This study is aimed to investigate the effectiveness of 4 allergic rhinitis (AR) drugs (loratadine, cetirizine, montelukast, and desloratadine) in reducing functional problems in patients, as indicated by rhinoconjunctivitis quality of life questionnaire scores. After an exhaustive search of electronic databases containing published scientific literature, high-quality randomized controlled trials relevant to our study were selected based on a stringent predefined inclusion and exclusion criteria. Statistical analyses were conducted using STATA 12.0 and comprehensive meta-analysis (CMA 2.0) software. The literature search broadly identified 386 studies, and after a multistep screening and elimination process, a total of 13 randomized controlled trials contributed to this network meta-analysis. These 13 high-quality studies contained a combined total of 6867 patients with AR on 4 different medications. The results of network meta-analysis revealed that, compared with placebo, all 4 medications treated AR effectively [cetirizine: mean: \(-0.62, 95\% \text{ confidence intervals (95\% CI)} = -0.90 \text{ to } -0.34, P < 0.001\); loratadine: mean: \(-0.32, 95\% \text{ CI} = -0.55 \text{ to } -0.097, P = 0.005\); montelukast: mean: \(-0.28, 95\% \text{ CI} = -0.54 \text{ to } -0.023, P = 0.033\); desloratadine: mean: \(-0.39, 95\% \text{ CI} = -0.60 \text{ to } -0.18, P < 0.001\)]. A comparison of surface under the cumulative ranking curve values of these 4 interventions clearly showed that cetirizine is the most optimal medication for AR treatment. In conclusion, this network meta-analysis provides the first evidence that cetirizine is the most efficacious treatment for AR compared with loratadine, montelukast, and desloratadine, significantly reducing the functional problems in patients with AR.

*Keywords:* allergic rhinitis, rhinoconjunctivitis quality of life questionnaire, loratadine, cetirizine, montelukast, desloratadine

INTRODUCTION

Allergic rhinitis (AR) is a symptomatic and inflammatory disorder of nasal mucosa, characterized by nasal itching, paroxysmal repetitive sneezing, watery rhinorrhea, reduced sense of smell, and nasal congestion.\(^1,2\) AR is classified as seasonal or perennial, depending on the sensitization to cyclic pollens or year-round allergens, such as dust mites, molds, and animal dander.\(^3\) Interestingly, the number of patients with AR, particularly with pollinosis, has markedly increased in recent years.\(^4\) Epidemiologic studies revealed that AR affects approximately 500 million people worldwide, with high prevalence reported from industrialized nations, especially English-speaking countries.\(^5\) AR can occur at any age, although most people first develop symptoms in early childhood or young adulthood.\(^6\) The underlying disease mechanisms indicate that AR is part of a systemic inflammatory response and is associated with other inflammatory disorders of mucous membranes, such as asthma, rhinosinusitis, chronic otitis media, and allergic conjunctivitis.\(^7,8\) Poorly controlled AR symptoms result in decreased

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health-related quality of life, daytime fatigue, poor sleep quality, impaired learning and cognitive functions, and decreased long-term productivity. 

The pathogenesis of AR involves both genetic and environmental factors and is aggravated by indoor and outdoor environmental allergens. 

Therapeutic approach to AR includes preventing allergen exposure or irritant contact, pharmacotherapy, and immunotherapy. 

Several previous studies have demonstrated that antihistamines and leukotriene (LT) antagonists are the commonly used agents for the treatment of AR. 

Histamine is the most common mediator in early allergic response and cause smooth muscle contraction, increase vascular permeability, and elevate mucus secretion and sensory nerve stimulation, among other symptoms of AR. 

The AR medications loratadine, cetirizine, and desloratadine are second-generation antihistamines effective in relieving histamine-mediated symptoms. 

Notably, loratadine and desloratadine have significantly reduced capacities to cross the blood-brain barrier; therefore, they exhibit reduced central nervous system side effects such as drowsiness. Although the 2 drugs effectively stabilize ocular and nasal symptoms, they have little effect in relieving nasal congestion and are generally combined with nasal decongestants in formulations. 

The safety and efficacy of cetirizine has been demonstrated in both perennial AR and seasonal allergic rhinitis (SAR). 

Cetirizine is effective in relieving allergic conjunctivitis symptoms and nasal congestion. LT antagonists also play significant roles in treatment of AR. 

Montelukast is one of the most commonly used agents in this category and is considered to be effective in patients with SAR and improves nasal obstruction. 

A number of studies have shown that loratadine, cetirizine, desloratadine, and montelukast have significant efficacy in AR management. 

However, the performance ranking of efficacy of these 4 drugs remains unknown, including the comparison of their rhinoconjunctivitis quality of life questionnaire (RQLQ) scores in patients with AR. 

Traditional meta-analyses combine the results of homogeneous studies conducted on the same topic, and the framework does not allow simultaneous comparisons between more than 2 interventions. 

However, compared with the traditional meta-analysis, network meta-analysis framework enables indirect comparison using a common comparator when a direct trial is not accessible and also combines direct and indirect analytical approaches to simultaneously compare several interventions. 

Therefore, this study conducted a systematic review including both traditional meta-analysis and network meta-analysis to evaluate more precisely the effects of loratadine, cetirizine, desloratadine, and montelukast on the RQLQ scores of patients with AR. 

MATERIALS AND METHODS 

Literature search 

This systematic review was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. To retrieve relevant literature comparing drugs treatment in AR, we comprehensively searched the following electronic databases: PubMed, Ovid, EBSCO, Springerlink, Wiley, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, and VIP databases (last updated search in October 2014), regardless of language. Keywords used included placebo, loratadine, cetirizine, montelukast, desloratadine and allergic rhinitis, Pollen Allergy and pollinosis in combination with the Boolean operators AND, OR, and NOT. We also manually searched related bibliographies to identify studies that were missed in the electronic search. 

Inclusion and exclusion criteria 

Studies were selected for our network meta-analysis if they met the following inclusion criteria: (1) study design: randomized controlled trial (RCT), (2) interventions: drugs treatment in study group versus placebo treatment in control group, (3) study subject: clinically diagnosed patients with AR based on the AR and its impact on asthma (ARIA) guideline revised by World Health Organization (WHO) in 2008, (4) course of treatment ≥2 weeks, and (5) RQLQ was used for the evaluation of quality of life for patients with AR. The exclusion criteria were (1) insufficient data, (2) non-RCT, (3) duplicated publications, and (4) combination use of drugs or treatments mixed with psychological intervention. 

Data extraction and quality assessment 

All data from eligible trials were extracted independently by 2 investigators using a standard form and the following information was collected: first author, publication year, country, ethnicity, language, disease, age, gender, and number of cases. Any disagreements on the merits of the extracted data were resolved by discussion with the third investigator. Methodological quality of the included RCTs was evaluated using Cochrane Collaboration’s tool for assessing risk of bias by 2 or more investigators. The risk of bias covers 6 domains, including random sequence generation, allocation concealment, blinding of participants or blinding outcome assessment, incomplete outcome data, selective reporting, and other bias. The detailed assessment criteria were (1) whether allocation sequence is generated properly, (2) whether the method used to
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Gender (M/F)</th>
<th>Age (yrs)</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Cauwenberge and Juniper</td>
<td>2000</td>
<td>USA</td>
<td>228</td>
<td>225</td>
<td>101/127</td>
<td>31.9 ± 12.22</td>
<td>Loratadine 10 mg</td>
</tr>
<tr>
<td>Murray et al</td>
<td>2002</td>
<td>USA</td>
<td>431</td>
<td>431</td>
<td>143/288</td>
<td>37.8 ± 10.8</td>
<td>Placebo</td>
</tr>
<tr>
<td>Nayak et al</td>
<td>2002</td>
<td>USA</td>
<td>301</td>
<td>149</td>
<td>110/191</td>
<td>37 ± 13</td>
<td>Cetirizine 10 mg</td>
</tr>
<tr>
<td>Nayak et al</td>
<td>2002</td>
<td>USA</td>
<td>155</td>
<td>149</td>
<td>53/102</td>
<td>35 ± 11</td>
<td>Montelukast 10 mg</td>
</tr>
<tr>
<td>Nayak et al</td>
<td>2002</td>
<td>USA</td>
<td>301</td>
<td>155</td>
<td>110/191</td>
<td>37 ± 13</td>
<td>Loratadine 10 mg</td>
</tr>
<tr>
<td>Noonan et al</td>
<td>2003</td>
<td>USA</td>
<td>202</td>
<td>198</td>
<td>63/139</td>
<td>35.8 ± 10.6</td>
<td>Placebo</td>
</tr>
<tr>
<td>van Adelsberg et al</td>
<td>2003</td>
<td>USA</td>
<td>180</td>
<td>451</td>
<td>61/119</td>
<td>39 ± 13 (15–79)</td>
<td>Placebo</td>
</tr>
<tr>
<td>van Adelsberg et al</td>
<td>2003</td>
<td>USA</td>
<td>448</td>
<td>451</td>
<td>147/301</td>
<td>36 ± 13 (15–82)</td>
<td>Placebo</td>
</tr>
<tr>
<td>van Adelsberg et al</td>
<td>2003</td>
<td>USA</td>
<td>180</td>
<td>448</td>
<td>61/119</td>
<td>36 ± 13 (15–82)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Philip et al</td>
<td>2004</td>
<td>USA</td>
<td>415</td>
<td>416</td>
<td>150/265</td>
<td>33.0 ± 13.2</td>
<td>Montelukast 10 mg</td>
</tr>
<tr>
<td>Hyo et al</td>
<td>2005</td>
<td>Japan</td>
<td>28</td>
<td>27</td>
<td>14/14</td>
<td>32.5</td>
<td>Placebo</td>
</tr>
<tr>
<td>Hyo et al</td>
<td>2005</td>
<td>Japan</td>
<td>30</td>
<td>27</td>
<td>14/16</td>
<td>34.1</td>
<td>Placebo</td>
</tr>
<tr>
<td>Hyo et al</td>
<td>2005</td>
<td>Japan</td>
<td>28</td>
<td>30</td>
<td>14/14</td>
<td>34.1</td>
<td>Cetirizine 10 mg</td>
</tr>
<tr>
<td>Pradalier et al</td>
<td>2007</td>
<td>France</td>
<td>234</td>
<td>249</td>
<td>121/113</td>
<td>32.7 ± 10.7</td>
<td>Placebo</td>
</tr>
<tr>
<td>Bachert and Maurer</td>
<td>2010</td>
<td>Belgium</td>
<td>242</td>
<td>245</td>
<td>126/116</td>
<td>29.8 ± 10.6</td>
<td>Placebo</td>
</tr>
<tr>
<td>Demoly et al</td>
<td>2009</td>
<td>France</td>
<td>118</td>
<td>115</td>
<td>58/60</td>
<td>40.3 ± 13.8</td>
<td>Placebo</td>
</tr>
<tr>
<td>Holmberg et al</td>
<td>2009</td>
<td>France</td>
<td>293</td>
<td>291</td>
<td>NR</td>
<td>39.2 ± 12.4</td>
<td>Placebo</td>
</tr>
<tr>
<td>Bousquet et al</td>
<td>2010</td>
<td>USA</td>
<td>360</td>
<td>358</td>
<td>151/209</td>
<td>34.0 ± 12.1</td>
<td>Placebo</td>
</tr>
<tr>
<td>Jauregui et al</td>
<td>2011</td>
<td>Spain</td>
<td>242</td>
<td>245</td>
<td>NR</td>
<td>33.9 ± 12.3</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

F, female; M, male; NR, not reported.
conceal the allocation sequence is appropriate, (3) whether the intended blinding was effective, (4) whether the incomplete outcome data are dealt with appropriately, (5) state how selective outcome reporting was examined and what was found, and (6) whether any other important concerns about bias are covered in the other domains in the tool.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (REC Central) and with the Helsinki Declaration of 1975, as revised in 2008.

Statistical analysis

Statistical analysis was conducted with STATA statistical software (version 12.0; Stata Corp, College Station, TX) and comprehensive meta-analysis (CMA 2.0) software. Standard mean difference (SMD) with 95% confidence intervals (95% CI) was calculated by applying a fixed-effects model or random-effects model for evaluating the effects of the intervention group and control group on RQLQ of patients with AR. The pooled effect size was assessed using Z test. The Cochran’s Q-statistic ($P < 0.05$ was considered significant) and $I^2$ test (0%, no heterogeneity; 100%, maximal heterogeneity) were also applied to reflect the heterogeneity among studies.

A random-effects model was applied on case of an evidence of significant heterogeneity ($P < 0.05$ or $I^2$ test exhibited $>50%$), otherwise a fixed-effects model was used. Network meta-analysis integrates data from a network of trials involving more than 2 interventions. The synthesis of indirect evidence (information about 2 intervention obtained from a common comparator) and direct evidence (studies comparing the interventions directly) enhances the precision in evaluation and produces a relative ranking of all the treatments for the studied outcome.

In each closed loop, we use the inconsistency factor (IF) to evaluate the heterogeneity among studies. If the 95% CIs of IF values are truncated at zero, it suggests that the direction of the IF is unimportant. Funnel plots to identify the presence of small-study effects provide further validation of the reliability of the results. The assumption of consistency models allows the presence of heterogeneity of the intervention effects among studies while no significant differences in study design. After the generation of heterogeneity matrix, frequentist method was used for the fitted model to calculate the ranking probabilities.

RESULTS

Baseline characteristics of included studies

A total of 386 articles relevant to drugs treatment in AR were initially reviewed. After excluding duplicates ($n = 2$), letters or reviews ($n = 5$), nonhuman studies ($n = 12$), and studies unrelated to research topics ($n = 307$) and 60 full-text articles remained. Thirteen studies ultimately met the inclusion criteria, after we removed studies that were not RCTs ($n = 18$) and studies not associated with AR ($n = 5$), and had no relevance to the network ($n = 24$). A combined total of 6867 patients with AR were enrolled in the 13 selected
RCTs (665 patients in loratadine group, 657 patients in cetirizine group, 975 patients in montelukast group, and 3157 patients in placebo group), and these studies were published between 1998 and 2014. Of these 13 high-quality RCTs, 1 study was performed in Asians and 12 studies were performed in whites. Three of the studies are 3-arm trials and the rest are 2-arm trials, a total of 19 comparisons. The baseline characteristics of included studies and Cochrane assessment of risk of bias are displayed in Table 1 and Figure 1, respectively.

Results of traditional meta-analysis

Heterogeneity test revealed a significant heterogeneity among studies ($I^2 = 99.1\%, P < 0.001$), thus a random-effects model was applied. Meta-analysis results revealed that compared with placebo treatment, 3 medications loratadine, cetirizine, and desloratadine effectively reduced the RQLQ scores of patients with AR (loratadine: SMD $= -1.88$, $95\%$ CI $= -2.73$ to $-1.03$, $P < 0.001$; cetirizine: SMD $= -1.36$, $95\%$ CI $= -2.38$ to $-0.34$, $P = 0.009$; desloratadine: SMD $= -0.91$, $95\%$ CI $= -1.80$ to $-0.02$, $P = 0.045$), whereas montelukast and placebo did not show statistically significant differences (SMD $= -1.64$, $95\%$ CI $= -3.53$ to $-0.25$, $P = 0.089$) (Figure 2).

The results of sensitivity analyses demonstrated that any single study had no significant influence on the overall effect size (SMRs) when comparing the differences of RQLQ scores of the 4 antihistamine drugs and placebo for AR treatment (Figures 3A–D).

Evidence network

The evidence network is shown in Figure 4. Connecting lines represent direct comparisons between 2 connected interventions and pairs of interventions without connection can be compared indirectly through network meta-analysis. The width of lines corresponds to the number of trials. The size of nodes corresponds to the overall sample size of intervention. The color of lines represents the risk of bias of enrolled trials. This study included 4 antihistamine drugs, loratadine, cetirizine, desloratadine, and montelukast.

Contribution plot of network meta-analysis

Each direct comparison in network meta-analysis contributes differently to the evaluation of the network pooled effects, and the details were shown in Figure 5: (1) 4 of the studies had the direct comparison between loratadine and placebo, whose percentage contribution to loratadine and cetirizine, loratadine and montelukast, and loratadine and desloratadine was 50%, 50%, and 50%, respectively; 25% to the whole network meta-analysis; (2) 3 of the studies had the direct comparison between cetirizine and placebo, whose percentage contribution to loratadine and cetirizine, cetirizine and montelukast, and cetirizine and desloratadine was 50%, 50%, and 50%, respectively; 25% contribution to the whole network meta-analysis; (3) 3 of the studies had the direct comparison between montelukast and placebo, whose percentage contribution to loratadine and montelukast, cetirizine and montelukast, and montelukast and desloratadine was...
50%, 50%, and 50%, respectively; 25% contribution to the whole network meta-analysis; (4) 6 of the studies had the direct comparison between desloratadine and placebo, whose percentage contribution to loratadine and desloratadine, cetirizine and desloratadine, and montelukast and desloratadine was 50%, 50%, and

---

### FIGURE 3

Sensitivity analysis about the effects difference in rhinoconjunctivitis quality of life questionnaire (RQLQ) scores of allergic rhinitis (AR) patients between intervention groups and placebo group: (A) loratadine group versus placebo group; (B) cetirizine group versus placebo group; (C) montelukast group versus placebo group; (D) desloratadine group versus placebo group.
Comparisons of efficacy

Network meta-analysis results demonstrated that compared with placebo, the 4 drugs, cetirizine, loratadine, montelukast, and desloratadine, effectively treated AR (cetirizine: mean: $-0.62$, 95% CI = $-0.90$ to $-0.34$, $P < 0.001$; loratadine: mean: $-0.32$, 95% CI = $-0.55$ to $-0.097$, $P = 0.005$; montelukast: mean: $-0.28$, 95% CI = $-0.54$ to $-0.023$, $P = 0.033$; desloratadine: mean: $-0.39$, 95% CI = $-0.60$ to $-0.18$, $P < 0.001$). After ignoring covariance, further analysis suggested significant differences among the results (Table 2). Relative efficacy of the 4 drugs is shown in Figure 7 (black corresponds to 95% CI and red corresponds to 95% predictive intervals).

Ranking of interventions

The cumulative probability ranking of interventions is shown in Figure 8. The surface under the cumulative ranking curve values of the 5 interventions were 8.5% for placebo, 50.3% for loratadine, 87.1% for cetirizine, 44.5% for montelukast, and 59.6% for desloratadine, suggesting that cetirizine is the most optimal drug for AR treatment compared with loratadine, montelukast, and desloratadine.

Assessment of publication bias

Figure 9 shows the funnel plot for the 5 interventions network, which provides an indication for the presence of small-study effect. All the included studies symmetrically distribute around the vertical line ($x = 0$), suggesting no small-study effect in the network.
DISCUSSION

The present network meta-analysis was based on 13 RCTs involving 6867 individuals and compared the effects of 4 drugs on the RQLQ scores in patients with AR. Our results demonstrated that compared with placebo, cetirizine, loratadine, montelukast, and desloratadine are effective in treating AR. Surface under the cumulative ranking curve values of these interventions suggested that cetirizine is the most optimal drug for the treatment of AR. Atopy is an exaggerated IgE-mediated immune response in a type I-hypersensitive reaction mounted against ubiquitous and innocuous environmental allergens, and AR is an atopic disease. In response to antigens entering into the mucous membrane, IgE antibodies in the regional lymphatic tissues and nasal mucosa bind to the antigens and cause release of histamine, proteases, and chemotactic factors. The antigen–antibody reaction also triggers production of other chemical mediators, such as prostaglandins and peptide LTs, which stimulates the sensory nerve endings and blood vessels of the nasal mucosa to cause pain, sneezing, pruritus, watery rhinorrhea, and nasal congestion. LTs and histamine generated by mast cells and other inflammatory cells cause vasodilation, nasal mucosal swelling, mucus hypersecretion, and increased capillary permeability. For these reasons, antihistamines and LT antagonists are widely used for the treatment of AR. Our study involved 3 antihistamine drugs, loratadine, cetirizine, and desloratadine. Previous RCTs showed that, compared with placebo, the second-generation antihistamines loratadine, cetirizine, and desloratadine are effective at relieving histamine-mediated symptoms in AR. Other studies revealed that compared with loratadine and desloratadine, allergic conjunctivitis symptom and nasal congestion were effectively treated with cetirizine, with an added benefit of lack of sedation. Montelukast is one of the most commonly used LT antagonist and is effective in patients with SAR and improves nasal obstruction. Recent studies have revealed that montelukast improves disease-specific quality of life in patients with persistent AR better than placebo. Consistent with most previous studies, our result confirm that compared with placebo, effective AR treatment is achieved with cetirizine, loratadine, montelukast, and desloratadine. However, ranking of efficacy of the 4 interventions in AR treatment is unknown.

Our study represents the first work to exploit network meta-analysis framework to simultaneously compare the effects of different drugs on RQLQ scores in patients with AR. The result of our study demonstrated

Table 2. Therapeutic efficacy of each drug compared with placebo.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic efficacy (correlation not ignored)</th>
<th>Therapeutic efficacy (correlation ignored)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean  95% CI        Z       P</td>
<td>Mean  95% CI        Z       P</td>
</tr>
<tr>
<td>Loratadine</td>
<td>−0.32  −0.55 to −0.097</td>
<td>−2.79  0.005</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>−0.62  −0.90 to −0.34</td>
<td>−4.30  0.000</td>
</tr>
<tr>
<td>Montelukast</td>
<td>−0.28  −0.54 to −0.023</td>
<td>−2.14  0.033</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>−0.39  −0.60 to −0.18</td>
<td>−3.62  0.000</td>
</tr>
</tbody>
</table>

FIGURE 6. Inconsistency test for direct and indirect comparison: (A) placebo; (B) loratadine; (C) cetirizine; (D) montelukast; (E) desloratadine.
that cetirizine is the optimal drug for the treatment of AR, when compared with 3 other interventions. The strengths of our network meta-analysis are first, we compared interventions indirectly when no head-to-head trial existed to obtain more precise efficacy estimates. Second, our updated integration of existing evidence provides new insights about the quality of life of patients with AR, with important implications in future research. Finally, the 95% CI of IF values are truncated at zero, suggesting there is no inconsistency in our network meta-analysis. Our study also has limitations. First, only 13 RCTs were enrolled in our study.

**FIGURE 7.** The confidence intervals of estimates (black corresponds to 95% CI and red corresponds to 95% predictive intervals).

**FIGURE 8.** Plots of the surface under the cumulative ranking curves for all treatments in the AR network.
study, and the number of included studies was relatively small. Second, because of the limited data on other drugs from our enrolled trials, we were able to analyze only 4 drugs and other drugs were not considered for analysis. Third, our network meta-analysis did not perform subgroup stratification based on drug dosage because of the lack of relevant details in selected studies. Finally, although all the enrolled RCTs mentioned the study design as a blinded, randomized, controlled method, there was no detailed evidence of randomization, which might have impacted our results.

CONCLUSIONS

This network meta-analysis provides strong evidence that cetirizine is the most optimal drug for the treatment of AR compared with placebo, loratadine, montelukast, and desloratadine. The use of cetirizine significantly reduced functional problems in patients with AR. Our conclusions will need to be confirmed by a more adequately designed study with large sample size and a more appropriate multivariate analysis for future clinical applications.

ACKNOWLEDGMENTS

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