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Real-world study of adverse events associated with triptan use in migraine treatment based on the U.S. Food and Drug Administration (FDA) adverse event reporting system (FAERS) database

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Abstract

Background Triptans selectively agoniste 5-Hydroxytryptamine(5-HT) receptors and are widely used in the treatment of migraine. Nevertheless, there is a dearth of comprehensive real-world clinical research on the safety of triptans. In light of the growing prevalence of migraine, it is imperative to gain a deeper understanding of the true extent of adverse events (AEs) associated with triptans in the clinical management of migraine.

Methods A database query of AEs reported to the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database for triptans was performed using the online platform Open Vigil 2.1. The query spanned the period from 1 January 2018 to 31 December 2023 and extracted all AEs for 'sumatriptan', 'zolmitriptan', 'rizatriptan', and 'naratriptan' from the 15–49 years old population and retrospective quantitative analyses. A proportional reporting ratio (PRR), reporting odds ratio (ROR), and Bayesian Confidence Propagation Neural Network (BCPNN) methodology were utilized to contrast AEs across the four triptans.

Results A total of 1.272 AEs reports for sumatriptan, 114 for zolmitriptan, 162 for rizatriptan, and 15 for naratriptan were identified. The ratio of females to males was approximately three times higher in all cases, with the highest number of reports originating from the Americas. A review of the FAERS database revealed that nervous system disorders were the primary SOC category for four drugs, with all four drugs exhibiting the AE indicative of reversible cerebral vasoconstriction syndrome, also classified as Nervous system disorders. The most frequently reported AE signal for sumatriptan was dyspnea, which is classified as respiratory, thoracic and mediastinal disorders. The most frequently reported AEs signals for the remaining three drugs were nausea, vomiting and terminal ileitis, all of which are classified as gastrointestinal disorders.

Conclusion Analyses have demonstrated that AEs are present in a range of systems, including cardiac, nervous, gastrointestinal, and musculoskeletal disorders. It should be noted, however, that the incidence and signal intensity

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of these AEs vary depending on the specific drug in question. In clinical practice, the selection of an appropriate drug and the monitoring of AEs should be tailored to the individual patient's and specific characteristics.

Keywords Triptan medications, Adverse events, Food and drug administration adverse event reporting system, Real-world, Pharmacovigilance

Introduction

Migraine is a prevalent chronic -neurological disorder that typically manifests as recurrent episodes of moderate to severe throbbing headaches and concomitant symptoms of autonomic dysfunction, including nausea, vomiting, photophobia, and phonophobia. Headaches may be unilateral, affecting one - side- of the head, or may become a full headache, which is more prevalent in women [1–3]. According to the Global Burden of Disease Study, migraine is the third leading cause of neurological health loss globally and is a major contributor to neurological disability as well as one of the leading causes of disability in people under 50 years of age [4–6]. Triptans are selective 5-hydroxytryptamine (5-HT) receptor agonists that have been developed for the acute treatment of migraine. It relieves migraine attacks by agonizing 5-HTIB/ID receptors on intracranial blood vessels (including arteriovenous anastomoses) and sympathetic nerves in the trigeminal system, constricting blood vessels and inhibiting the release of peripherally active neuropeptides, such as calcitonin gene-related peptide (CGRP) [7–9].

The introduction of the first-generation drug sumatriptan represented a significant advancement in the treatment of acute migraine. However, the second-generation triptan analogues (zolmitriptan, rizatriptan and naratriptan), which exhibit a superior pharmacokinetic profile compared to sumatriptan, demonstrate comparable pharmacodynamic properties and are currently employed for the management of moderate to severe migraine attacks [10–12]. The instructions for the use of drugs such as triptans indicate that they are contraindicated in patients with cardiovascular diseases, including but not limited to heart disease, angina pectoris, myocardial infarction, etc. Adverse reactions are often observed, including but not limited to neurological (headache, dizziness, drowsiness, etc.), cardiac (palpitations, arrhythmias, etc.), gastrointestinal (nausea, vomiting, etc.) and allergic reactions [13]. To date, the majority of clinical trials have demonstrated the safety, efficacy, and tolerability of triptans in the treatment of migraine [10, 14]. Patients with vascular disease due to the vasoconstrictive potential of triptans are frequently excluded from Phase III studies. Furthermore, individuals over the age of 65 are often excluded. In consequence of the aforementioned considerations, the instructions for all Triptan drugs indicate that they are contraindicated in patients with various vascular diseases. Nevertheless, an Austrian study demonstrated that the prevalence of vascular disease in users of the drugs over the age of 50 remained unchanged. This indicates that the use of the drugs does not elevate the risk of vascular events in this age group [15]. Due to the rigorous inclusion criteria for trial populations and constraints on sample size and follow-up duration, the occurrence of AEs and long-term medication safety concerns may be underestimated or overestimated at this juncture. The dearth of post-marketing safety data for triptans in pharmaceuticals underscores the necessity for comprehensive real-world studies.

The FAERS database, which collates data on AEs and medication errors occurring within and outside the United States, represents a significant source of real-world data on AEs, and may provide insight into the occurrence of drug AEs [16]. In previous studies, scholars investigated the drug-related vascular adverse events associated with triptans from 2004 to 2010. Their findings revealed a strong association between ischemic cerebrovascular events, aneurysms and artery dissections, and pregnancy-related vascular events and triptans [17]. And then Sharma [18] et al. explored the data of cardiovascular adverse events of Triptans from 1997 to 2023 in people aged 18–85 years, but no quantitative analyses such as year, region, gender etc. were done to compare with the drugs. The recent advances in pharmacological treatments and the growing prevalence of common adverse reactions have prompted a shift in the way clinicians and related professionals approach drug utilisation in the real world. This necessitates a comprehensive and up-to-date investigation of the subject.The objective of this study was to conduct pharmacovigilance analyses of triptans and AEs - using the FAERS database. This was done with the intention of providing insights into the post-marketing safety of triptans, as well as to inform personalised treatment decisions for clinicians, patients and regulators.

Methods

Data sources

The data for this study were retrieved from the publicly available FAERS database, which collates spontaneous AE reports from a variety of sources, including

healthcare professionals, patients, pharmaceutical manufacturers, and others in different regions. This can reflect the true incidence of AEs [19]. This retrospective study used Open Vigil 2.1 to query the FAERS database and retrieve reports of the target drug for the last 6 years between 1 January 2018 and 31 December 2023, which better represents the current real-world AE realities of the drug The generic name of the target drug is the first generation drug: 'sumatriptan', with second-generation drugs: 'zolmitriptan', 'rizatriptan', and 'naratriptan'. The age limit of 15–49 years was set primarily due to the relatively high incidence and prevalence of migraine in this age group and the fact that AE in this age group has not been extensively investigated in previous studies [20]. In the present study, we selected reported cases defined as AEs in which the reporter identified the target drug as the 'prime suspect'. We then classified and described the AEs according to the preferred terminology (PT) and the system organ classification (SOC) in the International Medical Dictionary for Regulatory Activities (MedDRA 27.0 Edition) [21]. Data sources are publicly available and therefore do not require ethical approval.

Statistical analysis

Proportional reporting ratio (PRR), reporting odds ratio (ROR) and Bayesian Confidence Propagation Neural Network (BCPNN) methods are commonly used to detect AE signals in pharmacovigilance [22]. PRR [23] can be employed to estimate relative risk; however, PRR methods are susceptible to false-positive signals. In contrast, ROR [24] is a consistent estimate of the ratio, or risk ratio, and is less biased than other indices. BCPNN [25]employs a neural network-supervised learning approach that utilises known adverse drug reactions as a machine-learning training set, which is relatively stable, even with a small number of reports. Therefore, we combined ROR, PRR and BCPNN methods to mine the AE signals of the target drugs, with the calculation of PRR and χ2 based on the ratio imbalance measure quadrangle table. Should the results of all three methods yield a positive outcome, it can be inferred that the criteria set forth in Table 1 have been met, thereby classifying the signal in question as a suspected AE signal [26]. We used Microsoft Office Excel 2021, R 4.3.1 software and online plotting platform (https://www.bioincloud.tech/) (https://www.chiplot.online/) (https://bioincloud.tech/) to statistically analyse and plot the data [27].

Results

Demographic information on the AE reports

A total of 968.550 AEs reports were identified from the FAERS database between 1 January 2018 and 31 December 2023. Of the four triptans, sumatriptan had the highest number of AEs reports, with 1,272 reports, followed by zolmitriptan with 114 reports, rizatriptan with 162 reports, and naratriptan with the lowest number of reports, at 15. With the exception of unknown reports, the ratio of females to males was approximately 3 times greater for all four drugs (Fig. 1C), demonstrating a wide range of differences. It is hypothesised that this may be due to the fact that migraines are more prevalent in women. Consequently, the population using triptans in the real world is predominantly female, which results in a higher number of AEs in women. The number of reports of sumatriptan was concentrated in 2018, with an overall downward trend (Fig. 1A). Furthemore, the most frequently reported age group was between 31 and 49 years of age, with the highest number of reports originating

Table 1 Formulas and signal detection criterias for reporting odds ratio (ROR), proportional reporting ratio (PRR) and bayesian confidence propagation neural network (BCPNN)

Algorithms	Equation	Criteria	
ROR	ROR=ad/bc	lower limitof 95%CI>1,a≥3	
	95%CI=eln(ROR)±1.96(1/a+1/b+1/c+1/d)^0.5		
PRR	PRR=a(c+d)/c/(a+b)	PRR>2,χ^2>4,a>3	
	χ^2=[(ad-bc)^2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]		
BCPNN	IC=$\log_2$a(a+b+c+d)(a+c)(a+b)	IC025 > 0	
	95%CI=E(IC)±2V(IC)^0.5		
Fourfold table of disproportionality measures.	Target AE	OtherAE	Total
Target drugs	a	b	a+b
Other drugs	c	d	c + d
Total	a+c	b + d	a+b + c + d

ROR reporting odds ratio, *CI* confidence interval, *PRR* proportional reporting ratio, *χ2* chi-squared, *BCPNN* bayesian confidence propagation neural network, *IC* information component, *IC025* the lower limit of 95%CI, of the IC

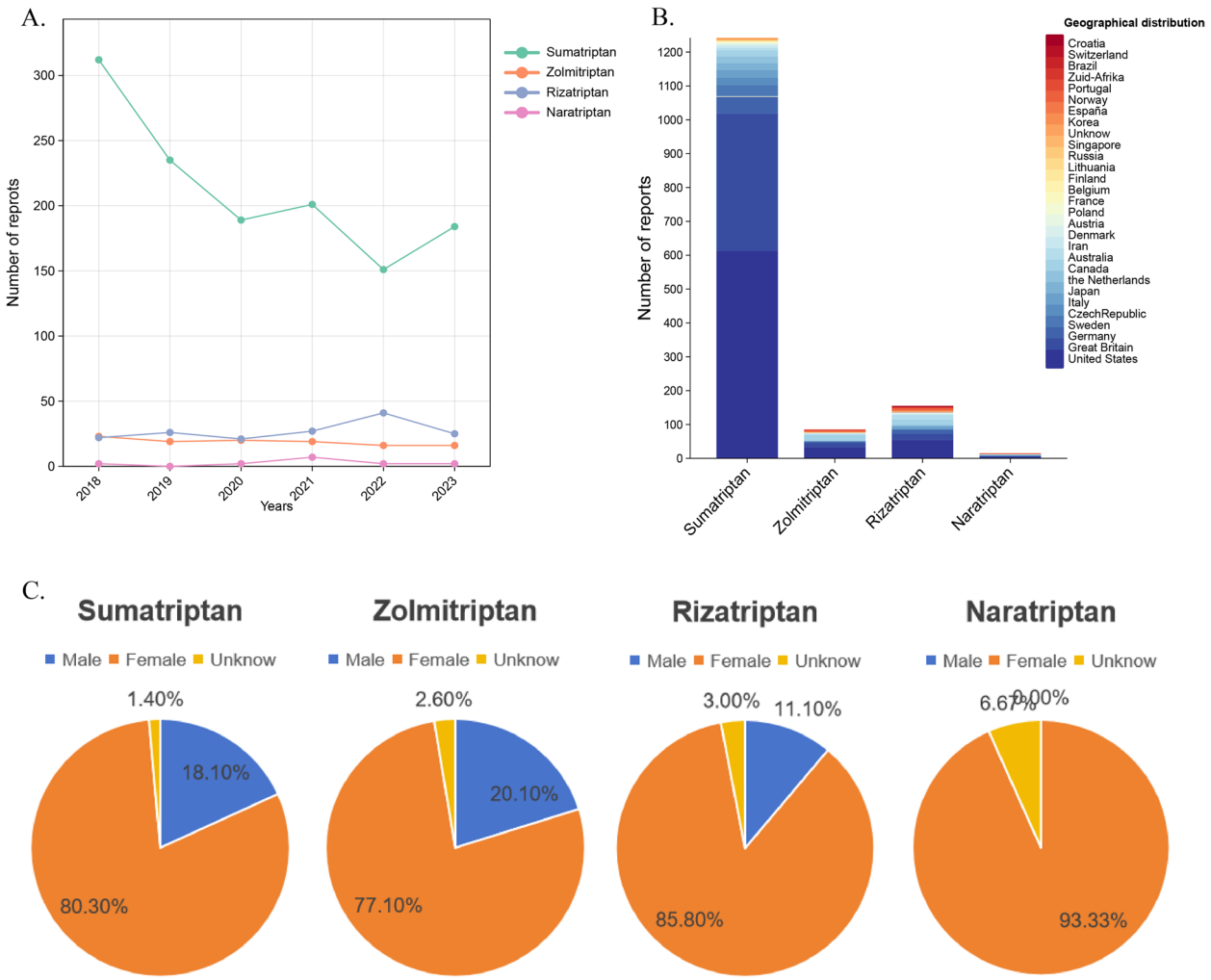

Fig. 1 Demographic information reported by AE in FAERS. **A** Number of four drugs reported per year; **B** Number of reports by region for the four drugs; **C** Rates were reported by sex for the four drugs

from - America- (Fig. 1B). The primary indication for the drug is the treatment of migraine. Please refer to Table 2 for further details.

Signal AE mining and analysis of AE signals at the PT level

In this study, the analysis of AE signals was conducted using ROR, PRR and BCPNN. A total of 164 AE signals were obtained for sumatriptan, following the removal of entry errors, incomplete information, and the screening and exclusion of signals pertaining to product quality, use problems, and drug indications. A total of 101 positive AE signals were obtained for zolmitriptan, 97 AE signals were obtained for rizatriptan, and 21 positive signals were obtained for naratriptan. All AE signals are presented in the Supplementary Material Table S1. We next analysed all signals at the PT level, focusing on the top 30 most frequent and highest signal intensity detections that occurred (Table 3; Fig. 2). The three most frequently reported AE associated with sumatriptan were dyspnoea, chest discomfort and dizziness- and the top 3 AE signals with PRR values were migrainous infarction, pityriasis lichenoides et varioliformis acuta, and subclavian artery thrombosis. The three most frequently reported AE signals associated with zolmitriptan were nausea, fatigue and pain. and the top 3 AE signals with PRR values were paraesthesia ear, vascular malformation and paranasal cyst. The three most frequently reported AE signals for rizatriptan were vomiting, chest discomfort, and myocardial infarction and the top 3 AE signals in terms of PRR values were broad ligament tear, hemiataxia, and thalamic infarction. The three most frequently reported AEs associated with naratriptan were terminal ileitis, nocturia, and abdominal pain. Among the AEs with the

Table 2 Demographic information reported by AE in FAERS

	Sumatriptan(*n*=1172)			Zolmitriptan(*n*=114)			Rizatriptan(*n*=106)			Naratriptan(n=15)		
		n	%		n	%		n	%		n	%
Sex	Male	231	18.1	Male	23	20.1	Male	18	11.1	Male	0	0.0
	Female	1022	80.3	Female	88	77.1	Female	139	85.8	Female	14	93.3
	Unknow	19	1.4	Unknow	3	2.6	Unknow	5	3.0	Unknow	1	6.7
Age (years)	15-18	74	5.82	15-18	5	4.4	15-18	4	2.5	15-18	0	0.0
	19-30	334	26.26	19-30	25	21.9	19-30	27	14.1	19-30	1	6.7
	31-49	864	67.92	31-49	84	73.7	31-49	131	67.9	31-49	14	93.3
Reporting year	2018	312	24.5	2018	23	20.1	2018	22	13.5	2018	2	13.3
	2019	235	18.4	2019	19	16.6	2019	26	16.0	2019	0	0.0
	2020	189	14.8	2020	20	17.5	2020	21	12.9	2020	2	13.3
	2021	201	15.8	2021	19	16.6	2021	27	16.6	2021	7	46.6
	2022	151	11.8	2022	16	14.0	2022	41	25.3	2022	2	13.3
	2023	184	14.4	2023	16	14.9	2023	25	16.4	2023	2	13.3
Geographical distribution	United States	613	48.1	United States	33	28.9	United States	54	33.3	United States	5	33.3
	Great Britain	405	31.8	France	29	25.4	Great Britain	18	11.1	Germany	3	20.0
	Germany	50	3.9	Canada	15	13.2	Canada	17	10.5	Norway	3	20.0
	France	32	2.5	Great Britain	13	11.4	Germany	13	8.0	Canada	2	13.3
	Sweden	32	2.5	Australia	5	4.4	Australia	13	8.0	Australia	1	6.7
	CzechRepublic	23	1.8	Germany	4	3.5	France	10	6.2	Japan	1	6.7
	Italy	22	1.7	España	3	2.6	Italy	8	4.9			
	Japan	20	1.5	Austria	2	1.8	Japan	5	3.1			
	the Netherlands	20	1.5	Norway	2	1.8	Norway	5	3.1			
	Canada	18	1.4	Portugal	2	1.8	Austria	3	1.9			
	Australia	7	0.6	Italy	1	0.9	España	3	1.9			
	Iran	7	0.6	Japan	1	0.9	India	3	1.9			
	Denmark	4	0.3	Korea	1	0.9	Unkown	2	1.2			
	Austria	3	0.2	the Netherlands	1	0.9	Croatia	2	1.2			
	Poland	3	0.2	Poland	1	0.9	Portugal	2	1.2			

Table 2 (continued)

	Sumatriptan(*n*=1172)			Zolmitriptan(*n*=114)			Rizatriptan(*n*=106)			Naratriptan(n=15)		
		n	%		n	%		n	%		n	%
	Switzerland	2	0.2	Zuid-Afrika	1	0.9	Brazil	1	0.6			
	France	2	0.2				Switzerland	1	0.6			
	Belgium	1	<0.1				Finland	1	0.6			
	Finland	1	<0.1				Zuid-Afrika	1	0.6			
	Lithuania	1	<0.1									
	Russia	1	<0.1									
	Singapore	1	<0.1									
	Unknow	6	0.5									
Indication	Migraine	788	62.0	Migraine	54	60.7	Migraine	98	60.5	Migraine	8	53.3
	Unknow	305	24.0	Headache	2	2.3	Headache	5	3.1	Headache	2	13.3
	Headache	65	5.1	Multiple sclerosis relapse	2	2.3	Cluster headache	3	1.9	Unknow	5	33.3
	Cluster headache	37	2.9	Tinnitus	2	2.3	Drug abuse	3	1.9			
	Ill-defined disorder	34	2.7	Cluster headache	1	1.1	Suicidal ideation	3	1.9			
	Other	43	3.4	Diaphragmatic hernia	1	1.1	Unknow	50	30.9			
				Unknow	22	30.2						

Table 3 Top 30 AEs with the highest percentage of signal detection in the FAERS database

	Sumatriptan					Zolmitriptan					Rizatriptan					Naratriptan				
No	PT	n(%)	PRR	χ2	ROR(95%CI)	PT	n(%)	PRR	χ2	ROR(95%CI)	PT	n(%)	PRR	χ2	ROR(95%CI)	PT	n(%)	PRR	χ2	ROR(95%CI)
1	Dyspnoea	79(5.36)	3.125	113.98	3.27(2.60 to 4.11)	Nausea	17(5.86)	3.7	32.213	4.21(2.51 to 7.07)	Vomiting	11(4.28)	2.89	12.07	3.04(1.64 to 5.62)	Terminal ileitis	2(7.69)	2306.038	2507.84	2690.21(589.43 to 12278.26)
2	Chest discomfort	71(4.82)	10.411	590.343	11.00(8.64 to 14.00)	Fatigue	11(3.79)	2.787	11.291	2.99(1.60 to 5.58)	Chest discomfort	8(3.11)	9.365	51.922	9.84(4.82 to 20.06)	Nocturia	2(7.69)	506.822	563.208	591.12(131.68 to 2653.66)
3	Dizziness	69(4.68)	2.346	53.084	2.43(1.90 to 3.10)	Pain	8(2.76)	2.78	7.628	2.92(1.42 to 6.01)	Myocardial infarction	7(2.72)	22.372	122.176	23.42(10.95 to 50.07)	Pollakiuria	2(7.69)	117.655	129.315	137.10(30.65 to 613.24)
4	Chest pain	60(4.07)	6.186	255.801	6.46(4.98 to 8.38)	Drug intolerance	7(2.41)	12.906	65.679	13.74(6.38 to 29.58)	Palpitations	7(2.72)	6.765	29.037	7.05(3.30 to 15.06)	Abdominal pain	2(7.69)	9.857	8.413	11.33(2.54 to 50.64)
5	Paraesthesia	58(3.93)	3.657	110.249	3.79(2.91 to 4.94)	Malaise	7(2.41)	3.694	11.385	3.88(1.80 to 8.36)	Somnolence	7(2.72)	3.947	12.738	4.09(1.92 to 8.74)	Malaise	2(7.69)	8.064	6.433	9.24(2.07 to 41.30)
6	Throat tightness	49(3.32)	21.97	935.993	22.86(17.11 to 30.53)	Vomiting	7(2.41)	2.578	5.409	2.69(1.25 to 5.79)	Coronary artery dissection	6(2.33)	230.571	1111.952	240.14(104.65 to 551.01)	Spinal cord infarction	1(3.85)	2767.246	664.241	2980.03(375.50 to 23649.77)
7	Somnolence	39(2.65)	2.731	41.413	2.79(2.03 to 3.84)	Dysphagia	6(2.07)	18.994	85.152	20.06(8.80 to 45.76)	Hypersensitivity	6(2.33)	4.709	14.125	4.86(2.15 to 11.01)	Cerebral vasoconstriction	1(3.85)	1471.939	359.347	1585.09(203.25 to 12361.95)
8	Coronary artery dissection	37(2.51)	215.911	6064.65	222.69(154.19 to 321.63)	Myalgia	6(2.07)	7.973	30.136	8.39(3.68 to 19.12)	Paraesthesia	6(2.33)	3.042	6.391	3.13(1.38 to 7.08)	Bronchial obstruction	1(3.85)	1080.955	265.108	1164.03(150.05 to 9030.24)
9	Musculoskeletal stiffness	34(2.31)	6.285	145.362	6.44(4.57 to 9.06)	Somnolence	6(2.07)	4.742	14.337	4.96(2.18 to 11.31)	Kounis syndrome	5(1.95)	131.22	512.184	135.71(55.16 to 333.87)	Consciousness fluctuating	1(3.85)	934.88	229.629	1006.72(130.03 to 7794.40)
10	Limb discomfort	33(2.24)	15.347	421.055	15.75(11.11 to 22.33)	Asthenia	6(2.07)	4.147	11.503	4.33(1.90 to 9.88)	Polyuria	5(1.95)	69.419	269.446	71.78(29.30 to 175.87)	Gluten sensitivity	1(3.85)	658.868	162.187	709.47(91.98 to 5472.47)
11	Loss of consciousness	24(1.63	3.041	30.944	3.08(2.06 to 4.62)	Angle closure glaucoma	5(1.72)	210.485	824.486	220.75(89.07 to 547.14)	Troponin increased	5(1.95)	67.11	260.288	69.39(28.32 to 169.99)	Incoherent	1(3.85)	345.906	85.069	372.44(48.49 to 2860.56)
12	Visual impairment	23(1.56)	3.711	42.897	3.06(2.03 to 4.63)	Nasal congestion	5(1.72)	14.669	50.83	15.34(6.25 to 37.67)	Sopor	5(1.95)	12.25	41.055	12.64(5.18 to 30.85)	Reversible cerebral vasoconstriction syndrome	1(3.85)	210.277	51.434	226.38(29.53 to 1735.50)
13	Vision blurred	23(1.56)	2.581	20.807	2.16(1.43 to 3.26)	Vertigo	5(1.72)	13.894	47.719	14.53(5.92 to 35.67)	Bradycardia	5(1.95)	11.062	36.301	11.41(4.67 to 27.85)	Faecal calprotectin increased	1(3.85)	178.763	43.6	192.44(25.11 to 1474.68)

Table 3 (continued)

	Sumatriptan					Zolmitriptan					Rizatriptan					Naratriptan				
No	PT	n(%)	PRR	χ2	ROR(95%CI)	PT	n(%)	PRR	χ2	ROR(95%CI)	PT	n(%)	PRR	χ2	ROR(95%CI)	PT	n(%)	PRR	χ2	ROR(95%CI)
14	Head discomfort	22(1.49)	17.26	314.468	2.61(1.73 to 3.95)	Nasopharyngitis	5(1.72)	5.196	13.115	5.40(2.20 to 13.26)	Hypoaesthesia	5(1.95)	3.976	8.427	4.08(1.67 to 9.95)	Subarachnoid haemorrhage	1(3.85)	177.844	43.371	191.45(24.98 to 1467.08)
15	Hypoaesthesia	22(1.49)	2.171	12.822	3.76(2.49 to 5.69)	Weight decreased	5(1.72)	5.048	12.545	5.25(2.14 to 12.88)	Paralysis	4(1.56)	34.945	99.665	35.88(13.25 to 97.12)	Gastrointestinal inflammation	1(3.85)	161.638	39.34	174.00(22.71 to 1333.05)
16	Hypersensitivity	21(1.42)	2.045	10.248	17.56(11.47 to 26.89)	Hypotension	5(1.72)	4.915	12.031	5.11(2.08 to 12.54)	Acute respiratory failure	4(1.56)	31.531	89.327	32.37(11.96 to 87.61)	Bronchospasm	1(3.85)	134.072	32.479	144.31(18.84 to 1105.19)
17	Peripheral coldness	20(1.36)	30.168	516.03	2.19(1.44 to 3.35)	Paraesthesia	5(1.72)	3.554	6.888	3.68(1.50 to 9.03)	Hallucination	4(1.56)	27.183	76.147	27.90(10.31 to 75.49)	Diarrhoea haemorrhagic	1(3.85)	114.728	27.661	123.48(16.13 to 945.40)
18	Pharyngeal swelling	20(1.36)	15.213	247.115	2.06(1.34 to 3.18)	Throat tightness	4(1.38)	19.805	53.837	20.54(7.55 to 55.81)	Pain in jaw	4(1.56)	23.648	65.424	24.27(8.97 to 65.65)	Sensation of foreign body	1(3.85)	96.353	23.083	103.69(13.55 to 793.68)
19	Neck pain	20(1.36)	5.933	76.811	6.02(3.86 to 9.37)	Disturbance in attention	4(1.38)	10.604	25.914	10.98(4.04 to 29.82)	Rhinorrhoea	4(1.56)	9.604	22.856	9.84(3.64 to 26.59)	Disorientation	1(3.85)	40.41	9.138	43.44(5.68 to 332.27)
20	Hot flush	19(1.29)	5.736	69.33	30.66(19.55 to 48.09)	Heart rate increased	4(1.38)	7.268	15.878	7.51(2.77 to 20.40)	Suicidal ideation	4(1.56)	3.55	5.034	3.62(1.34 to 9.78)	Anger	1(3.85)	37.825	8.494	40.66(5.32 to 310.97)
21	Angina pectoris	18(1.22)	19.29	287.403	15.45(9.89 to 24.14)	Palpitations	4(1.38)	5.417	10.394	5.59(2.06 to 15.18)	Tremor	4(1.56)	3.539	5.002	3.61(1.34 to 9.74)	Mobility decreased	1(3.85)	33.244	7.353	35.73(4.67 to 273.22)
22	Pain in jaw	18(1.22)	13.349	190.49	5.81(3.69 to 9.16)	Tremor	4(1.38)	4.961	9.062	5.12(1.88 to 13.89)	Thalamic infarction	3(1.17)	605.25	1148.26	617.58(187.05 to 2039.10)					
23	Skin discolouration	17(1.15)	8.797	108.778	19.57(12.22 to 31.34)	Hypoaesthesia	4(1.38)	4.459	7.613	4.59(1.69 to 12.47)	Vasospasm	3(1.17)	387.36	756.605	395.25(121.91 to 1281.43)					
24	Colitis ischaemic	16(1.09)	45.359	615.664	13.54(8.47 to 21.64)	Back pain	4(1.38)	4.015	6.348	4.13(1.52 to 11.22)	Acute coronary syndrome	3(1.17)	75.362	150.32	76.88(24.35 to 242.71)					
25	Syncope	15(1.02)	2.528	12.385	4.10(2.54 to 6.62)	Vascular malformation	3(1.03)	1429.085	2566.898	1470.28(428.57 to 5044.00)	Arteriospasm coronary	3(1.17)	64.346	127.858	65.64(20.81 to 207.02)					

Table 3 (continued)

	Sumatriptan					Zolmitriptan					Rizatriptan					Naratriptan				
No	**PT**	**n(%)**	**PRR**	**χ2**	**ROR(95%CI)**	**PT**	**n(%)**	**PRR**	**χ2**	**ROR(95%CI)**	**PT**	**n(%)**	**PRR**	**χ2**	**ROR(95%CI)**	**PT**	**n(%)**	**PRR**	**χ2**	**ROR(95%CI)**
26	Serotonin syndrome	14(0.95)	4.97	40.355	8.91(5.50 to 14.41)	Paranasal cyst	3(1.03)	1044.331	1946.11	1074.43(320.24 to 3604.76)	Reversible cerebral vasoconstriction syndrome	3(1.17)	59.229	117.401	60.42(19.16 to 190.47)					
27	Arteriospasm coronary	13(0.88)	35.714	387.403	45.95(27.68 to 76.29)	Acute myopia	3(1.03)	522.166	1023.799	537.20(165.14 to 1747.47)	Gastrointestinal pain	3(1.17)	45.465	89.19	46.37(14.73 to 146.02)					
28	Reversible cerebral vasoconstriction syndrome	13(0.88)	32.785	354.98	2.55(1.53 to 4.24)	Mastoiditis	3(1.03)	512.313	1005.429	527.06(162.12 to 1713.48)	Ischaemic stroke	3(1.17)	41.562	81.172	42.39(13.47 to 133.43)					
29	Joint stiffness	13(0.88)	9.917	94.427	5.02(2.96 to 8.51)	Otitis media	3(1.03)	195.342	393.527	200.95(63.01 to 640.88)	Affect lability	3(1.17)	39.607	77.152	40.40(12.84 to 127.13)					
30	Discomfort	13(0.88)	2.676	12.026	36.09(20.65 to 63.09)	Renal infarct	3(1.03)	176.316	355.459	181.37(56.94 to 577.77)	Hyperaesthesia	3(1.17)	34.96	67.588	35.65(11.33 to 112.17)					

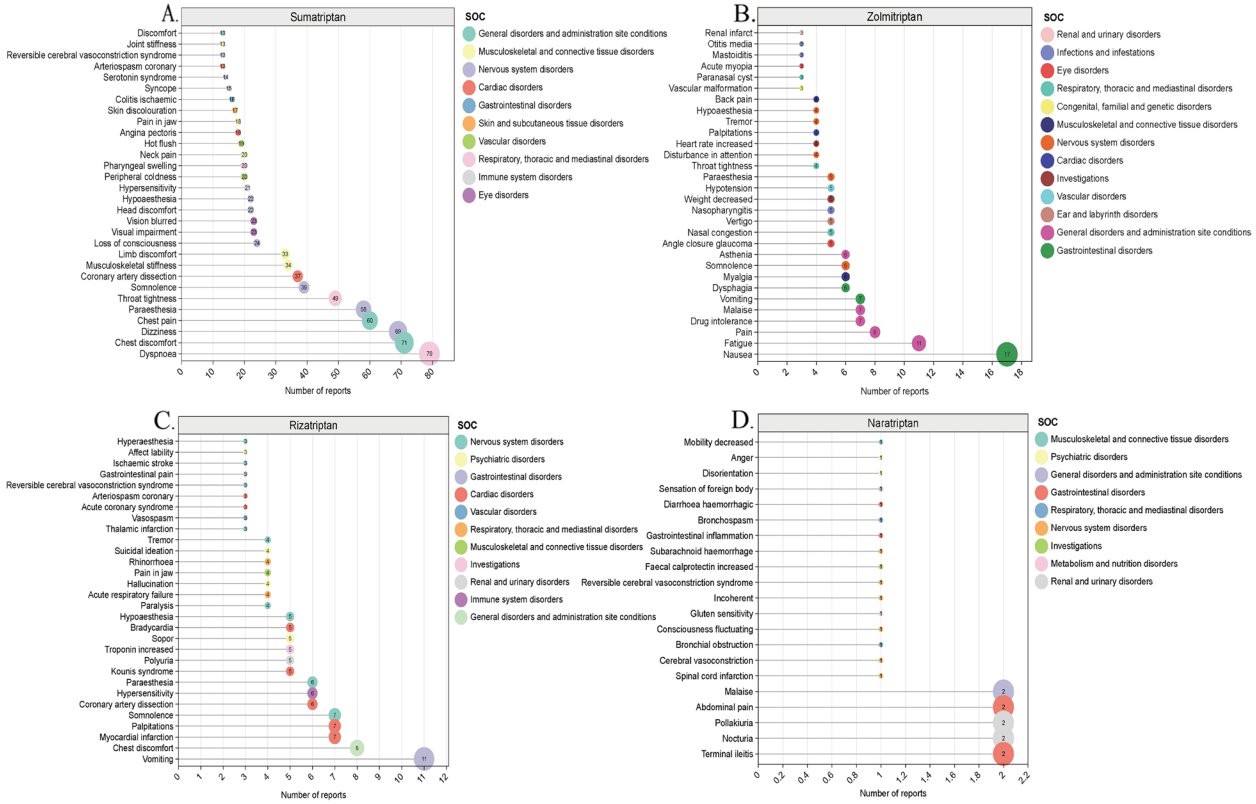

Fig. 2 The names and numbers of the top 30 AEs with the highest percentage of 4 drug signals detected in the FAERS database and their corresponding SOCs

highest PRR, the top three were spinal cord infarction, terminal ileitis, and cerebral vasoconstriction.

AE report stratified analysis by SOC and relationship between main AE signals detection and SOCs

The AE signals of the four drugs were classified according to the SOC for the involved organs and systems using the MedDRA27.0. Additionally, a visual analysis was conducted to examine the PT signals and their corresponding SOCs. Our findings revealed that nervous system disorders constituted the primary SOC category for the four triptans within the FAERS database (Table 4; Fig. 3, Figure S1-S3).

Subsequently, we concentrated on the ROR 95% confidence interval (CI) intensity of the signal among the top 30 most frequent AEs where the drug appeared (Table 3) for the purpose of forest plot visualisation analysis (Fig. 4). With regard to sumatriptan, the strongest signal (ROR = 222.69 (154.19 to 321.63)) was coronary artery dissection, which is classified as a cardiac disorder. The clinical use of sumatriptan has yielded a robust signal for the heart, which aligns with its contraindication in patients with preexisting cardiovascular disease and adverse cardiac effects. For zolmitriptan, the strongest signal was vascular malformation [ROR = 1470.28 (428.57 to 5044.00)]. The highest AE associated with rizatriptan was thalamic stroke no infarction (ROR = 617.58 [187.05 to 2039.10]), a neurological disorder. This was followed by vasospasm (ROR = 395.25 [121.91 to 1281.43]) and coronary artery dissection (ROR = 240.14 [104.65 to 551.01]). This indicates that it can cause a range of neurological disorders, as well as the possibility of cardiocerebral adverse effects. Naratriptan has been associated with a range of neurological disorders, with the highest incidence being spinal cord infarction (ROR = 2980.03 (375.50 to 23649.77)). It is speculated that cell death may be caused by ischaemia in the spinal cord due to excessive vasoconstriction of the blood vessels. Additionally, it has been linked to adverse reactions affecting the gastrointestinal system. Still awaiting further confirmation. The main AEs of the drugs are related to cardiac disorders, nervous system disorders, gastrointestinal disorders and respiratory system, and patients suffering from related system disorders should be closely monitored for adverse effects during the clinical use of triptans.

Table 4 Distribution of AE signals in each SOC

SOC	Sumatriptan n(%)	Zolmitriptan n(%)	Rizatriptan n(%)	Naratriptan n(%)
Nervous system disorders	42(25.6)	16(15.8)	22(24.2)	6(28.6)
General disorders and administration site conditions	15(9.1)	8(7.9)	3(3.3)	2(9.5)
Vascular disorders	14(8.5)	3(3.0)	2(2.2)	0(0)
Eye disorders	11(6.7)	4(4.0)	1(1.1)	0(0)
Musculoskeletal and connective tissue disorders	11(6.7)	9(8.9)	4(4.4)	1(4.8)
Respiratory, thoracic and mediastinal disorders	9(5.5)	14(13.9)	10(11.0)	2(9.5)
Investigations	8(4.9)	7(6.9)	2(2.2)	1(4.8)
Gastrointestinal disorders	7(4.3)	7(6.9)	5(5.5)	4(19.0)
Psychiatric disorders	7(4.3)	5(5.0)	8(8.8)	2(9.5)
Cardiac disorders	6(3.7)	6(5.9)	10(11.0)	0(0)
Skin and subcutaneous tissue disorders	6(3.7)	2(2.0)	3(3.3)	0(0)
Pregnancy, puerperium and perinatal conditions	5(3.0)	0(0)	1(1.1)	0(0)
Infections and infestations	4(2.4)	9(8.9)	3(3.3)	0(0)
Reproductive system and breast disorders	4(2.4)	0(0)	1(1.1)	0(0)
Endocrine disorders	3(1.8)	1(1.0)	0(0)	0(0)
Renal and urinary disorders	3(1.8)	1(1.0)	1(1.1)	2(9.5)
Blood and lymphatic system disorders	2(1.2)	0(0)	0(0)	0(0)
Ear and labyrinth disorders	2(1.2)	5(5.0)	4(4.4)	0(0)
Social circumstances	2(1.2)	0(0)	1(1.1)	0(0)
Congenital, familial and genetic disorders	1(0.6)	1(1.0)	1(1.1)	0(0)
Immune system disorders	1(0.6)	2(2.0)	5(5.5)	0(0)
Metabolism and nutrition disorders	1(0.6)	1(1.0)	1(1.1)	1(4.8)
Hepatobiliary disorders	0(0)	0(0)	2(2.2)	0(0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0(0)	0(0)	1(1.1)	0(0)

Comparison of SOCs

A comparative analysis was conducted to evaluate the AE signals associated with the four triptans. According to the FAERS database, sumatriptan exhibited the highest frequency of positive AE signals among the four triptans. A total of one AE was reported for all four drugs, namely reversible cerebral vasoconstriction syndrome, a disorder of the nervous system (Fig. 5). Consistent with the presence of adverse events in the drug insert. This comparison elucidates the interrelated nature of some of the AEs associated with these drugs, while also underscoring the distinctive attributes of each drug. It thus offers a comprehensive and nuanced perspective on their safety in clinical settings.

Discussion

The introduction of triptan medication has broadened the spectrum of potential migraine treatments, offering a greater array of options for clinicians and patients alike. In addition to evaluating the efficacy of these drugs, it is imperative to ensure their safety. This study explored the risk status of its AEs from the perspective of signalling risk by accessing triptan data from the FAERS database and performing signal mining. By undertaking a comparative and analytical examination of the AEs of sumatriptan, zolmitriptan, rizatriptan, and naratriptan as reported in the FAERS database, this study offers a comprehensive understanding of the similarities and differences in the safety profiles of these four drugs in common, novel, and rare AEs. In clinical practice, AEs associated with triptans affect multiple organ systems, including the neurological, gastrointestinal, and cardiac systems. Our data mining process identified all of the AEs listed in the drug's package insert. The four drugs share an AE, which is Reversible cerebral vasoconstriction syndrome.

The initial triptan developed by GlaxoSmithKline ® and introduced to the market in 1991 was sumatriptan (GR43175). While it demonstrated efficacy in the acute treatment of migraine, particularly when administered parenterally, the low oral bioavailability of sumatriptan prompted the development of a second generation of triptans [28]. In the present study, the highest number of AEs was reported for the first generation of

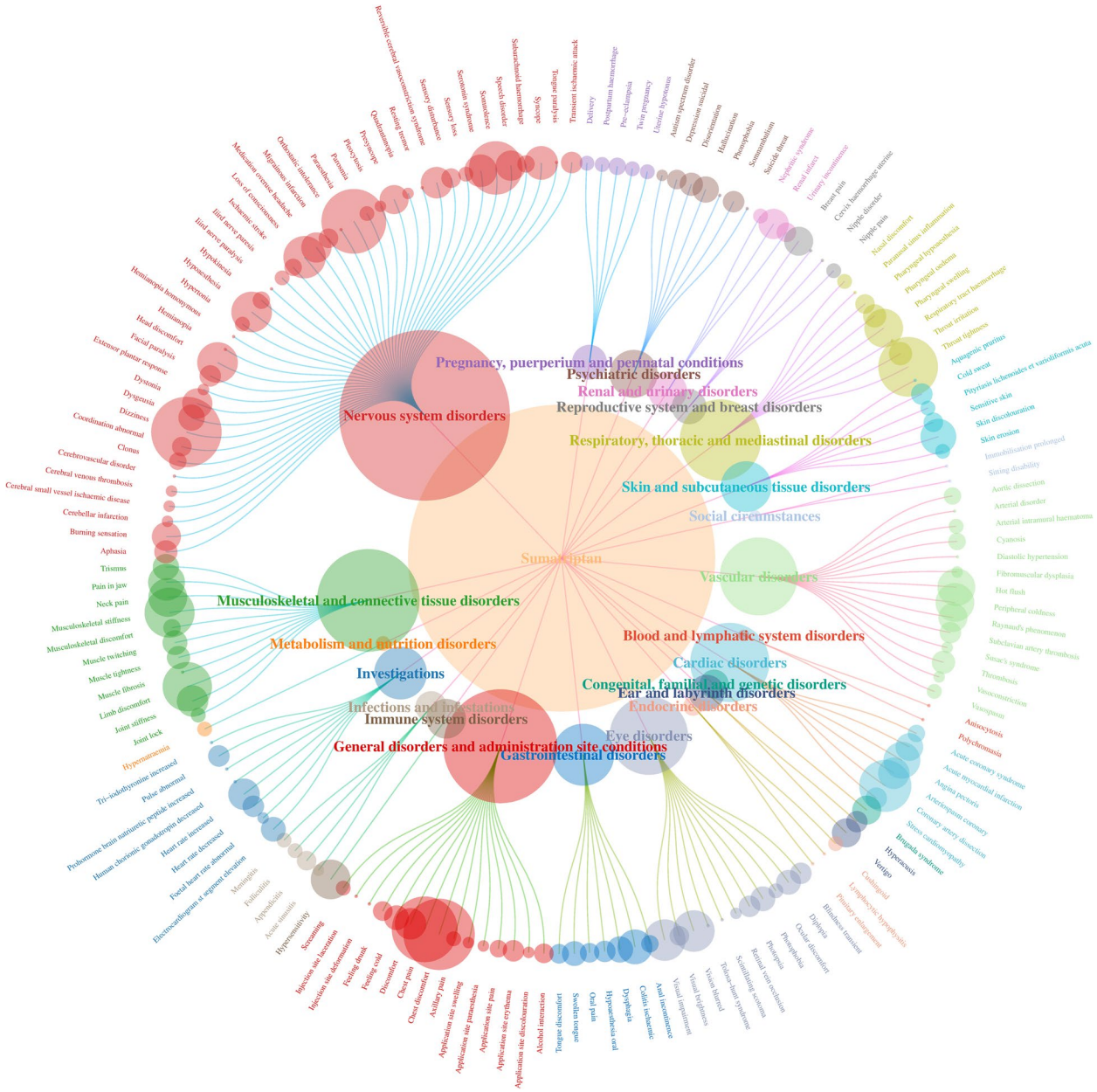

Fig. 3 Distribution network plot of AE signals in each SOC for the Sumatriptan. The root node represents the name of the drug and the number of AE signals, with the SOC in the inner ring and the AE signal name in the outer ring

sumatriptan. This may be attributed to the fact that it is the earliest triptans to be introduced on the market and therefore more widely used in clinical practice. With regard to age and gender, the data revealed a higher incidence of AEs in female patients. This finding may be attributable to the elevated prevalence of migraine in women, which may result in a greater utilization of triptans in women in clinical practice. This finding indicates that, in the future development of new drugs, consideration could be given to the creation of a new generation of drugs for different genders and age groups. For example, a formulation of the triptans class specifically targeting premenstrual migraine in women could be developed and could be combined with the mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) with a view to reducing the incidence of associated AEs.

In the course of our study, AEs associated with triptans were observed to affect multiple organ systems, including the nervous system and the heart, in actual clinical

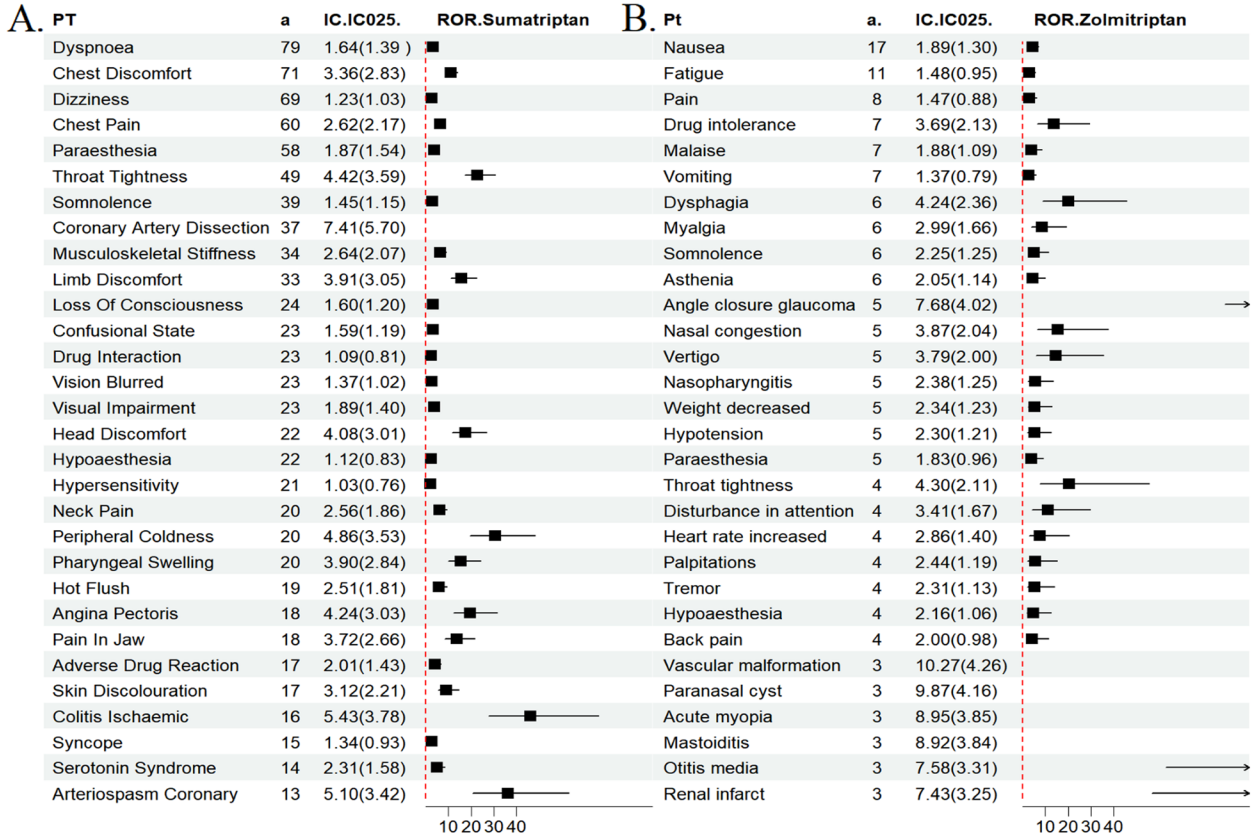

Fig. 4 Signal detection results of AE reports and ROR (95%CI)

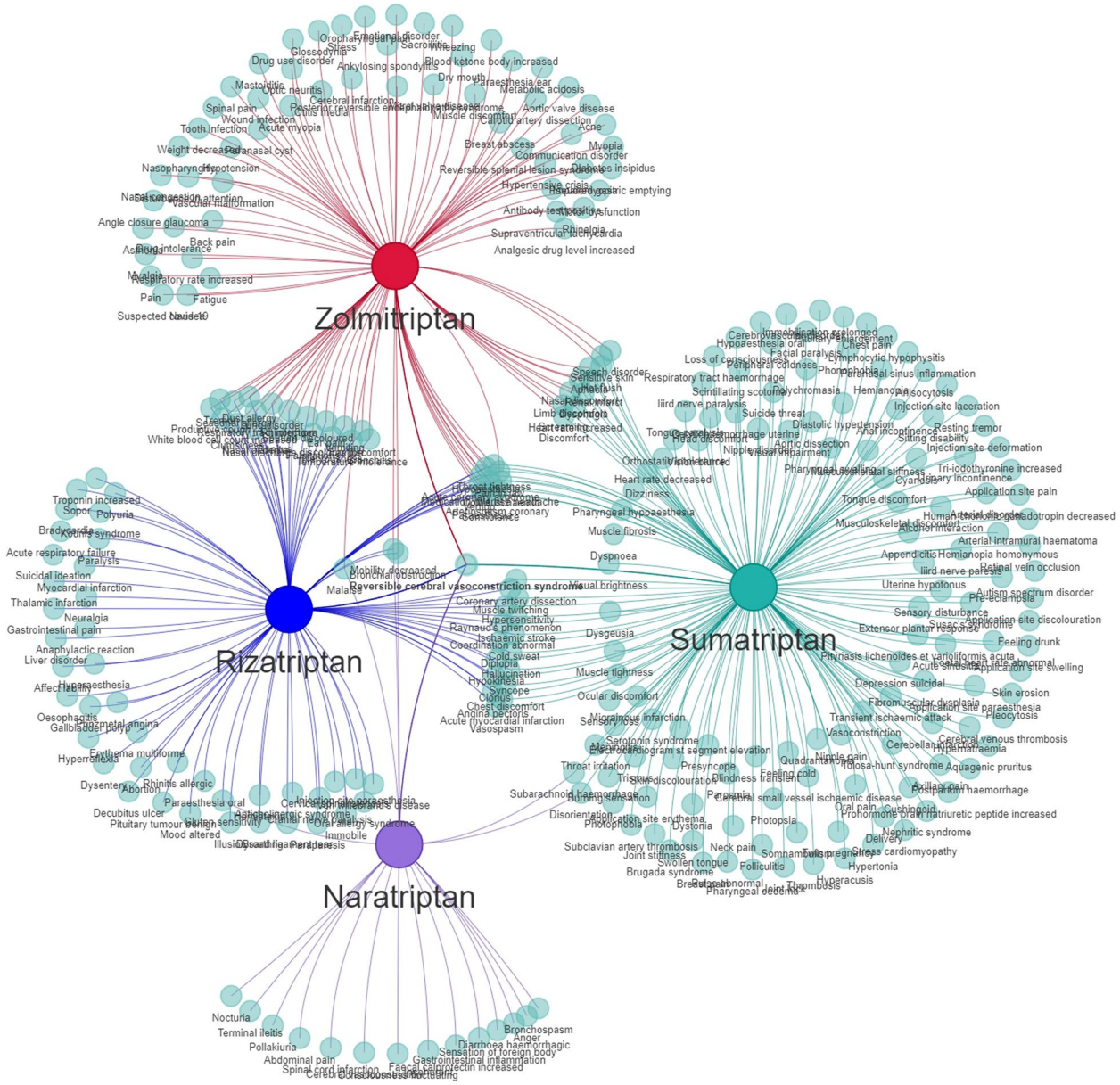

Fig. 5 Network Venn diagrams of PT-positive signals in the FAERS database for the four triptans

practice. In the context of cardiac disorders and cardiovascular disease AEs, clinical trials and drug inserts for triptans indicate that the use of this medication is contraindicated in patients with risk factors for cardiovascular disease and the cardiac system. These risk factors include, but are not limited to, the following: ischemic coronary artery disease (e.g., angina pectoris, history of myocardial infarction) and a history of stroke or transient ischemic attack [29–31]. Our study also confirms that sumatriptan may lead to adverse events such as Coronary artery dissection ($n=37$), Angina pectoris ($n=18$), Arteriospasm coronary ($n=13$), rizatriptan may lead to Myocardial infarction ($n=5$) and zolmitriptan may lead to Palpitations ($n=4$). The aforementioned data collectively indicate the presence of a potential risk factor for cardiac disease in the context of triptans utilized in actual clinical practice. Triptan has vasoconstrictive properties and exerts its pharmacological effects mainly by acting on the 5-HT receptor. The affinity for different subtypes of 5-HT receptors varies among the different triptan analogues. In the cerebral vasculature, some triptans selectively constrict dilated intracranial blood vessels, thereby

relieving migraine symptoms. However, in the peripheral vasculature, such as the coronary arteries, their effects are more complex [10, 32, 33]. Clinical trials and research reports have identified the potential effects of triptan on cardiac function. In a small number of cases, cardiovascular ischaemic events (myocardial infarction, cerebral vasoconstriction), as well as other symptoms including palpitations and arrhythmias, have been reported. However, the incidence of these events is relatively low [34–37]. It has been postulated that Tretinoin may also induce related cardiac adverse effects via its influence on neurotransmitter release and vascular endothelial function, among other mechanisms. Further investigation is required to elucidate the precise mechanism of action. The data presented herein underscore the potential risks associated with triptans in individuals with pre-existing cardiac disorders. Consequently, it is imperative that future drug development prioritise the creation of more selective and relevant analogues, with the aim of reducing vascular-related AEs.

Given the expression of 5-HT1B and 5-HT1D receptors in multiple regions of the central nervous system (CNS), it is reasonable to hypothesise that triptan may induce adverse central effects, which may depend on lipid solubility [38]. The present study identified nervous system disorders as the primary SOC category for four drugs in the FAERS database. Additionally, it was determined that the AE "reversible cerebral vasoconstriction syndrome," which is common to all four drugs, also belongs to the Nervous system disorders category. It is hypothesised that the lipid solubility of some triptans and the disruption of the blood-brain barrier during a migraine attack may facilitate the penetration of anti-migraine drugs into the CNS [39, 40]. It is particularly important in the future to update the new generation of tretinoin based on pharmacological mechanisms. A further avenue for investigation is the potential rational adjustment of the lipid solubility of the new generation of triptans, without compromising their pharmacological efficacy or pharmacokinetics, or whether 5-HT should be highly selected for the treatment of migraine through targeting.

We also observed that the first 30 most frequent and highest signal intensity detections for all four drugs involved gastrointestinal disorders. The AEs with the highest frequency associated with zolmitriptan, rizatriptan, and naratriptan medications are all classified as gastrointestinal disorders. It has been reported that triptans may cause gastrointestinal complications, including ischemic colitis, a finding that was also confirmed in our study [41]. Respiratory, thoracic and mediastinal disorders (dyspnoea, chest pain, etc.) had the first frequency of sumatriptan, which is consistent with AE reports from previous studies [40]. AEs for gastrointestinal disorders are a common occurrence in a diverse range of pharmaceutical agents employed for the management of pain, including NSAIDs such as ibuprofen and acetylsalicylic acid, as well as opioids [42, 43]. In clinical practice, a significant proportion of patients express concern that oral medications may cause damage to the gastrointestinal tract, which can lead to AEs such as nausea and vomiting. In the case of triptans for migraine, AEs on the gastrointestinal system have also been observed, which provides a valuable reference point for clinical use. It may be advisable for patients with digestive disorders to be administered drugs with a lesser propensity for side effects or the early development of new dosage forms that do not need to be absorbed through the gastrointestinal tract.

The results of a recent meta-analysis have demonstrated that four of the tretinoin analogues (sumatriptan, zolmitriptan, rizatriptan, and eletriptan) are more efficacious in the treatment of migraines than the recently marketed and more expensive drugs lasmiditan, rimegepant and ubrogepant. Consequently, these four tretinoin analogues should be considered as the drugs of choice for the treatment of migraines [44]. Previous studies have explored the adverse effects associated with gepants, which are used for the prophylactic and acute treatment of migraine, and which have a different mechanism of action than triptans. Researchers have also identified AEs related to the gastrointestinal system and have shown that it is more suitable for patients with a history of cardiovascular disease compared to triptans cardiovascular side effect risk, however comparative and real-world studies between triptans in recent years remain unexplored [45]. The safety and efficacy of migraine treatment are contingent upon the characteristics of the drug in question, as well as the patient's specific circumstances, including the use of multiple medications. Consequently, further investigation into the adverse effects associated with the triptans is currently a priority. Our study addresses a current gap in the literature by analysing AE signals at multiple levels. The findings can be used to inform treatment choices and facilitate informed decision-making between patients and clinicians. Future research should focus on a detailed characterisation of the specific mechanisms of action of 5-HT receptors in migraine and other related pain conditions. Additionally, efforts should be made to minimise potential side effects in response to current real-world adverse effects, and the development of more specific drugs to optimise migraine treatment strategies by precisely targeting therapy should be a priority.

Limitations

Limitations of this study include the fact that FAERS is a self-reporting database in the U.S., which has limitations such as incomplete reporting information and uncertainty about the causal relationship between reported

events and medications. Nevertheless, the results of this comprehensive data mining exercise offer guidance on the safe and rational use of medications. It is important to note that all signal detection results are only indicative of statistical associations. They do not determine prevalence or confirm causality. Consequently, future research should build on the AE signals identified in this paper and conduct further high-quality studies to elucidate the prevalence of these AEs in real-world use scenarios. Further evaluation is required to ascertain whether there are clear causal associations.

Conclusion

This study employed the FAERS database to examine the potential AEs of representative treprostinil analogues utilized for the treatment of migraine. Analyses have demonstrated that AE is present in a range of systems, including those pertaining to the cardiac, nervous, gastrointestinal, and musculoskeletal and connective tissue disorders. The clinical significance of this warrants careful consideration. It is recommended that future studies should aim to develop a new generation of highly selective analogues based on the possible mechanisms underlying the generation of these AEs, with a view to developing targeted therapies to reduce patient suffering.

Abbreviations

5-HT	5-Hydroxytryptamine
AEs	Adverse events
FDA	Food and Drug Administration
FAERS	U.S. Food and Drug Administration Adverse Event Reporting System
PRR	Proportional reporting ratio
ROR	Reporting odds ratio
BCPNN	Bayesian Confidence Propagation Neural Network
PT	Preferred terminology
SOC	System organ classification
NSAIDs	Non-steroidal anti-inflammatory drugs
CNS	Central nervous system

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-024-01913-0.

Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

In this study, WL: Data curation, Funding acquisition, Project administration, Resources, Investigation, Supervision, Writing review & editing. HH: Data curation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. CL: Conceptualization, Investigation, Visualization, Writing – original draft. QS and CL: Conceptualization, Formal analysis, Methodology, Project administration, Writing – review & editing. AL、YL and YZ: Formal analysis, Methodology, Visualization, Writing – review & editing. BF and PM: Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – original draft.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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