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Neuropsychiatric side reactions of leukotriene receptor antagonist, antihistamine, and inhaled corticosteroid: A real-world analysis of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS)

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ABSTRACT

Background: There are limited real-world studies on the differences in leukotriene receptor antagonists (LTRA), H1-antihistamines (H1-AH), and inhaled corticosteroids (ICS) associated neuropsychiatric events. In this study, we aimed to analyze the characteristics of drug associated neuropsychiatric events, and compare the differences among different drug categories.

Methods: Disproportionality analysis and Bayesian analysis were used in data mining to identify suspected neuropsychiatric events associated with LTRA, H1-AH, and ICS based on the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) from January 2004 to September 2020. Demographic information, time interval to onset, and death rates of LTRA, H1-AH, and ICS-associated neuropsychiatric events were also analyzed.

Results: A total of 9475 neuropsychiatric events were identified. The number of neuropsychiatric events related to LTRA, H1-AH, and ICS were 5201 (54.89%), 3226 (34.05%), and 1048 (11.06%), respectively. LTRA related neuropsychiatric events were more common in patients aged 4–6 years (18.66%). H1-AH and ICS related neuropsychiatric events were more common in patients aged 18–44 years (29.92%) and older than 65 years (30.60%), respectively. Montelukast was highly associated with neuropsychiatric events, with a high reporting odds ratio (ROR). Most neuropsychiatric symptoms occurred within the first 10 days after drug initiation (78.63% for LTRA, 91.39% for H1-AH, and 84.07% for ICS). The death rate due to neuropsychiatric events of first generation H1-AH was significantly higher than that of LTRA and ICS ($p < 0.001$).

Conclusions: LTRA associated neuropsychiatric events reported in FAERS were most frequent in 4 to 6-year-old children. Most reported cases occurred within the first 10 days after drug initiation.

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The second generation H1-AH was relatively safe for neuropsychiatric events compared with the first generation. The fatality rate due to first generation H1-AH associated neuropsychiatric events was higher than that of LTRA and ICS. More attention should be paid to specific patients treated with LTRA and H1-AH.

Keywords: Neuropsychiatric event, Leukotriene receptor antagonist, Antihistamine, Inhaled corticosteroid

INTRODUCTION

The H1-antihistamines (H1-AH), leukotriene receptor antagonists (LTRA), and inhaled corticosteroids (ICS) are commonly used in patients with atopic diseases, including allergic rhinitis (AR), allergic asthma, or both.[1,2] The global strategy for asthma management and prevention of the Global Initiative for Asthma (GINA) recommends ICS or the ICS-long-acting beta$_2$-agonist (LABA) as the preferred daily controller medication for patients with asthma, with LTRA as other options.[3] Local side effects of ICS include oropharyngeal candidiasis and growth suppression, especially in children;[4,5] thus, LTRA is favored in children with asthma. However, due to cases reported by post marketing surveillance and several studies,[6–9] the United States Food and Drug Administration (FDA) has issued warnings about the risk of neuropsychiatric side effects related to the use of montelukast. Since then, more attention has been paid to LTRA associated neuropsychiatric events. In March 2020, the FDA announced that montelukast (Singulair) required a boxed warning about serious mental health side effects. In fact, both H1-AH and ICS have also been associated with neuropsychiatric adverse reactions.[10–12] These 2 drugs are commonly used in patients with atopic diseases. However, few pharmacovigilance studies have analyzed the neuropsychiatric events related to the use of these drugs in real-world clinical practice. In this study, we aimed to analyze the reports of neuropsychiatric adverse reactions related to LTRA, H1-AH, and ICS, and compare the differences among the different drug categories. This study was based on the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).

METHODS

Data source

A retrospective pharmacovigilance study was conducted based on the FAERS database from January 2004 to September 2020. The FAERS database is a public, voluntary, spontaneous reporting system (SRS). It includes information about adverse drug events and medication error reports submitted by health professionals, patients, and manufacturers from both the United States of America (USA) and other regions of the world. The FAERS data files contained 7 types of datasets. The datasets included patient demographic and administrative information (DEMO), drug information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), therapy start dates and end dates for reported drugs (THER), and indications for drug administration (INDI).

In total, 14 970 649 reports were acquired from the FAERS database, and duplicated records were removed according to the FDA recommendations. The latest FDA_DT (date FDA received case) was selected when the CASEIDs (number for identifying a FAERS case) were the same. The higher PRIMARYID (unique number for identifying a FAERS report) was chosen when the CASEID and FDA_DT were the same. A total of 12 552 899 reports were obtained (Fig. 1). This study was approved by the institutional review board (IRB) of Peking Union Medical College Hospital (S-K1699).

Adverse event and drug identification

Neuropsychiatric symptoms were taken from the REAC files according to the Medical Dictionary for

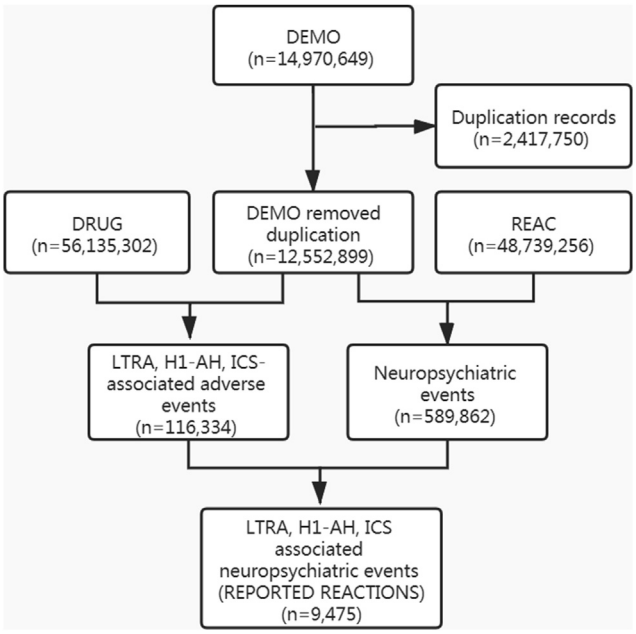

Fig. 1 Flowchart of the selection of cases of LTRA, H1-AH, ICS-associated neuropsychiatric events from the Food and Drug Administration Adverse Event Reporting System database

Regulatory Activities (MedDRA, version 22.1) at the Preferred Term level. The following terms were considered as associated with neuropsychiatric symptoms, especially in the scenario when LTRA, H1-AH, and ICS were administered: "anxiety (10002855)", "agitation (10001497)", "attention deficit disorder (10001497)", "cognitive disorder (10057668)", "disturbance in attention (10013496)", "learning disability (10024092)", "depression (10012378)", "irritability (10022998)", "impulse-control disorder (10061215)", "anger (10002368)", "aggression (10001488)", "sleep disorder (10040984)", "suicidal behavior (10065607)", "suicidal ideation (10042458)", "suicidal intention (10068557)", "behavior disorder (10004207)", "autism spectrum disorder (10063844)", "hallucination (10019063)".

We selected the generic and brand names for LTRA, H1-AH, and ICS, using IBM Micromedex as the dictionary during the data mining process (Table 1).

Data mining

Based on the basic principles of the Bayesian analysis and non-proportional analysis, the reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network, and multi-item gamma Poisson shrinker algorithms were used to investigate the association between the drugs and the selected adverse events. The equations and criteria for each of the 4 algorithms are listed in Table 2.[13-20] Correlations between the neuropsychiatric symptoms and different kinds of drugs were compared. The specific kind of drug was identified as "primary suspect" in the ROLE_COD (Code for the drug's reported role in event) field of the DRUG files.

We further analyzed the time to onset of the neuropsychiatric symptoms for the different kinds of drugs. This was defined as the interval between the EVENT_DT (adverse event onset date) and the START_DT (start date of the drugs administration). Records with incorrect entries or incorrect inputs (EVETN_DT earlier than START_DT) were excluded.

In addition, reports of fatal events induced by neuropsychiatric adverse drug events were summarized. The mortality rate was analyzed by dividing the number of fatal events by the total number of neuropsychiatric reactions due to the drugs.

Statistical analysis

Descriptive analysis was performed to summarize the demographic features of the patients from the FAERS database. The onset times of the drug-associated neuropsychiatric symptoms among different kinds of drugs were compared using non-parametric tests (the Mann-Whitney *U* test for dichotomous variables and the Kruskal-Wallis test for more than 2 subgroups of respondents). Pearson's chi-squared test or Fisher's exact test was used to compare the death rates among different kinds of drugs. $p < 0.05$ with 95% confidence intervals was considered to be statistically significant. All data mining and statistical analyses were performed using SPSS (version 16.0, SPSS Inc, Chicago, IL, USA).

RESULTS

Demographic characteristics

In total, 589 862 adverse events related to LTRA, H1-AH, and ICS were documented in the FAERS database dated from January 2004 to September 2020, of which 9475 reports were related to neuropsychiatric events. The age and

Generic name	Brand name
LTRA	
Montelukast	Montelukast sodium, Montelukast sodium tablets, Nra-montelukast, Q-montelukast, M-montelukast, Singulair
Zafirlukast	Accolate, Accolate tab 20 mg
Zileuton	Zyflo, Zyflo CR
H1-AH	
Cetirizine	Quzyttir, Reactine 20 mg tablet, Rhinaris relief, Zerviate, Zyrtec, Zyrtec af
Levocetirizine	Levocetirizine dihydrochloride, Xyzal
Chlorpheniramine	Chlorpheniramine maleate injection usp, Chlortripolon inj 10 mg/ml
Dexchlorpheniramine	
Diphenhydramine	Benadryl, Benadryl inj.50 mg/ml, Dicopanol, Diphenhydramine Hcl inj usp 50 mg/ml, Diphenhydramine Hcl injection usp, Diphenhydramine hydrochloride injection, Diphenhydramine hydrochloride injection usp, Diphenist 50 mg/ml, Scheinpharm diphenhydramine inj.50 mg/ml
Desloratadine	Aerius, Clarinex, Clarinex reditabs, Desloratadine teva, Neoclarityn
Fexofenadine	Allegra, Fexofenadine hydrochloride
Ketotifen	Zaditen, Zaditen-DPS 1 mg/ml
Loratadine	
ICS	
Budesonide	Pulmicort flexhaler, Pulmicort nebuamp, Pulmicort respules, Pulmicort turbuhaler
Fluticasone	Fluticasone furoate, Arnuity ellipta, Fluticasone propionate, Aermony respiclick, Armonair digihaler, Armonair respiclick, Flovent, Flovent Diskus, Flovent hfa, Flovent inhalers-Aem inh-orl
Mometasone	Mometasone furoate, Asmanex, Asmanex HFA, Asmanex twisthaler
Beclometasone Dipropionate	Beclodisk-Pwr inh, Beclodisk-PWR, Becloforte, Becloforte inhaler-Aem inh, Beclomethasone dipropionate oral inhaler, Beclovent-Aem, Beclovent rotacaps-inh, Beclovent rotacaps, Qvar, Qvar redihaler, Vanceril Aem

Table 1. Summary of Food and Drug Administration-approved leukotriene receptor antagonist (LTRA), H1-antihistamine (H1-AH) and inhaled corticosteroid (ICS). *LTRA: leukotriene receptor antagonist, H1-AH: H1-antihistamine, ICS: inhaled corticosteroid*

gender of the patients who experienced neuropsychiatric events are summarized in Table 3. More than half of the events were reported in North America, and then Europe. LTRA related events were more common in men, while H1-AH and ICS related events were more common in women. Anxiety was the most common type of neuropsychiatric event reported (2865 reports, 30.24%), followed by depression (2625 reports, 27.70%) and aggression (2010 reports, 21.21%) (Supplemental Table 1).

The LTRA related events reported increased until it peaked in 2008, while there was a gradual increase for the H1-AH and ICS related events reported from 2004 to 2020. All the 3 categories of drugs had a greater increase of neuropsychiatric events in 2020 than in 2004 ($p < 0.001$). Excluding reports with unspecified age, LTRA related

Algorithms	Equation*	Criteria
Reporting odds ratio (ROR)	$ROR = (a/b)/(c/d)$	95% CI > 1, N ≥ 2
	$95\%\ CI = e^{\ln(ROR)\pm 1.96(1/a+1/b+1/c+1/d)^{0.5}}$	
Proportional reporting ratio (PRR)	$PRR = (a/(a+c))/(b/(b+d))$	PRR≥2, $\chi^2 \geq 4$, N ≥ 3
	$\chi^2 = \Sigma((O\text{-}E)2/E)$; (O = a, $E = (a+b)(a+c)/(a+b+c+d)$)	
Bayesian confidence propagation neural network (BCPNN)	$IC = \log_2 a(a+b+c+d)/((a+c)(a+b))$	IC025 > 0
	$IC025 = e^{\ln(IC)-1.96(1/a+1/b+1/c+1/d)^{0.5}}$	
Multi-item gamma Poisson shrinker (MGPS)	$EBGM = a(a+b+c+d)/((a+c)(a+b))$	EBGM05 > 2, N > 0
	$EBGM05 = e^{\ln(EBGM)-1.64(1/a+1/b+1/c+1/d)^{0.5}}$	

Table 2. Summary of major algorithms used for signal detection. **a: number of reports containing both the suspect drug and the suspect adverse drug reaction. b: number of reports containing the suspect adverse drug reaction with other medications (except the drug of interest). c: number of reports containing the suspect drug with other adverse drug reactions (except the event of interest). d: number of reports containing other medications and other adverse drug reactions. Abbreviations: CI, confidence interval; N, the number of co-occurrences; χ^2, chi-squared; IC, information component; IC025, the lower limit of the 95% two-sided CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower 90% one-sided CI of EBGM*

neuropsychiatric events were more common in patients aged 4–6 years (18.66%). The H1-AH and ICS related neuropsychiatric events were more common in patients aged 18–44 years and older than 65 years, respectively. For neuropsychiatric events occurred before 1 year old, H1-AH accounted for the most (68.42%), while LTRA and ICS accounted for 15.79% and 15.79%, respectively. For events occurred between 1 and 17 years of age, LTRA accounted for the most. In adults (after 18 years of age), H1-AH accounted for the most again. Percentage of each kind of drug associated neuropsychiatric events reported in each age group was significantly different ($p = 0.004$) (Table 3).

Disproportionality analysis and Bayesian analysis

Neuropsychiatric events were screened for all the drugs, depending on the criteria for the 4 algorithms (Table 4). Among all drugs, Montelukast was considered to have a high relationship with neuropsychiatric events, with the highest ROR, PRR, and empirical Bayesian geometric mean (EBGM). Among the H1-AH drugs, chlorpheniramine had the highest ROR and had a high association with neuropsychiatric events. Of the ICS drugs, Mometasone showed a relatively weaker relationship with neuropsychiatric events, with a low ROR. The association between different drugs and different kinds of neuropsychiatric events is shown in Supplemental Table 2.

Time interval between drug initiation and neuropsychiatric symptoms

Most neuropsychiatric symptoms occurred within the first 30 days after drug initiation. Nearly half (49.77%) of the events of LTRA, 83.24% of the events associated with H1-AH, and 74.59% of the ICS events occurred within the first 30 days. There was a small second peak in events at 1–5 years after drug initiation (Fig. 2). Further analysis of the first 30-day time interval showed that most neuropsychiatric symptoms occurred within 10 days after drug initiation (78.63% for LTRA, 91.39% for H1-AH, and 84.07% for ICS).

The mean time to onset of neuropsychiatric events among different kinds of drugs was significantly different (Kruskal-Wallis test, $p < 0.001$). The median time from drug initiation to onset of neuropsychiatric events of LTRA, H1-AH, and ICS was 31 (interquartile range (IQR) 1–306) days, 1 (IQR 0–9) days, and 3 (IQR 0–31) days, respectively.

Characteristics	Total number of neuropsychiatric events (9,475)	Reports (n, %)		
		LTRA (5,201, 54.89%)	H1-AH (3,226, 34.05%)	ICS (1,048, 11.06%)
Reporting region				
North America	6503 (100)	3546 (54.53)	2088 (32.11)	869 (13.36)
Europe	2484 (100)	1430 (57.57)	940 (37.84)	114 (4.59)
Asia	144 (100)	47 (32.64)	71 (49.31)	26 (18.06)
Oceania	122 (100)	99 (81.15)	16 (13.11)	7 (5.74)
South America	41 (100)	14 (34.15)	17 (41.46)	10 (24.39)
Africa	10 (100)	6 (60.00)	4 (40.00)	0 (0)
Unspecified	171 (100)	59 (34.50)	90 (52.63)	22 (12.87)
Reporting year				
2004	114 (1.20)	30 (0.58)	72 (2.23)	12 (1.15)
2005	107 (1.13)	25 (0.48)	63 (1.95)	19 (1.81)
2006	147 (1.55)	29 (0.56)	93 (2.88)	25 (2.39)
2007	177 (1.87)	42 (0.81)	74 (2.29)	61 (5.82)
2008	1289 (13.60)	1040 (20.00)	183 (5.67)	66 (6.30)
2009	617 (6.51)	443 (8.52)	117 (3.63)	57 (5.44)
2010	490 (5.17)	322 (6.19)	129 (4.00)	39 (3.72)
2011	357 (3.77)	193 (3.71)	112 (3.47)	52 (4.96)
2012	359 (3.79)	170 (3.27)	110 (3.41)	79 (7.54)
2013	711 (7.50)	520 (10.00)	142 (4.40)	49 (4.68)
2014	442 (4.66)	171 (3.29)	191 (5.92)	80 (7.63)
2015	473 (4.99)	148 (2.85)	263 (8.15)	62 (5.92)
2016	563 (5.94)	194 (3.73)	308 (9.55)	61 (5.82)
2017	703 (7.42)	287 (5.52)	347 (10.76)	69 (6.58)
2018	853 (9.00)	404 (7.77)	336 (10.42)	113 (10.78)
2019	1078 (11.38)	606 (11.65)	377 (11.69)	95 (9.06)
2020	963 (10.16)	556 (10.69)	300 (9.30)	107 (10.21)
2020 annualized	1284 (13.11)	741 (13.76)	400 (12.03)	143 (13.19)
Unspecified	32 (0.34)	21 (0.40)	9 (0.28)	2 (0.19)
Gender of patients				
Male	3968/8626 (46.00)	2539/4871 (52.12)	1032/2754 (37.47)	397/1001 (39.66)
Female	4658/8626 (54.00)	2332/4871 (47.88)	1722/2754 (62.53)	604/1001 (60.34)
Unknown or missing	849/9475 (8.96)	330/5201 (6.34)	472/3226 (14.63)	47/1048 (4.48)
Age groups (years)				
0y	19/7226 (0.26)	3/4238 (0.07)	13/2243 (0.58)	3/745 (0.40)
1-3y	666/7226 (9.22)	450/4238 (10.62)	149/2243 (6.64)	67/745 (8.99)
4-6y	1012/7226 (14.00)	791/4238 (18.66)	140/2243 (6.24)	81/745 (10.87)
7-9y	897/7226 (12.41)	726/4238 (17.13)	123/2243 (5.48)	48/745 (6.44)

(continued)

Characteristics	Total number of neuropsychiatric events (9,475)	Reports (n, %)		
		LTRA (5,201, 54.89%)	H1-AH (3,226, 34.05%)	ICS (1,048, 11.06%)
10-12y	491/7226 (6.79)	393/4238 (9.27)	67/2243 (2.99)	31/745 (4.16)
13-17y	659/7226 (9.12)	446/4238 (10.52)	195/2243 (8.69)	18/745 (2.42)
18-44y	1420/7226 (19.65)	658/4238 (15.53)	671/2243 (29.92)	91/745 (12.21)
45-64y	1264/7226 (17.49)	573/4238 (13.52)	513/2243 (22.87)	178/745 (23.89)
≥65y	798/7226 (11.04)	198/4238 (4.67)	372/2243 (16.58)	228/745 (30.60)
Unknown or missing	2249/9475 (23.74)	963/5201 (18.52)	983/3226 (30.47)	303/1048 (28.91)

Table 3. (Continued) Demographic characteristics of patients with drug-associated neuropsychiatric adverse drug reactions sourced from the FAERS database (January 2004 to September 2020). *LTRA: leukotriene receptor antagonist, H1-AH: H1-antihistamine, ICS: inhaled corticosteroid*

Death rate due to LTRA, H1-AH, and ICS-associated neuropsychiatric events

We also analyzed the death rate due to the adverse neuropsychiatric events associated with different kinds of drugs to evaluate prognosis. The number of deaths associated with LTRA, first generation H1-AH, second generation H1-AH, and ICS due to neuropsychiatric adverse events was 69 (1.54%), 76 (11.86%), 16 (1.13%), and 7 (1.21%), respectively. Death rate of first generation H1-AH was significantly higher than that of LTRA ($p < 0.001$), and ICS ($p < 0.001$). However, no difference in the death rate between LTRA and ICS was observed ($p = 0.72$) (Fig. 3). Death in patients with depression accounted for the majority of deaths ($n = 77$) when each type of neuropsychiatric event was analyzed (Supplemental Table 1).

DISCUSSION

Drugs belonging to LTRA, H1-AH, and ICS are most commonly used in patients with atopic diseases. The association between LTRA and neuropsychiatric adverse effects has attracted increasing attention. In this study, we compared the neuropsychiatric events after the use of LTRA, H1-AH, and ICS based on the FAERS pharmacovigilance database.

In this study, we found that there was a peak of LTRA associated neuropsychiatric events in 2008. The FDA updated the product labeling in 2008 to include information about neuropsychiatric events reported with the application of montelukast. This might have influenced the subsequent reporting rate of neuropsychiatric events because of increased awareness,[21] and may explain why the peak occurred in 2008. The high paroxysmal age for neuropsychiatric events was different due to different drug categories. The onset of LTRA associated neuropsychiatric events was most frequent in 4 to 6-year old patients. In a retrospective cohort study of 1-to 17-year-old children initiated on montelukast, neuropsychiatric adverse drug reactions were observed. The median age was 5 (3–8) years,[22] which was similar to our study. In a real-world setting, some doctors may prefer montelukast over ICS when treating children with asthma. This is because many parents are afraid of the potential growth-related adverse events associated with ICS, which would explain the increased number of neuropsychiatric events reported in children aged 4–6 years. Children were observed to be overrepresented with neuropsychiatric events compared with adults, which was similar to another study on montelukast associated adverse reaction reports.[6] Some studies have found that neuropsychiatric adverse drug reactions can impair the quality of life in children with asthma.[23] Therefore, children especially preschool children should be paid more attention to the occurrence of neuropsychiatric symptoms.

Drug	Number of neuropsychiatric events (n)	ROR (95% two-sided CI)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
LTRA					
Montelukast	5171	10.35 (10.00,10.70)	7.21 (28,742.37)	2.84 (2.74)	7.15 (6.95)
Zafirlukast	19	1.38 (0.87,2.20)	1.36 (1.87)	0.44 (0.28)	1.36 (0.92)
Zileuton	11	1.66 (0.90,3.08)	1.61 (2.70)	0.69 (0.37)	1.61 (0.97)
H1-AH					
Chlorpheniramine	84	4.35 (3.43,5.50)	3.76 (178.21)	1.91 (1.51)	3.76 (3.08)
Desloratadine	208	2.65 (2.29,3.06)	2.46 (188.25)	1.30 (1.12)	2.46 (2.18)
Diphenhydramine	591	1.43 (1.31,1.55)	1.40 (70.67)	0.48 (0.45)	1.40 (1.30)
Loratadine	339	1.22 (1.09,1.36)	1.21 (12.57)	0.27 (0.24)	1.21 (1.10)
Cetirizine	1163	1.11 (1.05,1.18)	1.11 (12.20)	0.14 (0.14)	1.11 (1.05)
Dexchlorpheniramine	2	4.51 (0.97,20.86)	3.87 (4.47)	1.95 (0.42)	3.87 (1.07)
Levocetirizine	244	0.97 (0.86,1.11)	0.98 (0.15)	−0.04 (/)	0.98 (0.88)
Ketotifen	13	0.58 (0.34,1.01)	0.59 (3.76)	−0.75 (/)	0.59 (0.38)
Fexofenadine	582	0.56 (0.51,0.60)	0.57 (200.58)	−0.82 (/)	0.57 (0.53)
ICS					
Beclometasone Dipropionate	118	1.01 (0.84,1.22)	1.01 (0.01)	0.01 (0.01)	1.01 (0.87)
Budesonide	389	0.90 (0.81,1.00)	0.90 (4.21)	−0.15 (/)	0.90 (0.83)
Fluticasone	447	0.60 (0.55,0.66)	0.61 (113.04)	−0.70 (/)	0.62 (0.57)
Mometasone	94	0.31 (0.26,0.39)	0.33 (138.16)	−1.62 (/)	0.33 (0.27)

Table 4. Association of different drugs with neuropsychiatric events. *ROR: reporting odds ratio; CI: confidence interval; PRR: proportional reporting ratio; χ^2: chi-squared; IC: information component; IC025: the lower limit of the 95% two-sided CI of the IC; EBGM: empirical Bayesian geometric mean; EBGM05: the lower 90% one-sided CI of EBGM*

We also observed that most LTRA related neuropsychiatric events (78.63%) occurred within the first 10 days after drug initiation. In a retrospective cohort study of 106 children, the median day from drug initiation to the onset of neuropsychiatric adverse drug reactions was 7 (IQR 2–14) days.[22] Some studies have suggested that sleep disorders, agitation, nervousness, and psychotic disorders develop within hours to a few days, while depression and suicidal behavior occur within months or years of treatment.[6] This suggests us to frequently observe for neuropsychiatric symptoms in the first 7–14 days after drug initiation, and after even a longer time for special events. However, another study found no positive association between LTRA and suicide outcomes (especially at the population level). At the individual level, there was insufficient evidence to disprove the association.[24]

However, few reports on H1-AH related neuropsychiatric events have been reported in the

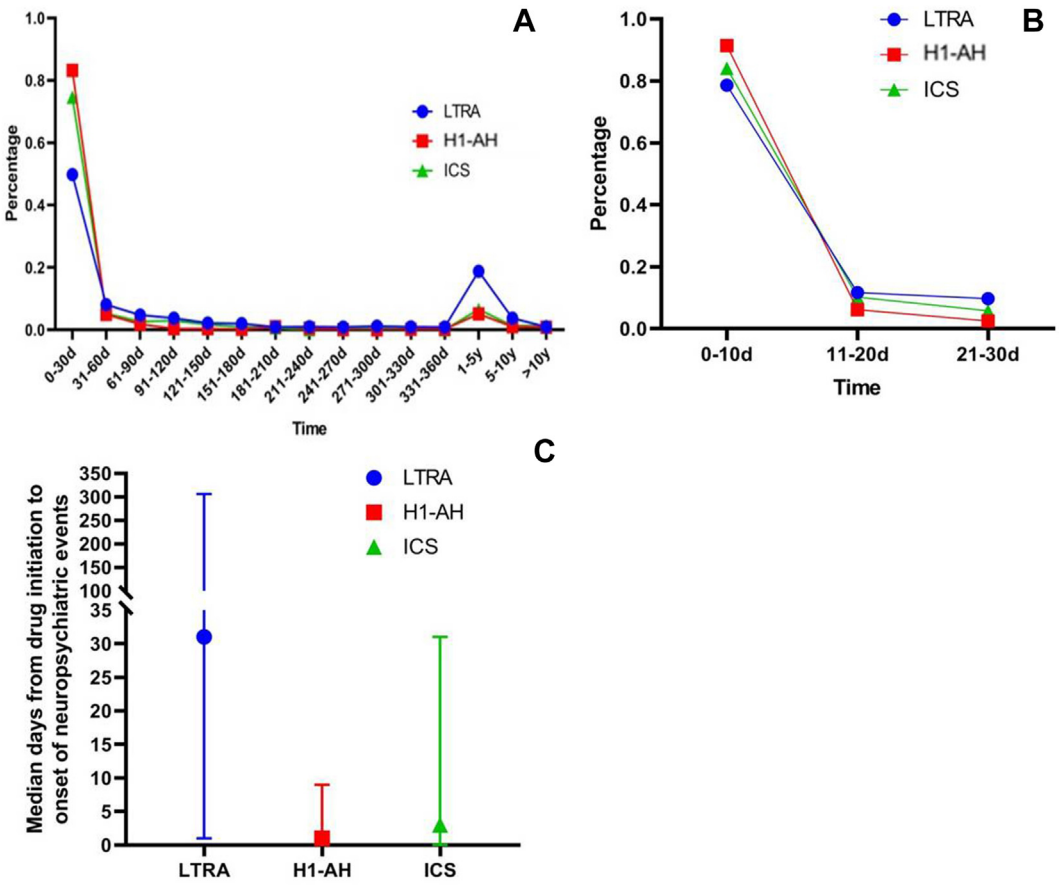

Fig. 2 Time interval between drug initiation and neuropsychiatric event. A&B. Percentage of each category of drug in different time interval between drug initiation and neuropsychiatric event. C. The median days from drug initiation to onset of neuropsychiatric event of each category of drug

literature. Some studies reported severe cardiac events, such as torsade de pointes, with H1-AH treatment.[25] We observed that 34.10% of neuropsychiatric events were related to H1-AH in the real world FAERS pharmacovigilance database. The H1-AH associated neuropsychiatric

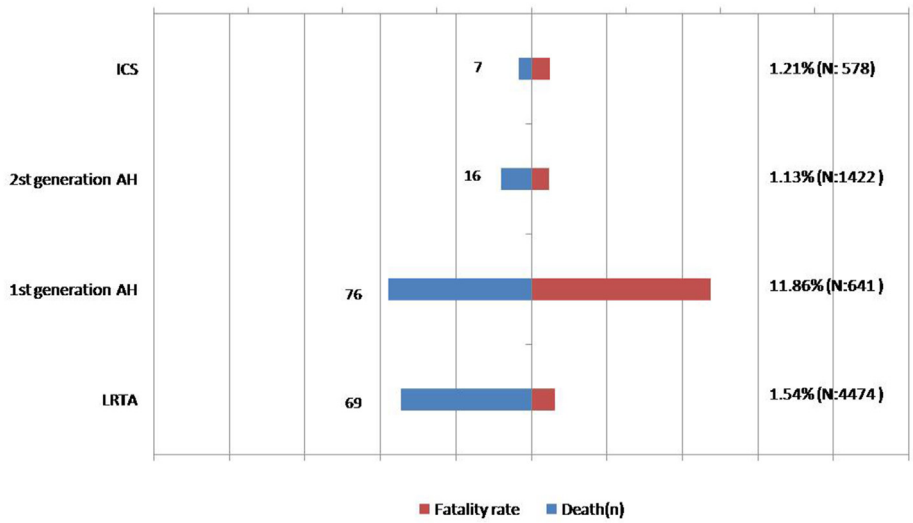

Fig. 3 Fatality rate due to different categories of drugs associated neuropsychiatric events. N: Death related neuropsychiatric adverse events reported

events were more frequent than the other 2 drug types, especially in infants less than 1 year of age and patients older than 18 years. This reminded us to be concerned about the H1-AH associated with neuropsychiatric events. These events were more common in the first 30 days after treatment initiation, and especially in the first 10 days. Therefore, patients should be observed frequently during this time interval.

We observed that ICS accounted for 11.05% of all the neuropsychiatric events reported, with a relatively lower association than LTRA. In a study of reported Individual Case Safety Reports concerning Swedish children (<18 years old) and psychiatric adverse reactions, montelukast, antihistamines, and ICS accounted for 9.2%, 1.5%, and 6.0% of adverse reactions, respectively.[10] Some studies reported that for every 1000 children treated with ICS for 23 weeks, 15 children experienced severe adverse effects.[26]

Montelukast was considered to be mostly associated with neuropsychiatric events, with the highest ROR of 10.35. This result was similar to that of another study concerning montelukast related neuropsychiatric events, which showed the relative risk of neuropsychiatric adverse effects from montelukast versus ICS was 12 (2–90).[22] Chlorpheniramine ranked second with lower ROR. The other H1-AH drugs had low RORs, suggesting that the second generation of H1-AH drugs relatively safe for neuropsychiatric events.

The underlying mechanism of frequent LTRA associated neuropsychiatric events was studied by some research. Cytochrome P450 (CYP) 2C8 was associated with hepatic metabolism and the elimination of montelukast, and SLCO2B1 codes for the transporter OATP2B1. This transporter modulates the blood-brain barrier and intestinal transport of montelukast.[27–30] Therefore, patients with polymorphisms of these genes had different elimination rates of LTRA, which might result in the different prevalence of adverse drug reactions. Neuropsychiatric events related to LTRA were more frequently reported in North America, and fewer reports have been reported in Asia, Oceania, South America, and Africa. This phenomenon may be explained by the above polymorphisms but will need confirmation in future studies. And underreporting in other regions could also be another reason for this result.

The fatality rates due to LTRA and ICS associated neuropsychiatric events were similar, while the fatality rate due to H1-AH associated neuropsychiatric events was higher. This suggests that although neuropsychiatric events were more common with LTRA, we should still pay attention to the events associated with H1-AH as they were more severe. Some studies have found that mindfulness interventions can increase the psychological resources of patients with asthma.[31]

Limitations

First, there was incomplete information for the reports, which may lead to the overestimation or underestimation of the results. The existence of a report did not establish a causative effect of the administration, and the information in the reports has not been verified. Second, the number of treated patients was unknown. Therefore, the frequency of adverse events for each suspected drug can't be established. Third, no underlying diseases were available in the FEARS and thus were not considered. However, some of the underlying diseases, as well as their severity, may have some relevant impact on the results. Fourth, reporting behaviours might be influenced by recent publication of a certain adverse event and media attention.[32,33]

CONCLUSIONS

In this study, we analyzed the LTRA, H1-AH, and ICS associated neuropsychiatric events reported in FAERS. Reported LTRA associated neuropsychiatric events were most frequent in 4 to 6-year-old children. Most reported cases occurred within the first 10 days after drug initiation. In addition, the fatality rate due to H1-AH associated neuropsychiatric events was higher than that due to LTRA and ICS. These results should remind practitioners to pay particular attention to specific patients treated with LTRA and H1-AH.

Abbreviations

FDA, Food and Drug Administration; FAERS, FDA Adverse Event Reporting System; LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid (ICS); ROR, reporting odds ratio; PRR, proportional reporting ratio.

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Availability of data and materials
All the available data are included in the manuscript.

Author contribution
Kai Guan and Bin Zhao designed the study, Bin Zhao directed the data mining in the FAERS database, Sainan Bian analyzed data and drafted the manuscript. Kai Guan, Bin Zhao, Lisha Li, Zixi Wang, Le Cui, and Yingyang Xu revised the manuscript. All authors read and approved the final manuscript.

Ethics statement
This study was approved by the institutional review board (IRB) of Peking Union Medical College Hospital (S-K1699).

Authors' consent for publication
All authors agreed to the publication of this work.

Submission declaration
We confirm this manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

Declaration of competing interest
The authors report no competing interests.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2021.100594.

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