BMC Pharmacology and Toxicology

RESEARCH Open Access

Data mining in FAERS: association of newer-generation H1-antihistamines with nervous system disorders

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Abstract

Background H1-antihistamines are widely used to treat symptoms depending on histamine release in a variety of conditions. However, neurological adverse events have been reported in post-marketing surveillance studies and there are limited literatures comparing the neurological disorders associated with newer-generation H1-antihistamines from real-world datasets.

Aims We performed a comparative analysis of nervous system disorders and several newer-generation H1-antihistamines including: cetirizine, loratadine, levocetirizine, desloratadine and fexofenadine.

Methods Disproportionality analysis was used to identify the suspected drug neurological adverse events associated with H1-antihistamines of interest via the Food and Drug Administration Adverse Event Reporting System. The proportional reporting ratio (PRR), χ^2 (chi-square) and the reporting odds ratio (ROR) with 95% confidence interval (CI) were used to estimate the association.

Results AE reports of 43,815 cases from 2017 to 2021 were extracted from FAERS. The H1-antihistamines included in our study were associated with various neurological adverse events that could be classified into 12 aspects, containing 42 preferred terms. The majority of adverse event reports were concentrated at somnolence: cetirizine [$N = 1342$, ROR (95%CI) = 11.8 (11.2–12.5), PRR = 10.8, $\chi^2 = 11755.4$], levocetirizine [$N = 1276$, ROR(95%CI) = 28.5 (26.7–30.3), PRR = 22.7, $\chi^2 = 26218.4$], loratadine[$N = 516$, ROR(95%CI) = 4.6 (4.2-5.0), PRR = 4.4, $\chi^2 = 1378.1$], desloratadine [$N = 33$, ROR(95%CI) = 6.1 (4.3–8.6), PRR = 5.8, $\chi^2 = 131.9$], fexofenadine [$N = 498$, ROR(95%CI) = 5.0 (4.6–5.5), PRR = 4.8, $\chi^2 = 1519.0$].

Conclusion Neurological AEs associated with individual newer generation H1-antihistamines of interest varies a lot, whereas somnolence was the most common AE reports. Fexofenadine was highly associated with headaches. Sedative effects associated with levocetirizine and cetirizine should arouse more concern. Seizures significantly associated with levocetirizine and desloratadine were infrequently reported, further research is needed to avoid

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possible serious outcomes. Patients taking cetirizine probably have higher risk of dystonia and anticholinergic syndrome.

Keywords H1-antihistamines, Nervous system disorders, FAERS, Adverse effects

Introduction

The newer-generation H1-antihistamines constitute the first-line treatment for urticarial and allergic rhinitis with a better safety profile [1, 2]. Neurological side effects, such as sedation, are most frequently associated with H1-antihistamines, which might lead to life-threatening outcomes for patients [3]. A recent cohort study conducted in 63 Chinese pediatric patients showed that *no adverse event* was induced by cetirizine either in the recommended dosage group or the overdose group [4]. A human lactation study incuding 32 women indicated that the transfer of cetirizine and levocetirizine into breast milk is low [5] and it is *safe* in the breastfed infant [5, 6]. Fexofenadine, levocetirizine, and cetirizine are *recommended for up-dosing* with chronic spontaneous urticaria (Grade A recommendation) [1]. Overall objective tests have not shown clinically relevant differences in the central nervous system effects of levocetirizine, cetirizine and loratadine [2]. Conversely, neurological adverse effects, such as *sedation and impaired psychomotor* function, had been documented in literatures [2, 7, 8]. Cetirizine probably had higher risk of central nervous system side effects compared to other second generation H1-antihistamines [9]. An animal experiment demonstrated that cetirizine and loratadine at a dose of 50 mg/kg could markedly inhibit memory retrieval of the rats [10]. Cetirizine, levocetirizne, loratadine, desloratadine and fexofenadine are listed in the Anticholinergic Burden Scale as low potency anticholinergics which could deteriorate cognitive impairment, especially for the elderly [11]. Some other studies showed that levocetirizine and desloratadine probably had adverse effects on cognitive and psychomotor performance, whereas cetirizine and loratadine showed dose-ranging impairment [12]. However, fexofenadine was free from these side effects [13, 14], even in a higher dose [14]. Moreover, levocetirizine was more likely to cause drowsiness and sedation than desloratadine and fexofenading [13, 15]. A recent study revealed that cumulative dose of the second generation H1-antihistamine raised elevated dementia risk [16]. Several cases of cetirizine-induced *dystonic* reactions had been reported, and most of the patients were children [17–22]. Additionally, it can cause *oculogyric crisis*, mainly impacting the pediatric group [21, 23, 24]. An association was found between *stabbing headaches* and levecetirizine [25]. A relationship was observed between desloratadine and epilepsy in some cases [26]. The nervous system impairment might lead to a poor academic performance [27] and lower work efficiency, as well as decreased quality of life [12].

To the best of our knowledge, limited real-world study has been conducted to evaluate the association between neurological disorders and newer-generation H1-antihistamines. FAERS is the largest post-marketing safety surveillance database for all marketed drug and therapeutic biologic products [28], which could provide the regulatory agencies with more than 80% of potential adverse drug reaction signals [29]. We aimed to raise awareness of the nervous system disorders associated with using newer-generation H1-antihistamines.

Methods

Data source

This was a real-word study based on FDA Adverse Events Reporting System (FAERS). AE reports, medication quality complaints and medication error reports were submitted to FAERS spontaneously by pharmacists, physicians, health professionals, consumers, lawyers and manufacturers [30]. Data sets from FAERS include: demographic and administrative information, report sources, drug information, preferred terms coded for the AEs, patient outcomes, therapy periods, drug administration and deleted cases.

A primary suspected drug coded as "PS" may have one or two more AEs, and it may also include concomitant medications. Each AE might be submitted more than once by different reporters, thus duplicated reports were removed by case ID. A total of 6,900,469 cases from 2017 to 2021 were retrieved. We searched the generic and brand names of each drug identified as "PS" in the data processing. Dmographic characteristics such as sex, age, reactions and reporters' type were collected. Finally, 43,815 cases were included: cetirizine (n=13,560), levocetirizne (n=6111), loratadine (n=12,479), desloratadine (n=609), fexofenadine (n=11,056). Duplicated AE reports and the records with incorrect or erred inputs were excluded. 10,663 neurological AE reports associated with drugs of interest were selected for further study. Data management were performed using My SQL5·7.

Definition of neurological AEs

Terminology is stratified into five levels in the Medical Dictionary for Regulatory Activities (MedDRA): system organ class (SOC), high level group terms (HLGT), high level terms (HLT), preferred terms (PT), and low level terms (LLT). AEs are coded by PT in the MedDRA (version-25·0) vocabulary in FAERS [28]. Neurological AEs

Table 1 Fourfold table of measures of PRR and χ2

	Drug of interest	All other drugs in FAERS
AEs of interest	a	b
All other AEs	c	d

Table 2 Major algorithms of disproportional analysis

Test method	Equations	Criteria of a positive signal
PRR	PRR=[a/(a+c)]/[b/(b+d)]	N ≥ 3
		PRR ≥ 2
	$\chi 2=(ad-bc)^2(a+b+c+d)/(a+b)(c+d)(b+d)(a+c)$	χ2 ≥ 4
ROR	ROR = ad/bc	N ≥ 3
	$95\%CI=e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)\wedge0.5}$	ROR 95%CI lower limit > 1

were identified by using SOC "Nervous System Disorders (MedDRA code: 10029205)".

Statistical analysis

Disproportionality analysis was used to identify statistical associations between drugs and AEs. These methods have been frequently used to detect risk signals with high sensitivity and reliability, reducing biases [31, 32]. The proportional reporting ratio (PRR), χ2 (chi-square) and the reporting odds ratio (ROR) with 95% confidence interval (CI) were calculated to report the signal strength (Tables 1 and 2). In each case, a particular adverse event that is more likely to be induced by a particular drug will typically get a higher score [33]. A positive signal of disproportionality was defined as ROR at least one, PRR at least two, χ^2 at least four, and three or more cases [34]. Data management was performed using MySQL 5.7 and statistical analysis was conducted using Microsoft Excel 2016.

Results

Summary characteristics of all AE reports submitted to FAERS

The number of neurological AE reports is of concern. Olopatadine was excluded from the study as the neurological AE reports number was zero (Fig. 1).

Basic characteristics

A total of 43,815 cases were obtained during the study period. Majority of the cases were reported by comsumers for cetirizine, levocetirizine, loratadine and fexofenadine. Most cases were reported by physician for desloratadine (n = 178; 29·2%) (Table 3).

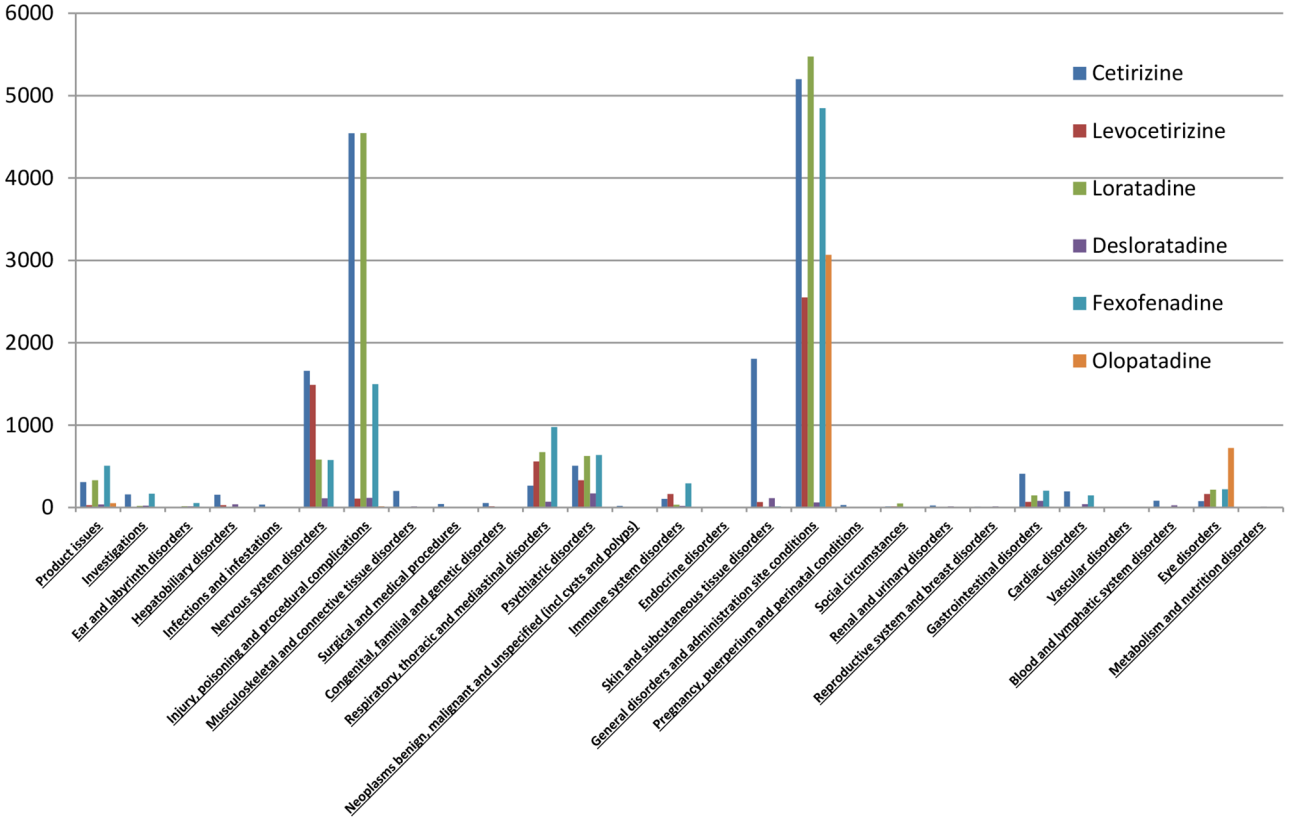

Fig. 1 Summary characteristics of all AE reports identified by SOC submitted to FAERS (x-axis: types of SOC associated with drugs of interest, y-axis: the number of AE reports)

Table 3 Demographic characteristics of AE reports submitted for H1-antihistamines of interest in FAERS

N(%)	Certirizine	Levocetirizine	Loratadine	Desloratadine	Fexofenadine
Variables					
Gender					
Female	6692(49·4%)	2396(39·2%)	6654(53·3%)	355(58·3%)	4556(41·2%)
Male	3392(25·0%)	869(14·2%)	3777(30·3%)	225(36·9%)	2188(19·8%)
Not Specified	3476(25·6%)	2846(46·6%)	2048(16·4%)	29(4·8%)	4312(39·0%)
Age					
0–18	1144(8·4%)	225(3·7%)	1562(12·5%)	103(16·9%)	346(3·1%)
19–65	3226(23·8%)	777(12·7%)	2438(19·5%)	253(41·5%)	1934(17·5%)
> 65	1616(11·9%)	530(8·7%)	2453(19·7%)	111(18·2%)	1809(16·4%)
Unknow	7574(55·9%)	4579(74·9%)	6026(48·3%)	142(23·3%)	6967(63·0%)
Reporters					
Consumers	11,074(81·7%)	5619(91·9%)	11,433(91·6%)	181(29·7%)	10,486(94·8%)
Physician	803(5·9%)	218(3·6%)	139(1·1%)	178(29·2%)	212(1·9%)
Health professionals	538(4·0%)	39(0·6%)	131(1·0%)	81(13·3%)	101(0·9%)
Pharmacists	275(2·0%)	176(2·9%)	51(0·4%)	45(7·4%)	125(1·1%)
Lawyers	2(0·0%)	0(0·0%)	2(0·0%)	0(0·0%)	1(0·0%)
Others	868(6·4%)	59(1·0%)	723(5·8%)	124(20·4%)	131(1·2%)
Total	13,560	6111	12,479	609	11,056

The newer-generation H1-antihistamines were associated with a series of neurological AEs defined by 42 PTs, which could be classified into 12 aspects: central nervous system vascular disorders, cranial nerve disorders (excl neoplasms), demyelinating disorders, headache, movement disorders (incl parkinsonism), mental impairment disorders, neurological disorders NEC, neurological disorders of the eye, neuromuscular disorders, peripheral neuropathies, seizures (incl subtypes), sleep disturbances (incl subtypes).There is variation in types and severity of neurological AEs across individual H1-antihistamines (Table 4).

Central nervous system vascular disorders, cranial nerve disorders (excl neoplasms), demyelinating disorders, neurological disorders of the eye, neuromuscular disorders, peripheral neuropathies in individual H1-antihistamines

Compared to other H1-antihistamines of interest, cetirizine was more likely to result in the emergency of positive signals in these aspects. Mild positive signals emerged in the context of lacunar infarction and transient ischaemic attack for levocetirizine and desloratadine respectively (Table 4).

Headache

Desloratadine tended to exhibit positive signals that emerged in migraine with aura, while others were more likely to result in sinus headache (Table 4).

Movement disorders (incl parkinsonism)

It was worth noting that significant positive signals emerged in the context of parkinsonism for desloratadine. Cetirizine tended to exhibit positive signals that emerged in psychomotor hyperactivity and dystonia. Positive signals were observed in the context of psychomotor hyperactivity for both loratadine and fexofenadine (Table 4).

Mental impairment disorders

Only desloratadine exhibited positive signals from this aspect (Table 4).

Neurological disorders NEC

Notably, strong positive signals were observed in the context of somnolence for all H1-anthistamines of interest, and the percentage of reports number is higher than 80% for individual H1-antihistamine. The calculations of PRR and $\chi 2$ are higher than 10 and 100,000 respectively for both levcetirizine and cetirizine (Table 4).

Positive signals were observed in the context of consciousness related AEs for levocetirizine and desloratadine. Significant positive signals were observed in regard to hyperpathia, hypercapnic coma and hyporesponsive to stimuli for cetirizine. Positive signals emerged in the coma, syncope, speech disorder and balance disorder for desloratadine (Table 4).

Seizures (incl subtypes)

Significant positive signals emerged in regard to febrile convulsion for levocetirizine and clonic convulsion for fexofenadine. Desloratadine tended to exhibit positive signals that emerged in epilepsy and seizure (Table 4).

Sleep disturbances (incl subtypes)

Levocetirizine is more likely to result in the emergency of positive signals in this aspect. Positive signals also

Table 4 Nervous system disorders associated with individual H1-antihistamines. (HLGT: high level group term, PT: preferred term,–: not a positive signal, n: total number of AE reports for individual drug)

HLGT	PT	Cetirizine (n = 1659)				Levocetirizine (n = 1488)				Loratadine (n = 582)				Desloratadine (n = 112)				Fexofenadine (n = 576)			
		N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2
Central nervous system vascular disorders	Carotid artery dissection	3	11.1(3.5–34.9)	11·1	27·0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Reversible cerebral vasoconstriction syndrome	11	8.2(4.5–14.9)	8·2	68·7	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cerebral vasoconstriction	3	6.3(2.0-19.7)	6·3	13·2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Subarachnoid haemorrhage	26	3.8(2.6–5.6)	3·8	53·1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Lacunar infarction	–	–	–	–	3	7.1(2.3–22.2)	7·1	15·7	–	–	–	–	–	–	–	–	–	–	–	–
	Transient ischaemic attack	–	–	–	–	–	–	–	–	–	–	–	–	5	7.0(2.9–16.8)	7·0	25·3	–	–	–	–
Cranial nerve disorders (excl neoplasms)	Facial paresis	7	3.2(1.5–6.7)	3·2	10·4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Demyelinating disorders	Demyelination	10	4.5(2.4–8.3)	4·5	26·5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Neurological disorders of the eye	Hemianopia homonymous	3	7.7(2.5–24.2)	7·7	17·3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Neuromuscular disorders	Anticholinergic syndrome	14	15.3(9.0-26.1)	15·3	181·5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Peripheral neuropathies	Guillain-Barre syndrome	7	2.5(1.2–5.3)	2·5	6·5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Headaches	Sinus headache	7	2.8(1.3–5.8)	2·8	7·8	9	7.9(4.1–15.3)	7·9	53·7	8	3.4(1.7–6.9)	3·4	13·6	–	–	–	–	15	7.3(4.4–12.1)	7·3	80·4
	Migraine with aura	–	–	–	–	–	–	–	–	–	–	–	–	3	35.0(11.2–109.0)	34·8	98·3	–	–	–	–
Movement disorders (incl parkinsonism)	Psychomotor hyperactivity	50	5.3(4.0–7.0)	5·2	170·0	–	–	–	–	28	3.2(2.2–4.6)	3·2	41·5	–	–	–	–	23	3.0(2.0-4.4)	2·9	29·4
	Dystonia	28	3.8(2.6–5.5)	3·8	57·1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Parkinsonism	–	–	–	–	–	–	–	–	–	–	–	–	5	20.8(8.6–50.2)	20·6	93·3	–	–	–	–
Mental impairment disorders	Amnestic disorder	–	–	–	–	–	–	–	–	–	–	–	–	4	256.3(94.8-692.6)	254·6	988·2	–	–	–	–
	Amnesia	–	–	–	–	–	–	–	–	–	–	–	–	5	2.9(1.2-7.0)	2·9	6·2	–	–	–	–

Table 4 (continued)

HLGT	PT	Cetirizine (n = 1659)				Levocetirizine (n = 1488)				Loratadine (n = 582)				Desloratadine (n = 112)				Fexofenadine (n = 576)			
		N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2
Neurological disorders NEC	Hyperpathia	6	160.5(64.1-401.8)	160·4	722·3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Hypercapnic coma	6	52.6(22.7-121.8)	52·5	274·9	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Somnolence	1342	11.8(11.2–12.5)	10·8	11,755·4	1276	28.5(26.7–30.3)	22·7	26,218·4	516	4.6(4.2-5.0)	4·4	1378·1	33	6.1(4.3–8.6)	5·8	131·9	498	5.0(4.6–5.5)	4·8	1519·0
	Hyporesponsive to stimuli	9	10.2(5.3–19.8)	10·2	73·4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Psychomotor skills impaired	10	5.3(2.8–9.8)	5·3	34·1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Formication	17	4.1(2.6–6.6)	4·1	39·5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Sedation	39	2.8(2.0-3.8)	2·8	43·5	16	2.5(1.5–4.1)	2·5	14·5	–	–	–	–	–	–	–	–	–	–	–	–
	Loss of consciousness	–		–	–	76	2.3(1.8–2.9)	2·3	55·2	–	–	–	–	–	–	–	–	–	–	–	–
	Altered state of consciousness	–	–	–	–	16	2.8(1.6–4.4)	2·7	16·7	–	–	–	–	3	5.0(1.6–15.7)	5·0	9·7	–	–	–	–
	Depressed level of consciousness	–	–	–	–	–	–	–	–	–	–	–	–	6	5.7(2.5–12.7)	5·6	22·9	–	–	–	–
	Head discomfort	–	–	–	–	–	–	–	–	30	2.6(1.8–3.7)	2·6	29·0	–	–	–	–	36	3.5(2.5–4.9)	3·5	64·0
	Coma	–	–	–	–	–	–	–	–	–	–	–	–	6	4.5-(2.0–10.0)	4·4	16·0	–	–	–	–
	Ageusia	–	–	–	–	–	–	–	–	–	–	–	–	3	4.5(1.4–13.9)	4·4	8·0	–	–	–	–
	Syncope	–	–	–	–	–	–	–	–	–	–	–	–	12	4.5(2.5–7.9)	4·4	31·8	–	–	–	–
	Speech disorder	–	–	–	–	–	–	–	–	–	–	–	–	5	3.5(1.5–8.5)	3·5	8·9	–	–	–	–
	Balance disorder	–	–	–	–	–	–	–	–	–	–	–	–	7	2.9(1.3–6.1)	2·9	8·5	–	–	–	–
Seizures (incl subtypes)	Tonic clonic movements	3	3.6(1.2–11.1)	3·6	5·5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Febrile convulsion	–	–	–	–	17	71.2(43.6-116.4)	71·0	1104·3	–	–	–	–	–	–	–	–	–	–	–	–
	Epilepsy	–	–	–	–	–	–	–	–	–	–	–	–	4	4.9(1.8–13.0)	4·9	12·2	–	–	–	–
	Seizure	–	–	–	–	–	–	–	–	–	–	–	–	11	2.6(1.4–4.6)	2·5	10·1	–	–	–	–
	Clonic convulsion	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4	12.8(4.8–34.4)	12·8	42·6

Table 4 (continued)

HLGT	PT	Cetirizine (n = 1659)				Levocetirizine (n = 1488)				Loratadine (n = 582)				Desloratadine (n = 112)				Fexofenadine (n = 576)			
		N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2	N	ROR (95% CI)	PRR	χ2
Sleep disturbances (incl subtypes)	Sleep paralysis	–	–		–	4	9.8(3.7–26.2)	9·8	31·3	–	–	–	–	–	–	–	–	–	–	–	–
	Hypersomnia	58	3.2(2.5–4.2)	3·2	87·4	68	8.4(6.6–10.7)	8·3	437·0	–	–	–	–	–	–	–	–	–	–	–	–
	Sleep deficit	–	–	–	–	3	4.6(1.5–14.3)	4·6	8·4	–	–	–	–	–	–	–	–	–	–	–	–

emerged in the context of hypersomnia for cetirizine (Table 4).

Discussion

The newer second-generation antihistamines can still cross the blood-brain barrier especially when taken in excess, though moderately, compared to the first-generation agents [35]. Neurological AEs associated with newer generation H1-antihistamines have been studied for long time. However, most of the literatures were limited by small samples or insufficient evidence. We performed a systematic and comprehensive analysis to detect signals of neurological AEs related to suspected H1-antihistamines of interest via the largest spontaneously AE reporting system, FAERS. We aimed to support the post-marketing safety surveillance. Due to the limitations of this database, such as "self-reporting" pattern that information in reports has not been verified. Thereby, some potential confounders could not be avoided. Moreover, the imperfection of disproportional analysis might lead to false positive signals. Thus, more studies should be provided to evaluate the association in further researches.

Cetirizine and the central nervous system vascular disorders

More significant signals were found in this aspect for cetirizine. Notably, reversible cerebral vasoconstriction syndrome (RCVS) and subarachnoid haemorrhage (SAH) had greater number of AE reports. RCVS is one of the main causes of severe and sudden-onset headaches [36, 37]. As one of the adverse reactions induced by cetirizine [38, 39], headaches are prone to impact children [20, 39]. SAH is a fatal cerebrovascular disease characterized by high mortality and very poor prognosis [40]. However, very few studies had been conducted to describe the association. This novel finding might provide physicians with significant insights.

Fexofenadine/levocetirizine and headache

Significant positive signals emerged in the context of sinus headache for fexofenadine and levocetirizine. In addition, fexofenadine was also associated with head discomfort in this study. Headache has wide range of clinical presentations and different etiologies [41]. A recent review demonstrated that headache is the most common AE associated with fexofenadine, while sinus headache was rarely reported [42]. Actually, most cases of sinus headache were misdiagnosed as either primary headaches or migraines in clinical practice [41], and migraine headache is a common clinical symptom of allergic rhinitis [43]. Our results might provide evidence for deeper research.

Levocetirzine induced headaches were infrequently reported [44]. One case report offered an unusual

conclusion that a pediatric patient suffered possibly levocetirizine-induced stabbing headaches [25]. Given the limited evidence and lower number of AE reports, this result should be evaluated more elaborately.

Cetirizine and anticholinergic syndrome

One study showed that there was no significant difference between second generation H1-antihistamine treatments for anticholinergic side effects [9]. However, as they can moderately pass through the blood-brain barrier [35], some of them, such as cetirizine, levocetirizne, loratadine, desloratadine and fexofenadine, are listed in the Anticholinergic Burden Scale as low potency anticholinergics which could deteriorate cognitive impairment [11]. Our results suggested that cetirizine had higher correlation with anticholinergic syndrome. Though, AEs of anticholinergic syndrome induced by second generation antihistamines are infrequently reported, the toxicity is possible for cetirizine when taken an over dosage [45]. Our advice is that a conservative dose of cetirizine might be necessary to avoid anticholinergic adverse effect.

Levocetirizine/cetirizine and sedation/somnolence/hypersomnia

In our study, all H1-antihistamines were highly associated with somnolence, compared with other neurological AEs. Notably, levocetirizine and cetirizine ranked top two, which is consistent with previous study [20]. Meanwhile, significant positive signals were also emeged in the context of sedation and hypersomnia for both of them, suggesting a high-risk of sedative effect for (levo) cetirizine. Moreover, levocetirizine was associated with sleep paralysis. Coincidence with our results, some literatures showed that levocetirizine was more likely to cause somnolence and sedation, compared to desloratadine and fexofenadine [15, 42, 44, 46]. Another literature indicated that in comparison with loratadine and fexofenadine, cetirizine was associated with increased somnolence and less motivation [7]. Moreover, compared to other second generation H1-antihistamines, sedative effects impacted slightest on subjects taking fexofenadine according to some currently available evidence [42]. Conversely, a review demonstrated that sedative effects of levocetirizine had no difference with other second-generation antihistamines [47]. The reason might be related to different administration time, as morning administration of levocetirizine was probably associated with greater risk of heightened somnolence [48].

Though most of the newer-generation H1-antihistamines have moderate sedative effects, physicians should be warned to consider more when prescribing (levo)cetirizine that might lead to serious adverse outcomes for patients [3].

Levocetirizine and the consciousness

In our study, another noteworthy finding was that loss of consciousness and altered state of consciousness were both associated with levocetirizine. To the best of our knowledge, very few evidence could be provided to explain the association. Over doses of sedative medication can cause loss of consciousness [49, 50]. Though, levocetirizine has moderate sedative effects, it does not produce deleterious effect on psychometric and cognitive functions [51]. Nevertheless, according to our results, levocetirizine was highly associated with sedative effects, such as somnolence, hyposomia, sleep paralysis and sedation. This study might initiate a brand new perspective on the sedative effect associated with levocetirizne.

Cetirizine and movement disorders

A novel finding was that the association between cetirizine and psychomotor hyperactivity was highly significant. Psychomotor hyperactivity is mostly found among people with ADHD (attention deficit hyperactivity disorder) [52]. Allergic rhinitis and ADHD might have joint mechanism and represent a comorbidity which connects the nervous system to the immune system [53]. Therefore, we presumed that some of these patients taking cetirizine probably had ADHD. Further researches are needed to analysis the association.

Hyporesponsive to stimuli and psychomotor skills impaired were both associated with cetirizine in our study. Consistent with this result, one study showed that cetirizine had slight negative impact on psychomotor performance and memory scanning speed, inducing marginal effect on cognition [54]. And available evidence on psychomotor function favors fexofenadine [42].

Dystonia associated with using cetirizine has been frequently reported [17–24]. The mechanisms are probably that cetirizine has weak dopamine receptor (D2 receptor) blockade property in the striatum of the basal ganglia and causes interference with postsynaptic dopamine release, thus may inhibit striatal γ-amino butyric acid (GABA) output and causes excitation in the primary motor cortex [55].

Desloratadine and mental impairement disorder

Our results indicated that desloratadine was associated with amnestic disorder and amnesia. Memory deficits associated with desloratadine had been reported but rarely [56]. The impact of H1-antihistamines on memory impairement remains unclear. We hope more elaborate studies should be conducted to examine the results.

Desloratadine/Levocetirizine and seizures

In our study, very strong positive signals were observed in the context of febrile convulsion for levocetirizine, and the reports number was 17. An animal experiment

demonstrated that toxic dosage of antihistamines could result in generalized seizure [57]. The possibility of febrile seizures in infants received levocetirizine treatment was of concern [58]. Epidemiological studies have linked prolonged febrile seizures with the development of epilepsy [59]. Nocturnal frontal lobe epilepsy is related to the impaired function of cholinergic receptors [60]. Mechanisms of drug induced febrile seizures are associated with anticholinergic medication [59]. We hope more studies should be conducted to explain this association in more detail.

Our results suggested that desloratadine was associated with seizure and epilepsy. Seizures associated with using desloratadine had been reported [26, 56]. A cohort study found a greater incidence rate of seizure during desloratadine exposed periods when compared to unexposed periods among individuals younger than 20, but no difference was observed in adults [61].

Physicians should be concerned regarding seizures in patients using levocetirizine or desloratadine, especially when treating patients with epilepsy.

Conclusion

Neurological AEs associated with individual newer generation H1-antihistamines of interest varies a lot, whereas somnolence was the most common AE reports. Fexofenadine was highly associated with headaches. Sedative effects associated with levocetirizine and cetirizine should arouse more concern. Seizures significantly associated with levocetirizine and desloratadine were infrequently reported, further research is needed to avoid possible serious outcomes. Patients taking cetirizine probably have higher risk of dystonia and anticholinergic syndrome.

Limitations

Continuous maintenance is necessary for the PT update of MedDRA. The ROR, PRR and χ^2 can only reflect the results of data obtained from self-reported AEs, as well as physician-reported AEs, which would be influenced by underreporting and reporting biases. The association between a drug and an AE in FAERS could not prove causality, and more typical clinical cases were needed to confirm the correlation [62]. The spontaneous reporting of AEs from FAERS is not valid, only reports from health providers are assured [63], **which is another potential confounder**. Most of our conclusions were assumptions, and resources of relevant ADR case reports and studies were limited to prove some of them from existing literatures of high quality. As ROR and PRR have the ability of high sensitivity, false positive errors might occur. However, this study might provide evidence for deeper research in the precise medicine approach.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-024-00822-x.

Supplementary Material 1

Acknowledgements

We thank Zhenyan Bo and Kai Tao for providing English language editing help.

Author contributions

L.L.Z. and W.P.H. contributed to the study conception and design. L.C. and W.P.H. analyzed the data and drafted the manuscript. L.H.L. and Z.L.N. critically revised the manuscript. G.J. and F.C.H. were involved in interpretation of data, and approved the final manuscript.

Funding

This study was supported by the National Natural Science Foundation of China (No. 82071686). The funding was used for data analysis.

Data availability

The data analyzed in the current study is publicly available, and supplementary information could be required from contacting with Li Chen (Email: chenl_hxey@scu.edu.cn).

Declarations

Ethical approval

The authors state that no ethical approval was needed.

Submission declaration

We confirm that this study is original and not being considered for publication elsewhere. It has not been posted to a preprint server as well.

Competing interests

The authors declare no competing interests.

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Received: 18 July 2023 / Accepted: 4 December 2024
Published online: 18 December 2024

References

1. Podder I, Dhabal A, Chakraborty SS. Efficacy and safety of Up-dosed second-generation antihistamines in uncontrolled chronic spontaneous urticaria: a review. J Clin Aesthet Dermatol. 2023;16(3):44–50.
2. Powell RJ, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. Clin Exp Allergy. 2007;37(5):631–50.
3. Izumi N, et al. Analysis of disease-dependent sedative profiles of H(1)-antihistamines by large-scale surveillance using the visual analog scale. Methods Find Exp Clin Pharmacol. 2008;30(3):225–30.

4. Liu W, et al. Model-based exploration of the rationality of off-label use of cetirizine in Chinese pediatric patients: a prospective cohort study. Front Pharmacol. 2024;15:1322788.
5. Nordeng H, et al. Transfer of cetirizine/levocetirizine into human breast milk and estimation of drug exposure to infants through breastfeeding: a human lactation study from the ConcePTION project. Basic Clin Pharmacol Toxicol. 2024;134(1):153–64.
6. Levocetirizine. Drugs and Lactation Database (LactMed®). National Institute of Child Health and Human Development: Bethesda (MD); 2006.
7. Ozdemir PG, et al. Assessment of the effects of antihistamine drugs on mood, sleep quality, sleepiness, and dream anxiety. Int J Psychiatry Clin Pract. 2014;18(3):161–8.
8. Carson S, Lee N, Thakurta S. 2010, Drug class reviews, in drug class review: Newer Antihistamines: Final Report Update 2. Oregon Health & Science University. Copyright © 2010 by Oregon Health & Science University, Portland, Oregon 97239. All rights reserved.: Portland (OR).
9. Chaichan W, et al. Comparative safety profiles of individual second-generation H1-Antihistamines for the treatment of Chronic Urticaria: a systematic review and network Meta-analysis of Randomized controlled trials. J Allergy Clin Immunol Pract. 2023;11(8):2365–81.
10. Nishiga M, et al. Effects of second-generation histamine H1 receptor antagonists on the active avoidance response in rats. Clin Exp Pharmacol Physiol. 2003;30(1–2):60–3.
11. Ramos H et al. CRIDECO anticholinergic load scale: an updated anticholinergic Burden Scale. Comparison with the ACB Scale in Spanish individuals with subjective memory complaints. J Pers Med 2022;12(2).
12. Isomura T, et al. Central nervous system effects of the second-generation antihistamines marketed in Japan–review of inter-drug differences using the proportional impairment ratio (PIR). PLoS ONE. 2014;9(12):e114336.
13. Shamil KS, et al. Old versus new antihistamines: effects on cognition and psychomotor functions. J Family Med Prim Care. 2022;11(10):5909–17.
14. Hindmarch I, Shamsi Z, Kimber S. An evaluation of the effects of high-dose fexofenadine on the central nervous system: a double-blind, placebo-controlled study in healthy volunteers. Clin Exp Allergy. 2002;32(1):133–9.
15. Layton D, et al. Comparison of the risk of drowsiness and sedation between levocetirizine and desloratadine: a prescription-event monitoring study in England. Drug Saf. 2006;29(10):897–909.
16. Su CH, et al. Cumulative dose effects of H1 antihistamine use on the risk of dementia in patients with allergic Rhinitis. J Allergy Clin Immunol Pract 2024.
17. Yılmaz-Topa Ö, et al. Cetirizine and albendazole induced dystonia in a child. Turk J Pediatr. 2015;57(4):407–8.
18. Esen I, et al. Cetirizine-induced dystonic reaction in a 6-year-old boy. Pediatr Emerg Care. 2008;24(9):627–8.
19. Rajput A, Baerg K. Cetirizine-induced dystonic movements. Neurology. 2006;66(1):143–4.
20. Naqvi A, Patel P, Gerriets V. Cetirizine, in StatPearls. StatPearls Publishing. 2024. Copyright © 2024, StatPearls Publishing LLC.: Treasure Island (FL) ineligible companies. Disclosure: Preeti Patel declares no relevant financial relationships with ineligible companies. Disclosure: Valerie Gerriets declares no relevant financial relationships with ineligible companies.
21. Bawany FI, et al. Cetirizine: an antihistamine associated with dystonia and oculogyric crises. J Pak Med Assoc. 2013;63(9):1216.
22. Pellecchia MT, et al. Drug induced oromandibular dystonia: a case related to prolonged use of cetirizine. Parkinsonism Relat Disord. 2014;20(5):566–7.
23. Fraunfelder FW, Fraunfelder FT. Oculogyric crisis in patients taking cetirizine. Am J Ophthalmol. 2004;137(2):355–7.
24. Fraunfelder FW, Fraunfelder FT. Adverse ocular drug reactions recently identified by the national registry of drug-induced ocular side effects. Ophthalmology. 2004;111(7):1275–9.
25. Biedroł A, Kacikski M, Skowronek-Bała B. Stabbing headache in an 8-year-old girl: primary or drug induced headache? Pediatrics. 2014;133(4):e1068–71.
26. Cerminara C, et al. Seizures induced by desloratadine, a second-generation antihistamine: clinical observations. Neuropediatrics. 2013;44(4):222–4.
27. Walker S, et al. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. J Allergy Clin Immunol. 2007;120(2):381–7.
28. FDA. FDA Adverse Event Reporting System (FAERS). 2017; https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers
29. Al-Azzawi F, et al. Developing an Artificial Intelligence-Guided Signal Detection in the Food and Drug Administration adverse event reporting System (FAERS): a proof-of-Concept Study using Galcanezumab and simulated data. Drug Saf. 2023;46(8):743–51.
30. FDA. https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers
31. Duggirala HJ, et al. Use of data mining at the Food and Drug Administration. J Am Med Inform Assoc. 2015;23(2):428–34.
32. Chen JJ, et al. Data mining for adverse drug reaction signals of daptomycin based on real-world data: a disproportionality analysis of the US Food and Drug Administration adverse event reporting system. Int J Clin Pharm. 2022;44(6):1351–60.
33. Zorych I, et al. Disproportionality methods for pharmacovigilance in longitudinal observational databases. Stat Methods Med Res. 2013;22(1):39–56.
34. Shen B. Healthcare+and+Big+Data+Management.pdf 2017:1028.
35. Specht T, Seifert R. Repurposing of H(1)-receptor antagonists (levo)cetirizine, (des)loratadine, and fexofenadine as a case study for systematic analysis of trials on clinicaltrials.gov using semi-automated processes with custom-coded software. Naunyn Schmiedebergs Arch Pharmacol. 2024;397(5):2995–3018.
36. Schmidbauer ML, et al. [Drug-induced reversible cerebral vasoconstriction syndrome: Ustekinumab as possible trigger?]. Schmerz. 2020;34(4):350–3.
37. Nesheiwat O, Al-Khoury L. Reversible cerebral vasoconstriction syndromes, in StatPearls. StatPearls Publishing. 2024. Copyright © 2024, StatPearls Publishing LLC.: Treasure Island (FL) ineligible companies. Disclosure: Lama Al-Khoury declares no relevant financial relationships with ineligible companies.
38. Sinha VV, et al. Comparative study of efficacy and safety of cetirizine and bilastine in patients of chronic spontaneous urticaria: Open-label, randomized, parallel-group study. Perspect Clin Res. 2023;14(4):180–6.
39. Nayak AS, et al. Randomized, placebo-controlled study of cetirizine and loratadine in children with seasonal allergic rhinitis. Allergy Asthma Proc. 2017;38(3):222–30.
40. Tan J, et al. Therapeutic potential of natural compounds in Subarachnoid Haemorrhage. Neuroscience. 2024;546:118–42.
41. Bernichi JV, et al. Rhinogenic and sinus headache - literature review. Am J Otolaryngol. 2021;42(6):103113.
42. Huang CZ, et al. Antihistamine effects and safety of fexofenadine: a systematic review and Meta-analysis of randomized controlled trials. BMC Pharmacol Toxicol. 2019;20(1):72.
43. Bernstein JA, et al. Allergic Rhinitis: Rev Jama. 2024;331(10):866–77.
44. Iriarte Sotés P, et al. Efficacy and safety of Up-dosing antihistamines in chronic spontaneous urticaria: a systematic review of the literature. J Investig Allergol Clin Immunol. 2021;31(4):282–91.
45. Renko A, et al. Unintentional cetirizine overdose causing anticholinergic syndrome. Am J Emerg Med. 2022;52:270. e1-270.e3.
46. Devillier P, Roche N, Faisy C. Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine: a comparative review. Clin Pharmacokinet. 2008;47(4):217–30.
47. Snidvongs K, et al. Sedative effects of Levocetirizine: a systematic review and meta-analysis of randomized controlled studies. Drugs. 2017;77(2):175–86.
48. Chen X, et al. Efficacy and safety of bilastine vs. levocetirizine for the treatment of chronic idiopathic urticaria: a multicenter, double-blind, double-dummy, phase III, non-inferiority, randomized clinical trial. Chin Med J (Engl). 2024;137(12):1480–2.
49. National Clinical Guideline C. National institute for health and clinical excellence: Guidance, in Sedation in children and young people: Sedation for diagnostic and therapeutic procedures in children and young people. Royal College of Physicians (UK). 2010. Copyright © 2010, National Clinical Guideline Centre.: London.
50. Li Y, Picheca L. CADTH Rapid Response reports, in Target-controlled infusion with propofol and remifentanil for moderate procedural sedation in medicine and dentistry: a review of clinical effectiveness, Cost-Effectiveness, and guidelines. Canadian Agency for Drugs and Technologies in Health. 2020. Copyright © 2020 Canadian Agency for Drugs and Technologies in Health.: Ottawa (ON).
51. Gandon JM, Allain H. Lack of effect of single and repeated doses of levocetirizine, a new antihistamine drug, on cognitive and psychomotor functions in healthy volunteers. Br J Clin Pharmacol. 2002;54(1):51–8.
52. *Conditions that are associated with Psychomotor hyperactivity*. https://www.ehealthme.com/symptom/psychomotor-hyperactivity/a/1/
53. Melamed I, Heffron M. Attention deficit disorder and allergic rhinitis: are they related? J Immunol Res. 2016;2016:p1596828.
54. van Ruitenbeek P, Vermeeren A, Riedel WJ. Histamine H1 receptor antagonist cetirizine impairs working memory processing speed, but not episodic memory. Br J Pharmacol. 2010;161(2):456–66.

55. Sharawat IK, Dawman L. Acute Focal Dystonia after a single dose of oral cetirizine in a 9-Year-old boy. Pediatr Emerg Care. 2019;35(2):e30–1.
56. Han X, et al. Epileptic convulsions probably induced by desloratadine: a case report. Eur J Hosp Pharm. 2023;30(4):e17.
57. Wills B, Erickson T. Chemically induced seizures. Clin Lab Med. 2006;26(1):185–209. ix.
58. Singh-Franco D, et al. Levocetirizine for the treatment of allergic rhinitis and chronic idiopathic urticaria in adults and children. Clin Ther. 2009;31(8):1664–87.
59. Dubé CM, Brewster AL, Baram TZ. Febrile seizures: mechanisms and relationship to epilepsy. Brain Dev. 2009;31(5):366–71.
60. Kim JB. Channelopathies Korean J Pediatr. 2014;57(1):1–18.
61. Ersbøll AK, et al. Desloratadine exposure and incidence of seizure: a nordic post-authorization Safety Study using a new-user Cohort Study Design, 2001–2015. Drug Saf. 2021;44(11):1231–42.
62. Teng C, et al. Torsades De Pointes and QT prolongation associations with antibiotics: a Pharmacovigilance Study of the FDA adverse event reporting system. Int J Med Sci. 2019;16(7):1018–22.
63. Nevin RL, Leoutsakos JM. Identification of a syndrome class of neuropsychiatric adverse reactions to Mefloquine from Latent Class modeling of FDA adverse event reporting System Data. Drugs R D. 2017;17(1):199–210.

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