Oral Antihistamines Alone vs in Combination with Leukotriene Receptor Antagonists for Allergic Rhinitis: A Meta-analysis

Guo Liu, MD\(^1\)*, Xu Zhou, MD\(^2\)*, Jianrong Chen, MD\(^3\), and Feng Liu, MD\(^1\)

**Abstract**

**Objective.** To evaluate whether an adjuvant therapy of leukotriene receptor antagonists (LTRAs) based on oral H\(_1\)-antihistamines (H\(_1\)) can increase efficacy of allergic rhinitis (AR) treatment.

**Data Sources.** The search involved databases of PubMed, EMBASE, and Cochrane Central Register of Controlled Trials, from inception up to September 23, 2017. Randomized controlled trials (RCTs) that compared efficacy of LTRAs + H\(_1\) vs H\(_1\) alone were eligible.

**Review Methods.** Pooled comparative effects were measured using weighted mean difference (WMD) and 95% confidence interval (CI). Subgroup analysis comparing seasonal vs perennial AR was prespecified to explore the source of heterogeneity. The evidence quality of each outcome was assessed by the GRADE approach.

**Results.** A total of 8 RCTs were included (n = 1886), and all measured outcomes used scaled scores. Compared with H\(_1\) alone, H\(_1\) + LTRAs were superior to improve overall daytime (WMD, –0.11; 95% CI, –0.19 to –0.03, high quality) and composite (WMD, –0.12; 95% CI, –0.23 to –0.01; low quality) nasal symptoms. Specifically, H\(_1\) + LTRAs had better efficacy against composite nasal rhinorrhea, sneezing, and daytime itching but not congestion. The effects were more pronounced in patients with perennial AR compared to those with seasonal AR. There were no significant differences in nighttime nasal symptoms and eye symptoms between the 2 groups.

**Conclusion.** The current evidence suggests that LTRAs + H\(_1\) can increase the therapeutic efficacy against daytime and composite nasal symptoms, including rhinorrhea, sneezing, and itching; however, it does not affect nighttime nasal symptoms and eye symptoms. The patients with perennial AR may benefit more from the combination therapy.

**Keywords**

antihistamines, leukotriene receptor antagonists, allergic rhinitis, meta-analysis
of the 2 drugs, combination use is expected to be more efficacious than either alone.

Consistent with this notion, previous clinical trials have shown that oral antihistamines plus LTRAs are superior to oral antihistamines\textsuperscript{12-14} or LTRAs alone\textsuperscript{12,13} for the symptoms of AR, especially nighttime symptoms.\textsuperscript{15,16} However, others have reported that the combination therapy is equivalent to oral antihistamines alone.\textsuperscript{15,17-20} To date, the use of oral antihistamines plus LTRAs is recommended in clinical guidelines despite inconsistent reports on their efficacy.\textsuperscript{1}

To optimize the clinical use of these 2 types of drugs, we conducted a meta-analysis of the published studies to compare the efficacy of oral H1-antihistamines (H1) plus LTRAs vs H1-antihistamines alone for AR.

**Methods**

We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)\textsuperscript{21} to report this systematic review.

**Selection Criteria**

Randomized controlled trials (RCTs) that compared the efficacy of H1 vs H1 plus LTRA in patients with AR were included in this review, without restriction regarding age. To be eligible, the RCTs also needed to report available data on at least 1 outcome of interest. The study outcomes should be assessed by validated scales, including score changes in daytime nasal symptoms, nighttime nasal symptoms, composite nasal symptoms (average score of nighttime and daytime nasal symptoms), and eye symptoms, as well as quality of life. Trials assessing withdrawn or nonapproved agents, involving nonallergic (eg, atrophic) rhinitis, or using a nonvalidated scale on assessment of outcome were excluded from the analyses.

**Search Strategy**

Three medical literature databases (PubMed, EMBASE, and Cochrane Central Register of Controlled Trials) were searched from inception to September 23, 2017. We combined medical subject headings and free-text terms to develop a highly sensitive search strategy using the keywords leukotriene antagonist and allergic rhinitis. Trials registered in clinicaltrials.gov or listed in published reviews were also screened for additional eligibility. The search strategy is described in Appendix 1 (available in the online version of the article).

**Study Screening and Data Extraction**

Study screening and data extraction were conducted in standardized forms in Microsoft Access (Microsoft, Redmond, Washington), including a pilot test. Two investigators independently screened titles and abstracts as well as full texts of published reports based on the selection criteria to determine the eligibility. They then extracted data on study characteristics (author, publication year, country, type of intervention, follow-up period, and follow-up rate), patient characteristics (type of AR, number of patients in total and in each arm), and outcome data from the included RCTs. Inconsistent results were addressed by discussion or adjudicated by a third reviewer.

**Risk of Bias Assessment**

Two investigators independently assessed risk of bias for RCTs included in the study using a modified Cochrane Risk of Bias assessment tool.\textsuperscript{22} This modification changed the original answer of “unclear” to “probably yes” or “probably no” to provide more precise appraisals.\textsuperscript{23,24} For assessing unclear methods of random sequence generation, we considered the answer was “probably yes” if the RCT reported an appropriate method to perform allocation concealment or blindness and “probably no” if the RCT simply reported “randomized” without any additional information about randomization. For assessing an unclear method of allocation concealment, we considered the answer was “probably yes” for studies with blindness appropriate for the trial and “probably no” for open-label studies or lack of information on blindness. For assessing unclear methods of blindness, we considered the answer was “probably yes” if the trial set a placebo control or claimed single blindness of patients, clinicians, or outcome assessors and “probably no” if the trial did not report any information about blinding status. For the item “free from attrition bias,” we judged as “definitely yes” those trials that lost less than 10% of the patients, “probably yes” those trials that lost 10% to 20% of the patients with balanced attrition rate and similar reasons for attrition across the groups, “probably no” those trials that lost 10% to 20% of the patients without balanced attrition rate and/or similar reasons for attrition across the groups or that lost 10% to 20% with balanced attrition rate and similar reasons for attrition across the groups, and “definitely no” those trials that lost 20% to 40% of the patients without balanced attrition rate and/or similar reasons for attrition across the groups or that lost more than 40% of the patients. For trials without published protocols or with registration on an open website, we considered the answer of “free from selective reporting” was “probably yes” or “probably no” according to whether the trial reported all important outcomes based on the purpose of research.

**Quality of Evidence**

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate the quality of evidence. In this approach, the default evidence quality from RCTs was defined as high (0 point) and was downgraded according to risk of bias, imprecision, inconsistency, indirectness, and publication bias. The quality of evidence for each outcome was finally appraised as high ($\geq$0 point), moderate (–1 point), low (–2 points), or very low (–3 points).

**Statistical Analysis**

Meta-analysis was conducted using a random-effects model regardless of the heterogeneity between primary studies.
The heterogeneity was assessed using Cochran’s $Q$ test and $I^2$ statistic, with the $P$ value in the $Q$ test lower than .10 or $I^2$ higher than 50%, indicating significant heterogeneity among studies. In the case where all included trials used an identical scale, weighted mean difference (WMD) and a 95% confidence interval (CI) were used to estimate pooled effects. In the case of different scales within studies, standardized mean difference (SMD) was used to calculate pooled effects. In fact, WMD was used in all outcomes because all included RCTs used identical scales to measure symptoms of AR or quality of life.

In additional analyses, we preset the type of AR (seasonal vs perennial) as a subgroup analysis variable to explore the source of heterogeneity. Efforts were made to eliminate studies with high risk of bias in sensitivity analyses to assess the robustness of results. We planned to detect publication bias based on funnel plot and Egger’s test, but no outcome met the condition of these statistical methods that at least 10 studies were included.

**Results**

**Study Characteristics**

The original search identified 1990 records, and 28 articles were considered as potentially eligible after eliminating duplicates and title and abstract screenings. Eventually, 8 RCTs were included in this meta-analysis after full-text screening (Figure 1). Three trials were conducted in the United States, and the remaining 5 trials were conducted in Turkey, India, Thailand, the United Kingdom, and Hong Kong, respectively. The eligible RCTs enrolled 1886 patients. The male-to-female ratio was 4:6, with mean age ranging from 11.9 to 38 years (1 trial only included adolescents). Based on a clinical history of AR for at least 1 or 2 years with a positive skin test, 4 RCTs enrolled patients with seasonal AR, while 4 others enrolled perennial AR, all with more than 1 year of the disease. One trial had a follow-up period of 24 weeks, and for the others, the period was 6 weeks or shorter (Table 1). All RCTs used a 3-point scale to evaluate symptoms of AR, and 2 RCTs used the Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) to evaluate quality of life; both were validated scales (details of 2 scales are present in Supplemental Table S1, Appendix 2, available in the online version of the article).

**Risk of Bias**

Four RCTs had good processes for allocation, blindness, follow-up, and reporting. They were considered to be at a low risk of bias. Two RCTs (reported in 1 article) were considered to have potential deficiencies in allocation concealment, blindness, or selective reporting but performed well in other categories. They were considered to be at a moderate risk of bias. The remaining 2 trials were considered to be at a high risk of bias because of selective reporting and inadequate allocation concealment and blindness. Details are shown in Appendix 3, Supplemental Table S2 (available in the online version of the article).

**Daytime Nasal Symptoms**

Seven RCTs reported data on changes in scores of daytime nasal symptoms, involving 852 and 747 patients in the LTRAs + H1 group and the H1-alone group, respectively. These trials applied a validated 3-point scale to assess the severity of daytime nasal symptoms (0 = none, 1 = mild, 2 = moderate, 3 = severe), including nasal congestion, rhinorrhea, sneezing, and itching. The total daytime nasal symptom (TDNS) score was the average of the 4 individual symptom scores. Figure 2 shows the meta-analytic results of TDNS. There was significantly more improvement in the scores of TDNS in the LTRAs + H1 group compared to the H1-alone group (WMD, –0.11; 95% CI, –0.19 to –0.03, $I^2 = 31$%). In the subgroup analysis comparing different types of AR, the patients with perennial AR had significantly more improvement of TDNS than those with seasonal AR (WMD, –0.06 [95% CI, –0.13 to –0.001]; interaction $P = 0.01$), and this subgroup analysis fully explained the statistical heterogeneity across the studies ($I^2 = 0\%$ in both of the subgroups).

Three trials further reported data on individual daytime nasal symptoms (n = 410 in each group). Results of meta-analyses suggested that the LTRAs + H1 group had significantly more reduction in scores of daytime nasal rhinorrhea (WMD, –0.18; 95% CI –0.32 to –0.03, $I^2 = 41\%$), sneezing (WMD, –0.21; 95% CI –0.38 to –0.03, $I^2 = 62\%$), and itching (WMD, –0.15; 95% CI –0.30 to –0.01, $I^2 = 45\%$) compared with the H1-alone group. There were no
significant between-group differences regarding changes in the score of daytime nasal congestion (LTRAs + H1 vs H1 alone: WMD, −0.12; 95% CI −0.25 to 0.02, $I^2 = 37\%$; Appendix 4, Supplemental Figure S1, available in the online version of the article).

**Nighttime Nasal Symptoms**

Four RCTs$^{13,15,25,27}$ reported data on changes in scores of nighttime nasal symptoms using the same scale system as for daytime nasal symptoms, with 458 and 457 patients in the LTRAs + H1 group and the H1-alone group, respectively. No significant difference was observed on changes in score of total nighttime nasal symptoms (TNNS) between the 2 regimens (WMD, −0.03; 95% CI −0.11 to 0.04, $I^2 = 0\%$). The subgroup analysis did not show any between-group differences when comparing seasonal vs perennial AR (interaction $P = .72$; Figure 3).

According to data reported in 2 trials$^{15,27}$ (324 and 323 patients in the LTRAs + H1 group and the H1-alone group), changes in the score of all individual nighttime nasal symptoms, including congestion (WMD, −0.07; 95% CI −0.23 to 0.08; 2 trials; $I^2 = 34\%$), rhinorrhea (WMD, −0.21; 95% CI −1.64 to 1.22; 1 trial), sneezing (WMD, −0.37; 95% CI −1.57 to 0.83; 1 trial), and itching (WMD, 0.18; 95% CI −0.93 to 0.57; 1 trial), were not statistically significant between the LTRAs + H1 group and the H1-alone group (Appendix 4, Supplemental Figure S2, available in the online version of the article).

**Composite Nasal Symptoms**

Seven RCTs$^{13,15,17,25,27}$ reported data on changes in scores of composite nasal symptoms (average of daytime and nighttime symptom scores), of which 1 RCT$^{14}$ only reported data on individual symptoms. The total composite nasal symptom (TCNS) score was the average of the 4 individual symptom scores. There were 861 and 714 patients in the LTRAs + H1 group and the H1-alone group, respectively. The pooling result suggested significantly more reduction in

---

**Table 1. Characteristics of Included Studies.$^a$**

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>Female, %</th>
<th>Age, y</th>
<th>History of AR, y</th>
<th>Type of AR</th>
<th>Follow-up Period, wk</th>
<th>Follow-up Rate, %</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cingi et al, 2010$^{14}$</td>
<td>Turkey</td>
<td>FEX</td>
<td>106</td>
<td>59.4</td>
<td>30.7 (7.1)</td>
<td>&gt;1 (total)</td>
<td>sAR</td>
<td>3</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FEX + MTK</td>
<td>112</td>
<td>58.9</td>
<td>29.7 (6.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FEX + PBO</td>
<td>57</td>
<td>54.4</td>
<td>30.2 (5.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gupta and Matreja, 2010$^{25}$</td>
<td>India</td>
<td>LCET</td>
<td>47</td>
<td>46.8</td>
<td>35.3 ± 12.6</td>
<td>&gt;1 (total)</td>
<td>pAR</td>
<td>6</td>
<td>93.1</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td>Li et al, 2009$^{27}$</td>
<td>Hong Kong</td>
<td>LCET + MTK</td>
<td>48</td>
<td>43.8</td>
<td>35.47 ± 11.93</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FEX + PBO</td>
<td>22</td>
<td>58.9</td>
<td>12.2 (10.4-14.4)$^c$</td>
<td>7.7 (5.2-11.1)$^c$</td>
<td>pAR</td>
<td>24</td>
<td>100</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FEX + MTK</td>
<td>22</td>
<td>42.5</td>
<td>11.9 (9.9-14.0)$^c$</td>
<td>7.0 (5.2-10.2)$^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lu et al, 2009 (study 1)$^{17}$</td>
<td>United States</td>
<td>LTD</td>
<td>116</td>
<td>64.7</td>
<td>34.8 ± 12.4</td>
<td>18.1 ± 11.0</td>
<td>sAR</td>
<td>2</td>
<td>99.8</td>
<td>1, 3</td>
</tr>
<tr>
<td>Lu et al, 2009 (study 2)$^{17}$</td>
<td>United States</td>
<td>LTD</td>
<td>174</td>
<td>61.5</td>
<td>34.0 ± 13.3</td>
<td>17.9 ± 11.7</td>
<td>sAR</td>
<td>2</td>
<td>99.8</td>
<td>1, 3</td>
</tr>
<tr>
<td>Meltzer et al, 2000$^{13}$</td>
<td>United States</td>
<td>LTD</td>
<td>92</td>
<td>53.3</td>
<td>34.5 (15-66)$^d$</td>
<td>19 ± 13</td>
<td>sAR</td>
<td>2</td>
<td>95.1</td>
<td>1, 2, 3, 4, 5</td>
</tr>
<tr>
<td>Nayak et al, 2002$^{15}$</td>
<td>Thailand</td>
<td>LTD</td>
<td>90</td>
<td>55.6</td>
<td>37 (15-74)$^d$</td>
<td>17 ± 12</td>
<td>sAR</td>
<td>2</td>
<td>88.7</td>
<td>1, 2, 3, 4, 5</td>
</tr>
<tr>
<td>Wilson et al, 2000$^{28}$</td>
<td>United Kingdom</td>
<td>CET</td>
<td>13</td>
<td>76.9</td>
<td>30 ± 9.0</td>
<td>NR</td>
<td>pAR</td>
<td>4</td>
<td>100</td>
<td>1, 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CET + MTK</td>
<td>11</td>
<td>63.6</td>
<td>31 ± 8.0</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AR, allergic rhinitis; CET, cetirizine; FEX, fexofenadine; LCET, levocetirizine; LTD, loratadine; MTK, montelukast; NR, not reported; pAR, perennial allergic rhinitis; PBO, placebo; sAR, seasonal allergic rhinitis.

$^a$Continuous data are presented as mean and standard deviation unless otherwise specified.

$^b$Outcome: 1, daytime nasal symptom; 2, nighttime nasal symptom; 3, composite nasal symptom; 4, eye symptom; 5, Rhinoconjunctivitis Quality-of-Life Questionnaire.

$^c$Median and interquartile range.

$^d$Median and range.

---
scores of TCNS in the LTRAs + H1 group than those in the H1-alone group (WMD, –0.12; 95% CI –0.23 to –0.01; Figure 4). The statistical heterogeneity was high ($I^2 = 70\%$). However, the type of AR fully explained the statistical heterogeneity in the subgroup analysis ($I^2 = 0\%$ within both of the subgroups). Improvement was significantly more in patients with perennial AR than those with seasonal AR (WMD, –0.30 [95% CI, –0.42 to –0.18] vs WMD, –0.05 [95% CI –0.10 to 0.01]; interaction $P = .0002$).

The pooled results of 3 trials14,27 (154 and 165 patients in the LTRAs + H1 group and the H1-alone group, respectively) further showed that patients in the LTRAs + H1 group had significantly improved individual composite nasal symptoms compared to those in the H1-alone group (congestion: WMD, –0.06 [95% CI, –0.12 to –0.01], $I^2 = 20\%$; rhinorrhea: WMD, –0.34 [95% CI, –0.53 to –0.14], $I^2 = 26\%$; sneezing: WMD, –0.30 [95% CI, –0.42 to –0.18], $I^2 = 0\%$), except for nasal itching (WMD, –0.11; 95% CI, –0.26 to 0.04, $I^2 = 71\%$; Appendix 4, Supplemental Figure S3, available in the online version of the article).

**Eye Symptoms**

Four RCTs13,15,25,28 reported data on changes in scores of eye symptoms using a 3-point scale (0 = none, 1 = mild, 2 = ...
moderate, 3 = severe). The individual symptoms included tearing, itching, redness, and puffiness, and the total eye symptom score (TES) was based on the average of the 4 individual symptom scores. There were 447 and 448 in the LTRAs \(1\) H1 group and the H1-alone group, respectively. The meta-analysis did not show statistically different changes in eye symptoms between the 2 groups (WMD, –0.05; 95% CI, –0.13 to 0.02, \(I^2 = 0\%\); Appendix 4, Supplemental Figure S4, available in the online version of the article).

Only 1 trial\(^{15}\) further reported data on individual eye symptoms (302 and 301 patients in the LTRAs \(1\) H1 group and the H1-alone group, respectively). The results suggested statistically similar changes in all individual eye symptoms in the 2 groups (tearing: WMD, –0.04 [95% CI, –0.14 to 0.06]; itching: WMD, –0.02 [95% CI, –0.12 to 0.08]; redness: WMD, –0.05 [95% CI, –0.14 to 0.04]; puffiness: WMD, –0.01 [95% CI, –0.10 to 0.08]; Appendix 4, Supplemental Figure S5, available in the online version of the article).

### Quality of Life

Two RCTs\(^{13,15}\) measured the quality of life in patients receiving the study treatments; both used the RQLQ, involving 388 patients in each study group. RQLQ is a 6-point scale that evaluates 7 domains (nasal symptoms, eye symptoms, nonrhinitis symptoms, activities, sleep, practical problems, and emotions). The total score is the average of all domain scores, and the higher score indicates the reduced quality of life. The meta-analysis pooling of the 2 trials revealed significantly more improvements (reduction in scores) in favor of LTRAs + H1 over H1 alone (WMD, –0.12; 95% CI, –0.16 to –0.09, \(I^2 = 0\%\); Appendix 4, Supplemental Figure S6, available in the online version of the article).

### Sensitivity Analysis

The meta-analyses of 4 outcomes included RCTs with a high risk of bias. The sensitivity analysis excluding 2 RCTs with a high risk of bias showed no significant changes in daytime nasal, nighttime nasal, and eye symptoms. However, the difference of the change from baseline in the score of composite nasal symptoms was marginally significant between 2 groups when 2 RCTs with a high risk of bias were excluded (WMD, \(-0.12\); 95% CI, \(-0.16\) to \(-0.09\); \(P = 0.05\); \(I^2 = 75\%\)). Details are shown in Appendix 5, Supplemental Figures S7 to S10 (available in the online version of the article).

### Quality of Evidence

We assessed the quality of evidence for all outcomes based on the GRADE approach. We considered that all the outcomes described above can directly measure the effects on symptoms of AR so that none of them were downgraded because of indirectness. The result relating to TDNS had no other major defect, and we considered it to be the only high-quality evidence in this review. The findings in 5 outcomes were considered to be of moderate quality because of limitations relating to risk of bias, imprecision, or inconsistency (ie, \(-1\) point, including daytime nasal sneezing, composite nasal rhinorrhea). The remaining findings had serious flaws in terms of evidence quality, relating to risk of bias, imprecision, inconsistency, and/or publication bias, and thus were judged as low (ie, \(-2\) points, including TCNS, TES, and quality of life) or very low (ie, \(-3\) points, including daytime nasal sneezing, composite nasal congestion, itching, and all individual nighttime nasal symptoms and eye symptoms). Details are shown in Appendix 6, Supplemental Table S3 (available in the online version of the article).
Discussion

Main Findings

We found that H1 plus LTRAs are more efficacious than H1 alone in treating patients with AR. The combination therapy effectively relieved nasal rhinorrhea, sneezing, and itching, especially during the daytime.

The studies enrolled in this meta-analysis all used score systems to assess the severity of nasal symptoms. In the overall analysis, we found that the treatment with H1 plus LTRAs could significantly reduce the scores of TDNS in patients but were not superior in decreasing the scores of TNNS. This is surprising. Some studies reported that H1 are more appropriate for daytime nasal symptoms, whereas LTRAs taken at the bedtime are better suited for nighttime. However, our findings do not support this notion, primarily due to a limited sample size in all studies included in this analysis.

Furthermore, we also analyzed individual nasal symptoms. The results showed that H1 plus LTRAs had more effects on daytime rhinorrhea, sneezing, and itching compared with H1 alone. However, the combination did not show superior efficacy in daytime congestion and individual nighttime nasal symptoms compared to H1 treatment alone. Interestingly, in a composite analysis that included day and night symptoms, the nasal congestion, which was marginally significant during the daytime, became statistically significant for the combination therapy. However, the magnitude of the difference is too small (WMD, –0.12; 95% CI –0.12 to –0.01). According to the reported articles, the anchor-based minimal clinically important difference (MCID) threshold value for AR symptom scales of 0 to 3 points was –0.07 in this review. Therefore, nasal congestion has statistical significance only, whereas nasal rhinorrhea (WMD, –0.34; 95% CI –0.53 to –0.14), sneezing (WMD, –0.30; 95% CI –0.42 to –0.18), and daytime nasal itching (WMD, –0.15; 95% CI –0.30 to –0.01) have both statistical and clinical significance. Thus, we believe that H1 plus LTRAs are more efficacious than H1 alone in treating nasal rhinorrhea, sneezing, and itching, especially during the daytime.

Meanwhile, the question remains of how long the combination therapy should last. A previous randomized, double-blind, placebo-controlled study that evaluated the effect of the combination therapy at 4, 16, and 24 weeks after the treatment began indicated that the leukotriene receptors gradually became saturated. The maximum effect occurred between 4 and 16 weeks, suggesting that the duration of the combined therapy should be considered.

It has been well established that monotherapy with LTRAs or H1 can improve the quality of life in patients with AR. Our results suggest that LTRAs plus H1 offer better relief to the patients, consistent with previous studies. However, the difference was not clinically significant (WMD, –0.12 vs MCID, –0.15). We consider the reason to be that the combination therapy has less effect on domains other than nasal symptoms (eg, eye symptoms and sleep).

For eye symptoms, efficient treatments are not explicitly recommended in all guidelines. One previous systematic review considered that the H1 plus LTRA therapy provided greater relief of eye symptoms compared with H1 alone. However, another systematic review questioned this conclusion because the research method of the former was not discussed in sufficient details. Our data strongly suggest that the H1 plus LTRA therapy does not offer better relief of ocular symptoms compared to H1 alone.

Due to the heterogeneity of seasonal and perennial AR, clinicians would prefer guidance as to the type of AR that would benefit more from a combination therapy. Our subgroup analysis shows that patients with perennial AR had statistically improved more on daytime and composite nasal symptoms than those with seasonal AR. The subgroup analysis also addressed the issue related to the heterogeneity in the results of both daytime and composite nasal symptoms. Therefore, we believe that the combination therapy is applicable to any type of AR, especially to alleviate daytime and composite symptoms of perennial AR.

Since the combination therapy is more efficacious, clinicians may be interested in another question: can intranasal antihistamines replace oral antihistamines to combine with LTRAs for AR treatment? With this question in mind, we searched for relevant literature but were unable to find any. In addition, none of the guidelines recommend this combination form. Therefore, intranasal antihistamines combined with LTRAs are not suggested based on the current evidence.

Strengths and Limitations

In this review, we comprehensively assessed nasal and eye symptoms and quality of life of patients with AR treated with either H1 or H1 plus LTRAs. We used revised tools to accurately evaluate the risk of bias and rigorous analytic methods to estimate pooled effects. We also applied the GRADE approach to assess the quality of evidence for the analysis. We demonstrated that LTRAs can provide additional efficacy regarding daytime and composite nasal symptoms based on the H1 treatment. For main outcomes (eg, overall daytime, nighttime, and composite nasal symptoms), most large studies included in the meta-analyses had a low to moderate risk of bias, and the heterogeneity was low or was addressed by subgroup analysis, suggesting that the findings are reliable.

There are several limitations to this study. First, the quality of evidence of individual nighttime symptoms, eye symptoms, and quality of life was mostly low or very low. This was mainly due to a high risk of bias of the included studies, imprecision due to small sample size, and the unsolved heterogeneity. Second, publication bias was not evaluated due to the limited number of studies included in the analysis. Third, some studies that reported outcomes of interest were excluded because they did not report either standard deviations or standard errors and we were unable to contact the authors to request more information. Fourth, there are
potentially different effects with regard to adult and pediatric use, but we could not perform subgroup analysis to assess this source of heterogeneity due to insufficient data.

**Conclusion**

The current evidence suggests that, compared with H1 alone, the combination of LTRAs and H1 increases efficacy for daytime and composite nasal symptoms, including rhinorrhea, sneezing, and itching in patients with AR. Patients with perennial AR could benefit more from the combination therapy. There is still substantial uncertainty on nasal congestion, nighttime nasal symptoms, eye symptoms, and quality of life. Further well-designed, large-sample studies with complete data reporting are warranted to address these gaps.

**Author Contributions**

Guo Liu, designed the study, screened articles, collected data, and drafted the manuscript; Xu Zhou, designed the study, developed the search strategy, collected data, performed data analyses, and drafted the manuscript; Jianrong Chen, designed the study, provided methodological and clinical advice, and critically revised the manuscript; Feng Liu, conceived and designed the study, developed the manuscript.

**Disclosures**

Competing interests: None.

Sponsorships: None.

Funding source: None.

**Supplemental Material**

Additional supporting information is available in the online version of the article.

**References**


