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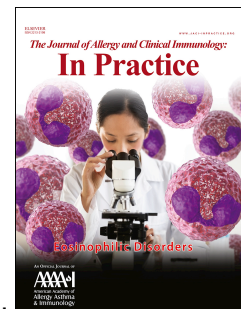
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[Title page]

Risk of neuropsychiatric diseases according to the use of a leukotriene receptor antagonist in middle-aged and older adults with asthma: a nationwide population-based study using health claims data in Korea

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Abstract

Background: Although leukotriene receptor antagonist (LTRA) is an effective drug for asthma, there has been increasing concern regarding neuropsychiatric (NP) adverse reactions. However, evidence for this association is not sufficient, especially in adults.

Objective: To investigate the association between the use of LTRA and risk of developing NP diseases in adults with asthma.

Methods: We performed a nationwide, retrospective, cohort study using data from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS). We selected asthma patients with no previous use of LTRA, and NP outcomes were defined by the registration of certain ICD-10 codes (F00-F59) during follow-up. We obtained the hazard ratio (HR) for NP diseases according to the use of LTRA.

Results: Overall, 61,571 asthma patients without LTRA experience were enrolled, and 12,168 of them took LTRA during the follow-up period. In the adjusted model, the HR for newly-diagnosed NP diseases showed no significant difference according to use of LTRA (HR, 1.01; 95% confidence interval, 0.83-1.23, $P = 0.952$). Subgroup analysis for associations between duration of LTRA use and risk of NP disease indicated no significance for all groups (< 6 , 6 to < 12 , 12 to < 24 , and ≥ 24 months). Common NP diseases included dementia (75.4% vs 76.1%), mood disorders (12.68% vs. 12.80%), and panic disorders (5.63% vs 3.53%) in LTRA users and non-LTRA users, respectively, and there was no significant difference in the prevalence of each NP disease in either group.

Conclusion: The current study showed the use or duration of LTRA exposure was not associated with the occurrence of NP diseases in Korean adult asthmatics.

Highlights box**What is already known about this topic?**

There has been increasing concern regarding the NP adverse reactions as the U.S. FDA stepped up warnings on montelukast in March 2020. However, there is insufficient evidence for this association, especially in adults.

What does this article add to our knowledge?

This study did not show any association between the use of LTRA and the occurrence of NP diseases in Korean adult asthmatics aged 40 or older.

How does this study impact current management guidelines?

The results could be one of the evidence for alleviating concerns about the occurrence of NP diseases due to LTRA in adult asthma patients.

Keywords: Leukotriene receptor antagonist; Neuropsychiatric diseases; Adult; Asthma

Abbreviations

LTRA: Leukotriene receptor antagonist

CysLT: Cysteinyl leukotriene

NP: Neuropsychiatric

NHIS-HEALS: the National Health Insurance Service-Health Screening Cohort

CCI: Charlson Comorbidity Index

Introduction

Because leukotrienes (LTs) play an important role in the pathogenesis of allergic inflammation, the inhibition of LTs is one of the main strategies to manage most allergic diseases, including asthma, allergic rhinitis, and atopic dermatitis.¹ There are two types of leukotriene modifying agents, which are classified according to their mechanism of action: 5-lipoxygenase (LO) inhibitors and leukotriene receptor antagonists (LTRAs). Whereas 5-LO inhibitors prevent the synthesis of leukotriene A₄ by inhibiting the catalytic activity of 5-LO, LTRAs block the cysteinyl LT (cysLT) receptor type 1 directly.^{1, 2}

Currently, the following LTRAs are available: pranlukast, montelukast, and zafirlukast, approved in 1995, 1998, and 2001, respectively.³ In the Republic of Korea (hereafter Korea), pranlukast was launched first in 1998, and now all three drugs can be prescribed. LTRA is commonly used as an add-on therapy for patients with asthma and/or allergic rhinitis. In particular, montelukast has been additionally approved for exercise-induced bronchoconstriction.⁴

Although montelukast is generally well-tolerated, the United States Food and Drug Administration (U.S. FDA) published a warning in 2008 related to serious neuropsychiatric (NP) adverse drug reactions reported in post-marketing studies.⁵ Recently, the U.S. FDA strengthened this warning to include serious behavior and mood-related changes.⁶ These NP events include agitation, aggressive behavior, anxiousness, depression, disorientation, disturbed attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal ideation and behavior (including completed suicides), and tremor.⁴⁻⁶ However, according to a systematic review conducted on NP events related to LTRA in 2018, more than half of the studies that observed NP events included only montelukast, and importantly, most of the previous studies included only children and adolescents, but not adults.⁴ Thus, we investigated the association between the

94 use of LTRA and occurrence of NP diseases among relatively older adults aged 40 or older,
95 using Korean nationwide health insurance claims data.

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Methods

Study population

In Korea, all legal residents are covered by the National Health Insurance Service (NHIS), including health insurance subscribers and medicare recipients. The NHIS has established several cohort databases (DB) including standard, qualified sample cohort DB, health screening cohort DB, and elderly cohort DB, using NHIS data collected from January 2002 to December 2015.⁷

We conducted a nationwide, retrospective, cohort study using the data from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS), which is a cohort of approximately 510,000 subjects who participated in health screening programs provided by the NHIS, aged 40 to 79 years at baseline, January 2002. The DB covers the period 2002-2015, and includes health care use, diagnosis statements by ICD-10 codes, details of prescriptions and medications, health screening results, sociodemographic variables, and cause of death.⁸

We selected 362,285 participants who had undergone health screening examinations between January 2009 and December 2010, and designated the date of each participants' examination as the start of follow-up. Among them, we selected 74,211 participants who already had an asthma diagnosis before the date of health screening, which is the start date. Having asthma was defined as two or more outpatient visits or at least one hospitalization for the ICD-10 code for asthma (J45-J46). We excluded participants who had taken any LTRA (montelukast, pranlukast, and zafirlukast) prior to the start date, or participants with NP diseases (F00-F59, and F99) before the start date. Finally, 61,571 patients were enrolled.

We defined the index date as outcome (NP diseases) that occurred, and follow-up was performed from the start date, which is each participants' health screening date, to the index date. In LTRA users, we detected the occurrence of NP diseases only after taking LTRA, not

before use of LTRA. If no outcome occurred, participants were followed up until death by any reason, censoring due to loss of health insurance eligibility, or the end of the follow-up day (31 December, 2015).

This study was approved by the Institutional Review Board of Ewha Womans University Medical Center (SEUMC 2019-11-015).

Variable definitions

Details of NP diseases were as follows: F00-F09 organic, including symptomatic mental disorders; F10-F19 mental and behavioral disorders due to psychoactive substance use; F20-F29 mood disorders; F40-F48 neurotic, stress-related and somatoform disorders; F50-F59 behavioral syndromes associated with physiological disturbances and physical factors; and F99 unspecified mental disorder. We excluded disorders of adult personality and behavior (F60-69), mental retardation (F70-79), psychologic developmental disorders (F80-89), and behavioral and emotional disorders with childhood and adolescent onset (F90-98), such as attention-deficit hyperactivity disorders or tic disorders, because these diseases usually occur in childhood and adolescence or have a strong genetic predisposition than environmental influence in the disease development.⁹ We also detected suicide attempt (X60-84) and suicidal ideation (R45.8).^{10, 11}

Asthma medications other than LTRA were also investigated, such as inhaled corticosteroids (ICS; beclomethasone, budesonide, triamcinolone, ciclesonide, fluticasone, or flunisolide), oral corticosteroids (OCS; methylprednisolone, prednisolone, hydrocortisone, dexamethasone, deflazacort), long-acting inhaled beta2-agonists (LABA; salmeterol or formoterol), long-acting inhaled muscarinic antagonists (LAMA; tiotropium, aclidinium, glycopyrronium, tiotropium, umeclidinium), and xanthine derivatives (theophylline and doxofylline).

We also included type 2 diabetes (T2DM; E11), essential hypertension (HTN; I10), chronic kidney disease (CKD; N18), cerebrovascular diseases (CVD; I60-I69), cancer (C00-C34, C39-C99, D00-D09), and other respiratory diseases such as interstitial lung disease (J84), rheumatoid lung disease (J99), and sarcoidosis (D86). For overall comorbidity, the Charlson Comorbidity Index (CCI) score was used.¹² Health behaviors (smoking status, pack-years of smoking, alcohol consumption, and physical activity) and body mass index (BMI; obtained as weight in kilograms divided by height in meters squared) were obtained from the results of the most recent national health screening examination of each participant between January 2009 and December 2010.

Statistical analyses

Statistical analysis of the general characteristics of the participants according to LTRA administration or the presence of NP disease was conducted using the Student's *t*-test for continuous variables and Pearson's χ^2 test for categorical variables. Proportional hazards regression (univariable and multivariable analysis) was performed to determine the risk of NP disease according to LTRA administration. We adjusted for possible confounders including age, sex, pack-years of smoking, alcohol consumption, physical activity, BMI, and comorbid diseases (T2DM, HTN, CKD, other respiratory diseases, and CCI score), and the use of other asthma medication. The strength of the association was expressed as the hazard ratio (HR) and 95% confidence intervals (CI), and a statistically significant difference was defined as a *P*-value of <0.05. All statistical analyses were conducted with SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

General characteristics

Overall, 61,571 asthmatic, LTRA-naïve participants were included in this study. The general characteristics of LTRA users and non-LTRA users are presented in Table 1. There were no significant differences in age or sex between groups, and their median age was approximately 61 years. During the follow-up period, NP disease, CVD, and lung cancer occurred in 1.09% vs 1.17%, 0.01% vs 0.01%, and 0.02% vs 0.02% patients in the LTRA user and non-LTRA user groups, respectively, all of which were not significantly different. There was no suicide attempt or suicidal ideation in both LTRA users and non-LTRA users. The mean follow-up period for any outcome was 47.6 ± 8.3 vs 46.5 ± 8.4 months for LTRA users and non-LTRA users, respectively ($P < .001$). The frequency of use of each LTRA in the total population was as follows: pranlukast (11.1%), montelukast (11.0%), and zafirlukast (0.24%).

Characteristics of the study participants according to the presence of neuropsychiatric disease

The NP disease group was significantly older (70.4 vs 60.9 years, $P < 0.001$) with fewer males (39.7% vs 45.8%, $P = 0.002$) compared with the control group. There were no significant differences in the frequency of LTRA use (20.9% vs 19.8%, $P = 0.473$), the duration of LTRA administration (99.7 ± 263.8 vs 77.4 ± 214.0 days, $P = 0.23$), or specific type of LTRA (8.22% vs 8.42%, $P = 0.717$ for montelukast, 10.13% vs 8.50%, $P = 0.252$ for pranlukast, 0.15% vs 0.24%, $P = 0.631$ for Zafirlukast) between the NP disease and control groups. The presence of comorbid diseases, the use of other asthma medication, and hospital visits were significantly higher in the NP group compared with the control group (Table 2).

Risk of the development of neuropsychiatric disease according to use of LTRA

We examined the association between the use of LTRA and the risk of newly-diagnosed NP diseases in Korean adults aged 40 and older. The HRs for NP disease were not significantly different according to use of LTRA in unadjusted (HR, 1.09; 95% CI, 0.91-1.32; $P = 0.357$) and adjusted models for potential confounders such as age, sex, BMI, smoking, alcohol consumption, comorbidities, use of other asthma medication, outpatient visit, hospitalization, and ER visit (HR, 1.01; 95% CI, 0.83-1.23, $P = 0.952$) (Table 3). We also performed subgroup analysis of the association between the duration of LTRA use and the risk of NP disease, and the results were not significant for all groups (< 6 , 6 to < 12 , 12 to < 24 , and ≥ 24 months).

The prevalence of each neuropsychiatric disease

We also studied whether there was a difference in the composition of the NP diseases between LTRA users and non-LTRA users. We found no significant difference in the prevalence of each NP disease between groups ($P = 0.722$). The prevalence was highest in the order of dementia [75.4% (107/142) vs 76.1% (410/539)], mood disorders [12.68% (18/142) vs. 12.80% (69/539)], and panic disorders [5.63% (8/142) vs 3.53% (19/539)] in LTRA users and non-LTRA users, respectively (Figure 1). There was also no significant difference in the prevalence of NP diseases according to the duration of LTRA use ($P = 0.27$) (Figure 2).

Discussion

In this study, we found that LTRA use did not increase the risk of developing NP diseases, and that the occurrence of NP diseases was not associated with the duration of LTRA administration. These results remained after adjusting for potential confounders. In LTRA users and non-LTRA users, dementia was the most common NP disease, followed by mood disorders, and panic disorders. When we analyzed the data according to the presence of NP diseases, there were no significant differences in the administration, duration, and specific type of LTRA between the NP disease and non-NP disease groups; however, the NP group was significantly older and contained more females, which might be related to the finding that dementia accounts for about 70% of NP diseases.¹³ The prevalence of NP disease in zafirlukast group was lower than that of montelukast and pranlukast, and this may be related to chemical difference of zafirlukast from montelukast and pranlukast.^{14, 15} In addition, the prevalence of comorbid diseases, such as chronic obstructive pulmonary disease, bronchiectasis, DM, HTN, CKD, and malignancy, was higher in the NP disease group, and outpatient visits, hospitalizations, and use of asthma medications were more common than in the non-NP disease group.

LTs are lipid inflammatory mediators synthesized from cell membrane phospholipids through phospholipase A2 and the 5-LO pathway.² Leukotriene A4, generated from arachidonic acid by 5-LO, is a precursor of two groups of LTs, leukotriene B4 and cysLTs, which contain the amino acid cysteine and have a primary role in allergic inflammation.^{1, 2} LTs induce bronchoconstriction, mucus secretion, type 2 inflammation, vascular permeability, and tissue remodeling; thus, inhibiting the action of LTs is one of the main treatment targets for allergic diseases such as asthma and allergic rhinitis.^{1, 16} CysLTs, including LTC4, LTD4, and LTE4, in particular, play a key role in allergic inflammation by signaling through two

types of cell surface receptors (CysLT type 1 and CysLT type 2 receptors). Of note, currently available LTRAs inhibit CysLT type 1 receptors.¹

The mechanism of the development of NP symptoms by LTRA has not been identified. Some studies suggest that the production of neurotransmitters, such as serotonin and noradrenalin, may be inhibited by LTRA that crossed the blood-brain barrier into the central nervous system,^{17, 18} whereas other studies propose that CysLT receptors, which are therapeutic targets for central nervous system diseases, such as Alzheimer's disease, Parkinson's disease, depression, and even brain injury, are a link between CysLTs and neuroinflammation.^{19, 20} One study showed that montelukast had beneficial effects on the recovery of cranial irradiated mice brain, and reduced proliferation in the hippocampus of normal mice brain,²² while another recent *in vitro* study found that montelukast could directly induce neurotoxicity in highly aggressively proliferating immortalized (HAPI) rat microglial cells and SH-SY5Y human neuroblastoma cells,²¹ and these conflicting findings may suggest the possibility of a dual effect of montelukast depending on the situation.²² Since the most of NP side effects due to montelukast occur in few patients, within 2 weeks of drug administration, it also may have relation with the presence of some genetic polymorphisms involving modification of the normal action or metabolism of LTRA.²³ Future research is needed to determine the pathophysiologic mechanism by which LTRA causes NP symptoms.

Montelukast is the most widely used LTRA, and since its approval for asthma treatment in 1998, its indications have been extended to seasonal allergic rhinitis in 2002, perennial allergic rhinitis in 2005, and exercise-induced bronchoconstriction in 2007.²⁴ Due to newly identified NP events during the post-marketing of montelukast, which were not detected in previous clinical trials, FDA in the U.S. generated warnings about tremor, depression, suicidal thinking and behavior, in 2008.²⁵ Warnings of NP events were also generated in 2009 for zafirlukast and zileuton, which are only approved for asthma.⁴ Recently in March 2020,

the U.S. FDA added a black box warning to montelukast to more effectively provide patients and healthcare professionals with information on serious mental health side effects; thus, the relationship between montelukast and the risk of NP events has become an issue again.⁶

The U.S. FDA evaluated all NP adverse reactions associated with montelukast reported from February 1998 to May 2019 in the FDA Adverse Event Reporting System (FAERS) database, and found that NP events began to increase after the initial announcement of NP adverse reactions by the FDA in 2008, which may be due to close monitoring during medication based on new information related to NP side effects.²⁶ In addition, the FDA conducted an observational study using data from the FDA Sentinel System from January 2010 to September 2015, which indicated no significant difference in depressive disorders and self-harm when the ICS group and montelukast group were matched 1:1.^{26, 27} Case reports submitted to FDA, the above mentioned observational study, and literature reviews including observational and animal studies, the FDA decided to add a black box warning to montelukast, to gain the attention of physicians and patients regarding the potential occurrence of NP events.^{6, 26}

A systematic review of 33 studies, conducted in 2018, investigated the NP safety of LTRAs.⁴ Four observational studies did not show a significant association,²⁸⁻³¹ whereas ten pharmacovigilance studies identified some psychiatric adverse reactions.³²⁻⁴¹ Although randomized controlled trials and observational studies, not intentionally searching for NP diseases, did not indicate any relevance, this systemic review concluded that the potential risk of NP occurrence associated with LTRA could not be ruled out, in consideration of the previous pharmacovigilance studies, case series, and case reports.⁴ Notably, almost half of the currently available studies included only children, adolescents, and young adults.^{29, 31, 34-36, 39,}

⁴¹ More recent pediatric studies also showed inconsistent results: one reported an increased risk of hospital visits for NP events associated with the use of montelukast,¹⁸ whereas another

reported no increase in the risk of attention-deficit or hyperactivity disorder.⁴² In summary, the previous studies showed various results depending on whether the study population contained children or adults, and which specific NP outcome was the main focus, leading to some confusion. There have been relatively few studies in elderly adults, and among several LTRAs, medication has been limited to montelukast.

In this study, we investigated the risk of NP diseases related to LTRA in adult patients; however, this study had some limitations. First, since the diagnosis of asthma was detected only by ICD-10 codes, without objective tests, there may be misclassification of asthma diagnosis. Second, because we also detected NP outcomes via ICD-10 code registration, we only recognized NP diseases, not temporary NP symptoms, which might cause the withdrawal of LTRA. Third, due to the nature of the NHIS-HEALS data, we only examined adults aged 40 and older. In addition, this study was conducted only for the Korean population, we was unable to detect possible ethnic differences. The risk of NP disorders due to LTRA use may be associated with genetic background, thus further research should be conducted in other ethnic groups. Finally, this was a retrospective cohort study, not a prospective study, and relied on exclusively medical insurance claim for the detection of the outcome of participants.

In conclusion, this study did not show any association between the use or duration of LTRA and the occurrence of NP disease in middle-aged and elderly Korean patients with asthma. Even though LTRA might cause the development of NP symptoms, excessive restrictions of its use might be a loss to both physicians and patients. Since LTRA is useful in treatment of some patients with asthma, these rare adverse NP symptoms should not withhold the physician from prescribing them in selected patients, but rather be accompanying the prescription by a word of caution in case any mood changes might occur. Further studies,

313 such as randomized controlled trials, are needed to reveal the association between the use of
314 LTRA and the risk of NP events and/or diseases.

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Figure legends

Figure 1. The prevalence of each neuropsychiatric disease in LTRA users and non-LTRA users.

Abbreviations: NOS, not otherwise specified; LTRA, leukotriene receptor antagonist.

Figure 2. The prevalence of neuropsychiatric diseases by duration of LTRA use.

Abbreviations: NP, neuropsychiatric; LTRA, leukotriene receptor antagonist.

443 **Table 1.** Characteristics of study participants.

Characteristics		Non LTRA users (n = 49,403)	LTRA users (n = 12,168)	P-value
Male, n (%)		22,657 (45.86)	5,530 (45.45)	0.411
Age, mean $\pm$ SD (years)		61.00 $\pm$ 9.48	61.07 $\pm$ 9.43	0.433
Age group, n (%)	40-49	5,086 (10.29)	1,185 (9.74)	0.185
	50-59	18,868 (38.19)	4,710 (38.71)	
	60-69	13,547 (27.42)	3,386 (27.83)	
	70-79	10,369 (20.99)	2,491 (20.47)	
	$\geq$ 80	1,533 (3.10)	396 (3.25)	
BMI (kg/m ²), n (%)	< 18.5 (underweight)	1,123 (2.27)	286 (2.35)	0.509
	18.5-22.9 (normal)	16,252 (32.91)	3,923 (32.25)	
	23-24.9 (overweight)	13,651 (27.64)	3,337 (27.44)	
	25-29.9 (obese)	16,571 (33.55)	4,165 (34.24)	
	$\geq$ 30 (morbidly obese)	1,788 (3.62)	452 (3.72)	
Smoking status, n (%)	Nonsmoker	34,373 (70.75)	8,488 (70.83)	<.001
	Past smoker	7,728 (15.91)	2,061 (17.20)	
	Current smoker	6,484 (13.35)	1,434 (11.97)	
Pack-years of smoking, n (%)	< 30	9,413 (19.37)	2,336 (19.49)	0.781
	$\geq$ 30	4,799 (9.88)	1,159 (9.67)	
Alcohol consumption, time/week		0.78 $\pm$ 1.50	0.71 $\pm$ 1.42	<.001
Exercise, time/week	None	25,028 (51.02)	6,155 (50.98)	0.899
	1-4	17,988 (36.67)	4,413 (36.55)	
	$\geq$ 5	6,042 (12.32)	1,505 (12.47)	
Respiratory diseases, n (%)	COPD (J41-J44)	26,245 (53.12)	7,921 (65.10)	<.001
	Bronchiectasis (J47)	1,858 (3.76)	810 (6.66)	<.001
	Tuberculosis (B90)	256 (0.52)	110 (0.90)	<.001
	Others*	19 (0.04)	4 (0.03)	0.775
History of DM, n (%)		14,511 (29.37)	3,778 (31.05)	<.001
History of HTN, n (%)		23,171 (46.90)	5,968 (49.05)	<.001
History of CKD, n (%)		2,412 (4.88)	662 (5.44)	0.011
History of cancer, n (%)		3,843 (7.78)	1,000 (8.22)	0.107
CCI scores, n (%)	0-1	10,428 (21.11)	2,256 (18.54)	<.001
	2-3	25,907 (52.44)	6,455 (53.05)	
	$\geq$ 4	13,068 (26.45)	3,457 (28.41)	
Other asthma medication, n (%)	Inhaled corticosteroid	7,187 (14.55)	4,678 (38.45)	<.001
	OCS burst	11,166 (22.60)	4,392 (36.09)	<.001
	LABA	153 (0.31)	204 (1.68)	<.001
	LAMA	315 (0.64)	280 (2.30)	<.001
	Theophylline	3,523 (7.13)	2,669 (21.93)	<.001
Hospital utilization, mean (SD) [†]	No. of outpatient visits	11.61 $\pm$ 23.00	28.53 $\pm$ 48.39	<.001
	No. of hospitalizations	0.17 $\pm$ 0.89	0.49 $\pm$ 1.84	<.001
	No. of ER visits	0.03 $\pm$ 1.03	0.09 $\pm$ 0.91	<.001
Neuropsychiatric disease, n (%)		539 (1.09)	142 (1.17)	0.473
Suicide, attempted, n		0	0	N/A
Cerebrovascular disease, n (%)		5 (0.01)	1 (0.01)	0.849
Lung cancer, n (%)		9 (0.02)	2 (0.02)	0.895
Follow-up period, mean $\pm$ SD (months)		47.65 $\pm$ 8.33	46.51 $\pm$ 8.42	<.001

*Includes interstitial lung disease (J84), rheumatoid lung disease (J99), and sarcoidosis (D86).

Abbreviations: SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; CCI, Charlson comorbidity index; OCS, oral corticosteroid; LABA, long-acting beta 2-agonists; LAMA, long-acting muscarinic antagonists; ER, emergency room; N/A, not applicable.

Table 2. Characteristics of the study population according to the presence of neuropsychiatric disease.

Characteristics		Neuropsychiatric diseases		P-value
		Yes (n = 681)	No (n = 60,890)	
Male, n (%)		272 (39.94)	27,915 (45.84)	0.002
Age, mean $\pm$ SD (years)		70.42 $\pm$ 8.98	60.91 $\pm$ 9.42	<.001
Age group, n (%)	40-49	16 (2.35)	6,255 (10.27)	<.001
	50-59	75 (11.01)	23,503 (38.60)	
	60-69	155 (22.76)	16,778 (27.55)	
	70-79	336 (49.34)	12,524 (20.57)	
	$\geq$ 80	99 (14.54)	1,830 (3.01)	
BMI (kg/m ²), n (%)	< 18.5 (underweight)	33 (4.85)	1,376 (2.26)	<.001
	18.5-22.9 (normal)	273 (40.09)	19,902 (32.70)	
	23-24.9 (overweight)	168 (24.67)	16,820 (27.63)	
	25-29.9 (obese)	178 (26.14)	20,558 (33.78)	
	$\geq$ 30 (morbidly obese)	29 (4.26)	2,211 (3.63)	
LTRA use, n (%)		142 (20.85)	12,026 (19.75)	0.473
Montelukast		56 (8.22)	5,127 (8.42)	0.717
Pranlukast		69 (10.13)	5,178 (8.50)	0.252
Montelukast + Pranlukast		16 (2.35)	1,577 (2.59)	0.838
Zafirlukast		1 (0.15)	144 (0.24)	0.631
Duration of LTRA use, mean $\pm$ SD (days)		99.70 $\pm$ 263.8	77.94 $\pm$ 214.0	0.230
Smoking status, n (%)	Nonsmoker	491 (73.61)	42,370 (70.73)	0.220
	Past smoker	93 (13.94)	9,696 (16.19)	
	Current smoker	83 (12.44)	7,835 (13.08)	
Pack-years of smoking, n (%)	< 30	93 (13.94)	9,696 (16.19)	0.156
	$\geq$ 30	83 (12.44)	7,835 (13.08)	
Alcohol consumption, time/week		0.65 $\pm$ 1.62	0.77 $\pm$ 1.48	0.041
Exercise, time/week	None	446 (65.68)	30,737 (50.85)	<.001
	1-4	165 (24.30)	22,236 (36.78)	
	$\geq$ 5	68 (10.01)	7,479 (12.37)	
Respiratory diseases, n (%)	COPD (J41-J44)	488 (71.66)	33,678 (55.31)	<.001
	Bronchiectasis (J47)	53 (7.78)	2,615 (4.29)	<.001
	Tuberculosis (B90)	4 (0.59)	362 (0.59)	0.981
	Others*	1 (0.15)	22 (0.04)	0.137
History of DM, n (%)		295 (43.32)	17,994 (29.55)	<.001
History of HTN, n (%)		426 (62.56)	28,713 (47.16)	<.001
History of CKD, n (%)		55 (8.08)	3,019 (4.96)	<.001
History of cancer, n (%)		72 (10.57)	4,771 (7.84)	0.008
CCI scores, n (%)	0-1	71 (10.43)	12,613 (20.71)	<.001
	2-3	304 (44.64)	32,058 (52.65)	
	$\geq$ 4	306 (44.93)	16,219 (26.64)	
Other asthma medication, n (%)	Inhaled corticosteroid	163 (23.94)	11,702 (19.22)	0.002
	OCS burst	219 (32.16)	15,339 (25.19)	<.001
	LABA	4 (0.59)	353 (0.58)	0.979
	LAMA	15 (2.20)	580 (0.95)	0.001
	Theophylline	109 (16.01)	6,083 (9.99)	<.001
Health care utilization, mean (SD)†	No. of outpatient visits	21.06 $\pm$ 36.59	14.89 $\pm$ 30.46	<.001
	No. of hospitalizations	0.78 $\pm$ 2.25	0.23 $\pm$ 1.13	<.001
	No. of ER visits	0.07 $\pm$ 0.60	0.04 $\pm$ 1.01	0.486

*Includes interstitial lung disease (J84), rheumatoid lung disease (J99), and sarcoidosis (D86).

Abbreviations: SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; CCI, Charlson comorbidity index; OCS, oral corticosteroid; LABA, long-acting beta 2-agonists; LAMA, long-acting muscarinic antagonists; ER, emergency room.

Table 3. Risk of neuropsychiatric disease according to use of LTRA.

Variables	Neuropsychiatric diseases			
	Unadjusted		Adjusted*	
	HR (95% CI)	P-value	HR (95% CI)	P-value
LTRA		0.357		0.952
No (n = 49,403)	1		1	
Yes (n = 12,168)	1.09 (0.91-1.32)		1.01 (0.83-1.23)	
Duration of LTRA (months)				
< 6 (n = 2,286)	1.05 (0.86-1.28)	0.634	1.01 (0.83-1.24)	0.904
6-11 (n = 503)	1.18 (0.53-2.63)	0.691	0.81 (0.36-1.84)	0.613
12-23 (n = 345)	2.27 (1.13-4.56)	0.021	1.37 (0.66-2.86)	0.399
≥ 24 (n = 331)	1.18 (0.44-3.16)	0.740	0.71 (0.26-1.98)	0.515

* adjusted for age, sex, pack-years of smoking, alcohol consumption, physical activity, BMI, and comorbid diseases (T2DM, HTN, CKD, other respiratory diseases, and CCI score), and the use of other asthma medication.

Abbreviations: LTRA, leukotriene receptor antagonist; HR, hazard ratio; CI, confidence interval.

Figure 1.

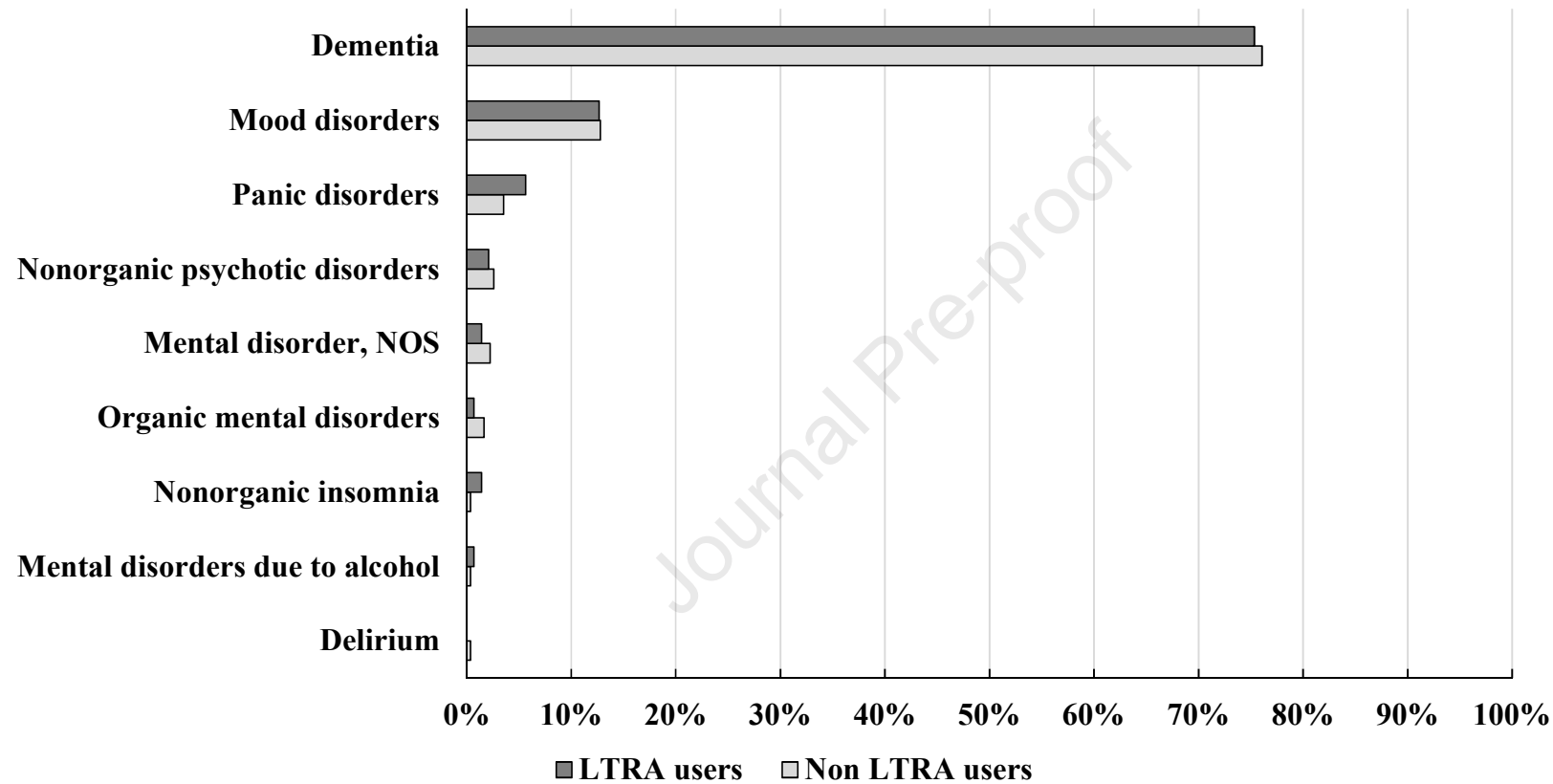


Figure 2.

