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Comparative Risk for Neuropsychiatric Events in Leukotriene Receptor Antagonist vs. Inhaled Corticosteroid in Children With Asthma: A Nationwide Observational Study With a Complementary Analysis Using Natural Language Processing

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Keywords: drug-related side effects and adverse reactions | leukotriene antagonists | natural language processing

ABSTRACT

Purpose: Leukotriene receptor antagonists (LTRAs) are widely prescribed as controller medications for pediatric asthma. However, there have been increasing concerns about potential neuropsychiatric adverse reactions associated with LTRAs. Findings from observational studies have been inconsistent, and direct comparisons of the risk of neuropsychiatric events (NPEs) between LTRAs and inhaled corticosteroids (ICS) remain limited in the pediatric population.

Methods: A retrospective cohort study was conducted utilizing a nationwide claims database (January 2018–April 2022) and a multicenter electronic health record (EHR) database (January 2006–March 2022) from South Korea. Patients aged 5–18 years diagnosed with asthma before initiating LTRA or ICS were included. The primary outcome was NPEs within 90 days of exposure, defined using two methods: diagnostic code-based analysis and natural language processing (NLP)-based analysis using clinical notes. After propensity score stratification, Cox proportional hazards models were used to estimate risks.

Results: The diagnostic code-based analysis on the claims database included 169 636 LTRA users and 28 845 ICS users. There was no statistically significant difference in the risk of NPEs between LTRA and ICS (calibrated hazard ratios [HRs], 1.14 [95% CI, 0.92–1.42]). In the NLP-based analysis using EHR database, 1641 LTRA users and 1607 ICS users were included. The results were consistent with those of the diagnostic code-based analysis (calibrated HR, 1.33 [95% CI, 0.66–2.68]).

Subin Kim and Chang Hoon Han contributed equally as co-first authors.

Conclusions: LTRA use was not found to be associated with a significantly increased risk of NPEs in children with asthma. These findings offer valuable insights to support clinical decision-making in pediatric asthma treatment.

1 | Introduction

Leukotriene receptor antagonists (LTRAs) block leukotriene-mediated inflammatory pathways, alleviating bronchoconstriction and airway inflammation [1]. As such, they are effective at treating asthma and are recommended by the Global Initiative for Asthma (GINA) guidelines as an alternative to inhaled corticosteroids (ICS) for the initial daily control of mild persistent asthma in children aged 6–11 years [2]. Although ICS is recommended as the preferred choice in the GINA guidelines, the choice between ICS and LTRA often depends on the preferences of physicians, patients, and their families [2, 3]. While general physicians may favor ICS due to their stronger potency in asthma control, pediatricians often choose LTRA over ICS because of their higher compliance with parental convenience and fewer concerns about related side effects, as ICS has been associated with oropharyngeal candidiasis and negative impacts on growth [3–5].

Nevertheless, post-market surveillance has raised concerns regarding LTRA-associated neuropsychiatric adverse effects, ranging from mild symptoms, including anxiety, irritability, and sleep disturbances, to severe outcomes, including suicidal thoughts and behaviors [6–8]. Repeated reports prompted the United States (US) Food and Drug Administration (FDA) to issue a boxed warning for montelukast, and the GINA guidelines now recommend that physicians inform patients of the potential neuropsychiatric risks before prescribing LTRAs [2, 9]. The risk of neuropsychiatric side effects is higher in children than in adults, which is concerning given the higher prescription rates of LTRAs in pediatric populations [10].

Nonetheless, previous observational studies comparing LTRA and ICS in children with asthma, including a large-scale cohort study in the US, failed to reach a consensus regarding the comparative risk of neuropsychiatric adverse events [11, 12]. Furthermore, under-documentation of neuropsychiatric symptoms in diagnostic code-based databases is common. Prior studies have highlighted discrepancies between coded data and chart reviews in reporting psychiatric symptoms and diagnoses [13–15].

This study directly compared the risk of neuropsychiatric adverse events between LTRA and ICS among children with asthma in South Korea, where LTRA prescriptions are more common, compared with those in other countries [16, 17]. We employed two complementary approaches—a coded data-based analysis using a nationwide claims database in South Korea and a multicenter analysis using a large language model (LLM)-based natural language processing (NLP) to extract neuropsychiatric symptoms from unstructured clinical notes.

2 | Methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of the Yonsei University Health System (IRB No. 4-2022-1475) and Ajou University Hospital (AUH) (IRB No. AJOUIRB-EX-2023-560), which waived the requirement for informed consent owing to the retrospective study design. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

2.1 | Data Sources

We used two electronic health record (EHR)-based databases and one nationwide administrative claims database in South Korea. The Yonsei University Health Systems (YUHS) database, an EHR database, contains data on over 5.7 million patients from three hospitals (Severance Hospital, Gangnam Severance Hospital, and Yongin Severance Hospital) between January 2006 and March 2022. The AUH database is an EHR database containing data on approximately 2.9 million patients who visited the Ajou University Medical Center between 1994 and 2023. EHR databases contain structured information on diagnoses, medications, procedures, and clinical measures, and unstructured free-text clinical notes.

The Health Insurance Review and Assessment Service (HIRA) is a nationwide claims database encompassing 20% of the South Korean population, sampled through age and sex stratification [18]. It contains health information on demographics, visit types, diagnoses, procedures, and medications from January 2018 to April 2022. All databases were standardized based on the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM).

2.2 | Study Cohorts and Exposure

We identified pediatric patients (aged 5–18 years) who were new users of LTRA and ICS, with at least 365 days of prior observation in the database. The index date was defined as the date of the first prescription of study drugs. Patients were eligible for inclusion if they had at least one diagnostic code for asthma in an outpatient clinic within 365 days before the index date and no history of acute lower respiratory disease within 7 days before the index date. We excluded patients who had been prescribed ICS (for the target cohort) or LTRA (for the comparator cohort) within 180 days before the index date or who had a previous history of neuropsychiatric events (NPEs). Further details of the cohort definitions are presented in Supporting Information S1. A graphical illustration of the study design is shown in Figure S1.

2.3 | Outcomes and Follow-Up

The primary outcome was newly developed NPEs, identified using two methods: diagnostic codes in the structured fields of the nationwide claims database and NLP to automatically review the free-text outpatient notes in the two EHR databases.

Summary

- This study compared the risk of neuropsychiatric events between LTRA and ICS in children with asthma.
- We used both structured claims data and unstructured outpatient clinical notes from a multicenter electronic health records database.
- Neuropsychiatric events, the primary outcome, were identified based on two methods: (1) diagnostic codes in structured data and (2) natural language processing (NLP) of unstructured outpatient clinical notes.
- Neither structured data analysis nor NLP-based analysis of clinical notes demonstrated a statistically significant association between LTRA use and an increased risk of neuropsychiatric events in children with asthma.

In the diagnostic code-based analysis, NPEs were defined as a composite of psychotic, mood, anxiety, sleep-related, cognitive, movement, and personality disorders and suicide-related outcomes (Supporting Information S2) [19]. For NLP-based analysis, we developed Bidirectional Encoder Representations from a transformer-based LLM for automated chart review. NPEs identified through NLP of the outpatient notes included anxiety, aggression, attention deficit, depression, hyperactivity, hallucinations, insomnia, referrals for psychiatric consultation, sleep disturbances, suicidal thoughts and behavior, and tics, as mentioned in the montelukast label. Detailed methods for developing our NLP algorithms are described in Supporting Information S3 and Table S1. The model performances for internal and external validation are presented in Table S2. Moreover, we validated the outcome definitions by assessing agreement between each definition and manual chart review. The detailed information and results of outcome validation are shown in Supporting Information S4 and Table S3.

In an intention-to-treat analysis, the follow-up period started on the day following the index date and continued for 90 days. Patients who did not have any outcomes were censored at death, loss to follow-up, or the end of data availability, whichever came first. Patients who did not have at least 1 day at risk were excluded from the study.

2.4 | Statistical Analysis

We used propensity score (PS) stratification to adjust for potential confounding biases due to between-group differences in baseline covariates. To calculate PS for each patient, we used large-scale regularized logistic regression with an L1 penalty, which shrinks the coefficients of less informative variables toward zero [20]. The model included over 4000 baseline covariates, including age, sex, year, and month of the index date, and medical history (diagnoses, drug exposures, device exposures, and historical procedures) over 30 and 365 days before the index date. All covariates except laboratory values were categorical variables, and all missing categorical variables were considered as not present and thus coded as no.

Patients were stratified into five strata based on PS. We assessed the differences in patient characteristics between the two study cohorts using the absolute standardized mean differences (aSMDs) before and after PS stratification. Incidence rates (IRs) per 1000 person-years (PY) were estimated. Cox proportional hazards models were applied to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). We then empirically calibrated the estimated HRs and 95% CIs to minimize potential unmeasured confounding biases [21]. For empirical calibration, negative control outcomes not known to be associated with LTRA or ICS use were applied. By fitting an empirical null distribution derived from these negative controls, we quantified the systematic error and calibrated the estimated HRs and corresponding 95% CIs. A total of 13 negative control outcomes were used in the diagnostic code-based analysis, whereas four were used in the NLP-based analysis (Supporting Information S5 and Figure S2).

We assessed study diagnostics to ensure the reliability of our study, quantifying empirical equipoise, defined as sufficient overlap in the preference score (a transformation of the PS accounting for differences in the prevalence of each treatment) distributions between the target and comparator cohorts [22]. If at least 25% of patients in both groups had preference scores between 0.3 and 0.7, we considered that empirical equipoise was achieved. An additional diagnostic study was conducted for covariate balance, which was considered sufficient if the aSMDs for all included covariates were <0.25 [23]. Results from data sources that did not meet the predefined diagnostic criteria were excluded from the primary analysis.

All analyses were performed using the R programming language version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a two-tailed $p<0.05$.

2.5 | Sensitivity Analyses

To evaluate the robustness of our findings, we performed sensitivity analyses using two PS adjustment methods (one-to-one PS matching and PS stratification) and five alternative time-at-risk windows (30, 60, 180, 365 days, and on-treatment periods). The on-treatment period was defined as the time from 1 day after the index date until the end of exposure to the drug or switching to the opposite drug or the end of a patient's record.

3 | Results

3.1 | Cohort Selection and Characteristics

A total of 198 481 patients were initially identified for diagnostic code-based analysis (Figure 1). Of these, 169 636 LTRA and 28 845 ICS users from the HIRA database were included in the diagnostic code-based primary analysis. For NLP-based analysis, 3248 patients were identified from the two EHR databases. Among them, 1641 LTRA users and 1607 ICS users were included in the NLP-based primary analysis. Patients from the AUH were excluded owing to low empirical equipoise and insufficient covariate balance after PS adjustment. The results of

the covariate balance assessment used in the diagnostic criteria are presented in Figure S3. The preference score distributions for each database are presented in Figure S4.

The baseline characteristics of the patients from the diagnostic code-based and NLP-based analyses are shown in Tables 1 and 2, respectively. In the diagnostic code-based analysis, 66% of LTRA users and 67% of ICS users were aged 5–9 years before PS stratification; the proportion of female participants was similar between the LTRA (46%) and ICS (47%) groups; and allergic rhinitis and bronchitis were the most common comorbidities in both groups. In the NLP-based analysis, the proportions of patients aged 5–9 years were 74% and 57% in the LTRA and ICS groups, respectively, while allergic rhinitis was the most frequent comorbidity in both groups (LTRA, 53%; ICS, 33%). Following PS adjustment, the aSMDs were less than 0.25 for all baseline characteristics between the LTRA and ICS users in all databases, except for the AUH database (Figure S3). The baseline characteristics of the patients excluded from the primary analyses are presented in Tables S4–S6.

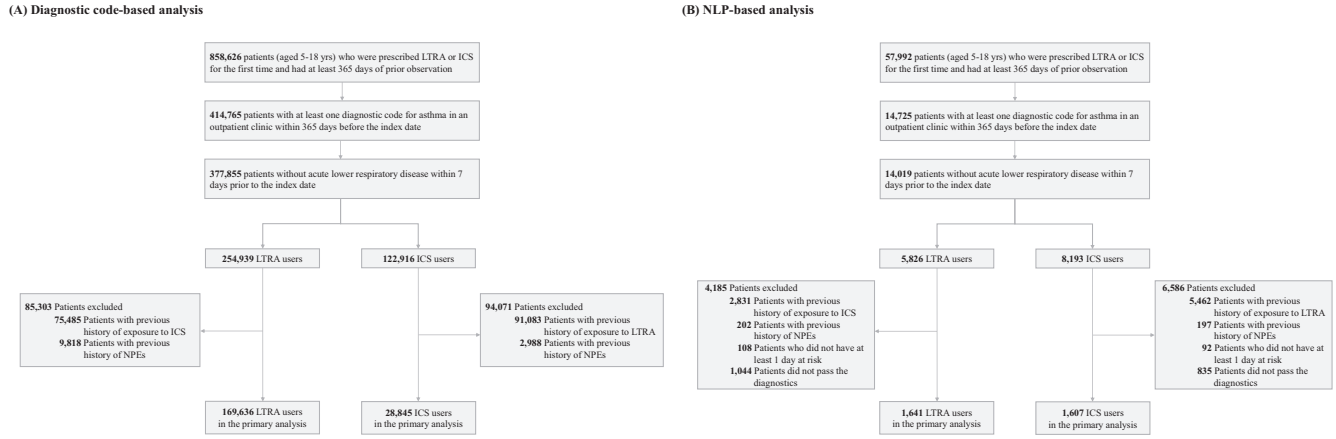

FIGURE 1 | Flowchart of patient selection. ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; NLP, natural language processing; NPE, neuropsychiatric event.

TABLE 1 | Baseline characteristics of patients included in the diagnostic code-based primary analysis.

	Before PS stratification			After PS stratification		
	LTRA ($N=169636$)	ICS ($N=28845$)	aSMD	LTRA ($N=169636$)	ICS ($N=28845$)	aSMD
Age group						
5–9	0.66	0.67	0.02	0.66	0.62	0.06
10–14	0.22	0.24	0.04	0.22	0.23	0.02
15–18	0.12	0.09	0.10	0.12	0.15	0.07
Sex (female)	0.46	0.47	0.03	0.46	0.46	0.01
Medical history						
Allergic conjunctivitis	0.29	0.23	0.14	0.28	0.26	0.04
Allergic rhinitis	0.99	0.92	0.37	0.99	0.98	0.10
Atopic dermatitis	0.19	0.15	0.10	0.18	0.18	0.02
Bronchiolitis	0.15	0.11	0.12	0.14	0.14	0.00
Bronchitis	0.96	0.97	0.05	0.96	0.96	0.02
Pneumonia	0.16	0.13	0.09	0.15	0.15	0.00
Rhinitis	0.99	0.92	0.36	0.99	0.98	0.10
Urticaria	0.28	0.24	0.08	0.27	0.27	0.00

Note: Values are presented as proportions of the patients (%) unless otherwise indicated.
Abbreviations: aSMD, absolute standardized mean difference; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; PS, propensity score.

TABLE 2 | Baseline characteristics of patients included in NLP-based primary analysis.

	Before PS stratification			After PS stratification		
	LTRA ($N=1641$)	ICS ($N=1607$)	aSMD	LTRA ($N=1641$)	ICS ($N=1607$)	aSMD
Age group						
5–9	0.74	0.57	0.37	0.67	0.67	0.00
10–14	0.18	0.28	0.25	0.23	0.22	0.01
15–18	0.08	0.14	0.21	0.11	0.11	0.01
Sex (female)	0.38	0.37	0.01	0.36	0.36	0.01
Medical history						
Allergic conjunctivitis	0.05	0.04	0.09	0.04	0.04	0.00
Allergic rhinitis	0.53	0.33	0.40	0.42	0.45	0.05
Atopic dermatitis	0.11	0.09	0.05	0.09	0.09	0.00
Bronchiolitis	0.02	0.02	0.05	0.02	0.03	0.07
Bronchitis	0.31	0.23	0.19	0.27	0.28	0.03
Pneumonia	0.04	0.05	0.03	0.04	0.05	0.02
Rhinitis	0.53	0.34	0.40	0.43	0.45	0.05
Urticaria	0.05	0.04	0.06	0.04	0.04	0.01

Note: Values are presented as proportions of the patients (%) unless otherwise indicated.
Abbreviations: aSMD, absolute standardized mean difference; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; NLP, natural language processing; PS, propensity score.

3.2 | Association Between LTRA and Diagnosed NPEs

The cumulative incidence curves for diagnosed NPEs over a 90-day period are presented in Figure 2A. During the follow-up period, the IR of NPEs was 24.04 per 1000 PYs for LTAR users and 22.70 per 1000 PYs for ICS users. IRs of individual diagnosed NPEs are shown in Table S7. The most prevalent diagnosed NPE was anxiety disorder.

We did not find evidence of an increased risk of NPEs in LTRA users compared with ICS users in the diagnostic code-based primary analysis. The uncalibrated HR was 1.08 (95% CI, 0.89–1.31), and the calibrated HR was 1.14 (95% CI, 0.92–1.42) (Table 3).

The cumulative incidence curves and HR for diagnosed NPEs in the EHR databases are presented in Figure S5A and Table S8. Consistent with the results of a nationwide population-based analysis, no statistically significant difference in the risk of NPEs was observed between the two drugs in the YUHS database.

3.3 | Association Between LTRA and NLP-Identified NPEs

Figure 2B presents the cumulative incidence curves of NPEs identified using NLP during the 90-day follow-up. The IR of NPEs was 148.77 per 1000 PYs for LTRA users and 122.78 per 1000 PYs for ICS users in the YUHS database. Detailed IRs for each NLP-identified NPE are provided in Table S7. Tic was the most frequently identified symptom among NLP-identified NPEs.

In this NLP-based primary analysis, the uncalibrated HR of NPEs was 1.01 (95% CI, 0.64–1.61), and the calibrated HR was 1.33 (95% CI, 0.66–2.68) (Table 3). The AUH results, which did not meet the study diagnostic criteria, are shown in Figure S5B and Table S8.

3.4 | Sensitivity Analyses

The results of the sensitivity analyses with various analytical settings for each outcome definition are presented in Figure S6. Across multiple analytical settings and different outcome definitions, we did not observe a statistically significant difference in NPE risk between LTRA and ICS users.

4 | Discussion

In our comparative analysis of neuropsychiatric burden associated with LTRA and ICS in children with asthma, we did not find evidence to suggest significant differences between the two drug classes. These results were consistent across different databases, analytical settings, and outcome measures, including both diagnostic code-based and NLP-identified analyses.

To our knowledge, this is the first study to compare adverse reactions of different drug classes using data extracted from unstructured clinical notes using an LLM-based NLP. This

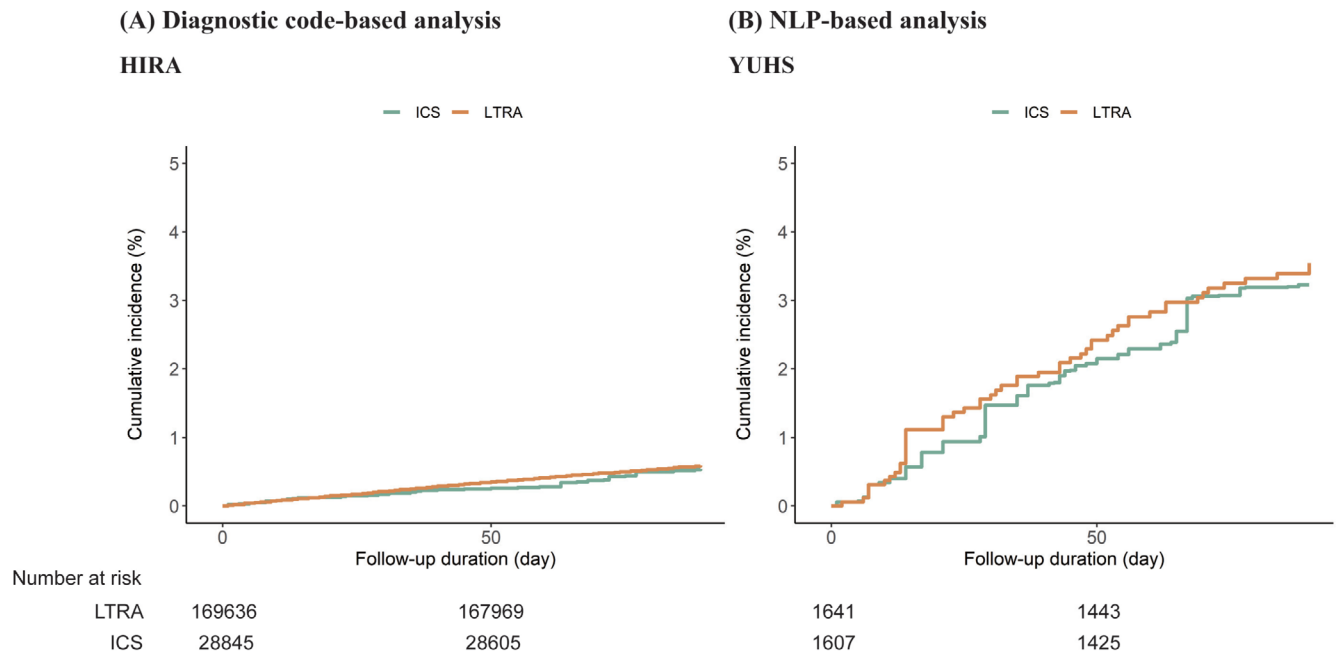

FIGURE 2 | Cumulative incidence curves for the risk of NPEs classified by outcome definitions. HIRA, Health Insurance Review and Assessment Service; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; NLP, natural language processing; NPE, neuropsychiatric events; YUHS, Yonsei University Health Systems.

TABLE 3 | Risk of NPEs between LTRA and ICS users in primary analysis.

	LTRA		ICS			
Source	**Total**	**Event**	**Total**	**Event**	**Uncalibrated HR (95% CI)**	**Calibrated HR (95% CI)**
Diagnostic codes						
HIRA	169 636	995	28 845	160	1.08 (0.89–1.31)	1.14 (0.92–1.42)
NLP-identified						
YUHS	1641	54	1607	44	1.01 (0.64–1.61)	1.33 (0.66–2.68)

Abbreviations: CI, confidence interval; HIRA, Health Insurance Review and Assessment Service; HR, hazard ratio; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; NLP, natural language processing; NPE, neuropsychiatric event; YUHS, Yonsei University Health Systems.

approach is valuable for detecting neuropsychiatric conditions and symptoms, which might be commonly underreported or inconsistently recorded in structured EHRs [13–15]. In our study, the IR of NPEs defined using diagnosis codes was 24.04 per 1000 PYs in LTRA users, which is compatible with previous studies [24, 25] (11.66–24.4 per 1000 PYs), while the IR of NLP-identified NPEs was 148.77 per 1000 PYs. One possible explanation for this underreporting is that certain symptoms or signs, while mentioned in clinical notes, may not reach the threshold required for clinicians to formally code them as diagnoses [14]. In addition, the social stigma surrounding mental health issues may discourage patients and clinicians from formally documenting symptoms [13]. By leveraging unstructured clinical notes, we identified NPEs that may otherwise have been overlooked. While manually reviewing all clinical notes from over 3000 participants would have been time-consuming and laborious, we streamlined this process by developing an NLP model fine-tuned to accomplish this specific task. Previous studies have demonstrated the efficacy of text mining for extracting depressive symptoms from unstructured clinical notes [26]. Our LLM-based NLP model further demonstrated acceptable performance when evaluated against manual chart reviews.

Our findings align with those of a large-scale US-based retrospective cohort study that compared 513 519 patients with asthma aged ≥ 6 years on montelukast with 1 332 431 patients on ICS and reported no evidence of increased risk in hospital admissions for depressive disorders (HR [95% CI] 1.06 [0.90–1.24]) and self-harm (HR [95% CI] 0.92 [0.69–1.21]) [12]. The study was limited to high-severity neuropsychiatric outcomes and relied on a claims-based structured database. Conversely, the NPE outcomes we examined encompassed a broader range of symptoms and diagnoses, and we complemented the structured data analysis with unstructured clinical notes; however, the findings did not suggest a marked difference in neuropsychiatric risk between LTRA and ICS. Other observational studies, including nested case–control studies or secondary analyses of clinical trials, further reported no association between LTRA and increased NPE [27–29]. Although our findings are consistent with those of these previous studies, they did not directly compare LTRA

and ICS. In contrast, our study relied on a comparison that more closely reflects real-world clinical practice, where clinicians choose between these two drug classes.

A prior retrospective study employing a matched cohort design reported a higher incidence of drug cessation due to neuropsychiatric adverse reactions in children with asthma initiated on LTRA compared to those initiated on ICS, based on direct interviews [11]. However, this prior study was limited by its small cohort size. In contrast, we utilized a nationwide database, allowing for more robust analyses. Recent observational studies have suggested that LTRA is associated with neuropsychiatric outcomes in various age groups [30–32]. Notably, one retrospective cohort study that also utilized the nationwide HIRA database compared patients with asthma on concomitant LTRA and ICS or ICS/long-acting b2-agonists (LABA) to those on ICS or ICS/LABA alone, reporting an increased risk of hallucinations and attention problems among the former; however, no increased risk of NPEs was observed among patients aged < 20 years who were treated with ICS or ICS/LABA with montelukast [33]. While this study focused on the additive effect of LTRA, rather than directly comparing them to other competing treatments, we compared LTRA with ICS, providing information directly applicable to clinical decision-making.

The causal mechanism underlying LTRA-associated NPEs remains unclear. One hypothesis is that montelukast, a widely used LTRA, can cross the blood–brain barrier, modulating leukotriene receptors implicated in neuroinflammatory pathways and influencing neurotransmitter regulation, potentially affecting mood and behavior [34]. Similarly, although ICS is characterized by minimal systemic absorption, its potential neuropsychiatric effects could arise indirectly from systemic corticosteroid exposure affecting neurotransmitter or hormone regulation [35]. Our findings suggest that the neuropsychiatric risk associated with LTRA may not be substantially greater than that associated with ICS, an alternative therapeutic choice, and thus may not clinically differentiate between these two treatments. However, due to the wide CIs observed in our analyses, we cannot entirely rule out the possibility of neuropsychiatric risk associated with LTRA.

Our study has several limitations. First, its retrospective design inherently introduces potential biases and confounding factors. Conducting randomized controlled trials to evaluate drug side effects is challenging, particularly among pediatric populations. Retrospective analyses using real-world data may better reflect actual clinical practice and provide more practical insights. Second, the HIRA database is based on insurance claims, which exclude drugs not approved at the time of use. Nonetheless, as all South Korean residents are obligated to enroll in the national health insurance system, the likelihood of significant omissions in drug use is minimal. Third, increased awareness of the potential neuropsychiatric side effects of LTRA may have led physicians, patients, or families to choose ICS over LTRA for patients with a prior history of neuropsychiatric conditions or symptoms. Although we excluded patients with NPE occurrence before the index date, we could not account for events outside the observation period or undocumented cases. Fourth, while we aimed to capture a broad range of neuropsychiatric symptoms when defining outcomes for the analysis, we only categorized them collectively, rather than examining each individual symptom. Considering that the results for neuropsychiatric symptoms as a whole may differ from those of individual symptoms, further studies on specific symptoms are warranted [33]. Fifth, our NLP-based analysis was limited to data from only two databases, which may have introduced bias owing to center-specific patient characteristics. Moreover, differences in the nature of databases, specifically between EHR-based data from a tertiary hospital comprising patients with higher clinical severity and national claims-based data addressing a general patient population, may have influenced our results, contributing to the substantially higher frequency of NPE observed in the NLP-based analysis conducted in YUHS compared to the code-based analysis conducted in HIRA. As the HIRA database does not contain clinical note data, this limitation is unavoidable. Large-scale studies using EHR databases from more centers would be beneficial to validate our findings. Sixth, the definition of NPEs differs across data sources. In the claims database, we used both inpatient and outpatient diagnosis codes, whereas in the EHR data, we used outpatient clinical notes to identify NPEs. Because of these differences, the results are not directly comparable and should be interpreted with caution. Finally, our NLP model was trained using a single database, potentially leading to overfitting and limiting generalizability to clinical notes with different stylistic patterns used by clinicians elsewhere. To address this concern, we validated the model's performance in a second database before applying it to the main analysis, demonstrating acceptable generalizability across institutions.

Despite these limitations, our study has several strengths. First, we leveraged the large-scale, nationwide HIRA database, capturing data across all areas of medical practice and representing the entire Korean population. Second, rigorous methodologies were employed to ensure an unbiased, robust comparison between the two drug classes. Large-scale PS adjustment allowed us to account for various covariates and extensively control confounding factors [36]. Empirical calibration and falsification endpoints were used to minimize residual bias. Multiple sensitivity analyses further strengthened the reliability of our findings. Third, we developed a high-performance NLP model that allowed for the efficient processing of unstructured clinical notes, ensuring consistency in reviewing large volumes of text, which is challenging with manual chart reviews.

In conclusion, our comprehensive analyses, using both structured diagnostic code-based and unstructured NLP-based outcomes, did not demonstrate a statistically significant difference in the risk of adverse NPEs between LTRA and ICS. These findings provide valuable insights for clinical decision-making in children with asthma. Further studies on the detailed safety profile of both LTRA and ICS are warranted.

4.1 | Plain Language Summary

There have been concerns regarding LTRAs, a type of asthma medication, that they may be linked to neuropsychiatric adverse

effects. In this study, we aimed to find whether children with asthma who are treated with LTRAs have a higher risk of developing NPEs compared to those treated with ICS, another common asthma medication. We analyzed two types of health records to address this question. First, we looked at a population-based claims database. Second, we analyzed hospital records, including physicians' clinical notes, using a LLM. In both analyses, children who used LTRAs did not have a higher risk of developing NPEs compared to ICS users. Our findings provide valuable insights to help clinicians make evidence-based decisions when treating children with asthma.

Acknowledgments

This study used HIRA OMOP-CDM data made by the Health Insurance Review and Assessment Service. The views expressed are those of the authors and not necessarily those of the HIRA and the Ministry of Health and Welfare (Ministry of Health, Welfare and Family Affairs), South Korea.

Ethics Statement

This study was approved by the Institutional Review Boards of the Yonsei University Health System (IRB No. 4-2022-1475) and Ajou University Hospital (IRB No. AJOUIRB-EX-2023-560), which waived the requirement for informed consent owing to the retrospective study design.

Conflicts of Interest

Seng Chan You reports being a chief executive officer of PHI Digital Healthcare and receiving grants from Daiichi Sankyo. The other authors declare no conflicts of interest.

Data Availability Statement

Data for the results is available on request to the authors. Requests to access the original full datasets from the HIRA database should be directed to the HIRA Big Data Department. The patient-level data and raw clinical notes cannot be shared due to concerns regarding patient privacy.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supporting Information.