exenatide (Byetta 4.5). Full confidence intervals, ROR, and chi-square values are reported in Table 1. The same-molecule contrast between diabetes- and obesity-indicated products is consistent with confounding by indication rather than a molecule-specific effect.

**Conclusions.** These results reproduce, with a transparent and fully reproducible method, the class-wide IGE disproportionate-reporting signal previously reported by independent groups. Disproportionality measures quantify reporting patterns, not incidence or risk, and cannot establish causality. The analysis is descriptive and hypothesis-generating; it makes no claim about clinical risk and requires confirmation in controlled cohort studies.

**Keywords:** pharmacovigilance; FAERS; disproportionality analysis; GLP-1 receptor agonists; impaired gastric emptying; signal detection

## 1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are widely used for type 2 diabetes and obesity. Delayed gastric emptying is a well-characterized, on-target pharmacological action of this class and contributes to both glycemic and satiety effects. As utilization has expanded, spontaneous reports describing impaired gastric emptying (IGE) and related upper-gastrointestinal events have increased, and regulatory labeling has evolved accordingly.

Spontaneous reporting databases such as the FDA Adverse Event Reporting System (FAERS) support hypothesis-generating signal detection through disproportionality analysis. Independent FAERS analyses have reported that GLP-1 RAs account for a substantial fraction of IGE reports, and controlled data indicate a measurable but bounded delay in gastric emptying. The objective of the present study is to provide a transparent, fully reproducible characterization of the IGE disproportionate-reporting signal across nine marketed GLP-1 RA products, using a single, correctly mapped MedDRA Preferred Term, with the analysis script and dataset available on request.

## 2. Methods

### *2.1 Data source and temporal scope*

Data were obtained from the public openFDA application programming interface to FAERS (api.fda.gov/drug/event.json). No date filter was applied; the analysis therefore reflects the full state of the database at the time of extraction rather than a predefined historical cutoff. Because openFDA continues to ingest reports, applying a date cap at the extraction date reproduces the reported figures from the public source; the analysis script and the exact analyzed dataset are available from the author upon reasonable request.

### *2.2 Outcome definition*

The outcome was the MedDRA Preferred Term “Impaired gastric emptying” (code 10021518), queried against the reaction field. We verified that the alternative term “Gastroparesis” is essentially absent in openFDA (on the order of single-digit reports per product) and therefore does not constitute a hidden case pool; the single Preferred Term captures effectively the entire reporting signal.

### *2.3 Products*

Nine products were analyzed, mapped to molecule and indication: semaglutide (Ozempic, type 2 diabetes; Rybelsus, oral type 2 diabetes; Wegovy, obesity), tirzepatide (Mounjaro, type 2 diabetes; Zepbound, obesity), dulaglutide (Trulicity, type 2 diabetes), liraglutide (Victoza, type 2 diabetes; Saxenda, obesity), and exenatide (Byetta, type 2 diabetes). Product-level counts used the medicinal-product field.

### *2.4 Statistical analysis*

For each product we constructed a 2×2 contingency table of product versus all other drugs, cross-classified by presence or absence of the IGE Preferred Term. We computed the proportional reporting ratio (PRR; Evans et al., 2001), the reporting odds ratio (ROR), log-normal 95% confidence intervals, and the Yates-corrected chi-square statistic. A signal was defined a priori by the conventional thresholds PRR $\geq 2$, $\chi^2 \geq 4$, and $N \geq 3$ reports. Reporting follows the READUS-PV recommendations for disproportionality analyses (Fusaroli et al., 2024). Analyses used only the Python standard library; the script and dataset are available on request.

## 3. Results

The background population comprised 20,328,575 reports, of which 11,456 contained the IGE Preferred Term. All nine products met the predefined signal criteria. Product-level results are shown in Table 1.

**Table 1. Disproportionate reporting of impaired gastric emptying (MedDRA 10021518) for nine GLP-1 RA products, FAERS/openFDA (full snapshot at extraction).**

| Product | Molecule | Indication | N (IGE) | Total | PRR (95% CI) | ROR | $\chi^2$ |
|---|---|---|---|---|---|---|---|
| Ozempic | semaglutide | T2D | 2,693 | 57,104 | 109.1 (104.6–113.8) | 114.4 | 220,669 |
| Rybelsus | semaglutide | T2D (oral) | 249 | 6,798 | 66.4 (58.7–75.1) | 68.9 | 15,640 |
| Trulicity | dulaglutide | T2D | 1,590 | 84,824 | 38.5 (36.5–40.5) | 39.2 | 49,959 |
| Wegovy | semaglutide | Obesity | 246 | 14,142 | 31.5 (27.8–35.7) | 32.1 | 7,088 |
| Mounjaro | tirzepatide | T2D | 1,260 | 84,847 | 29.5 (27.8–31.2) | 29.9 | 30,852 |
| Victoza | liraglutide | T2D | 495 | 41,142 | 22.3 (20.4–24.4) | 22.5 | 9,606 |
| Saxenda | liraglutide | Obesity | 76 | 7,030 | 19.3 (15.4–24.2) | 19.5 | 1,293 |
| Zepbound | tirzepatide | Obesity | 134 | 53,599 | 4.5 (3.8–5.3) | 4.5 | 354 |
| Byetta | exenatide | T2D | 132 | 52,082 | 4.5 (3.8–5.4) | 4.5 | 357 |

*PRR, proportional reporting ratio; ROR, reporting odds ratio; T2D, type 2 diabetes. All values reproduce from the public openFDA source at the extraction date.*

Semaglutide-based products showed the strongest disproportionality, with injectable semaglutide for diabetes (Ozempic) highest. Within a single molecule, products indicated for type 2 diabetes showed higher disproportionality than products indicated for obesity (Mounjaro 29.5 vs. Zepbound 4.5 for tirzepatide; Victoza 22.3 vs. Saxenda 19.3 for liraglutide). This pattern is concordant with the higher baseline prevalence of gastrointestinal dysmotility in diabetic populations and differing time on market, and is therefore most parsimoniously interpreted as confounding by indication rather than a molecule-specific safety difference.

## 4. Discussion

### *4.1 Principal findings*

Across nine marketed GLP-1 RA products, impaired gastric emptying generated a consistent, class-wide disproportionate-reporting signal. The ordering of products is biologically coherent and consistent with the established pharmacology of the class. These observations reproduce, rather than newly assert, the pattern already described in the peer-reviewed literature, and the present contribution is methodological: a single correctly mapped Preferred Term and a transparent, re-runnable pipeline.

### *4.2 Consistency with prior evidence*

These findings are consistent with independent published analyses. A peer-reviewed FAERS analysis reported that five GLP-1 RAs accounted for roughly half of all impaired-gastric-emptying reports among the most frequently implicated drugs (Huang et al., 2025), and a subsequent FAERS analysis found that the same five substances accounted for the majority of IGE reports among the most implicated drugs (Tu et al., 2026). A separate FAERS study identified gastrointestinal disorders, including delayed gastric emptying, as a dominant reported category for GLP-1 RAs (Bhagavathula, 2024). Semaglutide-specific FAERS work has likewise identified gastrointestinal disorders as the dominant reported system organ class (Shu et al., 2022; Du et al., 2024). At the same time, the clinical magnitude of the underlying effect appears bounded: a systematic review and meta-analysis found a pooled solid-phase emptying delay of approximately 36 minutes with no significant delay on liquid testing, which the authors characterized as limited relative to standard peri-procedural fasting intervals (Hiramoto et al., 2024). Controlled cohort data report elevated but imprecisely estimated gastrointestinal hazards (Sodhi et al., 2023). The disproportionate-reporting signal reported here should therefore be read as qualitatively concordant with, but not a quantitative substitute for, this body of evidence. Notably, delayed gastric emptying is recognized in the approved FDA prescribing

information for semaglutide as an on-target pharmacological effect, and the label was recently updated to add a Warnings and Precautions subsection on pulmonary aspiration during general anesthesia or deep sedation (Ozempic Prescribing Information, 2025); the present reporting signal is therefore concordant with, rather than antecedent to, regulatory recognition of this effect.

### 4.3 Limitations

Disproportionality analyses are subject to well-recognized limitations and quantify reporting patterns rather than incidence, risk, or causation. Spontaneous reporting is voluntary and incomplete, and report volume is influenced by media attention and litigation. The notoriety bias—increased reporting of an event after it receives public or regulatory attention—is particularly relevant for this drug class given the contemporaneous litigation and media environment (Pariente et al., 2007), although analyses of modern FAERS suggest that classical stimulated-reporting and Weber-effect patterns are less pronounced than once assumed (Hoffman et al., 2014a; Hoffman et al., 2014b), and an empirical evaluation of safety-alert-driven notoriety found no measurable inflation of disproportionality estimates (Neha et al., 2021). Differential duplication across heavily reported products cannot be excluded and may inflate the relative magnitude of the strongest signals; accordingly, the product ordering should be regarded as suggestive rather than definitive. Confounding by indication, differing time on market, and the absence of a denominator of exposed patients further constrain interpretation. We did not apply Bayesian shrinkage estimators (for example, the empirical-Bayes geometric mean or the information component); incorporation of these methods is planned for future work.

### 4.4 Conclusions

GLP-1 RAs show a robust, reproducible, class-wide disproportionate-reporting signal for impaired gastric emptying that is consistent with both the known pharmacology and independent published evidence. The signal is hypothesis-generating and of bounded clinical magnitude; it does not establish incidence, risk, or causality and requires confirmation in controlled cohort studies.

## Declarations

**Funding.** None.

**Conflicts of interest.** The author declares no competing financial or non-financial interests.

**Data and code availability.** All underlying data are publicly available from the FDA Adverse Event Reporting System (FAERS) via the openFDA API (api.fda.gov/drug/event.json) and are in the public domain. The analysis script reproduces every reported value directly from this public source; because openFDA is a moving snapshot, a date cap at the extraction date reproduces the reported figures. The script and the exact analyzed dataset are available from the author upon reasonable request.

**Ethics.** This study used only publicly available, de-identified aggregate data and did not involve human subjects.

## References

1. Bhagavathula AS. Gastrointestinal safety assessment of GLP-1 receptor agonists in the US: a real-world adverse events analysis from the FAERS database. Diagnostics (Basel). 2024;14(24):2829.

2. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, De Freitas RM. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998;54(4):315–321.

3. Du Y, Zhang M, Wang Z, Hu M, Xie D, Wang X, et al. A real-world disproportionality analysis of semaglutide: post-marketing pharmacovigilance data. J Diabetes Investig. 2024;15(10):1422–1433.

4. Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10(6):483–486.

5. Fusaroli M, Salvo F, Begaud B, AlShammari TM, Bate A, Battini V, et al. The Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): development and statement. Drug Saf. 2024;47(6):575–584.

6. Hiramoto B, McCarty TR, Lodhia NA, Jenkins A, Elnaiem A, Muftah M, et al. Quantified metrics of gastric emptying delay by glucagon-like peptide-1 agonists: a systematic review and meta-analysis with insights for periprocedural management. Am J Gastroenterol. 2024;119(6):1126–1140.

7. Hoffman KB, Dimbil M, Erdman CB, Tatonetti NP, Overstreet BM. The Weber effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): analysis of sixty-two drugs approved from 2006 to 2010. Drug Saf. 2014a;37(4):283–294.

8. Hoffman KB, Demakas AR, Dimbil M, Tatonetti NP, Erdman CB. Stimulated reporting: the impact of US Food and Drug Administration-issued alerts on the Adverse Event Reporting System (FAERS). Drug Saf. 2014b;37(11):971–980.

9. Huang H, Hu C, Liu F, Ji F, Fu Y, Cao M. Glucagon-like peptide-1 receptor agonists and impaired gastric emptying: a pharmacovigilance analysis of the US Food and Drug Administration Adverse Event Reporting System. Br J Anaesth. 2025;134(5):1486–1496.

10. Neha R, Subeesh V, Beulah E, Gouri N, Maheswari E. Existence of notoriety bias in the FDA Adverse Event Reporting System database and its impact on signal strength. Hosp Pharm. 2021;56(3):152–158.

11. Ozempic (semaglutide injection) Prescribing Information. Novo Nordisk; 2025. U.S. Food and Drug Administration, accessdata.fda.gov.

12. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf. 2007;30(10):891–898.

13. Shu Y, He X, Wu P, Liu Y, Ding Y, Zhang Q. Gastrointestinal adverse events associated with semaglutide: a pharmacovigilance study based on the FDA Adverse Event Reporting System. Front Public Health. 2022;10:996179.

14. Sodhi M, Rezaeianzadeh R, Kezouh A, Etminan M. Risk of gastrointestinal adverse events associated with glucagon-like peptide-1 receptor agonists for weight loss. JAMA. 2023;330(18):1795–1797.

15. Tu YY, et al. Risk factors for drug-related impaired gastric emptying: a pharmacovigilance analysis of the FDA Adverse Event Reporting System. Front Pharmacol. 2026;17:1844057.