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南京中医药大学第十届“汪受传奖学金”申请审批表

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<tr><td colspan="2">循证医学原理及中医临床应用</td><td>93</td><td colspan="2"></td><td></td></tr>
<tr><td colspan="2">学术规范与实验室安全</td><td>94</td><td colspan="2"></td><td></td></tr>
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课程	学分	学期	成绩
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课程	学分	学期	成绩
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学术成果目录

1. 学术论文

2. 江苏省研究生科研创新计划

学术论文1

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Leukotriene Receptor Antagonists and Risk of Neuropsychiatric Entities: A Meta-Analysis of Observational Studies.

By: Bai, Le; Xu, Yong; Fan, Lingyu; Zhang, Ying; Zhou, Xianmei; Xu, Jie

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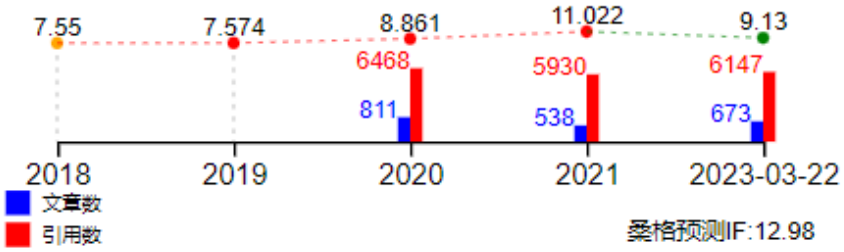

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Original Article

Leukotriene Receptor Antagonists and Risk of Neuropsychiatric Entities: A Meta-Analysis of Observational Studies

Le Bai, MD[a,*], Yong Xu, MD[b,*], Tingyu Pan, MD[a,*], Ying Zhang, MD[c], Xianmei Zhou, MD, PhD[a,d], and Jie Xu, MD, PhD[a,d]
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What is already known about this topic? Case reports and pharmacovigilance studies have indicated that leukotriene receptor antagonists (LTRAs) might lead to neuropsychiatric (NP) entities, whereas the conclusions in observational studies were inconsistent.

What does this article add to our knowledge? The association between LTRA use and NP entities was not statistically significant at the population level. However, increased NP risk may exist in particular groups (eg, patients with allergic rhinitis or NP history). More studies specific to these subjects are required to further examine the relationship between LTRAs and NP entities and identify the underlying mechanisms.

How does this study impact current management guidelines? Patients with allergic rhinitis or NP history should be well informed about the possible NP risks when prescribed LTRAs. Persistent follow-up and timely reports of adverse reactions are critical for further evaluation of clinical benefits and risks.

BACKGROUND: Leukotriene receptor antagonists (LTRAs) are commonly prescribed to patients with allergic diseases. Several case reports and pharmacovigilance studies have indicated that LTRAs might increase the risk of neuropsychiatric (NP) entities. However, the results are mixed in observational studies. Thus, the association between LTRAs and NP entities remains controversial.
OBJECTIVE: To quantitatively evaluate the NP risk with LTRAs based on current observational studies to provide a reference for clinical practice.
METHODS: We systematically reviewed the literature in Medline, Embase, Web of Science, Cochrane Library, Scopus, and PsycINFO. A meta-analysis of observational studies that investigated the association between LTRA use and the risk of NP entities was performed. Odds ratios (OR) with 95% confidence intervals (CI) were used to measure the effect; heterogeneity was evaluated using I-squared (I^2) statistics. Subgroup and sensitivity analyses were conducted to assess bias.
RESULTS: Eleven articles were included in the primary analysis. No significant association was found between LTRA use and NP entities (OR: 1.08, 95% CI: 0.93-1.24, $I^2 = 93.7\%$). In patients with allergic rhinitis (AR), a mildly increased NP risk was found (OR: 1.099, 95% CI: 1.004-1.202). The association between LTRA use and NP entities was not significant in patients with asthma (OR: 1.06, 95% CI: 0.90-1.26). LTRAs increased the risk of NP entities in a single study using data from an asthma clinic (OR: 9.00, 95% CI: 1.20-69.50), but not in studies from databases (OR: 1.07, 95% CI: 0.93-1.23).
CONCLUSION: At the population level, LTRAs and NP entities were unrelated. However, the association may exist in particular groups (eg, patients with AR or NP history). Subject-specific studies are required to further examine the relationship between LTRAs and NP entities and identify the underlying mechanisms. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2023;11:844-54)

Key words: *Leukotriene receptor antagonist; Neuropsychiatric entities; Meta-analysis*

Leukotriene receptor antagonists (LTRAs), including montelukast, pranlukast, and zafirlukast, were developed in the 1990s. They have been licensed by the US Food and Drug Administration (FDA) for the prevention and treatment of asthma; they inhibit airway inflammatory mediators and relax bronchial smooth muscle.[1,2] LTRAs have been adopted as first-line or add-on treatments

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Abbreviations used
AR- Allergic rhinitis
CI- Confidence interval
FDA- Food and Drug Administration
HR- Hazard ratio
LTRA- Leukotriene receptor antagonist
NOS- The Newcastle-Ottawa Scale
NP- Neuropsychiatric
OR- Odds ratio
RCT- Randomized controlled trial
RR- Relative risk
SCCS- Self-controlled case series

for asthma in most national guidelines.[3,4] In addition, montelukast has been approved for the treatment of allergic rhinitis (AR) and is currently the most prescribed drug worldwide.[5]

Although LTRAs were considered safe and well tolerated,[6,7] postmarketing reports and pharmacovigilance studies have indicated a possible relationship between LTRAs and neuropsychiatric (NP) entities.[8] Therefore, the FDA announced a label change for montelukast in 2008 to draw attention to its NP risk. Concerns have been raised about whether the FDA was overreacting as such adverse reactions were not reported in the initial trials.[9] A subsequent pooled analysis of randomized controlled trials (RCT) indicated that LTRA use did not significantly increase the risk of NP entities.[10] Clinical trials cannot be expected to detect rare adverse events. However, evidence from observational studies is limited as well.[11,12] In addition, systematic review results have been contradictory. Dixon et al[13] found an increased NP risk in children and young people (<18 years) who were prescribed LTRAs, whereas 2 other systematic reviews were inconclusive and emphasized the poor evidence quality that supported a positive association.[14,15]

In 2020, the FDA issued a new boxed warning for montelukast, aiming to overcome its potential NP risk. However, whether a statistical correlation exists between LTRAs and NP entities still remains controversial. Previous cohort or case-control studies have reported inconsistent results, and available systematic reviews have failed to reach a consensus.[10-14,16,17] Moreover, several large observational studies published recently have involved new evidence.[18-24] Consequently, we conducted a comprehensive meta-analysis of current observational studies to further examine evidence linking LTRA use to NP entities.

METHODS

We performed a meta-analysis and wrote the manuscript according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[25]

Literature search and selection criteria

Databases, including Medline, Embase, Web of Science, Cochrane Library, Scopus, and PsycINFO, were searched for eligible studies published in any language before May 31, 2022. The following items were used as keywords: ("leukotriene modifying agent" OR "leukotriene modifying agents" OR "leukotriene receptor antagonist" OR "leukotriene receptor antagonists" OR "montelukast" OR "pranlukast" OR "zafirlukast") AND ("cohort study" OR "case-control study" OR "observational study"). We also reviewed the references in relevant articles in case of omission of possible studies.

The previously conducted RCTs were primarily aimed at assessing the efficacy of LTRAs in patients with asthma or AR, and most of them were conducted before the montelukast label change. Two previous studies have pointed out that NP entities may be underreported due to a lack of awareness of the connection between LTRAs and NP risk.[10,14] Thus, in the present meta-analysis, observational studies specifically designed to evaluate the NP risk in LTRA users were selected. In individual studies, the association between them needed to be measured by odds ratio (OR), relative risk (RR), or hazard ratio (HR) to be included in the analysis. Studies with incomplete data for the meta-analysis were excluded.

Data extraction and quality assessment

Two researchers (LB and YX) independently screened the literature according to the inclusion and exclusion criteria, and extracted data from the full text of eligible articles. A third researcher (TP) was consulted in case of any disagreements. The extracted information included first author; country or region; study design, population, and sample size; exposure factors; NP entities in each study; covariates, and OR (or RR/HR) with 95% confidence interval (CI).

The methodological quality of the case-control or cohort studies was assessed using the Newcastle-Ottawa Scale (NOS; see Table E1 in this article's Online Repository at www.jaci-inpractice.org).[26] It was developed to evaluate the quality of nonrandomized studies[27] and has been the most commonly reported tool (39%) in systematic reviews.[28] It takes several common sources of bias in observational studies into consideration, including the selection of groups (comparability), exposure, and confounding factors. The thresholds for converting the NOS to the Agency for Health care Research and Quality standards (good, fair, and poor) are provided in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org). Two researchers (LB and YX) independently assessed the quality of the included studies and consulted a third researcher (TP) in case of disagreements.

Data synthesis and analysis

All statistical analyses were performed using Stata 15.0 (StataCorp, College Station, Texas). Because the absolute risk of NP entities was low (incidence rate < 10%), the OR, RR, and HR were considered similar.[29-31] We employed OR with 95% CI as the effect measure for the relationship between LTRAs exposure and the incidence of NP entities. Forest plots were used to display the individual and pooled results. Heterogeneity was evaluated using the I-squared (I^2) statistic. When it was considered notable ($I^2 > 50\%$), the random-effects model was selected; otherwise, the fixed-effects model was selected.

Subgroup analyses were also conducted to adjust for potential confounding factors such as: (1) the data source (databases or clinical studies only [ie, excluding studies from databases]); (2) the study design (case-control or cohort studies); (3) participant type (patients with asthma or AR); (4) age (children, adolescents, or middle-aged and elderly adults); and (5) region (or race). In addition, the label change of montelukast, which might affect the reporting rate of NP entities in LTRA users, was also considered. We also performed a sensitivity analysis for bias assessment, and a funnel plot was used to evaluate publication bias.

RESULTS

Study selection and characteristics

A total of 1217 publications were obtained from all databases, and 811 duplicates were eliminated. We screened the abstracts

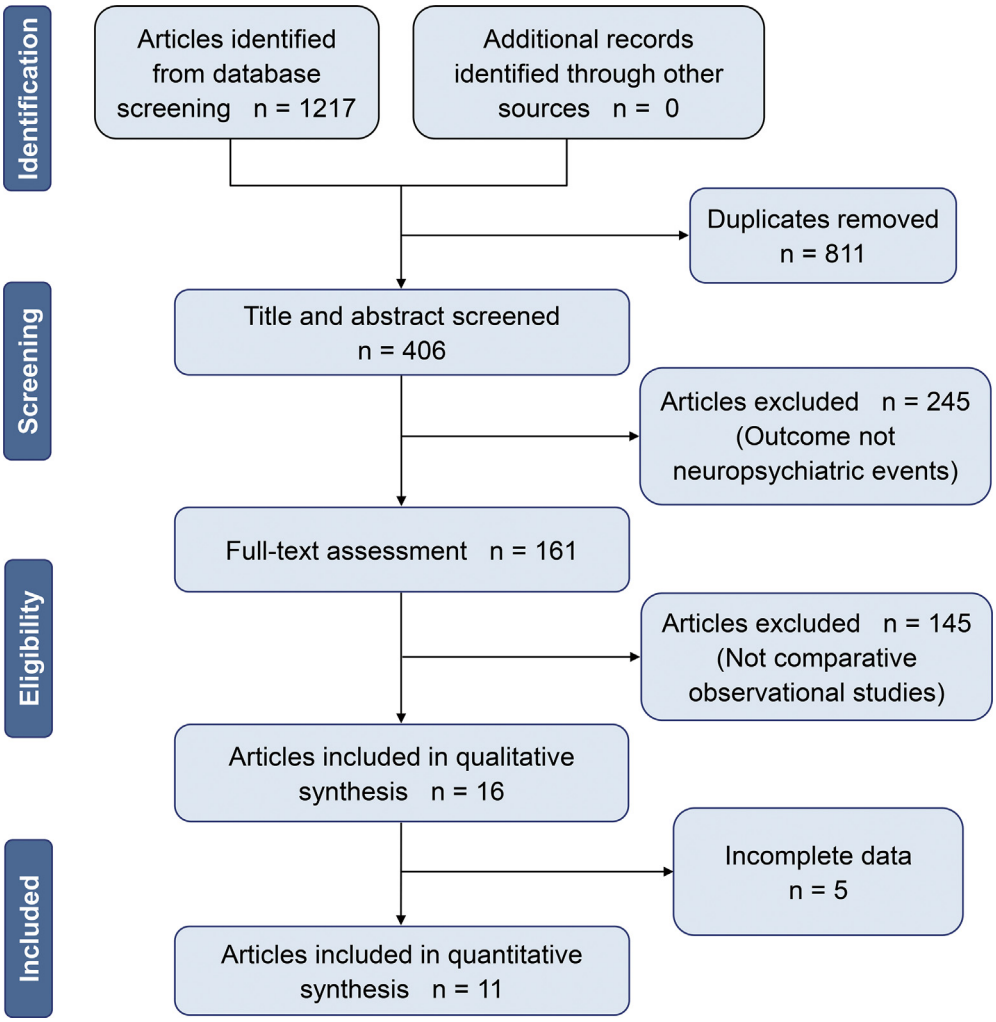

FIGURE 1. Flow chart of the study selection.

and full texts of the remaining articles and eliminated 395 studies that did not meet the inclusion criteria. Ultimately, 4 nested case-control studies, 6 cohort studies, and 1 self-controlled case series (SCCS)[11,12,16-24] were included in the meta-analysis. Traditional epidemiologic designs include cohort and case-control studies, which assess the relationship between the exposure and outcome of interest. However, several biases (eg, confusion bias) would be present in these studies. The nested case-control study can be considered as a case-control study within a cohort study, in which controls are matched to cases to control for the effect of confounders.[32] The SCCS method is also based on the principles of a cohort study. In a cohort study, a comparison is made between different individuals with and without exposure to the incidence of an outcome. In an SCCS study, a comparison is made between different periods the same people with and without exposure to determine the outcome incidence. Therefore, confounding factors are better balanced in an SCCS study than in a cohort study.[33] The entire study selection process is shown in Figure 1.

Table I summarizes the characteristics of each eligible study including the first author, region, study design, period, population, and sample size. Patients with asthma or AR who were prescribed LTRAs were compared with patients without LTRA exposure. Ten studies were conducted based on primary care databases,[11,12,17-24] and 1 study was conducted using retrospective data from an asthma clinic.[16] Five studies[12,18,20,22,23] chose LTRAs as the exposure and the rest[11,16,17,19,21,24] chose montelukast. We summarized the components of NP entities and covariates that were adjusted for in each study (Table I).

All the cohort and case-control studies were identified to be of good quality as assessed using NOS (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). The methodological quality of the SCCS study was assessed using the tool proposed by Wachira et al,[34] which is an adaptation of the NOS assessment (Table E4, available in this article's Online Repository at www.jaci-inpractice.org); the SCCS study was considered to be of high quality (Table E5, available in this article's Online Repository at www.jaci-inpractice.org).

Meta-analysis and bias analysis

Eleven studies[11,12,16-24] with 1,274,695 participants were included in the meta-analysis (Figure 2). The incidence of NP entities did not significantly increase in patients prescribed LTRAs than in non-LTRA users (OR: 1.08, 95% CI: 0.93-1.24,

TABLE I. Characteristics of the studies included in the meta-analysis

First author	Design	Study period	Region	Age (y)	Exposure	Sample size	Neuropsychiatric entities	Covariates adjusted for	OR/RR/HR (95% CI)
S. Dresden Glockler-Lauf[17]	Nested case-control study	2004-2015	Canada	5-18	Montelukast	898 patients with asthma, 3497 controls matched for age, sex, and residence	Anxiety, sleep disturbance, mood, substance related, personality, schizophrenia, agitation	Socioeconomic status, asthma severity, number of asthma drugs used, and corticosteroid prescriptions	1.91 (1.15-3.18)
Sang Oh Kang[22]	Nested case-control study	2003-2013	Korea	>60	LTRAs	31,922 patients with asthma, 31,922 controls matched for sex, age, income	Mood disorder, sleep disorder, anxiety disorder, personality disorder, substance-related disorder, agitation, schizophrenia, self-harm disease	Comorbidities	1.67 (1.58-1.78)
Mir M. Ali[11]	Nested case-control study	1998-2009	United States	1-17	Montelukast	1920 patients with asthma, and 5760 controls matched for sex, age, region	All mental illnesses, extrapyramidal and abnormal movement disorders, and hallucinations	Asthma severity, comorbidities, drug exposures, socioeconomic status	1.01 (0.88-1.14)
Po-Yu Huang[24]	Retrospective cohort study	1997-2013	Taiwan	<12	Montelukast	12,806 patients with asthma and 12,806 controls matched for sex, age, region	Attention-deficit/ hyperactivity disorder	Asthma severity, comorbidities	1.04 (0.93-1.17)
Glen T. Schumock[12]	Nested case-control study	1997-2006	United States	5-24	LTRAs	344 patients with asthma and 3438 controls matched for sex, age, region	Suicide attempt	Asthma severity, comorbidities, drug exposure	0.74 (0.46-1.20)
Yumi Ishikura[23]	Retrospective cohort study	2006-2015	Japan	>50	LTRAs	20,942 patients with asthma	Dementia	Sex, age, comorbidities, drug exposure	0.42 (0.20-0.87)

(continued)

TABLE I. *(Continued)*

First author	Design	Study period	Region	Age (y)	Exposure	Sample size	Neuropsychiatric entities	Covariates adjusted for	OR/RR/HR (95% CI)
Ji-Su Shim[20]	Retrospective cohort study	2002-2015	Korea	40-79	LTRAs	61,571 patients with asthma	Organic mental disorders; behavioral syndromes associated with physiological disturbances and physical factors; mood disorders; neurotic, stress-related, and somatoform disorders; unspecified mental disorders	Age, sex, smoking, alcohol drinking, physical activity, BMI, comorbidities, other asthma medications	1.01 (0.83-1.23)
Veronica Sansing-Foster[21]	Retrospective cohort study	2000-2015	United States	>6	Montelukast	914,754 patients with asthma	depressive disorder	Sex, age, asthma severity, comorbidities, medication use, history of psychiatric disorders, psychotropic medications use	Inpatient 0.63 (0.37-1.07)*
									Outpatient 1.07 (0.98-1.17)*
Brigitte Benard[16]	Retrospective cohort study	2011-2016	Canada	1-17	Montelukast	168 patients with asthma	NA	Age, sex, ethnicity, asthma phenotype and control, drug use, predisposing conditions, montelukast dose, and genetic factors.	9.00 (1.20-69.50)
Ji Soo Park[18]	Self-controlled case series study	2005-2018	Korea	3-30	LTRAs	17,001 patients with asthma or AR	Psychotic, mood, anxiety, cognitive, movement, sleep, and personality disorders	Age	1.05 (0.96-1.15)

Tapio Paljarvi[19]	Retrospective cohort study	2015-2019	United States	15-64	Montelukast	72,490 patients with asthma	Psychotic, mood, anxiety, dissociative, stress-related, somatoform, and other nonpsychotic mental disorders; adult personality and behavior disorders; sleep disorders; and nonfatal self-harm	Age, race, sex, comorbidities, history of NP diagnoses and medications use	1.11 (1.04-1.19)
						82,456 patients with AR			1.07 (1.01-1.14)

AR, Allergic rhinitis; *BMI*, body mass index; *CI*, confidence interval; *HR*, hazard ratio; *LTRA*, leukotriene receptor antagonist; *NA*, not available; *NP*, neuropsychiatric; *OR*, odds ratio; *RR*, relative risk.
*HRs for NP entities in patients without an NP history were selected in case of heterogeneity and possible bias.

$I^2 = 93.7\%$), which indicated that LTRA use was not associated with NP risk.

Considering the notable heterogeneity among the studies, we performed subgroup and sensitivity analyses (Table II and Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). In a meta-analysis of studies[12,18,21,24] where the participants were children (<12 years), LTRA use did not increase the risk of NP entities (OR: 0.88, 95% CI: 0.70-1.11, $I^2 = 75.2\%$), which was similar to the results obtained in studies aimed at adolescents[12,18,21] (12-18 years; OR: 0.95, 95% CI: 0.69-1.32, $I^2 = 85.4\%$) and middle-aged and elderly adults[20,22,23] (>40 years; OR: 1.02, 95% CI: 0.61-1.70, $I^2 = 94.4\%$) (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). Similarly, no positive association was observed between LTRA use and NP entities irrespective of regional (or racial) (North America vs Asia; Figure E3, available in this article's Online Repository at www.jaci-inpractice.org) and study design (cohort studies vs case-control studies; Figure E4, available in this article's Online Repository at www.jaci-inpractice.org) differences. In the analysis of studies[11,12,18,21] conducted before the montelukast label change, we found a negative association between LTRAs and NP entities (OR: 0.92, 95% CI: 0.86-0.98, $I^2 = 0\%$); the association was not significant in studies[16,18,19,21] using data after the label change (OR: 1.06, 95% CI: 0.94-1.18, $I^2 = 92.5\%$; Figure 3). In patients with AR, LTRA use mildly increased the risk of NP entities (OR: 1.099, 95% CI: 1.004-1.202, $I^2 = 32.8\%$); however, in patients with asthma, the association was not significant (OR: 1.06, 95% CI: 0.90-1.26, $I^2 = 93.9\%$; Figure 4). Ten studies[11,12,17-24] were conducted using databases, and our meta-analysis indicated that LTRA use did not increase the risk of NP entities (OR: 1.07, 95% CI: 0.93-1.23, $I^2 = 94.1\%$; Figure E5, available in this article's Online Repository at www.jaci-inpractice.org). Meanwhile, in a single study based on retrospective data from one asthma clinic,[16] a significantly increased NP risk was found in patients exposed to LTRAs (OR: 9.00, 95% CI: 1.20-69.50). Visual assessment of the funnel plot indicated publication bias (Figure 5).

DISCUSSION

In the present meta-analysis, we did not find a significant increase in the NP risk in patients who were prescribed LTRAs, which indicated that LTRA use was not clinically relevant in the development of NP entities. In subgroup analyses, the outcomes remained consistent irrespective of age, region, study design, and montelukast label change. However, a mildly increased risk of NP entities was found in patients with AR, whereas the association was not significant in patients with asthma. In addition, heterogeneity across the included studies was notable ($I^2 = 93.7\%$), which limited the interpretation of our results.

Two previous systematic reviews did not reach a conclusion;[14,15] NP risk was detected in case reports and pharmacovigilance studies; however, the outcomes of case-control and cohort studies were inconsistent. Pooled analysis was not conducted because of insufficient observational studies. Law et al[14] proposed the need of more well-designed epidemiological studies on a larger population to quantify the NP entities risk. We performed a meta-analysis of previously published, high-quality cohort, case-control, and latest observational studies. The results indicated that LTRA use and NP entities were not

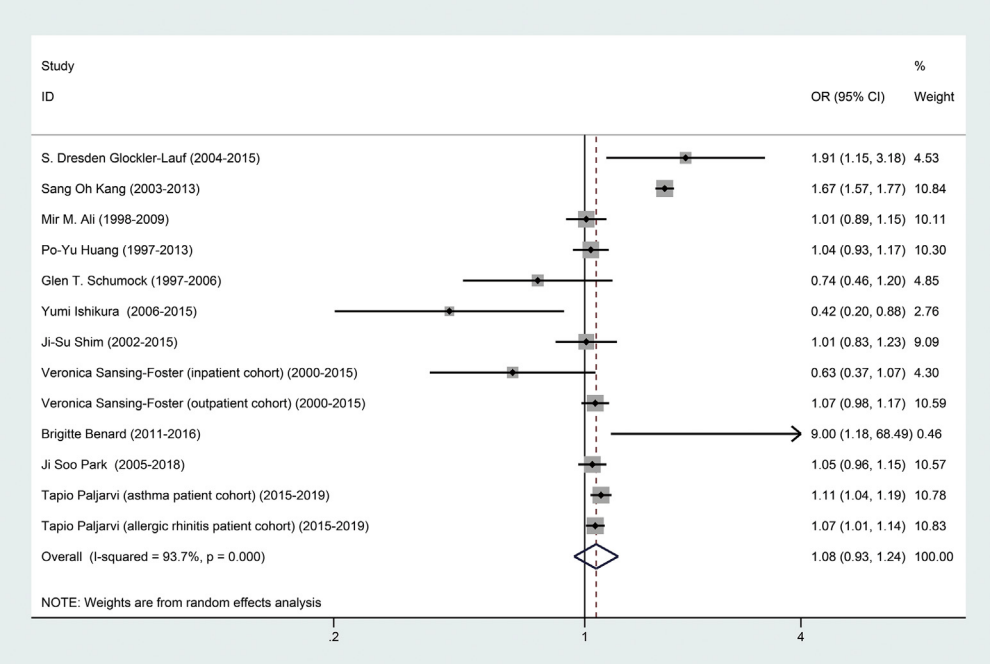

FIGURE 2. Forest plot of individual and overall effect of odds ratio (OR) for neuropsychiatric entities and leukotriene receptor antagonists. *CI*, Confidence interval.

TABLE II. Subgroup analyses

Study characteristic	No. of studies	OR	95% CI	Heterogeneity
Studies based on data before the label change[11,12,18,21]	4	0.92	0.86-0.98	$I^2 = 0\%$
Studies based on data after the label change[16,18,19,21]	4	1.52	1.05-2.19	$I^2 = 92.5\%$
Studies on children[12,18,21,24]	4	0.88	0.70-1.11	$I^2 = 75.2\%$
Studies on adolescents[12,18,21]	3	0.95	0.69-1.32	$I^2 = 85.4\%$
Studies on middle-aged and elderly adults[20,22,23]	3	1.02	0.61-1.70	$I^2 = 94.4\%$
Studies from North America[11,12,16,17,19,21]	6	1.06	0.98-1.15	$I^2 = 59.1\%$
Studies from Asia[18,20,22-24]	5	1.06	0.79-1.42	$I^2 = 96.6\%$
Cohort studies[16,19-21,23,24]	6	1.05	0.98-1.13	$I^2 = 56.2\%$
Case-control studies[11,12,17,22]	4	1.25	0.85-1.84	$I^2 = 94.8\%$
Clinical studies only (ie, excluding studies from databases)[16]	1	9.00	1.20-69.50	–
Studies on databases[11,12,17-24]	10	1.07	0.93-1.23	$I^2 = 94.1\%$

Children: <12 years, adolescents: 12-18 years, middle-aged and elderly adults: >40 years.
CI, Confidence interval; *OR*, odds ratio.

associated, at least at the population level. The evidence from the present meta-analysis is persuasive because the results of non-comparative studies (eg, case reports and pharmacovigilance studies) were easily confounded, especially considering that AR and asthma are related to various NP entities, such as sleep disorders and anxiety.[35-39] A Danish study discovered that the risk of depression was more likely to be associated with asthma than montelukast use.[40] We cannot neglect the fact that extreme NP entities, such as suicide, could not be fully evaluated in observational studies, which might influence the accuracy of the results. Suicidal tendencies were detected in several analyses of global adverse-events reporting databases.[41,42] However, a British study discovered that the suicide rate in patients taking montelukast was not higher than that in the normal population.[43] Schumock et al[44] found a negative association between LTRA use and suicide rate in the United States. These results were consistent with those of a retrospective review of LTRA clinical trials by the FDA,[45] none of which suggested that LTRAs increased the risk of suicide.

In 2 previous meta-analyses of RCTs,[10,46] no statistical correlation was found between montelukast and NP entities. Concerns were raised about this conclusion because these clinical trials were not specifically aimed at evaluating NP risk, and thus, could not adequately assess the occurrence of adverse drug effects.[10,14] However, we obtained similar results in a meta-analysis of currently available observational studies. In addition, the montelukast label change was considered as one of the confounders, as several studies have observed a significant increase in the reporting rate of NP entities after the drug safety communications.[8,47] However, the subgroup analysis indicated that

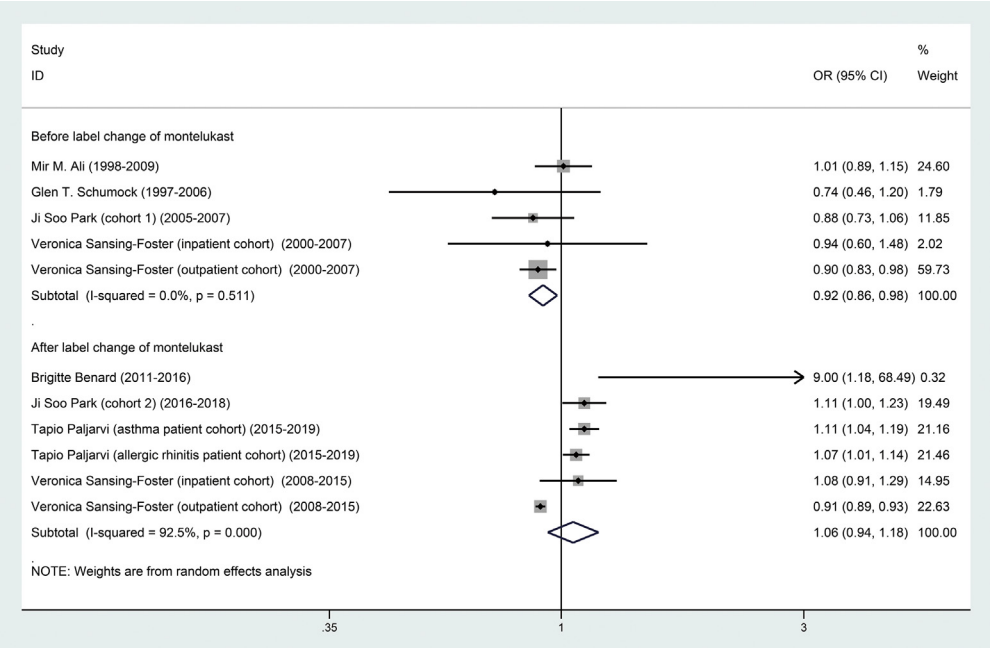

FIGURE 3. Forest plot of individual and overall effect of odds ratio (OR) for neuropsychiatric entities and leukotriene receptor antagonists in studies based on data before and after the montelukast label change. *CI*, Confidence interval.

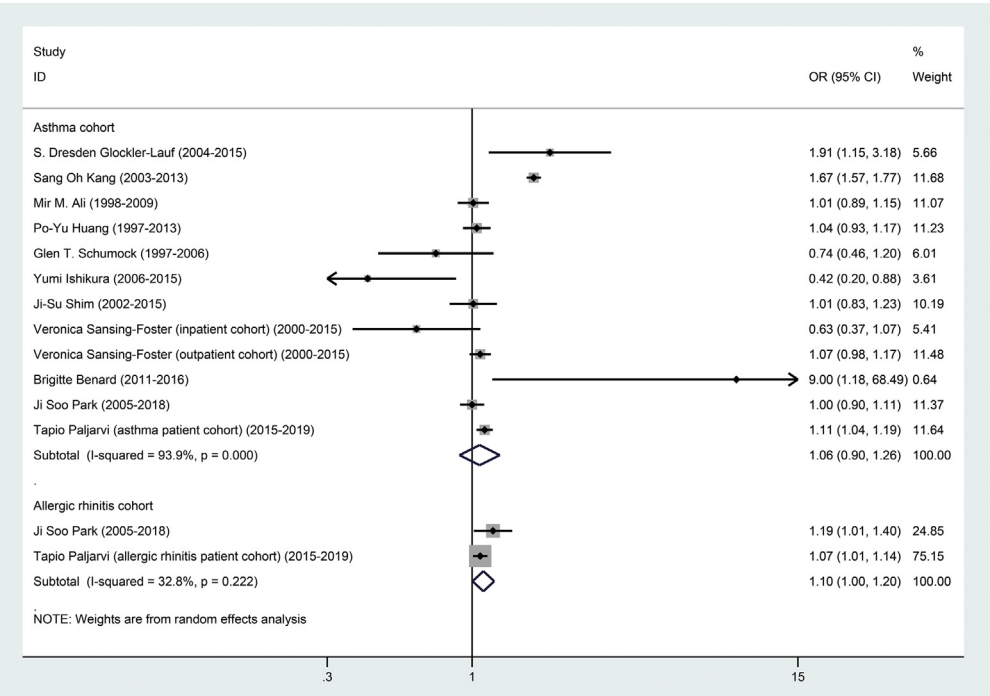

FIGURE 4. Forest plot of individual and overall effect of odds ratio (OR) for neuropsychiatric entities and leukotriene receptor antagonists in patients with asthma and allergic rhinitis. *CI*, Confidence interval.

LTRAs were not associated with the risk of NP entities either in studies before the label change or in those after the label change.

Our findings were contrary to those of the recent systematic review by Dixon et al,[13] which suggested that LTRA use was related to a significantly increased NP risk in young people (<18 years). Dixon et al[13] also included an RCT (MASCOT study), in which patients prescribed fluticasone and montelukast reported more NP entities (7 patients [33.3%] reporting 37 NP entities) than those prescribed fluticasone alone (5 patients [26.3%] reporting 13 NP entities).[48] Nevertheless, several points should

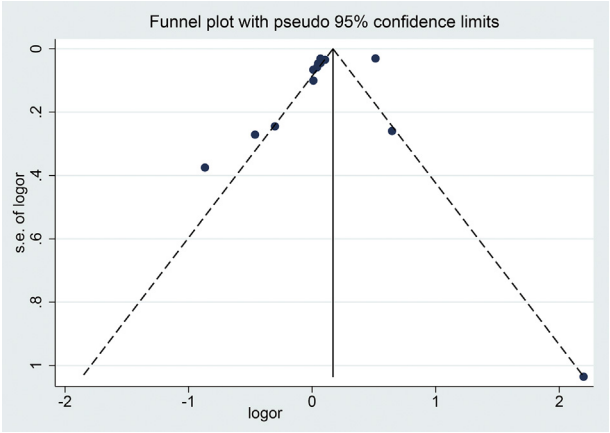

FIGURE 5. Funnel plot for the assessment of publication bias. s.e., Standard error.

be noted. First, the MASCOT study was concluded prematurely because of poor recruitment; inadequate sample size may have led to false-positive outcomes. Second, NP entities reported in the fluticasone and montelukast group significantly increased, to a considerable degree, owing to 1 patient experiencing 20 NP entities. This seems to indicate that the association between LTRAs and NP entities is specific to individuals rather than general groups. Finally, even if an excess of NP entities truly exists, it cannot be ascertained whether they are caused by LTRAs, in view of the overlap with behavioral changes associated with normal development in children.[49]

The current meta-analysis suggested that patients with AR seemed to have a higher LTRA-associated NP risk than patients with asthma. Caution should be exercised with regard to the interpretation of such results. The increased NP risk in patients with AR was mild (OR: 1.099, 95% CI: 1.004-1.202), which may be confounded. AR symptoms are common in patients with asthma;[50] however, increased NP risk was not found in these subjects. In addition, because only 2 studies[18,19] evaluated the association between LTRAs and NP entities in patients with AR, the reduction of statistical power in the subgroup analysis should be taken into consideration. Therefore, more evidence is required to reach a definitive conclusion.

The biological mechanisms of LTRAs and NP entities remain unknown. Nitric oxide, which is produced when LTRA binds to leukotriene receptors, is considered to be a potential cause for NP entity-induced brain tissue injury.[51] The reduction of LTRA-induced neuroinflammation reportedly improves memory impairment.[52] LTRAs are widely used as anti-inflammatory drugs for the treatment of allergic diseases. Nevertheless, in clinical practice, only a portion of patients in whom leukotrienes play a major role in inflammatory reactions may benefit from them.[7] Several single nucleotide polymorphisms (rs12436663 in MRPP3, rs517020 in GLT1D1, etc) were found to have a bearing on different responses (mainly manifested as improvement of lung function) to LTRA therapy.[53] Thus, it was hypothesized that adverse drug reactions have a genetic basis.[54] Umetsu et al[55] searched drug-gene interaction databases, including DGIdb, STITCH, and DSigDB, and found several potential genes (eg, hypocretin neuropeptide precursor genes and kalirin RhoGEF kinase genes) that linked montelukast and mood disorders or depression. A new hypothesis has been proposed that genetic variation might affect the LTRA metabolism, thereby producing neuroactive substances.[54] However, this still requires further demonstration in pharmacogenomic studies.

An obvious limitation of our study was the high heterogeneity, which was not satisfactorily explained in the subgroup analyses. Heterogeneity could be relevant for multiple reasons. First, the definition of NP entities differed widely among the included studies, ranging from mild symptoms to suicides. In reality, the incidence of various NP entities differs. For instance, the incidence of sleep disturbance or depression is approximately 0.1% to 1%, whereas that of suicidal thoughts and actions is $<0.01\%$.[49] As a result, the conclusions of individual studies may be contradictory. Pooled analyses of studies with the same NP outcomes were not conducted, given that each study reported different NP entities. However, we noticed that increased NP risks were detected only in studies where the outcome was a composite of NP entities;[17,19,22] in studies where the outcome was a single NP entity, no significant association was observed.[12,21,23,24] Therefore, a standardized nomenclature of defining NP entities is necessary. Previous studies have indicated that very rare NP outcomes, such as suicidal thoughts or actions, were unlikely to result from LTRA use.[12,43,44] Future studies can be more specific to the NP entities that have been frequently reported or found potentially associated with LTRAs (eg, agitation, mood disorders, and sleep disturbances).[49] Second, partial subjects in Paljarv et al's[19] study had an NP history, whereas other studies excluded patients with a history of NP diagnosis.[11,12,16-18,20-24] This could possibly explain the heterogeneity. In the study by Sansing-Foster et al,[21] most NP entities (93%) occurred in subjects with a history of NP diagnosis, which indicated that patients with and without an NP history might have different risks for development of NP entities. Third, most included studies were conducted using health insurance claims databases, in which several covariates, such as genetic background, could not be adjusted. If development of LTRA-associated NP entities exists only in a specific population, retrospective studies derived from large databases are not suitable, because the sign of increased risk could be easily masked. Finally, recall bias from retrospective studies and publication bias of the included studies could also be possible sources of heterogeneity.

In summary, LTRA use does not seem to be a definite risk factor for the development of NP entities at the population level, based on currently available evidence. However, for particular groups (eg, patients with an AR or NP history), an association may exist and should be considered. In clinical practice, these subjects should be well informed about the possible NP risks when prescribing LTRAs. Persistent follow-up and timely reports of adverse reactions are critical for the evaluation of clinical benefits and risks. In addition, prospective studies are required to further identify the groups who may have a higher risk of developing NP entities when exposed to LTRAs. For individuals who definitely develop NP entities, studies (eg, pharmacogenomics studies) are needed to investigate the underlying mechanisms. These will help to guarantee the safety of clinical administration.

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independently performed the literature search, data extraction, and quality assessment. T. Pan and Y. Xu were responsible for the data analysis. L. Bai and Y. Xu wrote the manuscript draft, and Y. Zhang reviewed the language. All the authors have read and approved the final manuscript for submission.

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江苏省研究生科研创新计划

南京中医药大学2023年江苏省研究生科研与实践创新计划项目 （校助面上、院助项目）

序号	培养单位	学号	申请项目 名　　称	项目类别 (科研计划/实践计划)	项目类型 (人文社科/自然科学)	一级学科或 专业学位类别	研究生层次 (博士/硕士)	资助类别	资助标准 （万元）
1	001 中医学院·中西医结合学院	20213001	《黄帝内经》泽泻饮改善阿尔兹海默病认知障碍的作用机制研究	科研计划	自然科学	1005 中医学	博士	校助面上	1.5
2	001 中医学院·中西医结合学院	20210022	益气活血方调控HIF-1α/BNIP3/Beclin-1信号通路促进破裂型腰椎间盘突出重吸收机制	科研计划	自然科学	1056 中药	硕士	校助面上	1.5
3	001 中医学院·中西医结合学院	20210006	基于“少阳主骨”理论研究少阳膝痹方调节胆固醇代谢改善膝骨关节炎的机制	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
4	001 中医学院·中西医结合学院	20210007	基于“宗气下陷”病机探讨重症肌无力的胸腺免疫病理机制	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
5	001 中医学院·中西医结合学院	20210008	OCF与顺铂联用在三阴性乳腺癌中的增效减毒作用研究	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
6	001 中医学院·中西医结合学院	20210011	基于EGFR/STAT3/Bcl-2信号通路探讨温润通脉方缓解阿霉素心肌损害机制	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
7	001 中医学院·中西医结合学院	20210015	紫参汤抗结直肠癌作用及分子机制的初步研究	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
8	001 中医学院·中西医结合学院	20220003	基于益气健脾法探究升陷汤通过肌肠轴治疗 EAMG的免疫分子机制	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
9	001 中医学院·中西医结合学院	20220005	基于PERK-ATF4-CHOP信号通路探讨防己黄芪汤治疗糖尿病肾病的机制	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
10	001 中医学院·中西医结合学院	20210025	芪术抗癌颗粒质量评价建立及其优选组分配　伍抗肿瘤效应探讨	实践计划	自然科学	1056 中药	硕士	院助项目	1.5
11	001 中医学院·中西医结合学院	20210027	基于NF-κB/JAK2/STAT3信号轴探讨苦参-黄连药对抑制CRA癌变作用机制	科研计划	自然科学	1056 中药	硕士	院助项目	1.5
12	001 中医学院·中西医结合学院	20220028	PIP@ZIF-8@PBZ@EXO通过清除ROS和增强BBB的通透性促进胡椒碱的抗抑郁作用	实践计划	自然科学	1056 中药	硕士	院助项目	1.5
13	001 中医学院·中西医结合学院	20210029	人参平肺散调控PI3K-Akt-mTOR通路抑制ECM沉积治疗IPF的效应机制研究	科研计划	自然科学	1056 中药	硕士	院助项目	1.5
14	001 中医学院·中西医结合学院	20210031	山茱萸-丹皮配伍对NAFLD糖脂代谢的影响	实践计划	自然科学	1056 中药	硕士	院助项目	1.5
15	001 中医学院·中西医结合学院	20210032	益气养阴降糖方调控GLP-1改善糖尿病认知障碍机制研究	科研计划	自然科学	1056 中药	硕士	院助项目	1.5
16	001 中医学院·中西医结合学院	20210034	温肾通督方通过调控IGF1-NLRP3活化小胶质细胞改善脊髓损伤的机制研究	科研计划	自然科学	1056 中药	硕士	院助项目	1.5
17	001 中医学院·中西医结合学院	20220020	基于破骨细胞铁死亡探讨补骨生髓方干预绝经后骨质疏松症的作用机制	科研计划	自然科学	1056 中药	硕士	院助项目	1.5
18	001 中医学院·中西医结合学院	20210030	温肾通督方通过Akt/mTOR通路激活自噬改善脊髓损伤的机制研究	科研计划	自然科学	1056 中药	硕士	院助项目	1.5
19	001 中医学院·中西医结合学院	20220007	基于Nrf2-ARE通路探讨泽泻化浊散改善药物性肝损伤机制	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
20	002 第一临床医学院	20213054	金敏汤通过调控Cer介导的p38 MAPK通路纠正Treg/Th17漂移改善风咳免疫炎症的机制研究	实践计划	自然科学	1057 中医	博士	校助面上	1.5
21	002 第一临床医学院	20223047	基于 IL-33/ST2 探讨消风宣窍汤治疗小儿鼻鼽作用机制研究	实践计划	自然科学	1057 中医	博士	院助项目	1.5
22	002 第一临床医学院	039315122	清灵润肺膏治疗儿童哮喘的临床疗效及其对气道上皮间充质转化的影响	实践计划	自然科学	1057 中医	博士	院助项目	1.5
23	002 第一临床医学院	20213026	基于AMPK-mTOR-DCs自噬依赖性凋亡探讨降气平哮方治疗哮喘的机制	科研计划	自然科学	1005 中医学	博士	院助项目	1.5
24	002 第一临床医学院	039216153	中药煎剂鼻腔冲洗对FESS术后鼻腔黏膜恢复效果的临床观察	实践计划	自然科学	1057 中医	硕士	院助项目	1.5
25	002 第一临床医学院	20210340	Treg来源的外泌体通过Hippo信号通路调控变应性鼻炎的Th1/Th2平衡及益气温阳方的干预作用	实践计划	自然科学	1057 中医	硕士	院助项目	1.5
26	002 第一临床医学院	20220217	基于传承的雷公藤治疗RA的配伍减毒增效机制探讨	实践计划	自然科学	1057 中医	硕士	院助项目	1.5
27	002 第一临床医学院	20210272	新加健脾润燥通络方治疗原发性干燥综合征合并胃食管反流的临床研究	实践计划	自然科学	1057 中医	硕士	校助面上	1.5
28	002 第一临床医学院	20210170	刮痧治疗强直性脊柱炎临床疗效及痧象客观化研究	实践计划	自然科学	1057 中医	硕士	院助项目	1.5
29	002 第一临床医学院	20210200	基于NLRP3/IL-β信号通路探讨热痹消颗粒治疗急性痛风性关节炎的临床疗效及机制	实践计划	自然科学	1057 中医	硕士	院助项目	1.5
30	002 第一临床医学院	039316128	基于 IFNγ-JAK1/2-STAT1 通路探讨麦冬地芍汤治疗干燥综合征的临床疗效	实践计划	自然科学	1057 中医	博士	校助面上	1.5
31	002 第一临床医学院	039216116	基于代谢组学的健脾布津法治疗干燥综合征的临床疗效及作用机制研究	实践计划	自然科学	1057 中医	硕士	院助项目	1.5
32	002 第一临床医学院	20210073	基于脂质组学探讨凉血化瘀清络方对狼疮鼠的干预机制	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
33	002 第一临床医学院	20213019	基于SIRT1/HIF-1α信号通路研究清络通痹复方配伍减轻雷公藤肝毒性的机制	科研计划	自然科学	1005 中医学	博士	院助项目	1.5
34	002 第一临床医学院	039316125	加味二妙颗粒靶向TAK1泛素化激活ALPK1/NF-kB通路促进hBD-3分泌清除HR-HPV的临床及机制研究	实践计划	自然科学	1057 中医	博士	校助面上	1.5
35	002 第一临床医学院	039217243	枸杞消窠汤联和16/8限时饮食法治疗围青春期PCOS-IR的临床研究	实践计划	自然科学	1057 中医	硕士	院助项目	1.5
36	002 第一临床医学院	20213053	滋阴补阳方序贯经lncRNA/miR-421-5p/Per2干预授时因子对卵巢功能影响的研究	实践计划	自然科学	1057 中医	博士	院助项目	1.5
37	002 第一临床医学院	20223046	基于蛋白质组学探讨补肾促排卵汤介导组蛋白修饰调控 SLPI改善DOR排卵障碍的研究	实践计划	自然科学	1057 中医	博士	院助项目	1.5
38	002 第一临床医学院	039316105	养心奠基汤对薄型子宫内膜的临床治疗作用及机制探讨	实践计划	自然科学	1057 中医	博士	院助项目	1.5
39	002 第一临床医学院	20210102	基于BDNF/TrkB探讨温经止痛方治疗寒凝血瘀证原发性痛经的机制	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
40	002 第一临床医学院	20223014	莪术、白术配伍抗肝损伤效应物质及作用机制研究	科研计划	自然科学	1005 中医学	博士	校助面上	1.5
41	002 第一临床医学院	20213020	以OSM/LIFR信号通路为关键靶点探讨黄葵总黄酮治疗 UC伴抑郁的机制研究	科研计划	自然科学	1005 中医学	博士	院助项目	1.5
42	002 第一临床医学院	20223038	基于外泌体介导线粒体自噬探讨柴胡通便汤治疗　STC 的作用机制	实践计划	自然科学	1057 中医（专业）	博士	院助项目	1.5
43	002 第一临床医学院	20220289	基于“癌毒”理论探讨“以毒攻毒”治法通过MMR基因调控结肠癌干细胞干性和抵抗失巢凋亡治疗　HNPCC 的机制研究	实践计划	自然科学	1057 中医（专业）	硕士	院助项目	1.5
44	002 第一临床医学院	039216160	基于MAGNIFI-CD指数探讨乌司奴单抗联合挂线引流治疗克罗恩病肛瘘的疗效	实践计划	自然科学	1057 中医（专业）	硕士	校助面上	1.5
45	002 第一临床医学院	20210288	肛周克罗恩病患者疲乏的患病率及危险因素分析	实践计划	自然科学	1057 中医（专业）	硕士	院助项目	1.5
46	002 第一临床医学院	039316110	基于PHD2/HIF-1α/P53氧化应激信号通路探讨右归饮调控 GA-ONFH的机制	实践计划	自然科学	1057 中医	博士	校助面上	1.5
47	002 第一临床医学院	20210095	威灵仙总皂苷复合丝素蛋白纳米微球抑制工程软骨血管侵袭的作用与机制研究	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
48	002 第一临床医学院	20210099	基于Nrf2/HO-1信号通路探讨温肾健骨方对成骨细胞氧化应激损伤的保护机制	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
49	002 第一临床医学院	20220082	基于PI3K-AKT-HIF-1α信号通路探讨“温经活血”外治法改善KOA滑膜纤维化的机制研究	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
50	002 第一临床医学院	20220085	虫类药“活血通络”干预绝经后骨质疏松症 H 型血管生成的机制研究	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
51	002 第一临床医学院	20210096	HMGB1信号轴参与KOA滑膜纤维化的作用机制及“温经活血”外治法的干预效应	科研计划	自然科学	1005 中医学	硕士	校助面上	1.5
52	002 第一临床医学院	20210098	基于小夹板固定下轴向应力通过Piezo1对犬胫骨骨折愈合的影响	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
53	002 第一临床医学院	039316126	麦味养肺汤治疗特发性肺纤维化的疗效观察与机制研究	实践计划	自然科学	1057 中医	博士	校助面上	1.5
54	002 第一临床医学院	20223026	“麦味养肺汤”调控 PI3K/Akt 信号通路抑制 II 型肺泡上皮细胞衰老发挥抗肺纤维化作用的机制研究	科研计划	自然科学	1006 中西医结合	博士	院助项目	1.5
55	002 第一临床医学院	20210075	基于肠-脑轴探究乌蔹对AD模型大鼠抗炎作用机制研究	科研计划	自然科学	1005 中医学	硕士	院助项目	1.5
56	002 第一临床医学院	20210237	潜阳育阴颗粒维持心脏能量稳态改善老年高血压心肌病研究	实践计划	自然科学	1057 中医	硕士	院助项目	1.5

江苏省研究生科研创新计划

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一级学科名称：　　中西医结合临床

研 究 方 向 ：特发性肺纤维化的基础与临床研究

申请项目名称：“麦味养肺汤”调控 PI3K/Akt 信号通路抑制 II 型肺泡上皮细胞衰老发挥抗肺纤维化作用的机制研究

指 导 教 师 ：　　周贤梅

所 在 学 校 ：　　南京中医药大学

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重要学术成果材料

学术论文：Leukotriene Receptor Antagonists and Risk of Neuropsychiatric Entities: A Meta-Analysis of Observational Studies

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Leukotriene Receptor Antagonists and Risk of Neuropsychiatric Entities: A Meta-Analysis of Observational Studies.

By: Bai, Le; Xu, Yong; Fan, Lingyi; Zhang, Ying; Zhou, Xianmei; Xu, Jie

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