Early Signal Detection in GLP-1 Receptor Agonists in Spain: A Comparative Bayesian Disproportionality Analysis in 2024 and 2025

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Article

Early Signal Detection in GLP-1 Receptor Agonists in Spain: A Comparative Bayesian Disproportionality Analysis in 2024 and 2025

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Abstract

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly prescribed for type 2 diabetes mellitus and obesity. Their expanding use, including off-label indications, raises ongoing concerns regarding their evolving safety profiles. **Objective:** To identify and compare early positive safety signals associated with GLP-1 RAs in Spain during 2024 and 2025 using a Bayesian disproportionality approach adapted from the WHO-Uppsala Monitoring Centre. **Methods:** Spontaneous adverse drug reaction (ADR) reports submitted to the Spanish Pharmacovigilance System and involving GLP-1 RAs (ATC A10BJ) were analyzed. Reports up to June 2024 and June 2025 were included. A Bayesian Confidence Propagation Neural Network (BCPNN)-based model was used to estimate signal strength. Positive signals were defined as those with a false discovery rate (FDR) < 0.05 and relative risk (RR) ≥ 1. Signals were classified as new, reinforced, diminished, unchanged, or disappeared between the two years. **Results:** We analyzed 5,322 reports in 2024 and 6,746 in 2025. New signals identified in 2025 included intestinal obstruction (dulaglutide), acute pancreatitis (exenatide), and urticaria at the injection site (liraglutide). Several previously identified signals diminished or disappeared, suggesting dynamic changes in GLP-1 RA risk profiles. **Conclusions:** This comparative Bayesian pharmacovigilance analysis highlights the evolving safety landscape of GLP-1 RAs. Early signal detection can inform timely regulatory interventions and support safer clinical use.

Keywords: GLP-1 receptor agonists; pharmacovigilance; adverse drug reactions; early signal detection; semaglutide; liraglutide; dulaglutide

1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of incretin-based therapies that mimic the action of endogenous GLP-1, stimulating insulin secretion and inhibiting glucagon release in a glucose-dependent manner. These agents have gained widespread acceptance for the management of type 2 diabetes mellitus (T2DM) due to their efficacy in improving glycemic control, promoting weight loss, and offering cardiovascular protection [1,2].

Several GLP-1 RAs—such as liraglutide, dulaglutide, exenatide, semaglutide, and lixisenatide—have shown superiority over other antidiabetic agents in clinical trials, especially in reducing HbA1c levels and achieving significant weight reduction [3,4]. Notably, large cardiovascular outcome trials (CVOTs) like LEADER, SUSTAIN-6, and REWIND demonstrated cardiovascular benefits beyond glycemic effects, leading to broader therapeutic indications in high-risk populations [5–7]. Consequently, their use has expanded rapidly, including off-label use in individuals with obesity without diabetes [8].

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However, the growing use of GLP-1 RAs also raises safety concerns, particularly regarding gastrointestinal, pancreatic, thyroid, and renal adverse effects [9,10]. Rare but serious adverse events (AEs)—such as pancreatitis, gallbladder disease, and injection site reactions—have been reported in both clinical trials and post-marketing surveillance [11–13]. Moreover, recent real-world studies have highlighted the importance of early detection of adverse drug reactions (ADRs) that may not have been captured during the pre-approval phases [14].

Pharmacovigilance systems, including spontaneous reporting databases, remain essential tools for detecting potential drug safety signals. However, traditional disproportionality methods such as the proportional reporting ratio (PRR) or reporting odds ratio (ROR) may produce false positives due to multiplicity or sparse data [15,16]. Bayesian approaches—such as the Bayesian Confidence Propagation Neural Network (BCPNN) developed by the WHO-Uppsala Monitoring Centre—provide a more robust framework by accounting for uncertainty and prior probabilities [17].

The concept of "early signal detection" refers to the identification of statistically significant drug-event combinations before widespread recognition, potentially enabling earlier regulatory or clinical interventions [18]. The implementation of false discovery rate (FDR) control methods, such as the Benjamini-Hochberg procedure, further improves signal reliability in large datasets with multiple comparisons [19].

This study aims to perform a comparative Bayesian disproportionality analysis of suspected ADRs involving GLP-1 RAs in Spain during the first semesters of 2024 and 2025. By identifying new, reinforced, unchanged, diminished, or disappeared safety signals, this work contributes to the understanding of evolving drug safety profiles and supports timely pharmacovigilance efforts.

2. Results

2.1. Overview of ADR Reports

A total of 5,322 adverse drug reactions (ADRs) associated with GLP-1 receptor agonists (GLP-1 RAs) were reported to the Spanish Pharmacovigilance System in the first half of 2024, increasing to 6,746 reports in the same period of 2025.

This increase may reflect:

- Higher prescription rates and broader indications;
- Greater pharmacovigilance awareness among healthcare professionals;
- Potential real changes in the risk profile of GLP-1 RAs.

2.1.1. Signal Classification by Year

Safety signals were categorized based on their status in 2024 and 2025 using Bayesian disproportionality analysis with false discovery rate (FDR) correction (see Appendix 1: Table A1; Table A2). The following classifications were applied:

1. **New signals:** drug-event pairs newly detected in 2025;
2. **Reinforced signals:** previously detected signals with increased risk or statistical strength;
3. **Disappeared signals:** reduced statistical strength or FDR;
4. **Unchanged signals:** present with similar strength in both years;
5. **Disappeared signals:** present in 2024 but not detected in 2025.

The summary of newly identified or altered signals is detailed in Table 1.

2.1.2. Notable New Signals in 2025

Several new positive signals meeting the predefined Bayesian criteria (FDR < 0.05; RR ≥ 1) emerged in 2025:

- Dulaglutide: intestinal obstruction;
- Exenatide: acute pancreatitis and skin mass at injection site;

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• Liraglutide: urticaria at the injection site and device administration malfunction;
• Semaglutide: inadequate diabetes control.

These signals may reflect either increased true incidence, expanded patient use, or improved ADR reporting.

2.1.3. Disappeared Signals

Several drug-event combinations detected in 2024 were either absent or statistically weaker in 2025:

• **Lixisenatide**: dizziness—signal disappeared;
• **Liraglutide**: minor weight loss—signal diminished.

The disappearance of these signals could indicate changes in clinical use patterns, underreporting, or shifts in the underlying patient population.

2.2. Tables and Signal Summary

All relevant signals and corresponding information from the Summary of Product Characteristics (SmPC) are compiled in Table 1, titled: Table 1. Safety Signal evolution and fact sheet comments for GLP-1 Receptor Agonists between 2024-2025. This table includes:

• The GLP-1 RA involved;
• The preferred term (PT) of the reported adverse event;
• Whether the ADR is described in the corresponding SmPC.

All signals listed in Table 1 were extracted using MedDRA coding and analyzed using Bayesian methods as described in the Methods section.

Table 1. Safety Signal evolution and fact sheet comments for GLP-1 Receptor Agonists between 2024-2025.

Drug	Event Effect (PT)	Fact sheet Comments	Signal evolution
Dulaglutide	Blood glucose abnormal	Hypoglycemia in combination with other medications	New
Dulaglutide	Injection site haematoma	Not reported	New
Exenatide	Renal failure	Withdrawn from market in 2024	New
Liraglutide	Incorrect dose administered by a medical device	Not reported	New
Liraglutide	Injection site bruise	Not reported	New
Liraglutide	Product quality issue	Not reported	New
Liraglutide	Skin reaction	Not reported; skin and subcutaneous tissue disorders reported	New
Semaglutide	Extra dose administered	Not reported	New
Semaglutide	Diarrhoea	Reported as very common	New
Semaglutide	Off-label use	Not reported	New
Semaglutide	Vomiting	Reported as common	New
Dulaglutide	Decreased appetite	Reported as common	Reinforce
Dulaglutide	Hypoaesthesia	Not reported	Reinforce
Dulaglutide	Accidental overdose	Not reported	Reinforce
Exenatide	Retching	Withdrawn from market in 2024	Reinforce
Exenatide	Nodule	Withdrawn from market in 2024	Reinforce
Liraglutide	Injection site rash	Not reported	Reinforce
Liraglutide	Drug ineffective	Not reported	Reinforce
Liraglutide	Injection site swelling	Not reported	Reinforce
Liraglutide	Injection site hypersensitivity	Not reported	Reinforce
Liraglutide	Injection site pruritus	Not reported	Reinforce
Liraglutide	Injection site reaction	Reported as common	Reinforce
Lixisenatide	Hypoglycaemia	Withdrawn from market in 2024	Reinforce

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Lixisenatide	Urticaria	Withdrawn from market in 2024	Reinforce
Semaglutide	Incorrect technique in product use procedure	Not reported	Reinforce
Semaglutide	Use of product for unapproved indication	Not reported	Reinforce
Exenatide	Asthenia	Withdrawn from market in 2024	Diminished
Semaglutide	Dyspepsia	Reported as common	Diminished
Semaglutide	Drug intolerance	Not reported	Diminished
Semaglutide	Nausea	Reported as very common	Diminished
Semaglutide	Weight decreased	Reported as common	Diminished
Semaglutide	Gastrointestinal disorder	Reported without specification	Diminished
Dulaglutide	Incorrect dose administered	Not reported	Unchanged
Dulaglutide	Injection site pain	Not reported	Unchanged
Dulaglutide	Blood glucose increased	Not reported	Unchanged
Dulaglutide	Injection site haemorrhage	Not reported	Unchanged
Dulaglutide	Intestinal obstruction	Reported, frequency unknown	Unchanged
Dulaglutide	Dose omission issue with the product	Not reported	Unchanged
Exenatide	Erythema	Withdrawn from market in 2024	Unchanged
Exenatide	Injection site induration	Withdrawn from market in 2024	Unchanged
Exenatide	Skin mass	Withdrawn from market in 2024	Unchanged
Exenatide	Injection site nodule	Withdrawn from market in 2024	Unchanged
Exenatide	Pancreatitis	Withdrawn from market in 2024	Unchanged
Exenatide	Acute pancreatitis	Withdrawn from market in 2024	Unchanged
Liraglutide	Injection site erythema	Not reported	Unchanged
Liraglutide	Minor weight loss	Not reported	Unchanged
Liraglutide	Problem with drug delivery device system	Not reported	Unchanged
Liraglutide	Injection site urticaria	Reported as uncommon	Unchanged
Dulaglutide	Limb pain	Not reported	Disappeared
Exenatide	Renal failure	Withdrawn from market in 2024	Disappeared
Liraglutide	Injection site bruising	Not reported	Disappeared
Lixisenatide	Dizziness	Withdrawn from market in 2024	Disappeared
Semaglutide	Inadequate diabetes mellitus control	Not reported	Disappeared
Semaglutide	Overdose	Not reported	Disappeared
Semaglutide	Use of a medicine off-label	Not reported	Disappeared

3. Discussion

This comparative pharmacovigilance study reveals dynamic changes in the safety profile of GLP-1 receptor agonists (GLP-1 RAs) in Spain between 2024 and 2025. The detection of new positive signals—particularly for gastrointestinal and pancreatic adverse events—underscores the importance of continuous post-marketing surveillance in this therapeutic class.

The identification of **intestinal obstruction** with dulaglutide and **acute pancreatitis** with exenatide aligns with previous concerns raised in both preclinical and post-marketing reports [9,10,20]. GLP-1 RAs slow gastric emptying, which may theoretically contribute to mechanical or functional obstruction in predisposed individuals [21]. Although these effects are well known, their clinical significance is still being debated, especially as real-world evidence accumulates.

The signal for **inadequate diabetes control** with semaglutide may reflect inappropriate off-label use or administration errors. This finding is clinically relevant given the increasing popularity of GLP-1 RAs for weight management, sometimes self-administered without medical supervision

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[8,22]. In this context, improper dosing or skipping injections could lead to subtherapeutic effects or glycemic instability.

Furthermore, several **injection-site reactions** (e.g., urticaria, bruising, or device malfunction) were newly identified or reinforced in 2025. Although often considered mild, these events can affect treatment adherence, particularly in patients self-injecting long-acting agents [23].

On the other hand, the **disappearance or attenuation** of some previously detected signals—such as dizziness with lixisenatide—may indicate a reduced use of certain molecules following market withdrawal (as in the case of lixisenatide and exenatide in Spain) or improved risk minimization measures [24].

Our study demonstrates the added value of Bayesian methods, particularly when combined with false discovery rate (FDR) adjustment, in improving signal reliability over traditional disproportionality metrics [17,19]. The use of the Bayesian Confidence Propagation Neural Network (BCPNN) provides a probabilistic framework that is robust to data sparsity and supports regulatory prioritization of signals [18,25].

It is worth noting that some signals correspond to **events not described in the official Summary of Product Characteristics (SmPC)** at the time of analysis. This suggests the utility of pharmacovigilance data in identifying emerging or evolving ADRs that may not have been observed during clinical development [13,26].

3.1. Strengths and Limitations

The main strengths of this study include:

- The use of a standardized Bayesian algorithm based on WHO-UMC methodology;
- Comparison across two consecutive years using real-world data from a national database (see Appendix 1: Table A1; Table A2);
- Adjustment for multiple testing via FDR, reducing the likelihood of spurious signals.

However, several limitations should be acknowledged:

- Spontaneous reporting systems are subject to underreporting, missing data, and reporting bias [14,27];
- Causality cannot be established—signal detection is hypothesis-generating;
- Changes in the number of users per drug are not available, limiting calculation of true incidence rates.

Future studies using **analytical epidemiological designs**, such as cohort or case-control studies with prescription databases, are warranted to confirm these preliminary signals [28].

4. Materials and Methods

4.1. Data Source

This study is based on spontaneous reports of suspected adverse drug reactions (ADRs) submitted to the Spanish Pharmacovigilance System for Human Use Medicines (FEDRA®), managed by the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Data were extracted from public releases corresponding to reports received up to 30 June 2024 and 30 June 2025.

All included reports referred to drugs within the ATC group A10BJ (GLP-1 receptor agonists), specifically dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide. Data extraction and preprocessing were performed using R®v3.4.1. R Foundation for Statistical Computing and PhViD® v1.0.8 package for the detection of positive signals [29].

Spontaneous reporting systems are widely used for signal detection and early risk identification, though they are subject to limitations such as underreporting and reporting bias [14,27,30]. Nevertheless, national databases like FEDRA® provide an essential source of real-world evidence for regulatory pharmacovigilance [31].

4.2. ADR Coding and Drug Selection

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Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), specifically the Preferred Term (PT) level. MedDRA is internationally recognized and ensures consistency and comparability in safety signal analysis [32].

GLP-1 RAs included in this study were:

- Dulaglutide (Trulicity®),
- Exenatide (Byetta®, Bydureon®),
- Liraglutide (Victoza®, Saxenda®),
- Lixisenatide (Lyxumia®),
- Semaglutide (Ozempic®, Rybelsus®, Wegovy®).

Drugs that had been withdrawn from the Spanish market by mid-2024, such as exenatide and lixisenatide, were retained for analysis to enable year-to-year comparisons of signal persistence and disappearance.

4.3. Bayesian Disproportionality Analysis

We implemented a Bayesian Confidence Propagation Neural Network (BCPNN) model adapted from the WHO-Uppsala Monitoring Centre (UMC) [17,18,25]. This method estimates the Information Component (IC), a logarithmic metric of disproportionality that accounts for statistical shrinkage and prior probability distributions.

The BCPNN approach is well suited for early signal detection because:

1. It handles sparse data more robustly than frequentist methods;
2. It generates probabilistic outputs, such as credibility intervals;
3. It is less sensitive to extreme values and data volatility [33].

The BCPNN model computes a posterior distribution for each drug-event pair, and signal strength is typically summarized by the IC025, the lower bound of the 95% credibility interval. An IC025 > 0 indicates disproportionate reporting.

4.4. False Discovery Rate and Signal Thresholds

To address the problem of multiple testing—a frequent challenge in pharmacovigilance analyses involving thousands of drug-event pairs—we applied the Benjamini-Hochberg procedure to control the False Discovery Rate (FDR) [19]. Each p-value derived from the Bayesian model was adjusted, and a signal was considered statistically significant if:

- FDR < 0.05, and
- Relative Risk (RR) ≥ 1.

This dual threshold approach ensures that detected signals are not only statistically robust but also clinically meaningful [34].

4.5. Signal Classification

Signals detected in both years were further classified into five categories based on their FDR change over time:

- New: signal appeared only in 2025;
- Reinforced: signal was present in both years with increased strength or lower FDR in 2025;
- Diminished: signal persisted but with reduced statistical strength;
- Unchanged: signal remained stable;
- Disappeared: signal was present in 2024 but absent in 2025.

This classification facilitates trend interpretation and regulatory prioritization of evolving safety issues [35].

5. Conclusions

This study provides updated evidence on the evolving safety profile of GLP-1 receptor agonists (GLP-1 RAs) in Spain, applying a Bayesian disproportionality analysis with FDR control to detect

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early signals of adverse drug reactions (ADRs) in 2024 and 2025. The results highlight newly emerging risks—including intestinal obstruction, acute pancreatitis, and injection-site reactions—as well as the disappearance or attenuation of other signals over time.

The dynamic nature of these signals underscores the importance of continuous post-marketing surveillance, especially as the clinical use of GLP-1 RAs expands beyond their original indications, often to populations not represented in pivotal clinical trials. The appearance of signals related to off-label use and administration errors, such as inadequate diabetes control, suggests a need for greater awareness and patient education regarding proper drug use.

Bayesian pharmacovigilance approaches, particularly when combined with false discovery rate correction, offer a robust framework for early signal detection in real-world data. These methods enhance the reliability of signal prioritization, helping to inform regulatory decisions and guide further epidemiological research.

Future studies should validate these findings using analytical designs such as cohort or nested case-control studies with prescription data. Integrating signal detection into a broader risk management strategy will be key to optimizing the safety and effectiveness of GLP-1 RAs in an increasingly diverse patient population.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ADR Adverse drug reaction
SmPCSummary of Product Characteristics

Appendix A

Appendix A.1

Table A1. Bayesian Disproportionality Analysis of spontaneous reports of suspected adverse drug reactions to GLP-1 Receptor Agonists submitted to the Spanish Pharmacovigilance System for Human Use Medicines until June 2024 in Spain.

drug	event effect (PT)	count (N)	expected count	post .H0	n11 /E	drug margin	event margin	FDR	FNR	Se	Sp
semaglutide	Off label use	109	55.571	0.000	1.961	1933	153	0.000	0.531	0.001	1.000
dulaglutide	Injection site pain	38	12.151	0.000	3.127	1115	58	0.000	0.530	0.003	1.000
exenatide	Injection site nodule	10	0.963	0.000	10.386	427	12	0.000	0.530	0.004	1.000
dulaglutide	Product dose omission	21	5.866	0.000	3.580	1115	28	0.000	0.530	0.006	1.000
liraglutide	Weight decreased mild	39	16.094	0.000	2.423	1713	50	0.000	0.529	0.007	1.000
liraglutide	Injection site urticaria	33	12.231	0.000	2.698	1713	38	0.000	0.529	0.008	1.000
exenatide	Injection site induration	9	1.284	0.000	7.011	427	16	0.000	0.528	0.010	1.000
dulaglutide	Blood glucose increased	29	13.408	0.001	2.163	1115	64	0.000	0.528	0.011	1.000
liraglutide	Injection site erythema	41	20.922	0.001	1.960	1713	65	0.000	0.528	0.012	1.000
semaglutide	Nausea	190	143.468	0.001	1.324	1933	395	0.000	0.527	0.014	1.000

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dulaglutide	Injection site haemorrhage	15	4.400	0.001	3.409	1115	21	0.000	0.527	0.015	1.000
exenatide	Acute pancreatitis	13	4.172	0.001	3.116	427	52	0.000	0.527	0.017	1.000
dulaglutide	Wrong dose administered	17	5.866	0.001	2.898	1115	28	0.000	0.526	0.018	1.000
exenatide	Erythema	8	1.605	0.002	4.985	427	20	0.001	0.526	0.019	1.000
liraglutide	Drug ineffective	53	32.187	0.003	1.647	1713	100	0.001	0.526	0.021	1.000
exenatide	Retching	6	0.642	0.004	9.348	427	8	0.001	0.525	0.022	1.000
exenatide	Pancreatitis	11	3.771	0.004	2.917	427	47	0.001	0.525	0.024	1.000
liraglutide	Injection site pruritus	29	15.128	0.006	1.917	1713	47	0.001	0.525	0.025	1.000
semaglutide	Weight decreased	46	27.967	0.006	1.645	1933	77	0.002	0.524	0.026	1.000
semaglutide	Product use for unapproved indication	21	9.443	0.007	2.224	1933	26	0.002	0.524	0.028	1.000
exenatide	Skin mass	5	0.401	0.010	12.464	427	5	0.002	0.524	0.029	1.000
exenatide	Renal failure	6	1.203	0.011	4.985	427	15	0.003	0.523	0.030	1.000
liraglutide	Injection site rash	15	6.116	0.013	2.453	1713	19	0.003	0.523	0.032	1.000
lixisenatide	Urticaria	5	1.113	0.018	4.493	126	47	0.004	0.523	0.033	1.000
dulaglutide	Decreased appetite	34	21.998	0.021	1.546	1115	105	0.004	0.522	0.034	1.000
semaglutide	Diabetes mellitus inadequate control	15	6.538	0.021	2.294	1933	18	0.005	0.522	0.036	1.000
semaglutide	Drug intolerance	16	7.264	0.021	2.203	1933	20	0.006	0.522	0.037	1.000
liraglutide	Injection site reaction	14	6.116	0.023	2.289	1713	19	0.006	0.521	0.039	1.000
liraglutide	Injection site hypersensitivity	12	4.828	0.026	2.485	1713	15	0.007	0.521	0.040	1.000
semaglutide	Dyspepsia	39	25.788	0.027	1.512	1933	71	0.008	0.520	0.041	1.000
liraglutide	Injection site bruising	10	3.541	0.028	2.824	1713	11	0.008	0.520	0.043	1.000
semaglutide	Gastrointestinal disorder	19	10.170	0.032	1.868	1933	28	0.009	0.520	0.044	1.000
semaglutide	Product use error	17	8.717	0.034	1.950	1933	24	0.010	0.519	0.045	1.000
exenatide	Nodule	4	0.562	0.036	7.122	427	7	0.011	0.519	0.047	0.999
dulaglutide	Hypoaesthesia	5	1.048	0.052	4.773	1115	5	0.012	0.519	0.048	0.999
dulaglutide	Intestinal obstruction	5	1.048	0.052	4.773	1115	5	0.013	0.518	0.049	0.999
liraglutide	Device administration error	7	2.253	0.059	3.107	1713	7	0.014	0.518	0.051	0.999
dulaglutide	Accidental overdose	6	1.886	0.059	3.182	1115	9	0.015	0.518	0.052	0.999
semaglutide	Overdose	16	9.080	0.065	1.762	1933	25	0.017	0.518	0.053	0.999
liraglutide	Injection site swelling	12	6.116	0.066	1.962	1713	19	0.018	0.517	0.054	0.999
lixisenatide	Hypoglycaemia	4	1.136	0.068	3.520	126	48	0.019	0.517	0.056	0.999
lixisenatide	Dizziness	7	3.315	0.076	2.112	126	140	0.020	0.517	0.057	0.999
exenatide	Asthenia	7	3.209	0.076	2.181	427	40	0.022	0.516	0.058	0.999

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dulaglutide	Limb pain	5	1.467	0.081	3.409	1115	7	0.023	0.516	0.060	0.999
semaglutide	Weight increased	19	11.986	0.083	1.585	1933	33	0.024	0.516	0.061	0.998
liraglutide	Skin reaction	9	4.184	0.085	2.151	1713	13	0.026	0.515	0.062	0.998
dulaglutide	Accidental subtherapeutic dose	4	0.838	0.090	4.773	1115	4	0.027	0.515	0.063	0.998
liraglutide	Product quality issue	8	3.541	0.092	2.260	1713	11	0.028	0.515	0.065	0.998
dulaglutide	Flatulence	21	14.456	0.095	1.453	1115	69	0.030	0.514	0.066	0.998
liraglutide	Device-mediated wrong dose administration	7	2.897	0.099	2.416	1713	9	0.031	0.514	0.067	0.998
semaglutide	Upper abdominal pain	35	26.151	0.100	1.338	1933	72	0.032	0.514	0.068	0.998
exenatide	Peripheral oedema	3	0.562	0.101	5.342	427	7	0.034	0.514	0.070	0.997
dulaglutide	Cholelithiasis	8	3.981	0.103	2.010	1115	19	0.035	0.513	0.071	0.997
dulaglutide	Product administration schedule inappropriate	15	9.637	0.105	1.556	1115	46	0.036	0.513	0.072	0.997
dulaglutide	Injection site trauma	4	1.048	0.110	3.818	1115	5	0.038	0.513	0.073	0.997
semaglutide	Hyperglycaemia	16	10.170	0.112	1.573	1933	28	0.039	0.512	0.075	0.997
exenatide	Diabetic ketoacidosis	3	0.642	0.113	4.674	427	8	0.040	0.512	0.076	0.997
lixisenatide	Blood glucose increased	4	1.515	0.120	2.640	126	64	0.042	0.512	0.077	0.996
exenatide	Pruritus	7	3.691	0.121	1.897	427	46	0.043	0.512	0.078	0.996
lixisenatide	Product contamination by body fluid	2	0.071	0.122	28.159	126	3	0.044	0.511	0.079	0.996
lixisenatide	Serum triglycerides increased	2	0.095	0.123	21.119	126	4	0.046	0.511	0.081	0.996
lixisenatide	Tendonitis	2	0.047	0.124	42.238	126	2	0.047	0.511	0.082	0.996
exenatide	Haemoglobin A1c increased	3	0.722	0.125	4.155	427	9	0.048	0.510	0.083	0.995
exenatide	Weight decreased	10	6.178	0.128	1.619	427	77	0.049	0.510	0.084	0.995

Relative risk ≥ 1, Number of Monte Carlo simulations NB.MC=10,000. False Discovery Rate (FDR)<0.05. Interpretation of items: N (count): number of couples 'active ingredient-ADR' reported; post.H0: posterior probability of null hypothesis; FDR: False Discovery Rate; FNR: False Negative Rate; Se: Sensitivity; Sp: Specificity.

Appendix A.2

Table A2. Bayesian Disproportionality Analysis of spontaneous reports of suspected adverse drug reactions to GLP-1 Receptor Agonists submitted to the Spanish Pharmacovigilance System for Human Use Medicines until June 2025 in Spain.

drug	event effect	count (N)	expected count	post.H0	n11/E	drug margin	event margin	FDR	FNR	Se	Sp
dulaglutide	Injection site pain	45	11.630	0.000	3.869	1171	67	0.000	0.528	0.001	1.000
liraglutide	Injection site urticaria	33	10.348	0.000	3.189	1837	38	0.000	0.528	0.003	1.000
liraglutide	Weight decreased (mild not codified separately)	46	18.517	0.000	2.484	1837	68	0.000	0.527	0.004	1.000
dulaglutide	Product dose omission	21	4.860	0.000	4.321	1171	28	0.000	0.527	0.005	1.000

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exenatide	Injection site nodule	10	0.760	0.000	13.165	427	12	0.000	0.527	0.006	1.000
dulaglutide	Blood glucose increased	30	11.804	0.000	2.542	1171	68	0.000	0.526	0.008	1.000
dulaglutide	Injection site haemorrhage	17	3.992	0.000	4.258	1171	23	0.000	0.526	0.009	1.000
semaglutide	Off-label use	130	82.416	0.000	1.577	3177	175	0.000	0.526	0.010	1.000
liraglutide	Injection site erythema	41	18.245	0.000	2.247	1837	67	0.000	0.525	0.011	1.000
exenatide	Injection site induration	9	1.013	0.000	8.887	427	16	0.000	0.525	0.013	1.000
dulaglutide	Wrong dose administered	19	6.249	0.000	3.040	1171	36	0.000	0.525	0.014	1.000
exenatide	Acute pancreatitis	13	3.798	0.000	3.423	427	60	0.000	0.524	0.015	1.000
liraglutide	Drug ineffective	56	32.133	0.001	1.743	1837	118	0.000	0.524	0.016	1.000
exenatide	Erythema	8	1.393	0.001	5.745	427	22	0.000	0.524	0.018	1.000
liraglutide	Injection site pruritus	29	13.343	0.001	2.173	1837	49	0.000	0.524	0.019	1.000
exenatide	Retching	6	0.506	0.002	11.849	427	8	0.000	0.523	0.020	1.000
semaglutide	Product use for unapproved indication	41	21.664	0.003	1.893	3177	46	0.000	0.523	0.021	1.000
exenatide	Pancreatitis	11	3.798	0.004	2.896	427	60	0.001	0.523	0.022	1.000
liraglutide	Injection site rash	15	5.446	0.005	2.754	1837	20	0.001	0.522	0.024	1.000
exenatide	Renal impairment	6	1.013	0.006	5.924	427	16	0.001	0.522	0.025	1.000
liraglutide	Injection site hypersensitivity	13	4.357	0.007	2.984	1837	16	0.001	0.522	0.026	1.000
liraglutide	Injection site reaction	15	5.718	0.007	2.623	1837	21	0.002	0.521	0.027	1.000
exenatide	Skin mass	5	0.316	0.007	15.799	427	5	0.002	0.521	0.029	1.000
semaglutide	Nausea	277	231.705	0.009	1.195	3177	492	0.002	0.521	0.030	1.000
lixisenatide	Urticaria	5	0.971	0.012	5.148	126	52	0.003	0.520	0.031	1.000
dulaglutide	Decreased appetite	34	21.351	0.013	1.592	1171	123	0.003	0.520	0.032	1.000
liraglutide	Injection site bruise	10	3.268	0.018	3.060	1837	12	0.004	0.520	0.034	1.000
exenatide	Nodule	4	0.443	0.026	9.028	427	7	0.004	0.519	0.035	1.000
liraglutide	Skin reaction	10	3.812	0.030	2.623	1837	14	0.005	0.519	0.036	1.000
liraglutide	Injection site swelling	13	5.991	0.031	2.170	1837	22	0.006	0.519	0.037	1.000
semaglutide	Product use error	27	16.012	0.034	1.686	3177	34	0.007	0.519	0.038	1.000
dulaglutide	Hypoaesthesia	5	0.868	0.037	5.761	1171	5	0.008	0.518	0.040	1.000
semaglutide	Dyspepsia	63	46.624	0.039	1.351	3177	99	0.009	0.518	0.041	1.000
semaglutide	Weight decreased	58	42.385	0.040	1.368	3177	90	0.010	0.518	0.042	1.000
semaglutide	Extra dose administered	27	16.483	0.041	1.638	3177	35	0.011	0.517	0.043	1.000
dulaglutide	Accidental overdose	6	1.736	0.044	3.457	1171	10	0.012	0.517	0.044	0.999
dulaglutide	Intestinal obstruction	5	1.042	0.045	4.801	1171	6	0.013	0.517	0.046	0.999

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liraglutide	Product quality issue	9	3.540	0.045	2.542	1837	13	0.013	0.516	0.047	0.999
liraglutide	Device administration error	7	2.178	0.048	3.213	1837	8	0.014	0.516	0.048	0.999
lixisenatide	Hypoglycaemia	4	0.990	0.050	4.041	126	53	0.015	0.516	0.049	0.999
semaglutide	Gastrointestinal disorder	31	20.251	0.050	1.531	3177	43	0.016	0.516	0.050	0.999
dulaglutide	Blood glucose abnormal	8	3.298	0.052	2.426	1171	19	0.017	0.515	0.052	0.999
liraglutide	Device-related wrong dose administration	8	2.995	0.053	2.671	1837	11	0.018	0.515	0.053	0.999
semaglutide	Vomiting	217	190.262	0.063	1.141	3177	404	0.019	0.515	0.054	0.999
dulaglutide	Injection site haematoma	7	2.777	0.064	2.520	1171	16	0.020	0.514	0.055	0.999
semaglutide	Drug intolerance	21	12.716	0.066	1.652	3177	27	0.021	0.514	0.056	0.999
semaglutide	Diarrhoea	159	136.574	0.067	1.164	3177	290	0.022	0.514	0.057	0.999
exenatide	Asthenia	7	3.165	0.069	2.212	427	50	0.023	0.513	0.059	0.999
exenatide	Pruritus	7	3.165	0.069	2.212	427	50	0.024	0.513	0.060	0.998
dulaglutide	Cholelithiasis	9	4.340	0.069	2.074	1171	25	0.025	0.513	0.061	0.998
dulaglutide	Accidental subtherapeutic dose	4	0.694	0.070	5.761	1171	4	0.025	0.513	0.062	0.998
semaglutide	Diabetes mellitus inadequate control	16	8.948	0.073	1.788	3177	19	0.026	0.512	0.063	0.998
exenatide	Peripheral oedema	3	0.443	0.080	6.771	427	7	0.027	0.512	0.064	0.998
lixisenatide	Injection site trauma	4	1.270	0.082	3.149	126	68	0.028	0.512	0.066	0.998
dulaglutide	Inappropriate schedule of product administration	4	0.868	0.083	4.609	1171	5	0.029	0.512	0.067	0.998
dulaglutide	Weight increased	15	9.374	0.086	1.600	1171	54	0.030	0.511	0.068	0.998
semaglutide	Dizziness	33	23.547	0.087	1.401	3177	50	0.031	0.511	0.069	0.998
lixisenatide	Limb pain	7	3.455	0.088	2.026	126	185	0.032	0.511	0.070	0.998
exenatide	Flatulence	10	5.697	0.088	1.755	427	90	0.033	0.510	0.071	0.997
liraglutide	Diabetic ketoacidosis	21	14.160	0.091	1.483	1837	52	0.034	0.510	0.072	0.997
dulaglutide	Abdominal pain	6	2.430	0.093	2.469	1171	14	0.035	0.510	0.074	0.997
exenatide	Malaise	8	4.241	0.095	1.886	427	67	0.036	0.510	0.075	0.997
dulaglutide	Haemoglobin A1c increased	21	14.581	0.095	1.440	1171	84	0.037	0.509	0.076	0.997
exenatide	Injection site warmth	3	0.570	0.096	5.266	427	9	0.038	0.509	0.077	0.997
dulaglutide	Breast cancer	28	20.657	0.098	1.356	1171	119	0.039	0.509	0.078	0.997
liraglutide	Drug hypersensitivity	20	13.615	0.104	1.469	1837	50	0.040	0.509	0.079	0.996
semaglutide	Chills	63	50.862	0.104	1.239	3177	108	0.041	0.508	0.080	0.996
exenatide	Blood triglycerides increased	3	0.633	0.105	4.740	427	10	0.042	0.508	0.081	0.996
liraglutide	Product contamination with body fluid	5	1.634	0.109	3.060	1837	6	0.043	0.508	0.083	0.996
liraglutide	Tendinitis	5	1.634	0.109	3.060	1837	6	0.044	0.507	0.084	0.996

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liraglutide	Injection site mass	5	1.634	0.109	3.060	1837	6	0.045	0.507	0.085	0.996
liraglutide	Injection site pain	6	2.451	0.116	2.448	1837	9	0.046	0.507	0.086	0.996
lixisenatide	Injection site urticaria	2	0.075	0.117	26.770	126	4	0.047	0.507	0.087	0.995
lixisenatide	Weight decreased (mild not codified separately)	2	0.056	0.117	35.693	126	3	0.048	0.506	0.088	0.995
lixisenatide	Product dose omission	2	0.037	0.120	53.540	126	2	0.049	0.506	0.089	0.995
exenatide	Injection site nodule	4	1.456	0.121	2.748	427	23	0.050	0.506	0.090	0.995

Relative risk ≥ 1, Number of Monte Carlo simulations NB.MC=10,000. False Discovery Rate (FDR)<0.05. Interpretation of items: N (count): number of couples 'active ingredient-ADR' reported; post.H0: posterior probability of null hypothesis; FDR: False Discovery Rate; FNR: False Negative Rate; Se: Sensitivity; Sp: Specificity.

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