Additional file 1

Increased Vision Impairment Reports Linked to Semaglutide: Analysis of FDA Adverse Event Data

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Methods (detailed)

We downloaded all reports from the FDA Adverse Event Reporting System (FAERS, accessed July 8, 2024 via the FAERS public dashboard [1]) for the drug generic names (number of reports in Table S1 of Additional file 1) provided in the *Search Terms* column in Table S2, Additional file 1.

For each treatment class, we only included monotherapy cases, i.e. we only included reports where no other substance was mentioned under *Suspect Product Active Ingredients.* Combinations within groups, i.e. *"Sitagliptin, Sitagliptin Phosphate"* were treated as monotherapy.

Cases were assigned to one or more indication groups if any of the group's search terms (Table 1) was mentioned under *Reason for Use*. Cases that were not in at least one of the specified groups were excluded from the analysis.

Cases were classified into one or more adverse event groups if any of the group's search term (Additional file 1: Table S4) was mentioned under *Reactions* in FAERS.

Indications and reactions were not treated as mutually exclusive, e.g. cases that mention both type 2 diabetes (T2D) and obesity were included in both the T2D and the obesity subgroup analysis, and cases that mention both NAION and other visual impairments were included in both subgroups. The reference group only contains cases for which none of the investigated reactions were mentioned. Reports were not filtered by country where the event occurred.

Reporting odds ratios (rOR) were calculated using the online statistical tool VassarStats, with p-values computed using Yates' correction for continuity. We excluded bupropion (n = 3/73)[a] and naltrexone (n = 1/49) from the statistical analysis due to an insufficient number of reports. Setmelanotide (n = 0/3) was also excluded as no cases of visual impairment were reported for this medication. The rORs were used to compare the proportion of vision impairment reports for semaglutide against those of other medications (Comparator Substance), providing a measure of the relative frequency of this adverse event.

We did all data preprocessing in Python 3.9.7 using the re (regex), numpy, and pandas packages, and we used GraphPad Prism version 8.0.1 for creating visual display of the data. We created the world map using the matplotlib, seaborn, and GeoPandas packages and with geographical data from www.naturalearthdata.com.

References

1. U.S. Food & Drug Administration (FDA). FDA Adverse Event Reporting System. Published October 22, 2012. Accessed July 8, 2024. https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard

[a]Reports numbers are written as follows: n = number of reports for visual impairment / total number of reports

Table S1. Number of reports per treatment group (monotherapy only) by indication

Treatment class	Number of reports for obesity	Number of reports for type 2 diabetes
Bupropion	27	49
Bupropion/Naltrexone	2934	130
DPP-4 inhibitors	14	21112
Metformin	97	14109
Naltrexone	4	47
Orlistat	8020	71
other GLP-1 receptor agonists	4153	111243
Phentermine	1199	5
Phentermine/Topiramate	253	200
Semaglutide	2513	9447
Setmelanotide	2	1
SGLT2 inhibitors	76	32799
Thiazolidinediones	3	95555
Topiramate	173	85

Table S1: Indications “Obesity” and “Type 2 Diabetes” can overlap since multiple indications can be provided per report.

Table S2. Treatment groups and search terms

Treatment class	Treatment name	Treatment search term
DPP-4 inhibitors	Anagliptin	Anagliptin
DPP-4 inhibitors	Evogliptin	Evogliptin
DPP-4 inhibitors	Evogliptin	Evogliptin Tartrate
DPP-4 inhibitors	Gemigliptin	Gemigliptin
DPP-4 inhibitors	Linagliptin	Linagliptin
DPP-4 inhibitors	Omarigliptin	Omarigliptin
DPP-4 inhibitors	Saxagliptin	Saxagliptin
DPP-4 inhibitors	Saxagliptin	Saxagliptin Benzoate Hydrate
DPP-4 inhibitors	Saxagliptin	Saxagliptin Hydrochloride
DPP-4 inhibitors	Sitagliptin	Sitagliptin
DPP-4 inhibitors	Sitagliptin	Sitagliptin Hydrochloride
DPP-4 inhibitors	Sitagliptin	Sitagliptin Phosphate
DPP-4 inhibitors	Trelagliptin	Trelagliptin Succinate
DPP-4 inhibitors	Vildagliptin	Vildagliptin
other GLP-1 receptor agonists	Albiglutide	Albiglutide
other GLP-1 receptor agonists	Dulaglutide	Dulaglutide
other GLP-1 receptor agonists	Exenatide	Exenatide
other GLP-1 receptor agonists	Exenatide	Exenatide Synthetic
other GLP-1 receptor agonists	Liraglutide	Liraglutide
other GLP-1 receptor agonists	Liraglutide	Liraglutide Recombinant
other GLP-1 receptor agonists	Lixisenatide	Lixisenatide
Semaglutide	Semaglutide	Semaglutide
other GLP-1 receptor agonists	Tirzepatide	Tirzepatide
Metformin	Metformin	Metformin
Metformin	Metformin	Metformin Er 500 Mg
Metformin	Metformin	Metformin Hydrochloride
Metformin	Metformin	Metformin Pamoate
SGLT2 inhibitors	Bexagliflozin	Bexagliflozin
SGLT2 inhibitors	Canagliflozin	Canagliflozin
SGLT2 inhibitors	Canagliflozin	Canagliflozin Anhydrous
SGLT2 inhibitors	Dapagliflozin	Dapagliflozin
SGLT2 inhibitors	Dapagliflozin	Dapagliflozin Propanediol
SGLT2 inhibitors	Empagliflozin	Empagliflozin
SGLT2 inhibitors	Ertugliflozin	Ertugliflozin
SGLT2 inhibitors	Ertugliflozin	Ertugliflozin Pidolate
SGLT2 inhibitors	Henagliflozin	Henagliflozin Proline
SGLT2 inhibitors	Ipragliflozin	Ipragliflozin
SGLT2 inhibitors	Ipragliflozin	Ipragliflozin L-Proline
SGLT2 inhibitors	Luseogliflozin	Luseogliflozin
SGLT2 inhibitors	Remogliflozin	Remogliflozin Etabonate
SGLT2 inhibitors	Sotagliflozin	Sotagliflozin
SGLT2 inhibitors	Tofogliflozin	Tofogliflozin
Thiazolidinediones	Lobeglitazone	Lobeglitazone Sulfate
Thiazolidinediones	Pioglitazone	Pioglitazone
Thiazolidinediones	Pioglitazone	Pioglitazone Hydrochloride
Thiazolidinediones	Rosiglitazone	Rosiglitazone
Thiazolidinediones	Rosiglitazone	Rosiglitazone Hydrochloride
Thiazolidinediones	Rosiglitazone	Rosiglitazone Maleate
Thiazolidinediones	Rosiglitazone	Rosiglitazone Tartrate
Bupropion	Bupropion	Bupropion
Bupropion	Bupropion	Bupropion Hydrobromide
Bupropion	Bupropion	Bupropion Hydrochloride

Treatment class	***Treatment name***	***Treatment search term***
Bupropion	Bupropion	Erythrohydrobupropion
Bupropion	Bupropion	Hydroxybupropion, (+/-)-
Naltrexone	Naltrexone	Naltrexone
Naltrexone	Naltrexone	Methylnaltrexone
Naltrexone	Naltrexone	Methylnaltrexone Bromide
Naltrexone	Naltrexone	Naltrexone Hydrochloride
Orlistat	Orlistat	Orlistat
Topiramate	Topiramate	Topiramate
Phentermine	Phentermine	Phentermine
Phentermine	Phentermine	Phentermine Hydrochloride
Setmelanotide	Setmelanotide	Setmelanotide

Table S2: Search terms used for downloading type 2 diabetes and obesity treatments from FAERS. Individual treatments were then pooled into the classes specified in the leftmost column.

Table S3. Reaction filter list

Reaction group	Reaction search term
Optic Ischaemic Neuropathy	Optic Ischaemic Neuropathy
Optic Neuritis	Optic Neuritis
Optic Neuropathy	Optic Neuropathy
Visual Impairment	Blindness
Visual Impairment	Blindness Transient
Visual Impairment	Blindness Unilateral
Visual Impairment	Central Vision Loss
Visual Impairment	Ischaemic Neuropathy
Visual Impairment	Sudden Visual Loss
Visual Impairment	Visual Impairment
Visual Impairment (extended)	Ocular Ischaemic Syndrome
Visual Impairment (extended)	Vision Blurred
Visual Impairment (extended)	Visual Acuity Reduced

Table S3: Search terms for classifying adverse events. For the primary analysis shown in Figure 1, we included all reaction groups except *Optic Neuritis*.

Table S4. Number of reports with at least one retinopathy term listed as reaction

Treatment class	Number of reports, T2D or obesity	Comparator reports
Bupropion	0	73
Bupropion/Naltrexone	0	2861
DPP-4 inhibitors	41	20760
Metformin	26	13928
Naltrexone	0	49
Orlistat	1	7963
other GLP-1 receptor agonists	150	112170
Phentermine	0	1175
Phentermine/Topiramate	0	405
Semaglutide	82	11071
Setmelanotide	0	3
SGLT2 inhibitors	23	32491
Thiazolidinediones	94	94427
Topiramate	1	224

Table S4: Number of reports with at least one retinopathy term listed as reaction, and number of comparator reports where no term for retinopathy and no search term for any type of visual impairment included in the main analysis is mentioned.

Table S5. Monotherapy reports with and without visual impairment for individual GLP-1 receptor agonists

Active ingredient	Report with VI	Reports without VI
Albiglutide	52	5673
Dulaglutide	709	26317
Exenatide	1036	50311
Liraglutide	211	18295
Lixisenatide	0	39
Tirzepatide	146	11368

Table S5: Monotherapy reports with and without visual impairment for individual GLP-1 receptor agonists with obesity or type 2 diabetes as indication, reporting odds ratio in comparison with semaglutide (rOR > 1 indicates higher reporting odds for semaglutide). Abbreviations: VI: visual impairment.

Figure S1. Number of included reports by country where the event occurred.

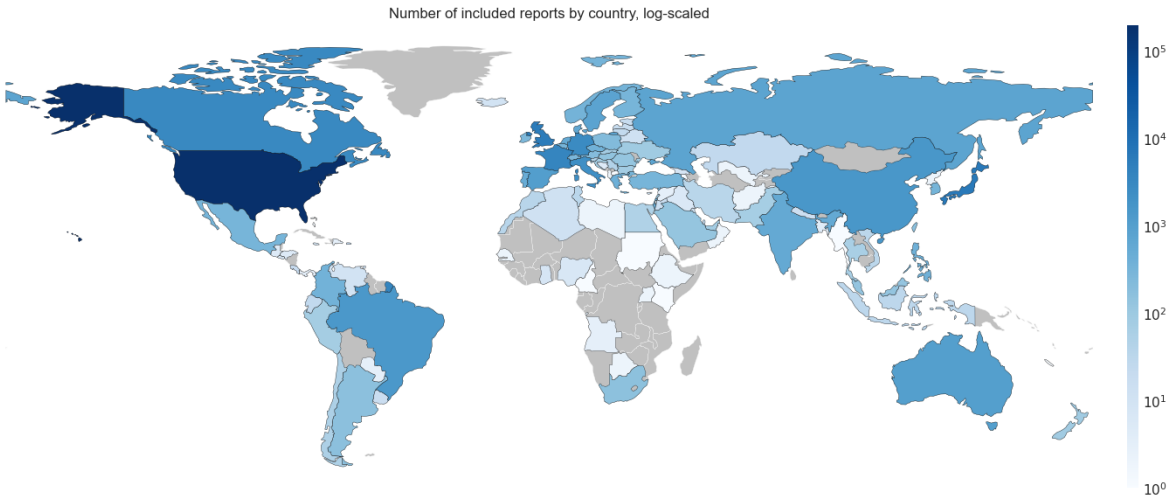

Figure S1: Number of reports submitted to FAERS with type 2 diabetes (T2D) or obesity as reason for use and T2D or obesity treatments as single suspect product active ingredient, by country. We included 302,706 reports, but 65,006 (21.5%) reports with unspecified country are not shown in this figure. Darker colors indicate more reports, and grey indicates no reports. Abbreviations: T2D: type 2 diabetes; FAERS: FDA Averse Event Reporting System.

Figure S2. Cases with at least one retinopathy-associated term mentioned in the reactions list showed an association between Semaglutide use and retinopathy risk

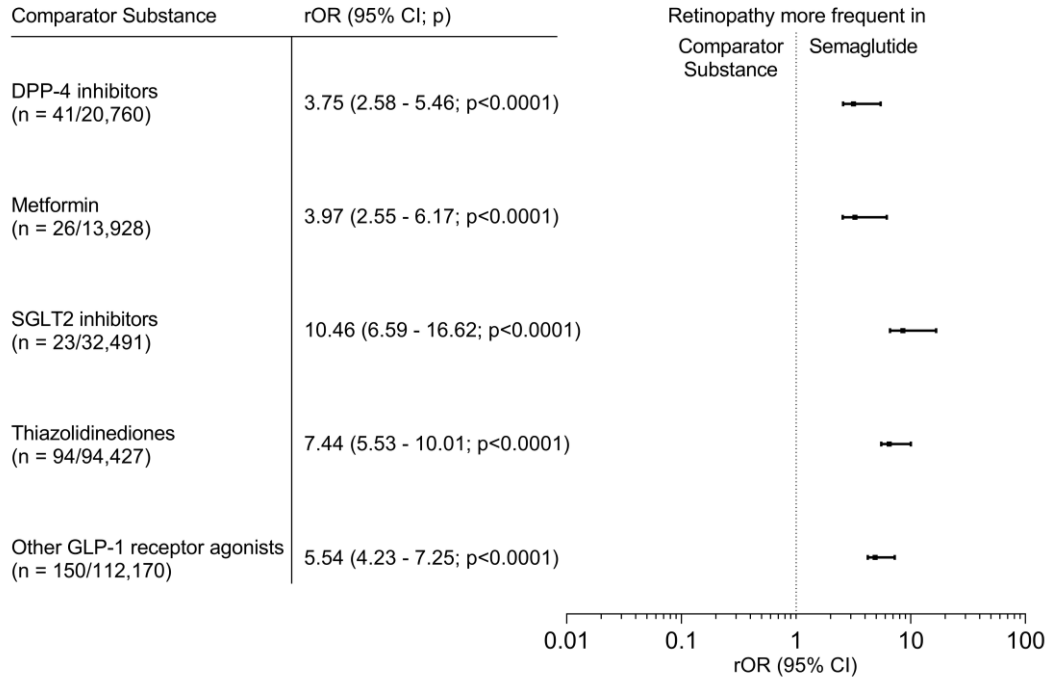

Figure S2: Analysis of FAERS reports of retinopathy (defined as all cases with at least one of the following terms mentioned in the reactions list: “Diabetic Retinopathy”, “Retinopathy”, “Retinopathy Haemorrhagic”, “Retinopathy Hypertensive”, “Retinopathy Proliferative”) in filtered reports with obesity or T2D as main indication for semaglutide and Comparator Substance (monotherapy). Reports for comparator substance were included when no term for retinopathy and no search term for any type of visual impairment included in the main analysis is mentioned (numbers are displayed in the graph as: report for visual impairment/total number of reports), except for semaglutide n=82/11,071. rORs were calculated with 95% CI and corresponding p-value (with Yates’ correction). Abbreviations: CI: confidence interval, FAERS: Food and Drug Administration (FDA) adverse event reporting system, rOR: reporting odds ratio, T2D: type 2 diabetes.

Figure S3. Semaglutide active ingredient drugs Ozempic, Rybelsus and Wegovy are associated with visual impairment or optic (ischemic) neuropathy compared to other substances, except topiramate

Figure S3: Analysis of FAERS reports of visual impairment (terms in Table S3, Additional file 1) in filtered reports with T2D or obesity as main indication for semaglutide and Comparator Substance (monotherapy). Numbers of reports for comparator substance are displayed in the graph (report for visual impairment/total number of reports), except for A) Ozempic n=348/8,132, B) Rybelsus n=47/1,207 and C) Wegovy n=13/1,107. rOR were calculated with 95% CI and corresponding p-value (with Yates' correction). Abbreviations: CI: confidence interval, FAERS: Food and Drug Administration (FDA) adverse event reporting system, rOR: reporting odds ratio, T2D: type 2 diabetes.

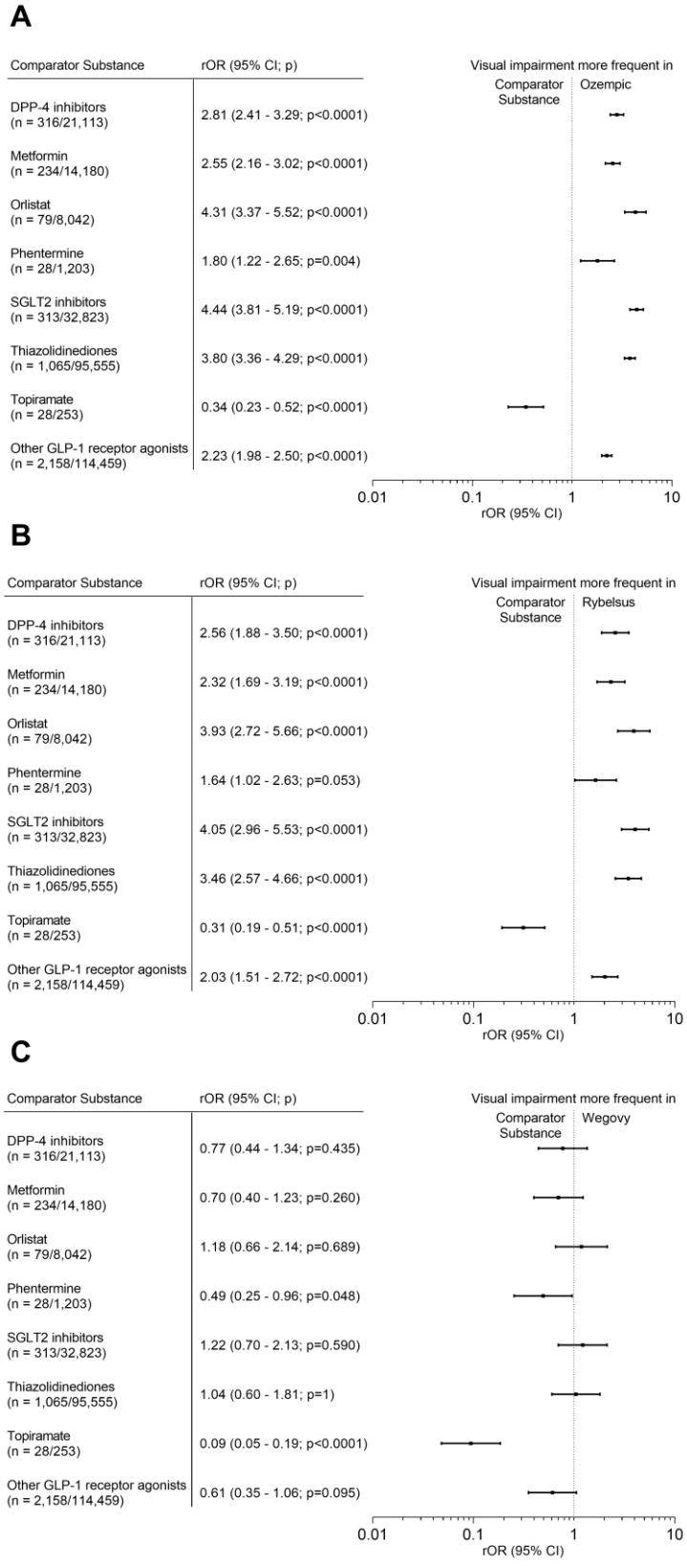

Figure S4. In cases without T2D as indication, the trend for Semaglutide association with visual impairment or optic neuropathy remains for orlistat and other GLP-1 receptor agonists

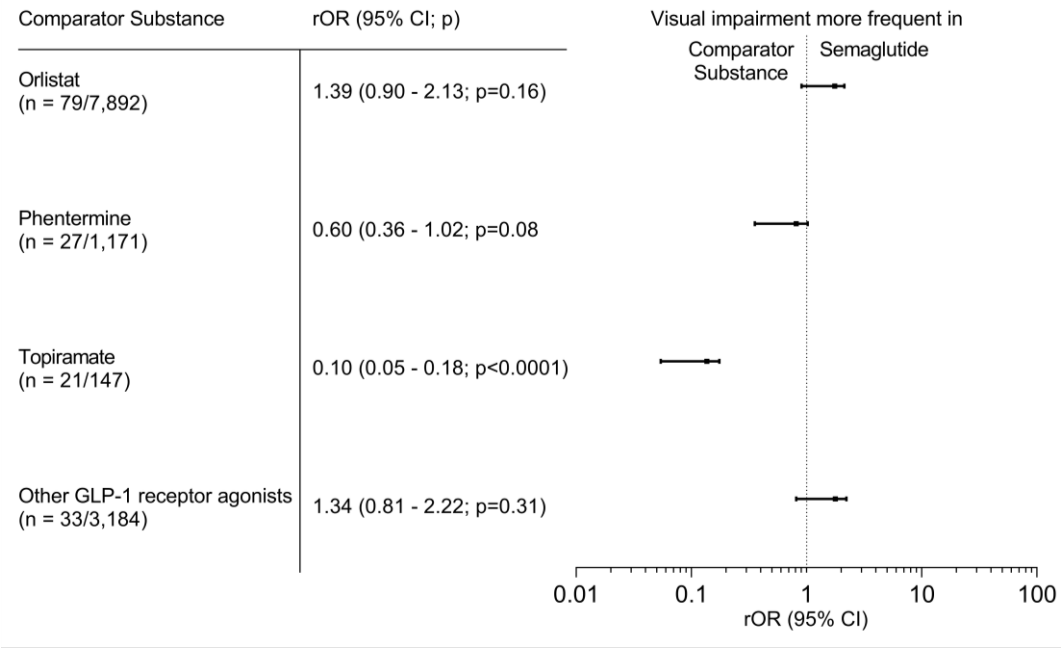

Figure S4: Analysis of FAERS reports of visual impairment (terms in Table S3, Additional file 1) in filtered reports with obesity only as main indication for semaglutide and Comparator Substance (monotherapy). Numbers of reports for comparator substance are displayed in the graph (report for visual impairment/total number of reports), except for semaglutide n=29/2,086. rORs were calculated with 95% CI and corresponding p-value (with Yates' correction). Abbreviations: CI: confidence interval, FAERS: Food and Drug Administration (FDA) adverse event reporting system, rOR: reporting odds ratio, T2D: type 2 diabetes.