Short report

Ischemic optic neuropathy with semaglutide: global observational analysis of sex- and formulation-specific risk

Moiz Lakhani [1], Abdullah Al-Ani [2], Marko Popovic [3], Étienne Bénard-Séguin [2], Edward Margolin [4]

[1]Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[2]Department of Surgery, Section of Ophthalmology, University of Calgary, Calgary, Alberta, Canada
[3]Department of Ophthalmology and Visual Sciences, University of Toronto, Toronto, Ontario, Canada
[4]Department of Ophthalmology, University of Toronto, Toronto, Ontario, Canada

Correspondence to
Dr Edward Margolin;
edmargolin@gmail.com

Received 17 August 2025
Accepted 22 November 2025

ABSTRACT

Ischaemic optic neuropathy (ION) is a rare but vision-threatening complication recently linked to GLP-1 receptor agonists, particularly semaglutide. Using over 30 million reports from the FDA Adverse Event Reporting System (2017–2024), we evaluated formulation- and sex-specific associations. Among 31 774 semaglutide cases, Wegovy demonstrated the strongest signal for ION (reporting odds ratio (ROR)=74.89) compared with Ozempic (ROR=18.81). Sex-stratified analyses showed higher odds in men (ROR=116.37), and multivariable regression confirmed greater risk with Wegovy versus Ozempic (adjusted OR (AOR)=4.74) and in men versus women (AOR=3.33). These findings highlight a potential dose-dependent safety concern that warrants urgent prospective evaluation to guide prescribing and regulatory policy.

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have transformed cardiometabolic care by improving glycaemic control, weight loss and cardiovascular risk. Recent reports link semaglutide to non-arteritic anterior ischaemic optic neuropathy (NAION), with severe vision loss in up to 15% and complete blindness in up to 5%, prompting an international safety review and regulatory action by the European Medicines Agency.[1] No prior study has evaluated formulation- or sex-specific patterns in semaglutide-associated events, and clinical trials are underpowered to detect rare events.

We conducted the first global, population-based observational study of over 30 million reports to compare ischaemic optic neuropathy (ION) risk with semaglutide formulations across diabetes and obesity.

METHODS

We retrieved and deduplicated FDA Adverse Event Reporting System (FAERS) reports from December 2017 to December 2024.[2] Institutional review board approval and informed consent were not required for deidentified public data. We included reports naming a GLP-1RA as the primary suspect for ION. Semaglutide was analysed both as a pooled category (Ozempic, Wegovy, Rybelsus and generic semaglutide) and by brand: Ozempic (weekly injectable for type 2 diabetes, up to 2 mg; FDA 2017), Wegovy (weekly injectable for obesity, up to 2.4 mg; FDA 2021) and Rybelsus (daily oral for type 2 diabetes; FDA 2019). Tirzepatide, a dual GLP-1/GIP agonist, was analysed as a pooled category (Mounjaro, Zepbound and generic tirzepatide) and by formulation: Mounjaro (for type 2 diabetes; FDA 2022) and Zepbound (for obesity; FDA 2023). Reports listing only the generic name (semaglutide or tirzepatide) were classified within the pooled categories. Comparator drugs were metformin, insulin and tirzepatide. Disproportionality was assessed using reporting odds ratios (RORs, 95%CIs). Signals met adapted Evans criteria (ROR>2, $\chi^2>4$, n≥3), Bonferroni-adjusted significance ($p<0.0056$; $p<0.0028$ for sex analyses) and Bayesian confirmation ($IC_{025}>0.3$) to minimise false positives.[3 4]

To complement disproportionality estimates, we conducted multivariable logistic regression adjusted for age and sex, generating adjusted odds ratios (AORs, 95%CIs) to evaluate whether associations persisted after controlling for demographic confounding.

RESULTS

Among 30 668 520 FAERS reports, 31 774 involved semaglutide (mean age=56.5±11.1 years; 54.1% female). Of these, 3070 were attributed to Wegovy (mean age=54.7 years) originating from 6 countries across three continents, and 20 608 to Ozempic (mean age=57.8 years) from 11 countries across four continents (table 1).

Ozempic generated about seven times more reports than Wegovy owing to its earlier approval in 2017 versus Wegovy's 2021 launch. Despite this difference in volume, Wegovy showed the strongest ION signal (n=28, ROR=74.89, 95% CI 51.79 to 108.29), exceeding Ozempic (n=47, ROR=18.81, 95% CI 14.11 to 25.07) and any form of semaglutide (n=85, ROR=21.37, 95% CI 17.40 to 26.65). No ION events were reported with Rybelsus. Other comparators showed no signal: tirzepatide (ROR=0.56), Mounjaro (ROR=1.02), Zepbound (none), metformin (ROR=1.35) and insulin (ROR=1.61) (figure 1). Sex-stratified analyses showed the highest signal for Wegovy in men (ROR = 116.37) and for Ozempic in women (ROR=26.86). All significant signals met $IC_{025}>0.3$.

► https://doi.org/10.1136/bjo-2025-329298

To cite: Lakhani M, Al-Ani A, Popovic M, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjo-2025-328483

Table 1 Demographic, clinical indication and dosing characteristics of ischaemic optic neuropathy cases reported with newer-generation glucagon-like peptide-1 receptor agonists in FAERS, December 2017 to December 2024

	GLP-1RAs					Controls	
	Semaglutide (n=85)	Ozempic (n=47)	Wegovy (n=28)	Tirzepatide (n=4)	Mounjaro (n=4)	Insulin (n=16)	Metformin (n=12)
Age, Mean±SD	56.53±11.10	57.77±12.11	54.65±9.25	55.00±1.41	55.00±1.41	66.44±6.89	42.88±8.13
Age (n)							
0–17 years	0	0	0	0	0	0	0
18–44 years	9	6	2	0	0	0	7
45–64 years	35	17	15	2	2	2	1
65–74 years	11	7	4	0	0	8	0
≥75 years	3	2	0	0	0	0	0
Unknown	27	15	7	2	2	6	4
Sex (n)							
Male	39	25	12	2	2	7	8
Female	46	22	16	1	1	9	0
Unspecified	0	0	0	1	1	0	4
Indications (n)							
Diabetes	17	15	0	3	3	13	12
Weight-related conditions							
Overweight	9	0	8	0	0	0	0
Obesity	12	3	8	0	0	0	0
Weight control	4	4	0	0	0	0	0
Other	2	2	0	0	0	0	0
Unknown	41	23	12	1	1	3	0
Year* (n)							
2004–2009	0	0	0	0	0	4	0
2010–2014	0	0	0	0	0	3	0
2015–2019	0	0	0	0	0	1	1
2020–2024	80	47	28	4	4	8	11
Unknown	5	0	0	0	0	0	0
Continent (n)							
Americas	36	21	9	4	4	11	0
Europe	40	20	18	0	0	3	1
Asia	2	1	1	0	0	0	11
Africa	0	0	0	0	0	0	0
Oceania	2	2	0	0	0	0	0
Other	5	3	0	0	0	2	0

*This table includes reports from 2004 to 2024 to reflect the full FAERS reporting period, as FDA approval dates varied across drugs. For disproportionality analyses, semaglutide and tirzepatide were restricted to December 2017–December 2024, and comparator drugs were restricted to reports on or after their respective FDA approval dates.
FAERS, FDA Adverse Event Reporting System.

In multivariable analysis adjusted for age and sex, odds were higher for Wegovy versus Ozempic (AOR=4.74, 95% CI 2.54 to 8.77, p<0.001) and for men versus women (AOR=3.33, 95% CI o 1.89 to 5.88, p<0.001).

DISCUSSION

Semaglutide, in any formulation, was the only agent significantly associated with ION (ROR=21.37), with the strongest signal for Wegovy (ROR=74.9) followed by Ozempic (ROR=18.8). These findings extend our prior global analysis and, whereas previous studies identified only an agent-specific association, this study provides the first evidence of a formulation- and dose-dependent ION risk, with the strongest association observed for Wegovy.[5]

Semaglutide is available as injectables (Ozempic for diabetes, Wegovy for obesity) and oral Rybelsus; injectables achieve high bioavailability and rapid systemic exposure, whereas oral absorption is ∼1%, yielding lower peaks and attenuated effects. Wegovy, approved at the highest dose (2.4 mg vs 0.5–2.0 mg for Ozempic), produces greater systemic exposure, faster weight loss and sharper metabolic shifts. These differences in route, dose and indication may influence prescribing patterns and safety signals, with high-dose Wegovy probably driving the stronger association by predisposing to optic nerve hypoperfusion through intravascular volume contraction, hypotension with nocturnal dips and autonomic instability, although no direct clinical link has been established.[6] In contrast, the limited absorption and slower uptake of Rybelsus probably explain the absence of a detectable signal.

Tirzepatide (Mounjaro, Zepbound), a dual GLP-1/GIP agonist titrated gradually across a broad dosing range, shows a favourable safety profile, with GIP agonism probably buffering GLP-1-mediated fluid shifts, stabilising vascular tone and reducing ischaemic vulnerability. High-dose semaglutide may also precipitate abrupt glycaemic correction that impairs optic nerve autoregulation, consistent with retinopathy flares observed in the SUSTAIN-6 Trial. Despite greater HbA1c and weight reductions, tirzepatide showed no signal for ION, suggesting that the risk of NAION may be GLP-1-specific rather than purely metabolic. Its dual receptor activity, gradual titration and broad dosing range (5–15 mg)

Drug	Sex	AE	All Other AE	ROR (95% CI)	P value	IC025
Insulin	T	15	72,711	1.61 (0.97–2.68)	0.066	-0.22
Insulin	F	8	37,995	2.96 (1.47–5.96)	0.0023	0.18
Insulin	M	7	28,292	1.06 (0.50–2.22)	0.88	-1.23
Metformin	T	12	69,480	1.35 (0.76–2.37)	0.31	-0.57
Metformin	F	0	32,381	1	1	1.00
Metformin	M	8	27,169	1.26 (0.63–2.52)	0.52	-0.90
Mounjaro	T	4	30,640	1.02 (0.38–2.71)	0.98	-1.75
Mounjaro	F	1	20,118	0.69 (0.10–4.92)	0.71	-4.16
Mounjaro	M	2	7,107	1.20 (0.30–4.82)	0.79	-2.38
Ozempic	T	48	20,392	18.81 (14.11–25.07)	< 0.0001	3.47
Ozempic	F	23	12,471	26.88 (17.68–40.87)	< 0.0001	3.37
Ozempic	M	25	6,504	16.79 (11.28–24.98)	< 0.0001	2.98
Rybelsus	T	0	3,220	1	1	1.00
Semaglutide	T	83	31,678	21.37 (17.40–26.65)	< 0.0001	3.82
Semaglutide	F	45	19,567	35.13 (25.85–47.74)	< 0.0001	4.08
Semaglutide	M	38	9,855	17.04 (12.32–23.57)	< 0.0001	3.23
Tirzepatide	T	4	55,337	0.56 (0.21–1.50)	0.25	-2.52
Tirzepatide	F	1	36,463	0.38 (0.05–2.71)	0.33	-4.83
Tirzepatide	M	2	11,307	0.76 (0.19–3.02)	0.69	-2.93
Wegovy	T	29	3,063	74.89 (51.79–108.29)	< 0.0001	4.42
Wegovy	F	16	2,294	100.33 (60.87–165.39)	< 0.0001	3.79
Wegovy	M	13	483	116.37 (66.86–202.54)	< 0.0001	3.52
Zepbound	T	0	10,151	1	1	1.00

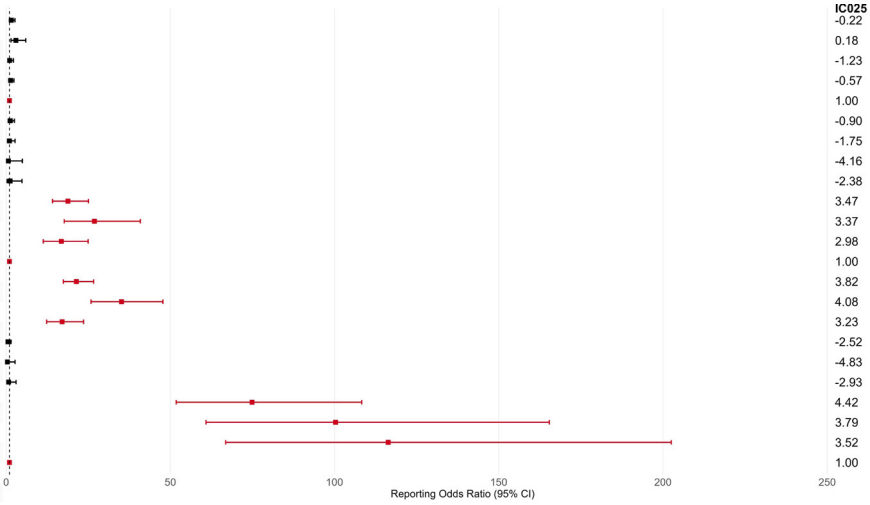

Figure 1 Risk of ischaemic optic neuropathy (ION) associated with glucagon-like peptide-1 receptor agonists (GLP-1RAs). The Forest plot shows reporting odds ratios (RORs) with 95% confidence intervals (CIs), stratified by sex. Rows are grouped first by active ingredient (insulin, metformin, semaglutide, tirzepatide) and then, when relevant, by individual brand names for semaglutide (Ozempic, Wegovy, Rybelsus) and tirzepatide (Mounjaro, Zepbound). Horizontal separators denote transitions between active-ingredient groups. Red points represent statistically significant disproportionality (p<0.05) or subgroups with n=0 when no adverse events were reported. Black points correspond to non-significant associations. AE, adverse event; F, female; IC_{025}, lower bound of the Bayesian information component 95% credibility interval; M, male; ROR, reporting odds ratio; T, total (sexes combined).

produce more moderate GLP-1 stimulation, potentially limiting gastrointestinal fluid loss and orthostatic hypotension.[7] By blunting abrupt haemodynamic shifts, these features may preserve vascular tone and autonomic stability, reducing ischaemic vulnerability, and may further lower NAION risk indirectly by improving sleep apnoea and oxygenation through fat loss.[7]

Overall, ION risk appears dose- and formulation-dependent, and highest with Wegovy. Although Wegovy produced fewer ION reports than Ozempic, its lower overall reporting yielded a higher ROR. Disproportionality reflects relative reporting rather than incidence and may be influenced by exposure, indication or media attention. Ozempic's earlier approval (2017) resulted in more FAERS reports than Wegovy (2021), yet Wegovy showed the stronger signal. Prescription audits and Novo Nordisk data confirm that Ozempic has consistently dominated semaglutide prescribing since 2017, with monthly fills exceeding 2 million by 2023, while Wegovy's uptake after 2021 remained lower owing to supply and coverage constraints.[8 9] This supports the suggestion that Wegovy's stronger disproportionality signal reflects higher reporting intensity rather than volume. As FAERS lacks denominator data, we could not determine true incidence or assess whether reports clustered following regulatory recognition. It also lacks comorbidity data (eg, diabetes) for adjustment and does not capture disease severity, laterality or other granular phenotypic characteristics. These constraints highlight the need for longitudinal pharmacoepidemiologic studies with exposure denominators. Although tirzepatide's shorter availability (~3 years vs >7 years for semaglutide) limits exposure, the reproducible semaglutide signal, supported by mechanistic plausibility and Bayesian evidence, highlights the need for individualised GLP-1 therapy and prospective risk stratification.

Contributors ML and EM had full access to all study data, directly verified the underlying data and take responsibility for the integrity of the data and accuracy of the analysis. Both authors are guarantors. Concept and design: ML, EM acquisition, analysis, or interpretation of data: ML, drafting of the manuscript: ML, critical revision of the manuscript for important intellectual content: all authors, statistical analysis: ML, administrative, technical, or material support: EM, supervision: EM.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer The views expressed are those of the authors and do not necessarily reflect those of the US Food and Drug Administration.

Competing interests Conflict of Interest: MP has received financial support (to the institution) from PSI Foundation and Fighting Blindness Canada. All other authors declare no financial or personal relationships with any organisations that could inappropriately influence (bias) the submitted work. This includes employment, consultancies, stock ownership, honoraria, paid expert testimony, patents, grants or travel funding within the past 3 years. No other relationships or activities have been identified as potential conflicts of interest for this manuscript.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data generated or analysed in this study are presented within the published article. De-identified adverse event reports and data dictionaries are publicly available via the FAERS Public Dashboard (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard). These data are freely accessible without restrictions and can be obtained immediately upon publication.

ORCID iDs
Moiz Lakhani https://orcid.org/0009-0009-4603-826X
Abdullah Al-Ani https://orcid.org/0000-0001-5057-7033
Marko Popovic https://orcid.org/0000-0002-0370-5968
Edward Margolin https://orcid.org/0000-0002-6738-7225

REFERENCES

1 Biousse V, Newman NJ. Ischemic Optic Neuropathies. *N Engl J Med* 2015;372:2428–36.
2 FDA adverse event reporting system (FAERS) public dashboard. US Food and Drug Administration; 2023. Available: https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard [Accessed 7 Dec 2023].
3 Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf* 2009;18:427–36.

4 Jiao X-F, Pu L, Lan S, *et al*. Adverse drug reaction signal detection methods in spontaneous reporting system: A systematic review. *Pharmacoepidemiol Drug Saf* 2024;33:e5768.
5 Lakhani M, Kwan ATH, Mihalache A, *et al*. Association of Glucagon-Like Peptide-1 Receptor Agonists With Optic Nerve and Retinal Adverse Events: A Population-Based Observational Study Across 180 Countries. *Am J Ophthalmol* 2025;277:148–68.
6 Kommu S, Whitfield P. Semaglutide. In: *Statpearls*. StatPearls Publishing, 2025.
7 Willard FS, Douros JD, Gabe MB, *et al*. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight* 2020;5:e140532.
8 Scannell C, Romley J, Myerson R, *et al*. Prescription Fills for Semaglutide Products by Payment Method. *JAMA Health Forum* 2024;5:e242026.
9 Berning P, Adhikari R, Schroer AE, *et al*. Longitudinal Analysis of Obesity Drug Use and Public Awareness. *JAMA Netw Open* 2025;8:e2457232.