Original Article

Efficacy and Safety of Oral Antihistamines for Allergic Rhinitis: Network Meta-Analysis

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What is already known about this topic? Oral antihistamines are one of the mainstays of the pharmacologic management of allergic rhinitis, being widely available and affordable.

What does this article add to our knowledge? Oral antihistamines are effective in improving rhinitis symptoms and quality of life. Cetirizine, ebastine, bilastine, and rupatadine were among the individual medications associated with the highest efficacy for improving nasal symptoms.

How does this study impact current management guidelines? This systematic review will inform the Allergic Rhinitis and its Impact on Asthma (2024-2025) guidelines. In particular, it will provide evidence on the efficacy and safety of individual oral antihistamines.

BACKGROUND: Oral H1-antihistamines (OAHs) are among the most frequently used medications for the treatment of allergic rhinitis (AR).

OBJECTIVE: To perform a systematic review and network meta-analysis comparing the efficacy and safety of individual OAHs in patients with AR.

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Abbreviations used
AE- adverse event
AR- allergic rhinitis
ARIA- Allergic Rhinitis and its Impact on Asthma
CoE- certainty of evidence
GRADE- Grading of Recommendations, Assessment and Evaluation
MD- mean difference
NMA- network meta-analysis
OAH- oral H1-antihistamine
PAR- perennial allergic rhinitis
RCT- randomized controlled trial
RoB- risk of bias
RQLQ- Rhinoconjunctivitis Quality-of-Life Questionnaire
SAR- seasonal allergic rhinitis
TNSS- Total Nasal Symptom Score
TOSS- Total Ocular Symptom Score

METHODS: We searched 4 electronic bibliographic databases and 3 clinical trial databases for randomized controlled trials assessing adults with perennial or seasonal AR, and comparing (1) OAH *versus* placebo or (2) different individual OAHs. We performed a network meta-analysis on the Total Nasal Symptom Score, Total Ocular Symptom Score, Rhinoconjunctivitis Quality-of-Life Questionnaire, development of adverse events, and withdrawals due to adverse events. Certainty of evidence for comparisons involving the most clinically relevant second-generation OAHs was assessed using Grading of Recommendations, Assessment and Evaluation approach to network meta-analysis.

RESULTS: We included 74 randomized controlled trials (21 on perennial AR and 53 on seasonal AR). Cetirizine, ebastine, bilastine, and rupatadine were among the individual medications associated with the highest efficacy for improving nasal symptoms. For other efficacy outcomes, the most efficacious interventions varied. A similar frequency of adverse events was observed among different individual second-generation OAHs, with serious adverse events being rare. For most comparisons, the certainty of evidence was rated as "low" or "very low," indicating substantial uncertainty regarding the treatment effects.

CONCLUSIONS: Although some OAHs seem to be more efficacious than others, most of the differences between individual second-generation medications are trivial or small. In addition, we did not find any relevant differences in the safety profiles of second-generation OAHs. **(J Allergy Clin Immunol Pract 2026;■:■-■)**

Key words: *Allergic rhinitis; Oral antihistamines; Network meta-analysis; Systematic review*

INTRODUCTION

Oral H1-antihistamines (OAHs) are one of the mainstays of the pharmacologic management of allergic rhinitis (AR).[1,2] Their widespread use is largely attributed to their accessibility, ease of use, and favorable safety profile (particularly when considering second-generation agents).[3] The Allergic Rhinitis and its Impact on Asthma (ARIA) 2020 guidelines[4] recommend OAHs especially for patients with mild symptoms or those who prioritize preference for oral treatments and tolerability over maximal efficacy.

Several randomized controlled trials (RCTs) have demonstrated that OAHs are more effective than placebo in reducing nasal and ocular symptoms of AR, with a variable impact on

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quality of life depending on the specific agent and allergic profile of the patient.[5] However, head-to-head comparisons among different OAHs are limited, and there is substantial uncertainty regarding their relative efficacy and safety. To date, previous systematic reviews have typically focused on specific individual agents[6,7] or symptoms,[8,9] or comparisons between intranasal and oral treatments,[10,11] rather than offering a comprehensive evaluation and comparison of individual agents.

Network meta-analysis (NMA) enables the simultaneous comparison of multiple interventions by integrating both direct and indirect evidence from a network of RCTs, thus allowing for more comprehensive and precise treatment rankings. This approach is particularly relevant for informing guideline development and optimizing individualized treatment strategies in AR. To date, 1 NMA has addressed the comparative effectiveness of OAHs, but it was limited in scope (having only included 18 RCTs) and did not stratify results by AR subtype, such as seasonal AR (SAR) and perennial AR (PAR).[12] Accordingly, a more comprehensive NMA focused on OAHs is warranted to provide clearer comparative insights into their efficacy and safety profiles—evidence that can directly support clinical decision making and guideline updates in the management of AR.

This systematic review and NMA aims to compare the relative efficacy and safety of OAHs in the treatment of seasonal and perennial AR, focusing on key patient-reported outcomes. Results of this study will inform the ARIA 2024-2025 guidelines.[13,14]

METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) checklist.[15] The study protocol has been previously published[16] and registered in PROSPERO (CRD42025635590). A comprehensive description of the methods is detailed in this article's Online Repository at www.jaci-inpractice.org.

Eligibility criteria

We included RCTs with a parallel design that evaluated first- or second-generation OAHs in patients 12 years or older with SAR or PAR. Eligible studies needed to report data on at least 1 of the following patient-reported outcomes: Total Nasal Symptom Score (TNSS), Total Ocular Symptom Score (TOSS), or Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) score. Studies were required to have a minimum follow-up period of (1) 2 weeks for SAR assessments or (2) 4 weeks for PAR assessments.[17] We included studies directly comparing different OAHs as well as those comparing OAHs with placebo. There were no restrictions based on language, publication date, or publication status.

Information sources and search strategy

We conducted a systematic literature search (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) on MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials. In addition, we manually searched clinicaltrials.gov, the GSK clinical study data set, and the AstraZeneca Clinical Trials Website. The search was conducted on May 10, 2024.

Study selection and data collection

Two reviewers independently evaluated each record first by title and abstract screening and then by full-text reading. Data from the included studies were independently extracted by 2 reviewers using a predefined online form. Disagreements between reviewers were resolved by consensus or by a third reviewer.

Risk of bias and certainty of evidence assessment

Two reviewers independently assessed the risk of bias (RoB) for each reported outcome using the Cochrane RoB tool.[18] Discrepancies in assessment were settled through discussion or arbitration by a third reviewer. The certainty of evidence (CoE) was evaluated on the basis of Grading of Recommendations, Assessment and Evaluation (GRADE) approach to network meta-analysis (GRADE-NMA[19,20]).

Synthesis of the evidence

Efficacy outcomes (TNSS, TOSS, and RQLQ score) were described using mean ± SD baseline and change-from-baseline values. Safety outcomes, including the occurrence of at least 1 adverse event (AE) and treatment withdrawal due to AE, were described using absolute and relative frequencies. Statistical analyses were conducted using the *netmeta* and *rjags* packages in R.

NMA: Main analysis

An NMA was performed for each efficacy and safety outcome, integrating both direct and indirect evidence to compare OAHs. For efficacy outcomes, random-effects NMA was applied to analyze mean differences (MDs) in change-from-baseline values. Only TNSS calculated as the sum of 4 symptoms (nasal congestion, itching, sneezing, and rhinorrhea) and TOSS calculated as the sum of 3 symptoms (eye itching/burning, tearing/watering, and redness) were considered for meta-analytical purposes. For safety outcomes, a random-effects NMA of risk ratios was conducted. Separate analyses were performed for SAR and PAR. Treatments were ranked on the basis of P scores, representing the probability of an intervention being associated with the most favorable outcome.[21] In this study, we focused the presentation of NMA results on a predefined subset of treatments ("main OAH") considered (1) more relevant to current clinical practice, and (2) more widely commercially available (further details in this article's Online Repository at www.jaci-inpractice.org).

NMA: Complementary approach

A complementary Bayesian meta-analytical approach was used to determine the probability that, for each pairwise comparison, observed differences corresponded to large, moderate, small, or trivial (clinically nonmeaningful) effects.

RESULTS

We identified 6209 records from bibliographic database searches and 27 records from clinical trials registries (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). After removing 2457 duplicate records, we assessed 410 full texts for eligibility. A total of 74 RCTs—published between 1985 and 2021—were included in the systematic review.

Tables E2 and E3 in this article's Online Repository at www.jaci-inpractice.org summarize the characteristics and results of studies on PAR (n = 21) and SAR (n = 53), respectively. Tables E4 to E10 in this article's Online Repository at www.jaci-inpractice.org present the raw data used for the NMA across all outcomes. Across studies, the median percentage of female participants was 56.3% (percentile 25-percentile 75 = 50.6%-63.0%), and the median average age was 34.3 years (percentile 25-percentile 75 = 31.9%-36.8%). Study sample

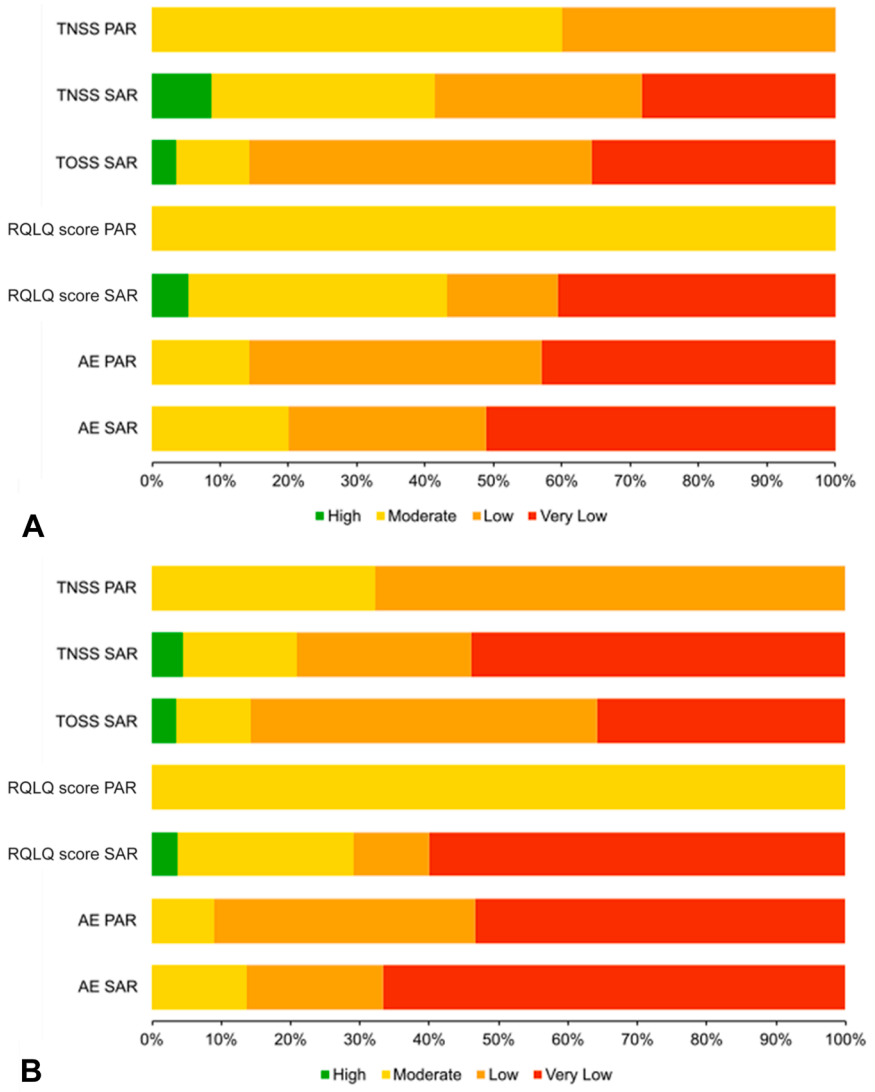

FIGURE 1. Percentage of comparisons for each outcome that were classified as associated with a high, moderate, low, or very low CoE (**A** = comparisons involving only main OAHs*; **B** = all comparisons). *"Main oral antihistamines": bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, rupatadine, and terfenadine.

sizes ranged from 27 to 1179 participants, with a mean of 437 participants per study. SAR studies had follow-up periods ranging from 2 to 8 weeks, whereas PAR studies had follow-up periods of 4 to 24 weeks. Regarding outcomes, the TNSS was assessed in 78.4% of the studies, whereas TOSS and RQLQ score were assessed in 28.4% and 44.6% of the studies, respectively. No studies evaluated the TOSS in patients with PAR.

RoB and overall CoE

Figure E2 in this article's Online Repository at www.jaci-inpractice.org presents the RoB assessments for the included studies. Most studies had a RoB for "blinding of outcome assessment" and "completeness of outcome data." However, inadequate reporting frequently led to unclear RoB for "random sequence generation" and "allocation concealment." The domains most frequently classified as of high RoB included "selective reporting" and "blinding of participants and personnel." Overall, 6 studies (8%) were classified as having low, 51 (67%) as unclear, and 17 (23%) as high RoB.

Figure 1 displays a summary assessment of the CoE, as evaluated according to GRADE-NMA. Overall, most outcomes were rated as having low (31%) or very low (49%) CoE. TNSS PAR (32%) and RQLQ SAR (26%) were the outcomes with the highest proportion of evidence rated as moderate or high CoE. Among comparisons involving main OAH treatments, 25% of the outcomes were rated as moderate, 35% as low, and 35% as very low CoE (Figure 1).

Meta-analytical results

A detailed description of meta-analytical results for all assessed outcomes is available in this article's Online Repository

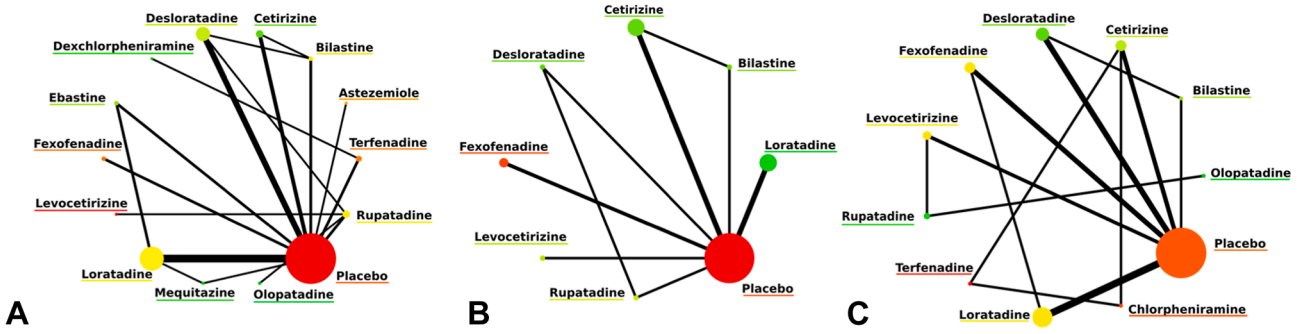

FIGURE 2. Graphical representation of the NMAs for the (**A**) TNSS, (**B**) TOSS, and (**C**) RQLQ score in patients with SAR. The thickness of the edges is proportional to the precision of the NMA, the sizes of the nodes are proportional to the number of studies, and the colors of the nodes and of the underlined text reflect the *P*-score ranks of the interventions (higher *P*-score ranks are marked in green and lower ranks in red).

	SAR					PAR				
	TNSS*	TOSS*	RQLQ score*	Any AE†	Withdrawal due to AE†	TNSS*	TOSS*	RQLQ score*	Any AE†	Withdrawal due to AE†
Placebo (reference)	−1.91	−1.70	−0.84	19.5%	1.2%	−2.32	-	−0.98	24.3%	2.3%
Bilastine	−0.76 (−1.18 to −0.34)	−0.64 (−1.04 to −0.24)	−0.34 (−0.58 to −0.10)	−0.87 (−0.70 to 1.09)	0.37 (0.08 to 1.65)		-		−1.03 (0.84 to 1.26)	1.32 (0.20 to 8.52)
Cetirizine	−1.07 (−1.39 to 0.75)	−0.65 (−0.89 to 0.41)	−0.30 (−0.48 to −0.13)	1.04 (0.83 to 1.30)	0.46 (0.12 to 1.81)	−0.67 (−1.13 to 0.22)	-	−0.32 (−0.47 to −0.17)	0.92 (0.79 to 1.07)	0.97 (0.45 to 2.10)
Desloratadine	−0.83 (−1.06 to −0.60)	−0.66 (−1.20 to 0.12)	−0.38 (−0.51 to −0.25)	1.10 (0.95 to 1.29)	0.88 (0.42 to 1.87)	−0.51 (−0.94 to 0.09)	-	−0.38 (−0.63 to −0.13)	0.99 (0.87 to 1.11)	1.08 (0.62 to 1.89)
Ebastine	−0.94 (−1.31 to 0.56)			1.00 (0.75 to 1.32)	0.79 (0.33 to 1.91)	−0.83 (−1.27 to 0.38)	-		0.76 (0.58 to 0.99)	1.46 (0.33 to 6.52)
Fexofenadine	−0.16 (−0.58 to 0.26)	−0.06 (−0.37 to 0.24)	−0.24 (−0.35 to 0.13)	1.09 (0.91 to 1.30)	0.96 (0.40 to 2.30)		-			
Levocetirizine	−0.80 (−0.15 to 1.75)	−0.57 (−0.97 to 0.17)	−0.23 (−0.41 to 0.05)	0.79 (0.60 to 1.05)	0.33 (0.07 to 1.48)		-	−0.48 (−0.67 to −0.29)	0.98 (0.88 to 1.08)	1.35 (0.46 to 3.93)
Loratadine	−0.73 (−0.90 to 0.56)	−0.84 (−1.10 to 0.58)	−0.24 (−0.32 to 0.15)	1.05 (0.95 to 1.17)	1.01 (0.63 to 1.61)	−0.43 (−0.86 to 0.00)	-		0.82 (0.64 to 1.04)	2.10 (0.61 to 7.28)
Rupatadine	−0.73 (−1.15 to 0.31)	−0.53 (−1.06 to 0.00)	−0.56 (−1.96 to 0.22)	1.29 (0.99 to 1.68)	0.33 (0.01 to 8.13)	−0.96 (−1.36 to 0.56)	-	−0.22 (−0.42 to −0.02)	1.12 (0.86 to 1.48)	0.57 (0.17 to 1.90)
Terfenadine	−0.20 (−0.67 to 0.28)		−0.33 (−0.16 to 0.84)	1.27 (0.99 to 1.62)	0.98 (0.19 to 5.13)		-			
Classification of the intervention (cell color)								**Certainty of the evidence (CoE) (letter color)**		
Beneficial effect		Harmful effect		No clear effect		No data		High/Moderate CoE	Low/Very Low CoE	Not assessed

FIGURE 3. Summary of the NMA results of the comparisons between each main OAH with placebo. *Results for placebo presented as mean change-from-baseline and results for the remaining interventions presented as MDs in change-from-baseline values (95% CI). †Results for placebo presented as cumulative incidences and results for the remaining interventions presented as risk ratios (95% CI).

at www.jaci-inpractice.org. Figure 2 and Figures E3 and E4 in this article's Online Repository at www.jaci-inpractice.org depict the network plots for all outcomes. A summary of the results comparing each main OAH against placebo for every outcome is available in Figure 3. Table I and Tables E11 to E15 in this article's Online Repository at www.jaci-inpractice.org display the full meta-analytical results for each efficacy and safety outcome. The probability that each intervention is associated with a clinically relevant difference in the assessed outcomes when compared with the remaining ones is displayed in Table E16 in this article's Online Repository at www.jaci-inpractice.org. Table E17 in this article's Online Repository at www.jaci-inpractice.org displays the *P* scores ranking the different interventions being tested.

TNSS: PAR. The NMA on TNSS in patients with PAR included 13 studies (4762 participants). The NMA displayed moderate heterogeneity (I^2 = 38.1%) and nonsignificant incoherence (P = .073). Except for loratadine, all active treatments were associated with significant improvements in the TNSS compared with placebo (Figure 3). In the comparison between active interventions, rupatadine displayed significantly better

TABLE I. Net league table displaying the NMA results for each efficacy outcome in PAR (top-right) and in SAR (bottom-left)

A. TNSS

Bilastine	—	—	—	—	—	—	—	—	
0.31 (−0.15 to 0.78)	**Cetirizine**	−0.16 (−0.78 to 0.46)	0.15 (−0.43 to 0.74)	—	—	−0.24 (−0.84 to 0.36)	0.29 (−0.27 to 0.84)	—	**−0.67 (−1.13 to −0.22)**
0.07 (−0.37 to 0.52)	−0.24 (−0.63 to 0.15)	**Desloratadine**	0.31 (−0.30 to 0.92)	—	—	−0.08 (−0.68 to 0.52)	0.45 (−0.14 to 1.03)	—	**−0.51 (−0.94 to −0.09)**
0.18 (−0.38 to 0.74)	−0.14 (−0.63 to 0.36)	0.63 (−0.46 to 1.71)	**Ebastine**	—	—	−0.39 (−0.87 to 0.08)	0.13 (−0.40 to 0.67)	—	**−0.83 (−1.27 to −0.38)**
−0.60 (−1.19 to 0.00)	**−0.91 (−1.44 to −0.38)**	−0.14 (−0.63 to 0.36)	**−0.78 (−1.34 to −0.21)**	**Fexofenadine**	—	—	—	—	—
−1.55 (−2.59 to −0.52)	**−1.87 (−2.87 to −0.87)**	**−0.91 (−1.44 to −0.38)**	**−1.73 (−2.75 to −0.72)**	−0.96 (−2.00 to 0.08)	**Levocetirizine**	—	—	—	—
−0.03 (−0.48 to 0.42)	−0.35 (−0.71 to 0.02)	**−1.87 (−2.87 to −0.87)**	−0.21 (−0.58 to 0.16)	**0.57 (0.11 to 1.02)**	**1.52 (0.56 to 2.49)**	**Loratadine**	**0.53 (0.01 to 1.04)**	—	−0.43 (−0.86 to 0.00)
−0.02 (−0.62 to 0.57)	−0.34 (−0.87 to 0.19)	**1.56 (0.61 to 2.51)**	−0.20 (−0.77 to 0.36)	0.57 (−0.03 to 1.17)	**1.53 (0.68 to 2.38)**	0.01 (−0.45 to 0.46)	**Rupatadine**	—	**−0.96 (−1.36 to −0.56)**
−0.56 (−1.19 to 0.07)	**−0.87 (−1.45 to −0.30)**	−0.34 (−0.87 to 0.19)	**−0.74 (−1.34 to −0.14)**	0.04 (−0.60 to 0.67)	1.00 (−0.06 to 2.05)	**−0.53 (−1.03 to −0.03)**	−0.53 (−1.17 to 0.10)	**Terfenadine**	—
−0.76 (−1.18 to −0.34)	**−1.07 (−1.39 to −0.75)**	**−0.87 (−1.45 to −0.30)**	**−0.94 (−1.31 to −0.56)**	−0.16 (−0.58 to 0.26)	0.80 (−0.15 to 1.75)	**−0.73 (−0.90 to −0.56)**	**−0.73 (−1.15 to −0.31)**	−0.20 (−0.67 to 0.28)	**Placebo**

B. TOSS

Bilastine	—	—	—	—	—	—	—	—	—
0.00 (−0.40 to 0.41)	**Cetirizine**	—	—	—	—	—	—	—	—
0.02 (−0.66 to 0.69)	0.01 (−0.58 to 0.60)	**Desloratadine**	—	—	—	—	—	—	—
—	—	—	**Ebastine**	—	—	—	—	—	—
-0.58 (−1.08 to −0.07)	**−0.58 (−0.97 to −0.20)**	−0.60 (−1.21 to 0.02)	—	**Fexofenadine**	—	—	—	—	—
−0.07 (−0.64 to 0.49)	−0.08 (−0.54 to 0.39)	−0.09 (−0.76 to 0.58)	—	**0.51 (0.01 to 1.00)**	**Levocetirizine**	—	—	—	—
0.20 (−0.28 to 0.67)	0.19 (−0.16 to 0.54)	0.18 (−0.42 to 0.78)	—	**0.77 (0.38 to 1.17)**	0.27 (−0.21 to 0.74)	**Loratadine**	—	—	—
−0.11 (−0.78 to 0.56)	−0.12 (−0.70 to 0.47)	−0.13 (−0.64 to 0.38)	—	0.47 (−0.15 to 1.08)	−0.04 (−0.71 to 0.63)	−0.31 (−0.90 to 0.28)	**Rupatadine**	—	—
—	—	—	—	—	—	—	—	**Terfenadine**	—
−0.64 (−1.04 to −0.24)	**−0.65 (−0.89 to −0.41)**	**−0.66 (−1.20 to −0.12)**	—	−0.06 (−0.37 to 0.24)	**−0.57 (−0.97 to −0.17)**	**−0.84 (−1.10 to −0.58)**	−0.53 (−1.06 to 0.00)	—	**Placebo**

C. RQLQ score

Bilastine	—	—	—	—	—	—	—	—	—
−0.04 (−0.34 to 0.26)	**Cetirizine**	0.06 (−0.23 to 0.35)	—	—	0.16 (−0.08 to 0.40)	—	−0.10 (−0.30 to 0.10)	—	**−0.32 (−0.47 to −0.17)**
0.04 (−0.20 to 0.28)	0.07 (−0.14 to 0.29)	**Desloratadine**	—	—	0.10 (−0.21 to 0.41)	—	−0.16 (−0.48 to 0.16)	—	**−0.38 (−0.63 to −0.13)**
—	—	—	**Ebastine**	——	—	—	**-**	—	—
−0.10 (−0.37 to 0.16)	−0.07 (−0.27 to 0.14)	−0.14 (−0.31 to 0.03)	—	**Fexofenadine**	—	—	—	—	—
−0.11 (−0.41 to 0.19)	−0.08 (−0.32 to 0.17)	−0.15 (−0.37 to 0.07)	—	−0.01 (−0.22 to 0.20)	**Levocetirizine**	—	−0.26 (−0.54 to 0.02)	—	**−0.48 (−0.67 to −0.29)**
−0.11 (−0.36 to 0.15)	−0.07 (−0.26 to 0.13)	−0.14 (−0.30 to 0.01)	—	−0.00 (−0.13 to 0.13)	0.01 (−0.19 to 0.20)	**Loratadine**	—	—	—
0.25 (−0.20 to 0.69)	0.28 (−0.13 to 0.70)	0.21 (−0.18 to 0.61)	—	0.35 (−0.04 to 0.74)	**0.36 (0.03 to 0.69)**	0.35 (−0.03 to 0.74)	**Rupatadine**	—	**−0.22 (−0.42 to −0.02)**
−0.67 (−1.24 to −0.10)	**−0.63 (−1.12 to −0.14)**	**−0.70 (−1.24 to −0.17)**	—	**−0.56 (−1.09 to −0.03)**	**−0.55 (−1.10 to −0.01)**	**−0.56 (−1.09 to −0.04)**	**−0.91 (−1.55 to −0.28)**	**Terfenadine**	—
−0.34 (−0.58 to −0.10)	**−0.30 (−0.48 to −0.13)**	**−0.38 (−0.51 to −0.25)**	—	**−0.24 (−0.35 to −0.13)**	**−0.23 (−0.41 to −0.05)**	**−0.24 (−0.32 to −0.15)**	**−0.59 (−0.96 to −0.22)**	0.33 (−0.19 to 0.84)	**Placebo**

Results are expressed as MDs (95% CI) and they concern the comparisons between interventions in columns *vs* interventions in rows for SAR, and between interventions in rows *vs* in columns for PAR. Results are presented only for the "main oral antihistamines" (the full net league tables are available in Tables E11 to E15). Significant results are presented in bold. The content of each cell should be interpreted as the difference in the score levels when comparing the OAH in the respective column with the OAH in the respective row. A negative value indicates that the OAH in the column is associated with a higher symptom improvement than the treatment in the row. A positive value indicates lower symptom improvement associated with the treatment in the columns. For example, bilastine is associated with an additional improvement of 0.76 points in the TNSS compared with placebo for SAR. However, cetirizine is associated with an additional improvement of 0.31 points compared with bilastine.

results than loratadine (MD = −0.53; 95% CI = −1.04 to −0.01) (Table I). In addition, ebastine, cetirizine, and rupatadine were associated with a higher than 50% probability of resulting in a clinically meaningful improvement in the TNSS when compared with loratadine (Table E16). Rupatadine (0.861) and ebastine (0.726) presented the highest *P*-score ranks (Table E17). Most comparisons (68%) between treatments were classified as of moderate CoE (see Table E18 in this article's Online Repository at www.jaci-inpractice.org).

TNSS: SAR. We included 38 studies in the NMA of TNSS on SAR (14,925 participants). The NMA on individual medications displayed moderate heterogeneity (I^2 = 49.3%) and significant incoherence (P = .002). All active treatments were associated with significant improvements in the TNSS compared with placebo, except for fexofenadine, levocetirizine, and terfenadine (Figure 3). Ebastine, cetirizine, and loratadine displayed better results than fexofenadine, levocetirizine, and terfenadine, and rupatadine was found to be more effective than desloratadine (MD = −1.56; 95% CI, −2.51 to −0.61) and levocetirizine (MD = −1.53; 95% CI, −2.38 to −0.68) (Table I). In addition, cetirizine, ebastine, loratadine, desloratadine, and rupatadine displayed a probability of higher than 50% of resulting in a clinically meaningful improvement in the TNSS when compared with fexofenadine, levocetirizine, and terfenadine (Table E16). Cetirizine (0.736) and ebastine (0.647) presented the highest *P* scores (Table E17). More than half of the comparisons (54%) were classified as of very low certainty (see Table E19 in this article's Online Repository at www.jaci-inpractice.org).

TOSS: SAR. Twelve studies (5675 participants) reported data on TOSS in patients with SAR. The NMA on individual medications displayed moderate heterogeneity (I^2 = 31.7%) and nonsignificant incoherence (P = .209). Except for fexofenadine and rupatadine, all active treatments were associated with significant improvements in TOSS compared with placebo (Figure 3). Bilastine, cetirizine, levocetirizine, loratadine, and rupatadine were found more effective than fexofenadine (>50% probability of resulting in a clinically meaningful improvement) (Table I; Table E16). Loratadine (0.868) and desloratadine (0.653) were associated with the highest *P* scores (Table E17). Most of the comparisons were classified as of low (50%) or very low (36%) certainty (see Table E20 in this article's Online Repository at www.jaci-inpractice.org).

RQLQ: PAR. The NMA on RQLQ in PAR included 6 studies (2586 participants). Heterogeneity was not detected (I^2 = 0%), and incoherence was not significant (P = .792). All active treatments were associated with significant improvements in the RQLQ score compared with placebo (Figure 3). No significant differences between active interventions were found (Table I), but levocetirizine presented a higher than 50% probability of being associated with a clinically meaningful improvement when compared with desloratadine and rupatadine (Table E16). Levocetirizine (0.903) and desloratadine (0.689) were associated with the highest *P* scores (Table E17). All comparisons were classified as of moderate certainty (see Table E21 in this article's Online Repository at www.jaci-inpractice.org).

RQLQ: SAR. Twenty-five studies on SAR (11,409 participants) reported RQLQ data. The NMA reported low heterogeneity (I^2 = 37.9%) but significant incoherence (P = .043). All active treatments were associated with significant improvements in RQLQ scores compared with placebo and terfenadine (Table I). Consistently, all active treatments were associated with a higher than 50% probability of resulting in a clinically meaningful improvement when compared with terfenadine. In addition, rupatadine was found to be more effective than levocetirizine (MD = −0.36; 95% CI, −0.69 to −0.03) and was associated with a higher than 50% probability of resulting in a clinically meaningful improvement when compared with all other active treatments (Table E16). Rupatadine (0.857) and desloratadine (0.734) were associated with the highest *P* scores, although the evidence for rupatadine was based on fewer RCTs and participants than that for desloratadine (Table E17). More than half of the comparisons were classified as of very low certainty (61%) (see Table E22 in this article's Online Repository at www.jaci-inpractice.org).

AE: PAR. Sixteen studies (7330 participants) reported data on AEs for patients with PAR. Heterogeneity was not detected (I^2 = 0%), and incoherence was not significant (P = .417). No active treatment showed a higher risk of AEs than placebo (Figure 3). Ebastine was associated with a lower risk of AEs than rupatadine (risk ratio = 0.67; 95% CI, 0.46-0.98). Most comparisons were classified as of low (38%) or very low (53%) CoE (see Table E23 in this article's Online Repository at www.jaci-inpractice.org).

AE: SAR. The NMA on AEs for SAR included data from 38 studies (15,568 participants). The NMA reported low heterogeneity (I^2 = 17.3%) but significant incoherence (P = .016). No significant differences in AE risk were found between active interventions and placebo (Figure 3). Bilastine and levocetirizine were associated with a lower risk of AEs than rupatadine and terfenadine. Most of the comparisons were classified as of low (23%) or very low (64%) certainty (see Table E24 in this article's Online Repository at www.jaci-inpractice.org).

Withdrawal due to AE: PAR. We included 14 studies (8663 participants) providing data on withdrawals due to AEs in PAR. The NMA reported low heterogeneity (I^2 = 16.4%) and no significant incoherence (P = .707). There were no significant differences in the comparisons against placebo (Figure 3) or between active treatments (Table E15).

Withdrawal due to AE: SAR. Thirty-eight studies (18,415 participants) were included in the NMA on withdrawals due to AEs in SAR. The NMA reported low heterogeneity (I^2 = 15.3%) and no significant incoherence (P = .191). There were no significant differences in the comparisons against placebo (Figure 3) or among active interventions (Table E15).

Serious AEs. In patients with PAR, serious AEs were reported in the bepotastine (N = 2 events/221 participants), cetirizine (N = 1/455), desloratadine (N = 1/1241), and placebo (N = 6/2050) groups. Among patients with SAR, serious AEs were reported in the terfenadine (N = 2/193), astemizole (N = 1/102), fexofenadine (N = 2/770), desloratadine (N = 2/1046), levocetirizine (N = 1/764), and placebo (N = 14/5658) groups. Among the main OAHs, none of the reported serious

AEs were related to the treatment. Because of the small number of events, meta-analysis was not performed.

DISCUSSION

In this systematic review, we evaluated the comparative efficacy and safety of OAHs in patients with AR. Although some OAHs appeared more efficacious than others, most differences between individual agents were trivial or small. In addition, the treatments identified as the potentially most efficacious often varied depending on the outcome assessed. Cetirizine, ebastine, bilastine, and rupatadine were among the OAHs that may be the most effective for improving nasal symptoms, whereas loratadine and desloratadine may be among the most effective in relieving ocular symptoms. Desloratadine may also be among the most effective OAH in improving the RQLQ score. In contrast, fexofenadine, terfenadine, and levocetirizine were frequently among the OAHs that may be the least effective. AEs occurred at a similar frequency across most second-generation OAHs, with serious AEs being rare. These findings underscore their generally favorable safety profiles. The CoE for most outcomes was rated low to very low, primarily due to imprecision and RoB, except for TNSS and the RQLQ score in PAR, which were mostly rated as moderate.

Several of our results merit some caution in their interpretation or further research. Rupatadine was found to be a highly effective OAH in improving TNSS and RQLQ score in patients with PAR, although its quality-of-life benefits are only supported by 2 studies, both with small sample sizes. However, some OAHs that are not widely commercially available (such as olopatadine, mequitazine, and dexchlorpheniramine) demonstrated apparently more favorable effects than some "main OAHs" for TNSS in patients with PAR. However, these findings are all supported by a single study with a small sample size, resulting in highly imprecise results. Finally, the fact that cetirizine may be more efficacious than levocetirizine in improving nasal symptoms deserves further mechanistic research.

To our knowledge, few systematic reviews have specifically compared the efficacy of individual OAHs for AR,[6,7,9,10] and only 1 previous review has conducted an NMA of direct and indirect comparisons among these treatments.[12] Several key differences distinguish the latter from the present review. First, our review improves upon earlier efforts by including a larger number of trials (74 vs 18), applying a Bayesian probabilistic framework for enhanced clinical interpretation, and incorporating GRADE to evaluate CoE. Notably, our NMA included outcomes not analyzed in the previous review (ie, RQLQ score and safety outcomes), which are critical for informing clinical decision making and patient self-management. In addition, by stratifying studies by SAR and PAR, we provide more tailored clinical insights based on these 2 allergic profiles. Even though it would be also relevant to provide stratified results based on AR severity, such information is not typically provided in RCTs. In terms of results, the previous review identified rupatadine as the most effective treatment for nasal congestion, rhinorrhea, and overall symptom control in AR.[12] Although we did not perform an analysis by individual nasal symptoms, our findings also suggest that rupatadine is one of the most efficacious OAHs in improving nasal symptoms, particularly in patients with PAR. However, in terms of the least efficacious OAHs, in contradistinction to our study, the other NMA identified them to be loratadine and desloratadine.[12] However, importantly, there are differences in the included RCTs and in the evaluated outcomes.

Despite its methodological rigor, our review has some limitations. The CoE for most outcomes was rated as low or very low, primarily due to imprecision and RoB. Imprecision was particularly influenced by RCTs with small sample sizes, especially among less frequently assessed OAH treatments. Moreover, a substantial proportion of trials were classified as having an unclear RoB, often resulting from inadequate reporting of allocation concealment, random sequence generation, and selective outcome reporting. Although our review applied comprehensive eligibility criteria, it is important to note that—for meta-analytical purposes—we included only those studies reporting the 4-symptom TNSS scale, excluding those using the 3-symptom TNSS scale. Although this approach improved outcome homogeneity and interpretability, it may have led to the exclusion of older trials, thus narrowing the evidence base. Moreover, there was scarce evidence for some relevant outcomes, most notably TOSS in PAR. Safety data were also predominantly derived from short-term studies with limited sample sizes, which may underestimate the risk of rare or long-term AEs. For example, in the included RCTs on terfenadine (or astemizole), there were no reported cases of arrhythmias. Nevertheless, terfenadine- (or astemizole-) induced torsade de pointes has been described in case reports and subsequently identified as a relevant serious AE of these drugs,[22] leading to their withdrawal. In addition, evaluating somnolence/drowsiness (a specific relevant patient-important AE) was found to be challenging: numerous studies did not provide information on the number of patients reporting somnolence, whereas others reported no or very few events (resulting in potentially imprecise estimates). This would limit our capacity to draw meaningful conclusions on the existing differences regarding this outcome. In this context, (1) there is a clear need for more high-quality, large-scale head-to-head RCTs with longer follow-up periods to strengthen the evidence base and allow for more definitive comparisons among OAHs, and (2) the ARIA 2024-2025 guidelines will not only consider results from RCTs but also those from pharmacovigilance when evaluating the safety of OAHs.[14] It is also worth noting that in real-world practice, many patients with AR receive combination therapies or are treated with doses above the ones tested in RCTs. Future studies should also explore the comparative effectiveness of OAHs in the context of multimodal treatment strategies. Finally, the included primary studies did not have all the same inclusion criteria (although differences were mostly minor) or follow-up period. However, sensitivity analyses restricted to studies with a follow-up of 2 weeks (SAR) or 4 weeks (PAR) provide similar results to analyses involving all RCTs (see Table E25 in this article's Online Repository at www.jaci-inpractice.org).

Nevertheless, this review has some strengths. First, stratification of results by AR subtype is a unique strength, because it captures disease-specific treatment effects often overlooked. For our analysis, we applied both frequentist and Bayesian network meta-analytical frameworks, enhancing not only statistical robustness but also the clinical interpretability of findings through probability-based effect estimates. The use of our Bayesian approach enables a better contextualization of the meta-analytical results as trivial ("not clinically meaningful"), small but meaningful, moderate, or large. The use of the GRADE methodology for NMA allowed for assessment of the CoE, which is particularly

relevant for integrating the NMA results in guideline development. In fact, the results of this NMA will inform the ARIA 2024-2025 guidelines. The ARIA 2024-2025 guideline question that motivated this systematic review was derived from an analysis of real-world online queries by patients with AR,[23] emphasizing its direct clinical relevance. The fact that we observed mostly trivial or small differences between individual OAHs does not diminish the impact of this systematic review. In fact, it highlights the importance of criteria other than desirable and undesirable effects ("efficacy and safety") for decision making in terms of choosing one OAH over others. The ARIA 2024-2025 guidelines adopt the GRADE Evidence-to-Decision framework, which requires evidence on 12 criteria for formulating health recommendations.[24,25] Finally, we observed low-to-moderate heterogeneity in most analyses.

Conclusion

This systematic review and NMA is the most comprehensive synthesis to date evaluating the comparative efficacy and safety of individual OAHs in RCTs for AR, integrating data from 74 RCTs and analyzing patient-reported outcomes across both SAR and PAR subtypes. Although most OAHs show efficacy and safety compared with placebo, our findings reveal some differences in their relative effectiveness, even though, in certain cases, such differences are trivial or small. Cetirizine, ebastine, and rupatadine were identified as the most efficacious medications for improving nasal symptoms, whereas loratadine and desloratadine displayed some favorable results in terms of ocular symptoms and rhinoconjunctivitis-related quality of life. However, limitations in evidence certainty warrant some caution in result interpretation. These findings support a more individualized, symptom-driven approach to antihistamine selection, considering both the allergic profile (SAR vs PAR) and patient-specific treatment priorities, such as symptom burden and tolerability. In doing so, this review helps bridge the gap between evidence synthesis and person-centered care. These results will directly inform the ARIA 2024-2025 guidelines, contributing to evidence-based recommendations on desirable and undesirable effects of OAHs, and identifying priorities for future research.

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