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Research On The Signal Mining Of Adverse Events Of Montelukast Sodium Based On FAERS

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Graphical Abstract

Tab. 1 Fourfold table of measures of disproportionality

Item	Target AE	Other AEs	Sum
Target drug	a	b	a+b
Other drugs	c	d	c+d
Sum	a+c	b+d	N=a+b+c+d

ROR= (a/c) (b/d); ROR 95%CI=exp(ln(ROR)±1.96)

PRR=[a/(a+b)]/[c/(c+d)]; PRR 95%CI=exp(ln(PRR)±1.96

Tab.2 Primary information of Montelukast related events reported in FAERS

nension	Subclass	case/n	Proportion
:	Male	2390	34.20
	Female	3694	52.85
	Unknown	905	12.95
e	<18	1827	26.14
	18~64	2366	33.85
	≥65	776	11.10
	Unknown	2020	28.90
orter	Physician	1144	16.37
	Consumer	3269	46.77
	Other professional staffs related to health care	1712	24.50
	Lawyer	7	0.10
	Pharmacist	682	9.76
	Unknown	175	2.50
orting country (Top 5)	US	2447	35.01
	UK	1919	27.46
	Canada	1019	14.58
	France	198	2.83
	Australia	167	2.39
sage form	Conventional tablets	2354	33.68
	Chewable tablets	522	7.47
	Coating tablet	451	6.45
	Granola	115	1.65
	Capsule	34	0.49

Abstract.

Objective *To conduct data-mining of montelukast-related adverse events after marketing to provide a reference for safe clinical medication.* ***Methods*** *We use reporting odds ratio (ROR) and proportional reporting ratio (PRR) methods to mine the adverse reaction signals of montelukast on the adverse reaction report data of 22 quarters from 2015Q1 to 2020Q2, extracted from the FAERS database.* ***Results*** *Totally 467 signals were detected with ROR and PRR, and the most relevant 50 preferred terms are conducted based on the signal strength and signal frequency, 55.32% of signals were not reported in the proved label. Adverse reaction signals of montelukast involve 27 systems and organs, in addition to psychiatric diseases, majority of adverse events included respiratory, thoracic, and mediastinal disorders and examination.* ***Conclusion*** *Clinical use of montelukast should pay attention to the patient's neuropsychiatric symptoms, especially those not reported in the proved label, such as*

1. Tab.3 Montelukast ADE signals and involved systems and organs

SOC	Signal	Proportion (%)	Cumulative number of adverse events (cases)	proportion (%)	Signals not mentioned in the drug description
Mental illness	107	22.91	8572	50.51	50
tory, thoracic and mediastinal diseases	68	14.56	2882	16.98	36
Various inspections	38	8.14	1037	6.11	32
ystemic diseases and responses to medication	28	6.00	900	5.30	27
nfection and infectious diseases	26	5.57	400	2.36	7
Various neurological diseases	22	4.71	646	3.81	10
n and subcutaneous tissue diseases	22	4.71	631	3.72	10
Immune system diseases	20	4.28	378	2.23	8
Gastrointestinal diseases	17	3.64	198	1.17	12
Cardiac organ diseases	16	3.43	289	1.70	15
Poisoning and Surgical Complications	12	2.57	115	0.68	11
ous surgical and medical operations	9	1.93	53	0.31	9
sculoskeletal and connective tissue diseases	8	1.71	91	0.54	4
n, malignant and unexplained tumors (including cystic and polypoid)	8	1.71	36	0.21	8
Eye organ diseases	8	1.71	83	0.49	8
Hepatobiliary diseases	7	1.50	73	0.43	1
genital familial hereditary diseases	7	1.50	35	0.21	7
vascular and lymphatic diseases	7	1.50	56	0.33	7
ear and labyrinth diseases	6	1.28	58	0.34	4
lood and lymph system diseases	6	1.28	85	0.50	3
Product issues	5	1.07	166	0.98	5
Social environment	5	1.07	40	0.24	4
letabolic and nutritional diseases	4	0.86	55	0.32	4
Endocrine system diseases	3	0.64	31	0.18	3
f pregnancy, puerperium and perinatal period	3	0.64	17	0.10	2
dney and urinary system diseases	3	0.64	35	0.21	3
oductive system and breast diseases	2	0.43	9	0.05	2
Sum	467	100	16971	100	293

Tab.4 The preferred terms of the top 50 ROR and top 50 reports of adverse event related to Montelukast in the FAERS database

PT（ranked by signal strength）	Cases	95%CI lower		PT（Ranked by frequency）	Cases	95%CI lower	
		ROR	PRR			ROR	PRR
Separation anxiety disorder*	33	388.14	387.86	Anxiety	1017	6.09	5.95
Sialadenosis*	6	356.14	356.11	Asthma	704	12.13	11.92
ergic granulomatous angiitis*	31	292.93	292.73	Depression	626	4.75	4.69
Eosinophilic granulomatosis with polyangiitis*	157	219.44	**218.57**	Aggression	579	22.63	22.30
Sleep terror*	346	200.92	199.08	Insomnia	481	2.79	2.77
Endocarditis fibroplastica*	10	191.8	191.77	Nightmare	466	22.18	21.92
Thumb sucking*	4	133.94	133.94	Suicidal ideation	460	9.13	9.03
inophilic pneumonia chronic	20	122.16	122.11	Cough	362	1.94	1.93
Post viral fatigue syndrome*	22	104.8	104.76	Anger	355	17.8	17.64
tal lung capacity*	3	102.09	102.08	Sleep terror	346	200.92	199.08
Physical abuse*	9	98.42	98.41	Urticaria	333	3.43	3.41
Autophobia*	24	98.22	98.18	Abnormal behaviour	317	13.98	13.87
School refusal*	11	83.12	83.11	Wheezing*	284	8.13	8.08
ediatric autoimmune neuropsychiatric sorders associated with streptococcal infection*	4	82.44	82.44	Crying*	233	10.22	10.16
sessive-compulsive symptom	24	80.31	80.27	Depressed mood	219	5.98	5.96
Sensory overload*	10	78.12	78.11	Blood pressure increased*	209	1.99	1.98
ak expiratory flow rate abnormal*	8	77.56	77.55	Agitation	198	4.47	4.45
Myxofibrosarcoma*	5	63.92	63.92	Irritability	196	4.74	4.72
unctional residual apacity decreased*	6	52.75	52.75	Sleep disorder	186	4.24	4.22
otal lung capacity increased*	10	51.04	51.04	Chest discomfort*	177	2.8	2.79
leuropsychological test abnormal*	4	48.67	48.67	Mood swings	160	7.46	7.43
Pulmonary renal syndrome*	13	48.22	48.21	Mood altered	159	8.96	8.93

Separation anxiety disorder, Sleep terror and PANDAS. For patients with mental history, phenylketonuria and autoimmune diseases who use the montelukast， relevant workers should pay attention to monitoring to ensure safe and rational medication.

Tab.5 The preferred terms of the top 50 ROR and top 50 reports of psychiatric diseases related to Montelukast in the FAERS database

Mental illness ADE (Ranked by signal strength)	Cases	95%CI Lower		Mental illness ADE(Ranked by frequency)	Cases	95%CI Lower	
		ROR	PRR			ROR	PRR
Separation anxiety disorder*	33	388.14	387.86	Anxiety	1017	6.09	5.95
Sleep terror*	346	200.92	199.08	Depression	626	4.75	4.69
Autophobia*	24	98.22	98.18	Aggression	579	22.63	22.30
School refusal*	11	83.12	83.11	Insomnia	481	2.79	2.77
Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection*	4	82.44	82.44	Nightmare	466	22.18	21.92
Obsessive-compulsive symptom	24	80.31	80.27	Suicidal ideation	460	9.13	9.03
Defiant behaviour	12	39.66	39.65	Anger	355	17.80	17.64
Attention-seeking behaviour*	7	34.65	34.65	Sleep terror*	346	200.92	199.08
Tic	99	32.85	32.77	Abnormal behaviour	317	13.98	13.87
Obsessive-compulsive personality disorder	9	30.90	30.89	Depressed mood	219	5.98	5.96
Negative thoughts	56	27.40	27.37	Agitation	198	4.47	4.45
Social fear*	7	26.23	26.23	Irritability	196	4.74	4.72
Neuropsychiatric symptoms	24	23.35	23.34	Sleep disorder	186	4.24	4.22
Neurodevelopmental disorder*	10	23.21	23.21	Mood swings	160	7.46	7.43
Aggression	579	22.63	22.30	Mood altered	159	8.96	8.93
Morbid thoughts	19	22.46	22.46	Hallucination	152	3.50	3.49
Nightmare	466	22.18	21.92	Panic attack	113	4.91	4.90
Social avoidant behavior*	88	20.56	20.52	Emotional disorder	107	3.25	3.25
Hostility	30	19.97	19.96	Mental disorder	103	4.37	4.36
Enuresis	58	18.66	18.63	Tic	99	32.85	32.77

* means PT not included in the specification.

Introduction

Montelukast(SINGULAIR, SINGULAIR helped) is a potent Leukotriene Receptor antagonist (LTRA). By selectively binding with I type ammonia acyl Leukotriene Receptor and competitive blocking Leukotriene biological activity, it can effectively control the asthma inflammation [1]. Such a drug is mainly applied to the prevention and chronic treatment of asthma in adults and children over 12 months old, and has a significant relieving effect on seasonal or perennial allergic rhinitis [2]. Montelukast is recommended in guidelines for bronchial asthma [3, 4], obstructive sleep apnea (OSA) in children [5], cough variant asthma (CVA) [6], etc. The applications of it remain wide. In March 2020, the US Food and Drug Administration (FDA) issued a black-box warning : the asthma and allergy treatment Drug Montelukast can cause severe neuropsychiatric adverse reactions(including Suicidal thoughts or behaviors), also, its use in allergic rhinitis is recommended to be limited. In the UK, Medicines and Healthcare Products Regulatory Agency (MHRA) proposed that the benefits and risks of continued treatment should be carefully considered if Neuropsychiatric reactions occur in patients treated with Montelukast. Although the package inserts of Montelukast clearly lists the possible adverse reactions of the mental system, including suicidal thoughts and behaviors, it does not arouse enough attention from physicians, patients and their families. Reports of adverse reactions related to Montelukast showed that children reported more depression, sleep disorders and suicidal behaviors than adults. However, most of these patients have related neurological/psychiatric symptoms themselves, and there is insufficient information to assess the relationship between the drug and adverse events. Adverse Events Reporting System (ARES) is a major source of information for exploring post-marketing

safety of drugs domestically and overseas due to its wide scope of monitoring and its ability to detect potential Adverse drug reactions (ADRs) early without being limited by time or space [7]. Till now, there is no research report on Montelukast adverse reaction signal mining based on spontaneous reporting system in China, to the best of our knowledge. Based on the FDA Adverse Event Reporting System(FAERS), this research plans to run an analysis on the safety of Montelukast using Reporting odd ratio(ROR) and Proportional reporting ratio(PRR). By quantifying the potential safety warning signals of the anti-asthma drug Montelukast, it provides objective reference data for clinical medication.

1. Materials and Methods

1.1 **Research data** Based on the information from FAERS and the FDA approved drugs and adverse reactions public dashboard(public dashboard), the researches retrieved the ASCII data from the first quarter of 2015 to the second quarter of 2019(220 quarters in total) using the general name(Montelukast) and the brand name(SINGULAIR) of the drug as the keywords. Then we imported the data into MySQL, using the DEMO list to wash out the repetition of the same patient information, then analyzed the adverse event report(AE) within which referred Montelukast as "Primary Suspect"(PS).

1.2 **Method** The adverse drug reactions of inspection Methods commonly used internationally and domestically mainly is Disproportionality Methods, which mainly includes reporting odds ratio(ROR) and proportional reporting ratio (PRR). The sensory thresholds of such methods are: (1) reporting cases a≥3； (2) floor of ROR 95% confidence interval >1; (3) PRR >2 (4) Chi-square >4. The fulfillment of all four conditions above indicates the occurrence of a suspective signal. The stronger the signal intensity of ADE indicates a higher correlation between the drug and ADR, but it should be noted that the signal only indicates a statistical association between the target drug and the target adverse event[7]. The algorithms of ROR and PRR are based on the four-lattice table, as shown in Table 1. Based on the preferred glossary of terms for adverse drug reactions of system organ class(SOC) and Preferred Terms(PT) in Medical Dictionary for Regularly Activities (MedDRA), the PT was mapped to the corresponding SOC and classified, and the TOP 50 PT was selected according to the signal frequency and signal strength respectively for the AE report in which the primary suspect(PS) drug is Montelukast. Enumeration data were described by the number of cases and composition ratio, and the statistical analysis of this study was completed by Microsoft Excel 2016.

Tab. 1 Fourfold table of measures of disproportionality

Item	Target AE	Other AEs	Sum
Target drug	a	b	a+b
Other drugs	c	d	c+d
Sum	a+c	b+d	N=a+b+c+d

ROR=（a/c）(b/d)；ROR 95%CI=exp(ln(ROR)±1.96)

PRR=[a/(a+b)]/[c/(c+d)]；PRR 95%CI=exp(ln(PRR)±1.96

2. Results and Discussion

2.1 **Basic features of adverse event reported cases** In this study, a total of 34,168 AE reports with Montelukast as the primary suspect were retrieved from the first quarter of 2015 to the second quarter of 2020. After washing out the repetition, there are 6989 cases in which Montelukast is the primary suspect, related events within are 1939 in total, with a 0.65 sex ratio. According to China's modern age segment [9], 26.14% of patients are less than 18 years old, 33.85% are between 18 and 64 years old, and 11.10% are ≥65 years old. Patients were the main reporting group, accounting for 46.77%. The United States reported the most cases, while China reported only 60 cases, accounting for 0.86%.The dosage forms were mainly ordinary tablets, accounting for 33.68%. The basic feature of the cases reported by AE were shown in Table 2.

Tab.2 Primary information of Montelukast related events reported in FAERS

Dimension	Subclass	case/n	Proportion
Sex	Male	2390	34.20
	Female	3694	52.85
	Unknown	905	12.95
Age	＜18	1827	26.14
	18~64	2366	33.85
	≥65	776	11.10
	Unknown	2020	28.90
Reporter	Physician	1144	16.37
	Consumer	3269	46.77
	Other professional staffs related to health care	1712	24.50
	Lawyer	7	0.10
	Pharmacist	682	9.76
	Unknown	175	2.50
Reporting country (Top 5)	US	2447	35.01
	UK	1919	27.46
	Canada	1019	14.58
	France	198	2.83
	Australia	167	2.39
Dosage form	Conventional tablets	2354	33.68
	Chewable tablets	522	7.47
	Coating tablet	451	6.45
	Granola	115	1.65
	Capsule	34	0.49

2.2 **Systems and organs involved in Adverse event safety alert signals** According to the filter condition mentioned before, we selected 467 alert signals from 16971 ADE report cases. These signals involved 27 SOC. Classified according to the MedDRA system, ranked by the number of involved systems, the top five SOC are mental derangement class (107), respiratory system, chest and mediastinal diseases (68), all kinds of inspection (38) application site reactions, systemic diseases and (28), infection and infection diseases (26). Involving ADE has reported cases accounted for SOC in the top five for psychotropic (8572 cases, 50.51%), respiratory system, chest and mediastinal diseases (2882 cases, 16.98%), all kinds of inspection (1037 cases, 6.11%), application site reactions and systemic disease (900 cases, 5.30%), infection and infection diseases (400 cases, 2.36%), as shown in table 3. By comparing English package inserts for the screening of 293 not in new security alert signals, which are mentioned in the leaflet distribution details shown in table 3, the nature of the unknown and benign and malignant tumor, eye organs disease, congenital genetic disease, metabolism and nutritional diseases, kidney and urinary system, endocrine system, reproductive system, these above AE signals are new.

3. Tab.3 Montelukast ADE signals and involved systems and organs

编号	SOC	Signal	Proportion (%)	Cumulative number of adverse events (cases)	proportion（%）	Signals not mentioned in the drug description
1	Mental illness	107	22.91	8572	50.51	50
2	Respiratory, thoracic and mediastinal diseases	68	14.56	2882	16.98	36
3	Various inspections	38	8.14	1037	6.11	32
4	Systemic diseases and responses to medication	28	6.00	900	5.30	27
5	Infection and infectious diseases	26	5.57	400	2.36	7
6	Various neurological diseases	22	4.71	646	3.81	10
7	Skin and subcutaneous tissue diseases	22	4.71	631	3.72	10
8	Immune system diseases	20	4.28	378	2.23	8
9	Gastrointestinal diseases	17	3.64	198	1.17	12
10	Cardiac organ diseases	16	3.43	289	1.70	15
11	Injury, Poisoning and Surgical Complications	12	2.57	115	0.68	11
12	Various surgical and medical operations	9	1.93	53	0.31	9
13	Musculoskeletal and connective tissue diseases	8	1.71	91	0.54	4
14	Benign, malignant and unexplained tumors (including cystic and polypoid)	8	1.71	36	0.21	8
15	Eye organ diseases	8	1.71	83	0.49	8
16	Hepatobiliary diseases	7	1.50	73	0.43	1
17	Congenital familial hereditary diseases	7	1.50	35	0.21	7
18	Vascular and lymphatic diseases	7	1.50	56	0.33	7
19	ear and labyrinth diseases	6	1.28	58	0.34	4
20	Blood and lymph system diseases	6	1.28	85	0.50	3
21	Product issues	5	1.07	166	0.98	5
22	Social environment	5	1.07	40	0.24	4
23	Metabolic and nutritional diseases	4	0.86	55	0.32	4
24	Endocrine system diseases	3	0.64	31	0.18	3
25	Status of pregnancy, puerperium and perinatal period	3	0.64	17	0.10	2
26	Kidney and urinary system diseases	3	0.64	35	0.21	3
27	Reproductive system and breast diseases	2	0.43	9	0.05	2

Sum		467	100	16971	100	293

2.3 Top 50 adverse event reports and signals In descending order according to signal frequency and 95%CI lower limit of ROR value, the top 50 AE security alert signals were obtained (Table 4), and 94 security alert signals were obtained after flittering. It includes 42 adverse reactions (44.68%) that have been included in the package inserts, and 52 signals (55.32%) that have not been included. AE safety warning signals that are not mentioned in the drug instructions and have strong signals worthy of clinical attention include: Psychiatric issues (separation anxiety disorder, sleep terrors, etc.), diseases of the gastrointestinal system (salivary gland benign hypertrophy), immune system disease (allergic granulomatous vasculitis, eosinophilic granulomatous vasculitis), heart organ disease (fiber proliferative endocarditis) application site reactions, systemic diseases and (thumb sucking addiction), infection and infection diseases (virus after fatigue syndrome), all kinds of inspection (total lung capacity change), social environment (physical abuse).

Tab.4 The preferred terms of the top 50 ROR and top 50 reports of adverse event related to Montelukast in the FAERS database

N	PT（ranked by signal strength）	Cases	95%CI lower		PT（Ranked by frequency）	Cases	95%CI lower	
			ROR	PRR			ROR	PRR
1	Separation anxiety disorder*	33	388.14	387.86	Anxiety	1017	6.09	5.95
2	Sialadenosis*	6	356.14	356.11	Asthma	704	12.13	11.92
3	Allergic granulomatous angiitis*	31	292.93	292.73	Depression	626	4.75	4.69
4	Eosinophilic granulomatosis with polyangiitis*	157	219.44	218.57	Aggression	579	22.63	22.30
5	Sleep terror*	346	200.92	199.08	Insomnia	481	2.79	2.77
6	Endocarditis fibroplastica*	10	191.8	191.77	Nightmare	466	22.18	21.92
7	Thumb sucking*	4	133.94	133.94	Suicidal ideation	460	9.13	9.03
8	Eosinophilic pneumonia chronic	20	122.16	122.11	Cough	362	1.94	1.93
9	Post viral fatigue syndrome*	22	104.8	104.76	Anger	355	17.8	17.64
10	Total lung capacity*	3	102.09	102.08	Sleep terror	346	200.92	199.08
11	Physical abuse*	9	98.42	98.41	Urticaria	333	3.43	3.41
12	Autophobia*	24	98.22	98.18	Abnormal behaviour	317	13.98	13.87
13	School refusal*	11	83.12	83.11	Wheezing*	284	8.13	8.08
14	Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection*	4	82.44	82.44	Crying*	233	10.22	10.16
15	Obsessive-compulsive symptom	24	80.31	80.27	Depressed mood	219	5.98	5.96
16	Sensory overload*	10	78.12	78.11	Blood pressure increased*	209	1.99	1.98
17	Peak expiratory flow rate abnormal*	8	77.56	77.55	Agitation	198	4.47	4.45
18	Myxofibrosarcoma*	5	63.92	63.92	Irritability	196	4.74	4.72
19	Functional residual capacity decreased*	6	52.75	52.75	Sleep disorder	186	4.24	4.22

20	Total lung capacity increased*	10	51.04	51.04	Chest discomfort*	177	2.8	2.79
21	Neuropsychological test abnormal*	4	48.67	48.67	Mood swings	160	7.46	7.43
22	Pulmonary renal syndrome*	13	48.22	48.21	Mood altered	159	8.96	8.93
23	Airway peak pressure increased*	10	46.69	46.68	Eosinophilic granulomatosis with polyangiitis*	157	219.44	218.57
24	Defiant behaviour	12	39.66	39.65	Hallucination	152	3.5	3.49
25	Female reproductive neoplasm*	3	38.9	38.90	Productive cough	149	3.83	3.82
26	Fight in school*	3	36.82	36.82	Palpitations	147	1.94	1.93
27	Retinal artery embolism*	8	35.72	35.72	Disturbance in attention	142	3.94	3.93
28	Attention-seeking behaviour*	7	34.65	34.65	Psychomotor hyperactivity	135	12.54	12.50
29	Hypereosinophilic syndrome	14	34.6	34.60	Nasal congestion	128	2.93	2.93
30	Mononeuropathy multiplex*	11	34.37	34.36	Panic attack	113	4.91	4.90
31	Tic	99	32.85	32.77	Product substitution issue*	112	2.71	2.70
32	Obsessive-compulsive personality disorder	9	30.9	30.89	Heart rate increased	112	1.75	1.75
33	Nodular vasculitis*	3	30.34	30.34	Emotional disorder	107	3.25	3.25
34	Gait deviation*	4	28.16	28.16	Sputum discoloured*	104	10.71	10.68
35	Chronic spontaneous urticaria	19	27.73	27.72	Mental disorder	103	4.37	4.36
36	Negative thoughts	56	27.4	27.37	Tic	99	32.85	32.77
37	Eosinophilic bronchitis	6	26.51	26.51	Lower respiratory tract infection*	97	2.43	2.43
38	Social fear*	7	26.23	26.23	Paranoia*	95	9.72	9.70
39	Hyperplastic cholecystopathy*	4	26.09	26.09	Blood pressure systolic increased*	94	5.17	5.17
40	Salpingo-oophorectomy unilateral*	5	25.91	25.91	Obstructive airways disorder*	93	11.16	11.14
41	Occupational exposure to dust*	4	25.47	25.47	Intentional self-injury	93	4.91	4.90
42	Neuropsychiatric symptoms	24	23.35	23.34	Obsessive-compulsive disorder	92	14.35	14.32
43	Neurodevelopmental disorder*	10	23.21	23.21	Fear*	89	5.92	5.91
44	Oropharyngitis fungal*	5	23.08	23.08	Rhinorrhoea	89	1.69	1.69
45	Aggression	579	22.63	22.30	Social avoidant behaviour*	88	20.56	20.52
46	Morbid thoughts	19	22.46	22.46	Personality change*	85	14.71	14.68
47	Amaurosis fugax*	12	22.22	22.22	Dyspnoea exertional*	84	2.61	2.61
48	Nightmare	466	22.18	21.92	Somnambulism	82	17.3	17.27
49	Asthma-chronic obstructive pulmonary disease overlap syndrome*	9	21.38	21.38	Abnormal dreams	80	4.98	4.97
50	Microscopic polyangiitis*	6	21.23	21.23	Thinking abnormal*	77	6.17	6.16

* means PT not included in the specification.

2.4 Top 20 psychiatric adverse event reports and signals

In descending order according to signal frequency and 95% lower limit of ROR value, the top 20 psychiatric AE security alert signals were obtained (Table 5), and 36 security alert

signals were obtained after screening. Within which are not included in the leaflet of adverse reactions are 9 (25%), according to the ROR the value of the 95% threshold descending sort of separation anxiety disorder, sleep terrors respectively, phobia, refused to go to school, children's correlation of streptococcus infection autoimmunity nerve disorder, attention seeking behavior, social phobia, neurodevelopmental disorder, social avoidant behavior.

Tab.5 The preferred terms of the top 50 ROR and top 50 reports of psychiatric diseases related to Montelukast in the FAERS database

N	Mental illness ADE（Ranked by signal strength）	Cases	95%CI Lower		Mental illness ADE(Ranked by frequency)	Cases	95%CI Lower	
			ROR	PRR			ROR	PRR
1	Separation anxiety disorder*	33	388.14	387.86	Anxiety	1017	6.09	5.95
2	Sleep terror*	346	200.92	199.08	Depression	626	4.75	4.69
3	Autophobia*	24	98.22	98.18	Aggression	579	22.63	22.30
4	School refusal*	11	83.12	83.11	Insomnia	481	2.79	2.77
5	Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection*	4	82.44	82.44	Nightmare	466	22.18	21.92
6	Obsessive-compulsive symptom	24	80.31	80.27	Suicidal ideation	460	9.13	9.03
7	Defiant behaviour	12	39.66	39.65	Anger	355	17.80	17.64
8	Attention-seeking behaviour*	7	34.65	34.65	Sleep terror*	346	200.92	199.08
9	Tic	99	32.85	32.77	Abnormal behaviour	317	13.98	13.87
10	Obsessive-compulsive personality disorder	9	30.90	30.89	Depressed mood	219	5.98	5.96
11	Negative thoughts	56	27.40	27.37	Agitation	198	4.47	4.45
12	Social fear*	7	26.23	26.23	Irritability	196	4.74	4.72
13	Neuropsychiatric symptoms	24	23.35	23.34	Sleep disorder	186	4.24	4.22
14	Neurodevelopmental disorder*	10	23.21	23.21	Mood swings	160	7.46	7.43
15	Aggression	579	22.63	22.30	Mood altered	159	8.96	8.93
16	Morbid thoughts	19	22.46	22.46	Hallucination	152	3.50	3.49
17	Nightmare	466	22.18	21.92	Panic attack	113	4.91	4.90
18	Social avoidant behavior*	88	20.56	20.52	Emotional disorder	107	3.25	3.25
19	Hostility	30	19.97	19.96	Mental disorder	103	4.37	4.36
20	Enuresis	58	18.66	18.63	Tic	99	32.85	32.77

* means PT not included in the specification.

2.5 Discussion

FAERS database used in this paper, through mining the montelukast special ADR signal and montelukast instruction ADR and broadly in line with a clinical trial results, including meng LuSi leaflet, sodium post-marketing experience recorded in the main adverse reactions included among the basic signal, and a strong signal, such as anxiety, depression, attack, nightmares, insomnia, etc, confirmed that the credibility of this research. At

present, clinicians and patients attach great importance to the neuropsychiatric response induced by montelukast. Therefore, this paper focuses on the safety warning signal of montelukast sodium in the aspect of mental damage, and interprets the new signal with strong signal extracted.

2.5.1 Security alert signals related to mental illness

As can be seen from Table 3, the SOC with the largest number of signal types and cumulative reported cases is "psychosis". According to literature review [10-13], oral absorption of Montelukast is rapid, and adverse reactions caused by montelukast occur within 30 min at the earliest. Adverse reactions caused by mental system disorders can occur after taking Montelukast sodium for 2h-10d. Currently, about montelukast, possible mechanisms of nervous system responses are: (1) [14], according to new research in rodents or the human brain, leukotriene receptor 1 (cysteinyl leukotriene 1, CysLT1) in the cortex, hippocampus and widely expressed in the substantia nigra striatum, specifically located in the cerebral vascular endothelial cells, astrocytes, microglia and several kinds of neurons.\ In pathological cases, CysLT1 and CysLT2 can be raised in the brain, and asthma patients taking selective CysLT1 montelulast drug through the blood-brain barrier and brain astrocytes and microglia CysLT1 combination, can break CysLT1 and CysLT2 balance in the brain, which affect CysLT1 and CysLT2 control microglial cells - neurons original interaction response and induce the nervous system. (2) Studies have also shown that [14] montelulast sodium can interfere with cyclic nucleotide phosphodiesterase and 5-lipoxygenase to raise the level of central nucleotide in brain cells and affect the dynamic balance between synthesis and hydrolysis of cAMP and cGMP, thus damaging the nervous system. (3) In addition, some researchers believe that the binding of montelulast sodium to the cysteine leukotriene receptor produces nitric oxide, which has a toxic effect on brain tissue [15]. As can be seen from Table 5, the new safety warnings with strong signals in montelulast -related mental impairment include Separation Anxiety disorder (SAD) (no. 1), sleeping terror, phobiasies, School refusal, and the Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). DSM-5 included "separation anxiety disorder" in the anxiety disorder group and removed the age limit (18 years in DSM-4) [16]. Typical symptoms of SAD in school-age children [17, 18] include overdependence, excessive worry, anger, refusal to go to school, and sleep problems (nightmares of being attacked or kidnapped).Typical manifestations in adults are agoraphobia [17]. SAD has been found to be associated with a variety of other disorders following the first episode[19], including internalized behavioral problems (major depression, bipolar disorder, social phobia, panic disorder, anxiety disorder) and externalized behavioral problems (adhd, disobedient disorders, conduct disorders). PANDAS face refers to compulsive disorder (OCD) and involuntary movement disorder (TD) caused by autoimmune after streptococcal infection. Sleeping terror is a kind of sleep disorder. Although it often occurs briefly in children, its damage to children's sleep quality can further affect their nervous system development [20].

Although there is no evidence to prove the cause-and-effect relationship between SAD, PANDAS and sleeping terrors and montelukast, due to the serious clinical consequences of these diseases, the following points should be noted in the clinical use of montelukast sodium. First, when patients start taking montelukast or increase the dose, medical staff should closely monitor the patient's nervous system response. Especially for children, the

development of the blood-brain barrier is not perfect, which is likely to lead to drugs passing through the blood-brain barrier and more likely to cause nervous system disorders. Therefore, the medical staff should inform the family of the child to observe whether the child has neurological and psychiatric abnormalities. In addition, the drug instructions [2] suggested that 4mg and 5mg Montelulst chewable tablets contained phenylalanine, and it was found that the content of phenylalanine increased in patients with severe asthma [21]. Therefore, for children with severe asthma who also suffer from phenylketonuria, chewable tablets should be avoided as far as possible to prevent the accumulation of phenylpyruvic acid in the body from damaging the brain, resulting in mental retardation. Finally, attention should be paid to streptococcal infection screening if mental disorders occur when using Montelulast, such as pharyngeal culture [22], or Garvey[23] and Snider[24] believe that penicillin and azithromycin can effectively prevent streptococcal infection. However, some studies [25] suggest that PANDAS should not overuse antibiotics.

2.5.2 Other new security alert signals

According to Table 4, 52 suspected ADR signals were found in this study, including benign hypertrophy of saliary glands in the gastrointestinal system (ranked second).Allergic granulomatous vasculitis and eosinophilic granulomatous polyvasculitis in immune system diseases;Cardiac organ diseases such as fibroproliferative endocarditis. Salivary gland benign hypertrophy can be divided into the salivary gland swelling and salivary gland swollen degenerative, clinical manifestations of the parotid gland can be gradually enlarged, swelling of the recurrent, sees more at old people, there is no evidence to prove that Montelulast can cause salivary gland lesions directly, may be related to Montelulast chewable tablet, for such patients, can consider to replace Montelulast dosage forms to ease the discomfort of the parotid gland swelling. Allergic granulomatous vasculitis, also known as Churg-Strauss syndrome (CSS), is a rare form of eosinophilic vasculitis associated with asthma. The CSS associated with Montelukast may be associated with a reduction in oral corticocholesterol treatment, or it may be caused by montelukast's hypersensitivity or leukotriene B4's chemotaxis to eosinophilic cells and neutrophils [26]. Therefore, patients receiving montelukast should be followed up and timely detection of CSS prevention. Fibroproliferative endocarditis is a clinically rare non-infective endocarditis. The instructions for montelulast suggest that it may cause palpitations, but there is no direct evidence that montelulast can induce cardiac lesions. Refer to table 3, the nature of unknown and benign and malignant tumor, eye organs disease, congenital genetic disease, metabolism and nutritional diseases, kidney and urinary system, endocrine system, reproductive system and mammary gland ADE signal has not been mentioned in the leaflet, the nature of unknown and benign and malignant tumor (mucus fibrosarcoma, female reproductive system tumor), kidneys and urinary tract (lung kidney syndrome) signal is strong. Lung-renal syndrome is a rare autoimmune disease characterized by cough, dyspnea, fever, and edema. The instructions for montelulast suggest edema as one of its adverse reactions, which may aggravate edema symptoms in asthma patients with autoimmune diseases such as systemic lupus erythematosus nephritis. There is no evidence that montelukast is carcinogenic.

3.1 **Research limitations** Using database to carry out the exploration of adverse drug events signal there are still many places need to improve and improve: (1) the institute adopts FAERS database for spontaneous reporting database, there is the possibility of omission, methodological basis for optimization and improvement of the database resources, focus

on improving the quality of spontaneous reporting system type database; A total of 6,989 cases with Montelukast as PS drugs were included in this study, and only 60 cases were reported in China. The lack of safety data related to the population in East Asia reminds us that the safety analysis results of montelukast should be further evaluated when applied in China. At the same time, only 11.10% of the elderly patients were reported in this study, while the proportion of patients over 65 years old included in the montelukast clinical trial was usually the smallest, and no age-specific subanalysis was conducted [27]. Nyenhuis et al. found that the lower level of cysteine leutriene in the airway of elderly patients with asthma may affect the therapeutic effect of LTRAs [28], so it is difficult to show that older patients have the same efficacy and safety as younger patients.In addition, unlike clinical trial data, FAERS data were reported when patients experienced adverse events after treatment. Therefore, the causal relationship between the drug and the reported event remains uncertain, which makes it more difficult to assess the safety of the drug.

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3.Conclusion

In this study, signal mining was conducted on the AE reports of Montelukast from the first quarter of 2015 to the second quarter of 2020 in the FAERS database, to explore the safety problems exposed after the extensive clinical application of montelukast, and to investigate the psychosis caused by montelukast sodium (SAD, sleeping terrors, PANDAS).Gastrointestinal system (benign hypertrophy of salivary glands);Diseases of the immune system (allergic granulomatous vasculitis, eosinophilic Wegener granuloma);Diseases of the heart (fibroproliferative endocarditis);Benign, malignant and unknown tumors (myxofibrosarcoma, female reproductive system tumors);Renal and urinary disorders (pulmonary and renal syndrome), which are not mentioned in the manual but have a high incidence in the real world, should be of particular concern.Should be ready before using Montelukast drug evaluation, especially patients with a history of mental illness, benzene acetone urine, the basic diseases such as autoimmune diseases, clinical doctors should pay close attention to children and the elderly in the process of drug nerve mental symptoms, and require active children guardians guardianship and promptly report to the doctor, take timely intervention measures, in order to ensure safe and rational medication.

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