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Adverse drug reactions of montelukast and pranlukast: Analysis of the Korea database

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Abstract

Background: Leukotriene receptor antagonists are recommended to treat asthma and allergic rhinitis. Although they had been used for a long time, recent studies have reported neuropsychiatric adverse drug reactions are associated with montelukast.

Objective: This study analyzed the adverse drug reactions of montelukast and pranlukast, which are the two most frequently prescribed leukotriene receptor antagonists, respectively in Korea.

Methods: This study retrospectively reviewed ADRs of 5,426 montelukast and 1,146 pranlukast reported in the Korea Adverse Event Reporting System between January 2014 and December 2018.

Results: When both drugs are classified by system organ class, the most adverse drug reactions were related to the gastro-intestinal system, followed by psychiatric events. The reported adverse drug reactions for both drugs were more common in women, and the ratio of adverse drug reactions to prescriptions was highest in the elderly. Women aged 19 to 64 years reported more than twice as many adverse drug reactions than men of the same age, and more than 5 times in insomnia.

Conclusions: When prescribing montelukast and pranlukast, attention would need to digestive and sleep disorders, especially women aged 19 to 64. After prescribing montelukast, physicians would need to pay more attention to agitation (5/396378 vs 0/82475), bad or vivid dreams (6/396378 vs 0/82475), anxiety (11/396378 vs 0/82475), depression (14/396378 vs 1/82475), tremor (53/396378 vs 7/82475), irritability (5/396378 vs 1/82475), insomnia (159/396378 vs 25/82475), and headache (68/396378 vs 10/82475), compared to when prescribing pranlukast. Further prospective research needs to elucidate the relationship between neuropsychiatric events and montelukast.

Key words: Leukotriene receptor antagonist, sleep disorder, neuropsychiatric events, insomnia, depression

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Abbreviations:

LTRA	Leukotriene Receptor Antagonist
FDA	Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
ADRs	Adverse Drug Reactions

Abbreviations (Continued):

HIRA	Health Insurance Review & Assessment Service
KAERS	Korea Adverse Event Reporting System
WHO-ART	World Health Organization-Adverse Reaction Terminology
SOC	System Organ Class
ARRN	Adverse Reaction Record Number
BBB	Blood-Brain Barrier

Introduction

Montelukast sodium is a specific leukotriene receptor antagonist (LTRA), first approved in 1998, to prevent asthma attacks and long-term asthma treatment in adults and children 1 year and older. Over time, the indication expanded to include seasonal allergic rhinitis in 2002, perennial allergic rhinitis in patients older than 6 months in 2005, and prevention of exercise-induced bronchoconstriction in 2007.

In Korea, the prescription of perennial allergic rhinitis for infants over 6 months is allowed. Montelukast is marketed under the brand name Singulair® and as a generic. It is now available in multiple formulations and dosages.[1]

Post-marketing studies with Singulair® reported neuropsychiatric events in adult, adolescent, and pediatric patients. An index case of suicide occurred in a 15-year-old man taking montelukast in August 2007. The U.S. Food and Drug Administration (FDA) initiated a safety review of montelukast and other LRTAs.[2] A review of the clinical trial safety database did not reveal a strong correlation for neuropsychiatric events or suicidality for montelukast or other leukotriene modifiers. The FDA also selected four reviews out of 71, of which two, nested case-control studies, indicated that montelukast and neuropsychiatric adverse events were not associated while the other two reviews indicated a possible relationship.[3-6]

Data from the FDA's Sentinel System from 2010 to 2015 did not support increased risk of psychiatric events when montelukast was used compared to inhaled corticosteroids. However, the study relied on outcomes of patients who sought medical attention that were recorded in health care claims. Thus, it could not evaluate either the entire spectrum of neuropsychiatric events or events that did not result in medical attention care. In one review study, observational studies did not find a significant association, while pharmacovigilance studies using different global databases detected the signal of NEs during LTRA treatment.[7] In studies analyzing VigiBase, more frequently reported than previously thought in practice.[8] The FDA also reviewed post marketing data in the FDA Adverse Event Reporting System (FAERS) for neuropsychiatric events.[9] Analysis of the FAERS from 1998 to 2019 identified 82 cases of completed suicide in patients using the drug. The review identified a broad set of neuropsychiatric adverse events reports that were typically non-serious and reversed with therapy cessation. Based on the review of post-marketing adverse event reports, the FDA recommended adding a precaution in the product labeling to describe the variety of neuropsychiatric events reported.

The FDA stated that there is no new information to elevate the risk of neuropsychiatric adverse drug reactions (ADRs) associated with montelukast to a Boxed Warning. However, despite FDA communication efforts and product label information, concerns have been raised that many doctors and patients are not aware of the dangers of neuropsychiatric events.

We were curious about ADRs of LTRAs reported in Korea. In Korea, two LTRAs are widely used. Montelukast is the most used, and pranlukast is the second. Although information and research on the ADRs of pranlukast are quite scarce, there is a recent paper using Korean data to analyze the administration of LTRAs and the occurrence of neuropsychiatric events in the elderly and confirm that there is a correlation.[10] Therefore, we tried to analyze the ADRs of two LTRAs using Korean data reported by experts.

Materials and Methods

Data source

We retrospectively reviewed all ADRs of montelukast and pranlukast reported to the KAERS between January 2014 and December 2018. The KAERS database, which is effectively a spontaneous ADR reporting system, was established by the Korea Institute of Drug Safety and Risk Management in 2012 and comprised 27 regional pharmacovigilance centers from 2014.[11-13] Because it is difficult to estimate the population, we tried to use the number of patients who were prescribed montelukast or pranlukast as the population. During the same period as the ADR reported to KAERS, the number of patients who were prescribed both drugs were received through the Health Insurance Review & Assessment Service (HIRA) in Korea. In Korea, 97.0% of the population is obliged to register in the Korea National Health Insurance Program. As almost all prescriptions are covered by health insurance, the total usage cases of montelukast or pranlukast from HIRA data are representative.[14] KAERS data contained almost all the spontaneous ADRs reports from twenty-two tertiary referral hospitals, four secondary referral centers, and the Korean pharmaceutical association. In view of this, we considered the population using montelukast or pranlukast in tertiary referral hospitals from HIRA data only; they accounted for 2.609% (prescribed montelukast 5 years population in tertiary referral hospital 396,378 / whole 5 years population: 515,191,983) and 1.612% (prescribed pranlukast 5 years population in tertiary referral hospital 82,475 / whole 5 years population 5,087,450) of the total usage cases in all medical institutions, respectively. We chose the data for 5 years as a population. This is because when the population was selected for patients who had been prescribed for 1 year, there was overlapping data when analyzing the data for 5 years. By selecting the 5-year prescription population, we were able eliminate duplicate data, which enhanced accuracy.

Assessment of ADRs

Each case included information on the patient's age, sex, administration montelukast or pranlukast, severity and symptoms of ADRs, and identified using the World Health Organization-Adverse Reaction Terminology (WHOART) coding dictionary without individual identification.[15] We considered that multiple ADR symptoms may be observed in each patient. In such cases, the data were divided into each ADR and processed. Data analyzed with system organ class (SOC) classification and Adverse Reaction Record Number (ARRN). The SOCs and ARRN were also coded using the WHO-ART. The causality assessment results for each ADR by the WHO criteria were recorded in the reporters' database. The serious ADRs included the following classifications: (1) death; (2) life-threatening event; (3) causing or prolongation of hospitalization; (4) causing persistent, significant disability or incapacity; (5) resulting in a congenital anomaly or birth defect; and (6) others of medical significance. The WHO causality assessment tool was used in the reported ADRs to confirm the relationship between suspected and adverse reactions. Six categories for the evaluation of the causal relationship were: (1) certain, (2) probable, (3) possible, (4) unlikely, (5) conditional or unclassified, or (6) inaccessible/unclassifiable. From these, we selected only three categories as causal ADRs: certain, probable, and possible.

Results

Characteristics of reported ADRs of montelukast & pranlukast

ADRs of montelukast and pranlukast increased over the years. Reports of ADRs increased especially in 2018 and similar trends were observed regardless of gender (**Figure 1A**). ADRs of montelukast were reported in 0.372% of cases during the total prescription of 5 years. Between 2014 and 2018, the number of patients who received montelukast increased by 19,484 (15.21%), and the number of patients who had been prescribed pranlukast slightly decreased. When looking at the prescriptions of antihistamines between 2010 and 2018, it was reported that the prescription of first-generation antihistamines decreased and the prescription of LTRAs increased. LTRAs are more effective when used in combination with other medications and are considered relatively safe for children, and by the end of 2017 LTRAs are reimbursed even when prescribed as a first-line treatment. In addition, montelukast had the advantage of being a once-a-day drug. For this reason, the prescriptions of montelukast would have increased.[16] However, in both LTRAs, compared with 2014, the number of ADRs reported cases increased by two-fold in 2018. It is possible that the sudden increase

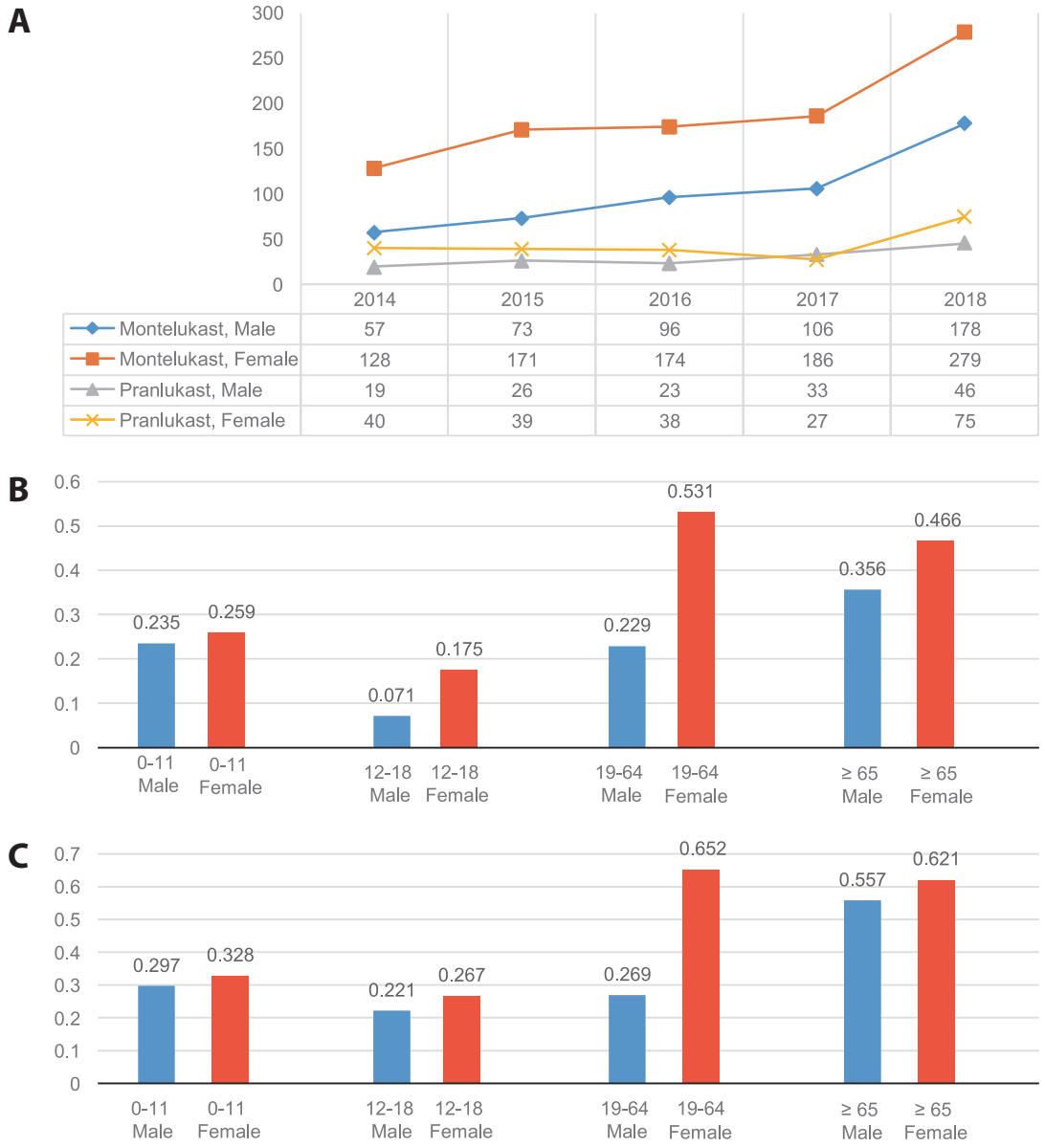

Figure 1.

A. ADRs of montelukast and pranlukast classified by years and sex

B. ADRs of montelukast classified by age and sex

The population was the number of patients for 5 years for whom the montelukast was prescribed, classified by age and sex, respectively. ADR reported by age and sex were divided into each population and compared in percentage (%).

C. ADRs of pranlukast classified by age and sex

The population was the number of patients for 5 years for whom the pranlukast was prescribed, classified by age and sex, respectively. ADR reported by age and sex were divided into each population and compared in percentage (%).

in the number of reported depressions in 2018 was an impact observed worldwide as a notable adverse effect of montelukast, or, conversely, it could be related to an increase in reporting of all ADRs. According to the 2019 Pharmaceutical Safety Information Report Trend prepared by the Korea Institute of Drug Safety and Risk Management, the number of ADRs reports is 183,554 in 2014, 198,037 in 2015, 228,939 in 2016, 252,611 in 2017, and 257,438 in 2018 (**Table 1**).[17]

We tried to determine the ADRs reporting rate compared to the number of patients prescribed by age and sex. The population was the number of patients for 5 years for whom the drug was prescribed, classified by age and sex, respectively. ADRs reported by age and sex were divided into each population and compared in percentage (%). The use and ADRs decreased in those aged 12 to 18 years. This may have been related to the nature of the disease for which the drug is used,

Table 1. Characteristics of reported montelukast & pranlukast ADRs.

Variables	Montelukast Cases no.		Pranlukast Cases no.	
	Reported ADRs (N = 1475)	Prescribed population*	Reported ADRs (N = 374)	Prescribed population**
Year				
2014	192 (0.177%)	108622	62 (0.279%)	22244
2015	247 (0.215%)	115022	66 (0.297%)	22203
2016	276 (0.227%)	121396	62 (0.276%)	22454
2017	296 (0.237%)	124965	61 (0.306%)	19951
2018	464 (0.362%)	128106	123 (0.601%)	20481
5 years	1475 (0.372%)	396378	374 (0.453%)	82475
Sex				
Male	510 (0.259%)	196904	147 (0.055%)	43441
Female	938 (0.47%)	199474	219 (0.088%)	39034
Blank	27		8	
Age (yr)	47.85 ± 23.96		45.92 ± 26.45	
0-11	217 (0.248%)	87625	79 (0.31%)	25499
Male	125 (0.235%)	53286	45 (0.297%)	15131
Female	89 (0.259%)	34339	34 (0.328%)	10368
Blank	3		0	
12-18	27 (0.112%)	24175	8 (0.236%)	3388
Male	11 (0.071%)	15584	5 (0.221%)	2265
Female	15 (0.175%)	8591	3 (0.267%)	1123
Blank	1		0	
19-64	804 (0.403%)	199645	180 (0.484%)	37206
Male	206 (0.229%)	89960	48 (0.269%)	17874
Female	582 (0.531%)	109685	126 (0.652%)	19332
Blank	16		6	
≥ 65	389 (0.417%)	93307	102 (0.595%)	17151
Male	152 (0.356%)	42661	48 (0.557%)	8615
Female	236 (0.466%)	50646	53 (0.621%)	8536
Blank	1		1	

The population is the number of patients who have been prescribed the montelukast* or pranlukast** for 5 years in tertiary referral hospital from HIRA data. ADRs are divided into each population and expressed as percent (%) in parentheses. ADRs: Adverse Drug Reactions, HIRA: Health Insurance Review & Assessment Service

such as asthma and allergic rhinitis.[18] People between the ages of 19 and 64 have had a high use of LTRAs, and this population has the most reported ADRs. Women reported approximately 1.81 times more ADRs than men. In those aged 12 to 18, ADRs were reported approximately 2.46 times more in women than in men and, in those aged 19 to 64, approximately 2.32 times more in women than in men. For those over 65 years old, the ratio of ADRs to prescriptions was highest at 0.417% (**Figure 1B, Table 1**).

ADRs of pranlukast were reported in 0.453% of cases during the total prescription of 5 years. The population receiving pranlukast showed little difference from year to year. But, compared to 2014, reported ADRs increased by approximately 1.98 times in 2018. Like montelukast, use and ADRs were reduced in those aged 12 to 18 years. The highest usage was among those aged 19 to 64 years old, as were the most reported ADRs. Over 65 years old, the ratio of ADRs to prescriptions was the highest at 0.595%. Women reported approximately 1.60 times more ADRs than men. ADRs were reported approximately 2.42 times more in women than in men in those aged 19 to 64 (**Figure 1C, Table 1**).

ADRs of montelukast and pranlukast classified by SOCs

ADRs of montelukast and ADRs of pranlukast were classified by SOCs of WHO-ART and four identical SOCs were selected in order of number of reports. These four SOCs account for 86.6% of the total ADRs of montelukast over five years. Gastro-intestinal (GI) system was the most common (27%) among men, followed by psychiatric system (26%). Among women, psychiatric system was the most common (30%), and gastro-intestinal system (29%) was the next (**Figure S1 A, B**). Gastrointestinal systems and psychiatric disorders in SOC accounted for more than half of ADRs. There was a slight difference in the ratio of SOC between genders, but the overall composition was similar. In comparison to the percentage, ADRs were 1.94 times higher in gastro-intestinal system, 2.07 times higher in psychiatric system, 1.75 times higher in central & peripheral nervous system, and 1.82 times higher in skin & appendages in women compared to men. Psychiatric ADRs were the most reported among patients aged 19 to 64, with women 2.42 times higher in comparison to the percentage than men. In other age groups, gastro-intestinal system ADRs were the most reported, and psychiatric system ADRs were second most reported (**Table 2**).

These four SOCs account for 88.2% of the total ADRs of pranlukast over five years. Among men, gastro-intestinal system was the most common (35%), and the psychiatric system (22%) was the next. Among women, gastro-intestinal system was the most common (40%), and the psychiatric system (20%) was the next (**Figure S1 C, D**) . Like montelukast gastrointestinal systems and psychiatric disorders in SOC accounted for more than half of ADRs. There was a slight difference in the ratio of SOC between genders, but the overall composition was similar. In comparison to the percentage, ADRs were 1.88 times higher in gastro-intestinal system, 1.49 times higher in psychiatric system, 1.93 times higher in central & peripheral nervous system, and 1.16 times higher in skin & appendages in women compared to men. At all ages, gastro-intestinal system ADRs were the most reported, and psychiatric ADRs were second most reported. Psychiatric ADRs were reported 3.05 times more in women than men in aged 19 to 64 in comparison to the percentage (**Table 2**).

ADRs of montelukast according to ARRN

To see the symptoms, ADRs of montelukast divided into ARRN which is the sub-item of SOC. 11 ARRNs were selected in order of number of reports. Diarrhea, nausea, dyspepsia, somnolence, insomnia, headache, dizziness, tremor, pruritus, rash, and urticaria accounted for 74.3% of the total ADRs. The most reported ADR was somnolence, followed by insomnia. The most common symptom in both men and women was somnolence; however, the second most common symptom in men was diarrhea, and the second most common symptom in women was insomnia (**Figure S1 E, F**). Under the age of 11, diarrhea was the most prevalent symptom, followed by insomnia and somnolence respectively. Somnolence and insomnia were reported first and second among those aged 19 to 64, compared with percentage 1.98 times more and 5.08 times more in women than men. Over 65 years old, insomnia was most reported, followed by dyspepsia and somnolence respectively (**Table 3**).

ADRs of pranlukast according to ARRN

ADRs of pranlukast were also divided into ARRN (**Table 4**). Based on the number of reports, 11 ARRNs were selected, including diarrhea, nausea, dyspepsia, constipation, dry mouth, somnolence, insomnia, dizziness, pruritus, rash and urticaria which accounted for 74.5% of the total ADRs. Compared to montelukast, 7 cases of headache and 3 cases of tremor were excluded from the table because of fewer reports. Instead, there were many reports of constipation and dry mouth. The most reported ADR was diarrhea, followed by somnolence. Among men, somnolence was the most common (16%), followed by diarrhea (12%) and rash respectively. Among women diarrhea was the most common symptom (13%), followed by somnolence (9%) and constipation respectively (**Figure S1 G, H**). Diarrhea was the most common symptom which is the same as montelukast for children below 11 years old. Somnolence and urticaria and pruritus were followed respectively. Somnolence was most commonly reported, followed by diarrhea among those aged 19 to 64. In comparison to the percentage, women aged 19 to 64 reported 2.12 times more in somnolence and 6.83 times more in insomnia than men. Over 65 years old, somnolence was the most reported, followed by dizziness and insomnia respectively (**Table 4**).

Severe ADRs of montelukast & pranlukast according to ARRN

We summarize the serious ADRs of montelukast and pranlukast (**Table 5**). It can be divided into ADRs that require hospitalization and ADRs that do not require hospitalization but that physicians should be pay attention. Among patients who were prescribed montelukast, 11 cases of serious ADRs required hospitalization in 5 years. 2 cases of depression and 1 case of somnolence were reported as medically important situations. Of the total ADRs, 12 cases of depression and 4 cases of convulsion were not reported as serious ADRs.

Table 2. ADRs of montelukast and pranlukast classified by SOC.

Variables	Montelukast Cases no.					Pranlukast Cases no.				
	Gastro - intestinal (600)	Psychiatric (500)	Central & peripheral nervous (410)	Skin & appendages (100)	Prescribed population	Gastro - intestinal (600)	Psychiatric (500)	Central & peripheral nervous (410)	Skin & appendages (100)	Prescribed population
Year										
2014	49	48	38	34	108622	27	6	5	11	22244
2015	73	58	43	42	115022	29	19	8	10	22203
2016	87	76	42	35	121396	25	8	11	10	22454
2017	71	99	53	46	124965	21	14	10	9	19951
2018	136	133	68	46	128106	39	32	18	18	20481
5 years	416	414	244	203	396378	141	79	52	58	82475
Sex										
Male	138 (0.07%)	131 (0.067%)	87 (0.044%)	67 (0.034%)	196904	52 (0.12%)	32 (0.074%)	19 (0.044%)	28 (0.064%)	43441
Female	272 (0.136%)	278 (0.139%)	154 (0.077%)	124 (0.062%)	199474	88 (0.225%)	43 (0.11%)	33 (0.085%)	29 (0.074%)	39034
Age (yr)	48.02 ± 25.21	48.43 ± 22.38	52.88 ± 20.58	46.44 ± 22.54		41.4 ± 27.71	47.67 ± 27.97	56.67 ± 20.9	40.7 ± 25.1	
0-11	71 (0.081%)	48 (0.055%)	15 (0.017%)	22 (0.025%)	87625	40 (0.157%)	16 (0.063%)	3 (0.012%)	12 (0.047%)	25499
Male	40 (0.075%)	22 (0.041%)	9 (0.017%)	14 (0.026%)	53286	21 (0.139%)	11 (0.073%)	2 (0.013%)	7 (0.046%)	15131
Female	31 (0.09%)	25 (0.073%)	5 (0.015%)	8 (0.023%)	34339	19 (0.183%)	5 (0.048%)	1 (0.01%)	5 (0.048%)	10368
12-18	9 (0.037%)	7 (0.029%)	2 (0.008%)	7 (0.029%)	24175	4 (0.118%)	2 (0.059%)	0 (0%)	2 (0.059%)	3388
Male	1 (0.006%)	4 (0.026%)	1 (0.006%)	2 (0.013%)	15584	2 (0.088%)	2 (0.088%)	0 (0%)	1 (0.044%)	2265
Female	7 (0.081%)	3 (0.035%)	1 (0.012%)	4 (0.047%)	8591	2 (0.178%)	0 (0%)	0 (0%)	1 (0.089%)	1123
19-64	212 (0.106%)	247 (0.124%)	136 (0.068%)	125 (0.063%)	199645	65 (0.175%)	34 (0.091%)	27 (0.073%)	30 (0.081%)	37206
Male	48 (0.053%)	62 (0.069%)	37 (0.041%)	38 (0.042%)	89960	11 (0.062%)	7 (0.039%)	6 (0.034%)	17 (0.095%)	17874
Female	161 (0.147%)	183 (0.167%)	98 (0.089%)	78 (0.071%)	109685	53 (0.274%)	23 (0.119%)	21 (0.109%)	13 (0.067%)	19332
≥ 65	116 (0.124%)	100 (0.107%)	82 (0.088%)	42 (0.045%)	93307	32 (0.187%)	27 (0.157%)	21 (0.122%)	12 (0.07%)	17151
Male	44 (0.103%)	39 (0.091%)	34 (0.08%)	13 (0.03%)	42661	18 (0.209%)	12 (0.139%)	11 (0.128%)	3 (0.035%)	8615
Female	71 (0.14%)	61 (0.12%)	48 (0.095%)	29 (0.057%)	50646	14 (0.164%)	15 (0.176%)	10 (0.117%)	8 (0.094%)	8536

ADRs, Adverse Drug Reactions; SOC, System Organ Class

Table 3. ADRs of montelukast classified by ARRN (SOC).

Variables	Cases no.											
	Diarrhea (600)	Nausea (600)	Dyspepsia (600)	Somnolence (500)	Insomnia (500)	Headache (410)	Dizziness (410)	Tremor (410)	Pruritus (100)	Rash (100)	Urticaria (100)	Prescribed population
Year												
2014	8	8	19	15	24	13	12	10	13	11	9	108622
2015	19	14	16	29	25	7	19	11	21	15	13	115022
2016	26	12	22	40	28	16	17	7	14	13	14	121396
2017	21	12	24	47	38	12	20	16	15	15	10	124965
2018	49	14	47	67	44	20	30	9	14	17	15	128106
5 years	123	60	128	198	159	68	98	53	77	71	61	396378
Sex												
Male	61	17	32	62	45	28	34	12	29	18	19	196904
Female	61	41	95	135	113	40	62	41	45	49	38	199474
Age (yr)	32.29 ± 28.33	52.10 ± 21.10	59.56 ± 15.09	48.68 ± 19.91	49.85 ± 23.67	55.75 ± 18.82	54.39 ± 18.64	47.00 ± 23.48	52.14 ± 21.41	46.08 ± 22.83	42.14 ± 23.32	
0-11	53	1	1	13	23	2	2	8	6	9	8	87625
Male	34 (0.064%)	0 (0%)	1 (0.002%)	5 (0.009%)	12 (0.023%)	2 (0.004%)	1 (0.002%)	5 (0.009%)	4 (0.008%)	4 (0.008%)	6 (0.011%)	53286
Female	19 (0.055%)	1 (0.003%)	0 (0%)	7 (0.02%)	11 (0.032%)	0 (0%)	0 (0%)	3 (0.009%)	2 (0.006%)	5 (0.015%)	2 (0.006%)	34339
12-18	1	4	2	6	0	0	1	0	2	2	4	24175
Male	0 (0%)	0 (0%)	1 (0.006%)	3 (0.019%)	0 (0%)	0 (0%)	1 (0.006%)	0 (0%)	1 (0.006%)	0 (0%)	1 (0.006%)	15584
Female	0 (0%)	4 (0.047%)	1 (0.012%)	3 (0.035%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.012%)	2 (0.023%)	2 (0.023%)	8591
19-64	45	34	80	135	85	38	61	30	43	44	38	199645
Male	15 (0.017%)	6 (0.007%)	18 (0.02%)	40 (0.044%)	12 (0.013%)	12 (0.013%)	17 (0.019%)	5 (0.006%)	14 (0.016%)	12 (0.013%)	10 (0.011%)	89960
Female	30 (0.027%)	26 (0.024%)	61 (0.056%)	95 (0.087%)	72 (0.066%)	26 (0.024%)	43 (0.039%)	25 (0.023%)	27 (0.025%)	28 (0.026%)	26 (0.024%)	109685
≥ 65	22	21	43	38	49	24	32	15	24	13	9	93307
Male	10 (0.023%)	11 (0.026%)	11 (0.026%)	12 (0.028%)	21 (0.049%)	11 (0.026%)	14 (0.033%)	2 (0.005%)	10 (0.023%)	2 (0.005%)	2 (0.005%)	42661
Female	12 (0.024%)	10 (0.02%)	32 (0.063%)	26 (0.051%)	28 (0.055%)	13 (0.026%)	18 (0.036%)	13 (0.026%)	14 (0.028%)	11 (0.022%)	7 (0.014%)	50646

ADRs, Adverse Drug Reactions; ARRN, Adverse Reaction Record Number; SOC, System Organ Class

Table 4. ADRs of pranlukast classified by ARRN (SOC).

Variables	Cases no.											
	Diarrhea (600)	Nausea (600)	Dyspepsia (600)	Somnolence (500)	Insomnia (500)	Headache (410)	Dizziness (410)	Tremor (410)	Pruritus (100)	Rash (100)	Urticaria (100)	Prescribed population
Year												
2014	5	0	10	9	2	1	4	2	6	1	4	22244
2015	8	6	2	3	7	13	4	4	5	4	3	22203
2016	12	6	2	2	0	6	1	7	3	0	6	22454
2017	7	2	4	4	2	8	6	5	3	3	2	19951
2018	15	4	4	8	4	16	10	7	6	8	3	20481
5 years	47	18	22	26	15	44	25	25	23	16	18	82475
Sex												
Male	18	9	8	8	3	23	6	8	9	10	8	43441
Female	29	9	14	18	12	20	17	17	14	6	9	39034
Age (yr)	26.67 ± 26.86	36.28 ± 29.71	57.50 ± 18.72	52.96 ± 25.39	51.33 ± 17.71	46.40 ± 25.87	53.04 ± 26.47	60.75 ± 15.86	39.29 ± 26.61	46.13 ± 23.28	35.17 ± 26.90	
0-11	25	5	1	5	0	7	4	0	6	2	6	25499
Male	14 (0.093%)	3 (0.02%)	0 (0%)	1 (0.007%)	0 (0%)	6 (0.04%)	2 (0.013%)	0 (0%)	3 (0.02%)	2 (0.013%)	3 (0.02%)	15131
Female	11 (0.106%)	2 (0.019%)	1 (0.01%)	4 (0.039%)	0 (0%)	1 (0.01%)	2 (0.019%)	0 (0%)	3 (0.029%)	0 (0%)	3 (0.029%)	10368
12-18	1	3	0	0	0	2	0	0	1	0 (0%)	0 (0%)	3388
Male	1 (0.044%)	1 (0.044%)	0 (0%)	0 (0%)	0 (0%)	2 (0.088%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2265
Female	0 (0%)	2 (0.178%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.089%)	0 (0%)	0 (0%)	1123
19-64	17	6	12	12	11	21	11	13	10	10	7	37206
Male	1 (0.006%)	1 (0.006%)	3 (0.017%)	3 (0.017%)	2 (0.011%)	6 (0.034%)	1 (0.006%)	2 (0.011%)	5 (0.028%)	7 (0.039%)	3 (0.017%)	17874
Female	16 (0.083%)	5 (0.026%)	9 (0.047%)	9 (0.047%)	9 (0.047%)	14 (0.072%)	8 (0.041%)	11 (0.057%)	5 (0.026%)	3 (0.016%)	4 (0.021%)	19332
≥ 65	4	4	9	9	4	14	10	11	4	4	5	17151
Male	2 (0.023%)	4 (0.046%)	5 (0.058%)	4 (0.046%)	1 (0.012%)	9 (0.104%)	3 (0.035%)	6 (0.07%)	1 (0.012%)	1 (0.012%)	2 (0.023%)	8615
Female	2 (0.023%)	0 (0%)	4 (0.047%)	5 (0.059%)	3 (0.035%)	5 (0.059%)	7 (0.082%)	5 (0.059%)	3 (0.035%)	3 (0.035%)	2 (0.023%)	8536

ADRs, Adverse Drug Reactions; ARRN, Adverse Reaction Record Number; SOC, System Organ Class

Table 5. Severe ADRs of montelukast and pranlukast classified by ARRN.

ARRN	Montelukast cases no.	Pranlukast cases no.
	Serious ADRs for admission	
Rash	1	
Sweating increased	1	
Palpitation	1	
Vomiting	1	
Abdominal pain	1	
Nausea	1	
Chest pain	1	
Fever	1	
Drug hypersensitivity syndrome	3	
Urticaria		1
Dyspnoea		1
Face oedema		1
	Serious ADRs for other	
Angioedema	1	
Depression	2	
Somnolence	1	
Nausea	1	
Stomatitis	1	
Thrombocytopenia	1	
Face oedema	2	
Fatigue	1	
Dizziness	2	1
Palpitation		1
Aortic stenosis		1
Cardiac failure		1
Anaphylactic shock		2
Heart valve disorders		1
Cardiomegaly		1
Anaphylactic reaction		1

ADRs, Adverse Drug Reactions; ARRN, Adverse Reaction Record Number

Among the patients who were prescribed pranlukast, 3 cases of serious ADRs required hospitalization in 5 years. Of the ADRs classified as medically important, depression has been reported 0 times. Of the total ADRs, 1 cases of depression and 1 cases of convulsion were not reported as serious ADRs. The standards were not clear and difficult to confirm due to reports by health professionals at each hospital.

Neuropsychiatric events of montelukast and pranlukast

By comparing montelukast with other LTRAs, pranlukast, which has the same mechanism of action, we tried to find out whether montelukast showed different ADRs than pranlukast. On the current montelukast product label (last updated 08/2019), patients and prescribers should be alert for neuropsychiatric events. According to FDA-approved patient labeling, 'PATIENT COUNSELING INFORMATION', health provider, patients, and parents are required to be cautious of the following neuropsychiatric events: agitation including aggressive behavior or hostility, memory problems, obsessive-compulsive symptoms, attention problems, restlessness, bad or vivid dreams, sleep walking, depression, stuttering, disorientation (confusion), suicidal thoughts, and actions (including suicide), feeling anxious, hallucinations (seeing or hearing things that are not really there), tremor, trouble sleeping, irritability, and uncontrolled muscle movements. Statistics and analysis based on the FAERS Database of montelukast's neuropsychiatric events can be found in an FDA document summarizing the Pediatric Advisory Committee Meeting September 27, 2019. Paresthesia, hypoesthesia, and headache are also remarkable neuropsychiatric events associated with the drug. We divided these items and the items presented in 'PATIENT COUNSELING INFORMATION' by WHO ARRN, then compared montelukast and pranlukast based on the KAERS database. ADRs that were not seen in both drugs were excluded. Restlessness, when divided by WHO ARRN, belonged to the agitation category. Agitation, bad or vivid dreams, stuttering, anxiety, or hallucination were not reported for pranlukast. Depression was reported 14 times in the context of montelukast usage, but only one time with pranlukast. Analyzed by age, depression was reported by two persons aged 0-11, one patient aged 12-18 years, 10 persons aged 19-64 years, and no one aged 65 years or older. Among these cases, all 0-11 years old were women, 12-18 years old were men. From 19-64 years old, there were 4 men and 5 women. Age was not known for 1 man. Three cases related to suicide were reported in montelukast, but since the association was not clear, it was excluded from the analysis. As the number of reports related to the above items was small, it was difficult to compare with the population as in the above analysis, so the comparison was made only by the number of reports (**Table 6**).

Table 6. Neuropsychiatric events of montelukast and pranlukast on FDA-approved patient labeling.

Variables	Cases no.													
	Agitation	Aggressive reaction	Bad or vivid dreams	Depression	Stuttering	Anxiety	Hallucination	Tremor	Somnolence	Insomnia	Irritability	Paresthesia	Convulsions	Headache
Montelukast														
Year														
2014	1	0	1	2	0	4	1	10	15	24	0	1	0	13
2015	0	1	0	0	0	2	0	11	29	25	0	2	1	7
2016	0	0	0	1	0	1	0	7	40	28	1	1	0	16
2017	1	1	1	2	0	3	1	16	47	38	3	4	1	12
2018	3	1	4	9	1	1	0	9	67	44	1	6	2	20
5 years	5	3	6	14	1	11	2	53	198	159	5	14	4	68
Sex														
Male	3	2	1	6	0	2	0	12	62	45	2	3	1	28
Female	2	1	5	7	1	9	1	41	135	113	3	11	3	40
Pranlukast														
Year														
2014	0	1	0	0	0	0	0	1	1	4	0	0	0	1
2015	0	0	0	0	0	0	0	1	13	4	0	1	0	2
2016	0	0	0	0	0	0	0	0	6	1	0	0	0	1
2017	0	0	0	0	0	0	0	2	8	6	0	0	0	3
2018	0	2	0	1	0	0	0	3	16	10	1	3	1	3
5 years	0	3	0	1	0	0	0	7	44	25	1	4	1	10
Sex														
Male	0	0	0	0	0	0	0	4	23	6	1	1	1	3
Female	0	3	0	1	0	0	0	3	20	17	0	3	0	7

FDA, Food and Drug Administration

Discussion

In our data, ADRs related to montelukast or pranlukast were more common in women. Especially, women aged 19 to 64 years reported more than twice as many ADRs than men of the same age, and more than 5 times in insomnia. Therefore, it is necessary to check for digestive discomfort and sleep disturbances after LTRAs was prescribed for 19 to 64 years women. Because the ratio of ADRs to prescriptions was highest in the elderly, education and continuous attention to health encounters is required. It seems that insomnia, somnolence, dyspepsia, and dizziness need to be noted in the elderly. People under the age of 11 need to be careful about diarrhea and somnolence and seem to be more careful about insomnia when receiving montelukast. Given the difficulty of explaining ADRs to children, physicians should instead explain ADRs to parents in detail and inform them that observation is necessary. When montelukast is prescribed, insomnia seems to be more cautious than pranlukast at all ages.

In montelukast, somnolence was reported as 159/396378, insomnia as 128/396378, and dyspepsia as 128/396378 in that order. In pranlukast, diarrhea was reported as 47/82475, somnolence as 44/82475 and constipation as 26/82475 constipation in that order. Montelukast and pranlukast differed in the ratio of ADRs classified as ARRN and in 2 of the 11 ARRN entries, but the composition looked similar. It is general knowledge that attention would need to neuropsychiatric events when prescribed these drugs. We separately analyzed the neuropsychiatric event that the FDA recommends that clinicians pay attention to. The total prescription amount of montelukast and pranlukast differed by 4.81 times and the total ADRs by 3.94 times over 5 years. In consideration of this, agitation, bad or vivid dreams, anxiety, depression, tremor, irritability, insomnia and headache that were reported more than 5 times in people who were prescribed montelukast compared to those who prescribed pranlukast (assuming 1 if the number of reports is 0). It seems that more attention should be paid when receiving montelukast for these neuropsychiatric events. However, it is difficult to derive accurate results by simple number comparison.

According to one study, depression was reported most frequently in the whole population of the global database VigiBase. In VigiBase, aggression was reported the most in children. In turn, headaches were reported most frequently in the Dutch database. Health professionals, patients, and some pharmaceutical companies report their experience of suspected ADRs to their national pharmacovigilance center.[19] In our study, when the ADRs of montelukast and pranlukast were classified as SOC, the GI system was the most common and the psychiatric system was the next. In one systemic review study, predominantly gastrointestinal and neuropsychiatric disorders.[20] This is particularly noticeable in women between the ages of 19 and 64. The effect of LTRAs on the GI system is also considered to be evaluated.

It is not clear whether LTRAs affects the human nervous system. But animal studies have suggested that montelukast can act directly on brain cells. Orally administered montelukast (10 mg/kg/day for 7 days) is detectable in the brain tissue and cerebrospinal fluid of rats, providing evidence of its ability to cross the blood-brain barrier (BBB).[21] One study suggested that there may be a mechanism for active transport of montelukast.[22]

In our study, the proportion of ADRs in elderly patients was higher than in those who were prescribed. In particularly, it was highly associated with sleep disorder. Originally, the elderly population was the age at which psychiatric problems appeared, and a study was conducted to determine whether it was related to this or whether it was related to the prescription of LTRAs. This study showed that the use of LTRAs was correlated with sleep disorder, mood disorder, and anxiety disorder. In addition, ADRs may occur immediately after stopping the drug, and the rate of ADRs occurring after 120 days of using the drug is low.[10] When older, brain declines in cognitive function due to neuroinflammation and BBB disruption. LTRAs also play a role in restoring the BBB, but this is situation dependent.[22] It also resulted in lower proliferation in the hippocampus under normal conditions.[23] When binding to the cysLT1 receptor, LTRA produces nitric oxide, which can damage brain tissue.[24] Rather, there are many things that need to be studied in the future whether it adversely affects the brain, which was in equilibrium, causing problems in behavior.

Only when a simple comparison is made compared to the prescribed amount, there are parts where montelukast reports more neuropsychiatric ADRs than pranlukast as shown in **Table 4**. Of course, montelukast is more commonly prescribed than pranlukast, and in fact, it is prescribed 5 times as often. This is because using it once a day is a huge advantage. In the real world, the prevalence of allergic rhinitis and the severity of asthma among prescribed patients may also differ. Some studies showed that pranlukast can also affect the brain.[25,26] One study reported that the leukotriene C4 synthase genotype had a greater effect, although plasma concentrations of pranlukast varied among individuals and had minimal clinical effects on asthma.[27] Although higher concentrations of pranlukast were required compared to montelukast, one study found that it improved seizures and dysfunction of the BBB.[25] Several studies were underway regarding the Cys-LT receptor antagonist effects on the nervous system, but precise mechanisms have not been revealed.[23] If montelukast passes through BBB and causes neuropsychiatric problems and if it is related to the function of LTRAs, we thought that other drugs in the same family could also cause neuropsychiatric problems. The US FDA has issued safety alerts and required manufacturers of LTRAs including montelukast, zafirlukast, and zileuton, to include suicide and neuropsychiatric warnings. Studies conducted by pharmaceutical companies reported neuropsychiatric events such as insomnia and depression associated to the use of zafirlukast and zileuton, but events related to suicidality were not reported.[28]

The limitation of this study is difficult to know the population, so it was estimated based on HIRA data. In addition, as mentioned above, it was difficult to accurately analyze neuropsychiatric events requiring attention because only the number of reports was compared. Also, underreporting may be possible as the ADRs data in Korea was reported by health professionals (physician, dentist, nurse, and pharmacist). Conversely, the strength of this paper is to select only ADRs

that have more than possible relationship with the judgment of the expert group. Analysis of the causes that may affect ADRs seems to be need. It may be necessary to consider the prevalence of general psychiatric diseases and the prevalence of psychiatric diseases in groups of diseases such as asthma and allergic rhinitis which mainly use montelukast. Some studies that reported the risk of suicidal ideation, attempts and mortality in asthmatics compared with non-asthmatics. Especially adolescent asthmatic patients had a more than 2-fold risk of suicide mortality compared to non-asthmatic controls.[29] The brains of mice with allergic rhinitis showed higher levels of proinflammatory cytokines and more behavioral problems compared to the control group. The mechanism by which cytokine increase affects hippocampus has not been elucidated.[30] We wanted to know about the improvement of symptoms after stopping the drug and the period of ADRs after using montelukast. However, the analysis was not possible due to the large amount of missing data.

In conclusion, both pranlukast and montelukast, attention should be paid to digestive problems and sleep disturbances. Especially women aged 19 to 64 seem to be cautious after prescribing LTRAs and whether insomnia should be checked after prescribing montelukast, physicians are more likely to pay more attention to agitation (5/396378 vs 0/82475), bad or vivid dreams (6/396378 vs 0/82475), anxiety (11/396378 vs 0/82475), depression (14/396378 vs 1/82475), tremor (53/396378 vs 7/82475), irritability (5/396378 vs 1/82475), insomnia (159/396378 vs 25/82475), and headache (68/396378 vs 10/82475) than when prescribing pranlukast. Prospective study is required to be certain about this.

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Conflict of interest Statement

All authors declare that they have no conflicts of interest to disclose.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent from participants was not required in accordance with local/national guidelines.

References

1. U.S. Food & Drug Adiministration (FDA). September 27, 2019: Meeting of the Pediatric and Drug Safety and Risk Management Committees. Vol. 2020. Silver Spring (MD): U.S. Food & Drug Adiministration (FDA); 2019.
2. U.S. Food & Drug Administration (FDA). Updated information on leukotriene inhibitors: montelukast (marketed as Singulair), zafirlukast (marketed as Accolate), and zileuton (marketed as Zyflo and Zyflo CR). Vol. 2020. Silver Spring (MD): U.S. Food & Drug Administration (FDA); 2009.
3. Schumock GT, Stayner LT, Valuck RJ, Joo MJ, Gibbons RD, Lee TA. Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: a nested case-control study. J Allergy Clin Immunol. 2012;130:368-75.
4. Ali MM, O'Brien CE, Cleves MA, Martin BC. Exploring the possible association between montelukast and neuropsychiatric events among children with asthma: a matched nested case-control study. Pharmacoepidemiol Drug Saf. 2015;24:435-45.
5. Glockler-Lauf SD, Finkelstein Y, Zhu J, Feldman LY, To T. Montelukast and Neuropsychiatric Events in Children with Asthma: A Nested Case-Control Study. J Pediatr. 2019;209:176-82 e4.
6. Benard B, Bastien V, Vinet B, Yang R, Krajinovic M, Ducharme FM. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. Eur Respir J. 2017;50:1700148.
7. Law SWY, Wong AYS, Anand S, Wong ICK, Chan EW. Neuropsychiatric Events Associated with Leukotriene-Modifying Agents: A Systematic Review. Drug Saf. 2018;41:253-65.
8. Aldea Perona A, Garcia-Saiz M, Sanz Alvarez E. Psychiatric Disorders and Montelukast in Children: A Disproportionality Analysis of the VigiBase((R)). Drug Saf. 2016;39:69-78.
9. U.S. Food & Drug Administration (FDA). FDA Adverse Event Reporting System (FAERS) public dashboard. Vol. 2020. Silver Spring (MD): U.S. Food & Drug Administration (FDA); 2019.
10. Kang SO, Min KH, Kim HJ, Kim TH, Kim W, Lee KE. The role of leukotriene modifying agent treatment in neuropsychiatric events of elderly asthma patients: a nested case control study. Asthma Res Pract. 2021;7:4.
11. Chae JI, Baek YH, Jeon HL, Lee EK, Shin J-Y. [The comparison of spontaneous adverse event reporting between consumers and healthcare professionals using Korea Adverse Event Reporting System (KAERS) database]. Journal of Korean Academy of Social & Managed Care Pharmacy. 2017;6:31-7.
12. Shin YS, Lee YW, Choi YH, Park B, Jee YK, Choi SK, et al. Spontaneous reporting of adverse drug events by Korean regional pharmacovigilance centers. Pharmacoepidemiol Drug Saf. 2009;18:910-5.
13. Choi NK, Park BJ. [Adverse drug reaction surveillance system in Korea]. J Prev Med Public Health. 2007;40:278-84.
14. An J, Jung H, Kwon OY, Kang Y, Lee JH, Won HK, et al. Differences in Adverse Reactions Among Iodinated Contrast Media: Analysis of the KAERS Database. J Allergy Clin Immunol Pract. 2019;7:2205-11.
15. Korea Institute of Drug Safety & Risk Management. [WHO-ART 092 Korean terminology]. Vol. 2020. Anyang-si, Republic of Korea: Korea Institute of Drug Safety & Risk Management; 2015.
16. Son J, Kim ES, Choi HS, Ha IH, Lee D, Lee YJ. Prescription rate and treatment patterns for allergic rhinitis from 2010 to 2018 in South Korea: a retrospective study. Clin Mol Allergy. 2021;19:20.
17. Korea Institute of Drug Safety & Risk Management. [2019 pharmaceutical safety information report trend]. Vol. 2020. Anyang-si, Republic of Korea: Korea Institute of Drug Safety & Risk Management; 2019.
18. Lee YJ, Kim CK. Montelukast use over the past 20 years: monitoring of its effects and safety issues. Clin Exp Pediatr. 2020;63:376-81.
19. Haarman MG, van Hunsel F, de Vries TW. Adverse drug reactions of montelukast in children and adults. Pharmacol Res Perspect. 2017;5: e00341.
20. Dixon EG, Rugg-Gunn CE, Sellick V, Sinha IP, Hawcutt DB. Adverse drug reactions of leukotriene receptor antagonists in children with asthma: a systematic review. BMJ Paediatrics Open. 2021;5:e001206.
21. Marschallinger J, Schaffner I, Klein B, Gelfert R, Rivera FJ, Illes S, et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. Nat Commun. 2015;6:8466.
22. Marschallinger J, Schaffner I, Klein B, Gelfert R, Rivera FJ, Illes S, et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. Nat Commun. 2015;6:8466.
23. Eriksson Y, Bostrom M, Sandelius A, Blennow K, Zetterberg H, Kuhn G, et al. The anti-asthmatic drug, montelukast, modifies the neurogenic potential in the young healthy and irradiated brain. Cell Death Dis. 2018;9:775.

24. Maes M, Bonifacio KL, Morelli NR, Vargas HO, Moreira EG, St. Stoyanov D, et al. Generalized Anxiety Disorder (GAD) and Comorbid Major Depression with GAD Are Characterized by Enhanced Nitro -oxidative Stress, Increased Lipid Peroxidation, and Lowered Lipid -Associated Antioxidant Defenses. Neurotoxicity Research. 2018;34: 489-510.
25. Lenz QF, Arroyo DS, Temp FR, Poersch AB, Masson CJ, Jesse AC, et al. Cysteinyl leukotriene receptor (CysLT) antagonists decrease pentylenetetrazol-induced seizures and blood-brain barrier dysfunction. Neuroscience. 2014;277:859-71.
26. Chu L-S, Wei E-Q, Yu G-L, Fang S-H, Zhou Y, Wang M-L, et al. Pranlukast reduces neutrophil but not macrophage/microglial accumulation in brain after focal cerebral ischemia in mice1. Acta Pharmacologica Sinica. 2006;27:282-8.
27. Asano K, Nakade S, Shiomi T, Nakajima T, Suzuki Y, Fukunaga K, et al. Impact of pharmacokinetics and pharmacogenetics on the efficacy of pranlukast in Japanese asthmatics. Respirology. 2009;14:822-7.
28. Schumock GT, Lee TA, Joo MJ, Valuck RJ, Stayner LT, Gibbons RD. Association between leukotriene-modifying agents and suicide: what is the evidence? Drug Saf. 2011;34:533-44.
29. Zhang Y, Cheng J, Li Y, He R, Choudhry AA, Jiang J, et al. Suicidality among patients with asthma: A systematic review and meta-analysis. J Affect Disord. 2019;256:594-603.
30. Yang S, Wu J, Zhang Q, Li X, Liu D, Zeng B, et al. Allergic Rhinitis in Rats Is Associated with an Inflammatory Response of the Hippocampus. Behavioural Neurology. 2018;2018:1-7.

Supplemental material

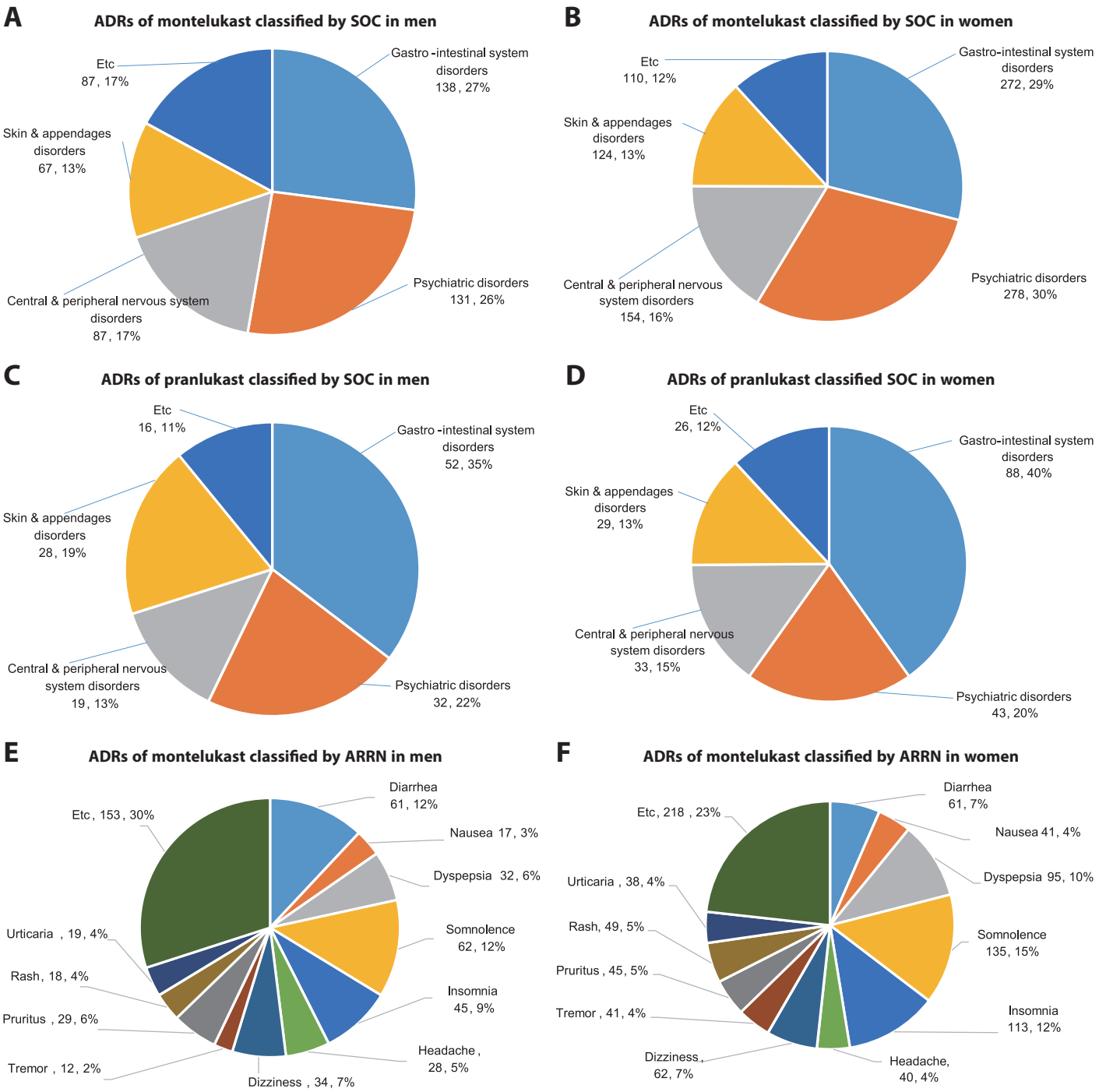

Figure S1.

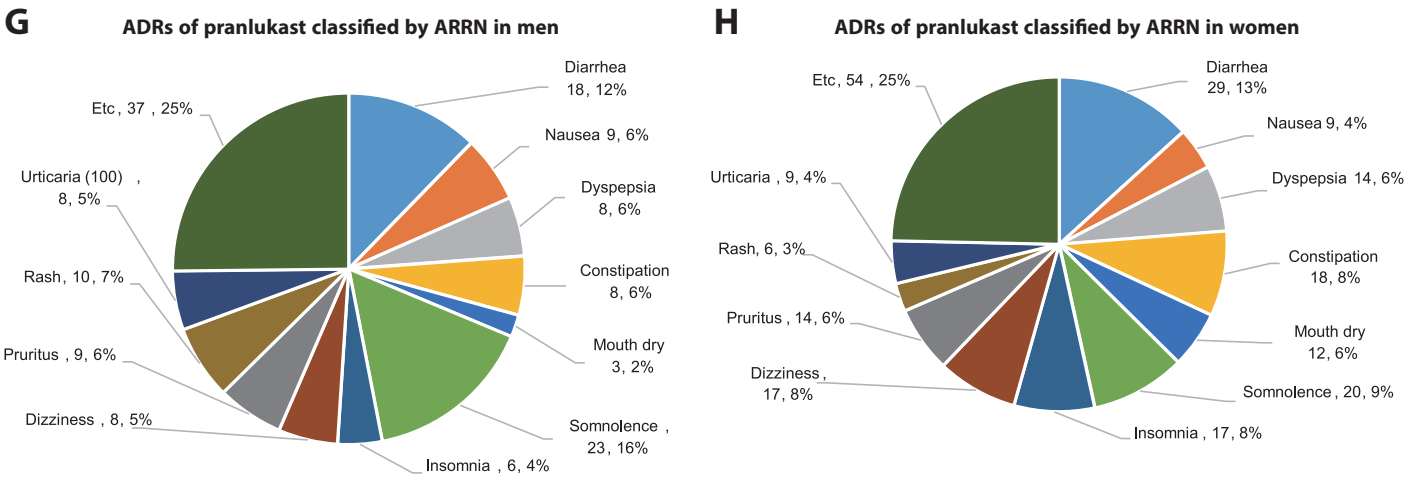

Figure S1. (Continued)