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Efficacy and safety of oral treatments for allergic rhinitis in children: A network meta-analysis

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Abstract

Background: Allergic rhinitis is the most common chronic disease in children. Information on efficacy and safety of oral allergic rhinitis treatments in children is scarce. We aimed to comprehensively evaluate the efficacy and safety of oral medications for allergic rhinitis in children.

Methods: We performed a systematic review, searching three bibliographic databases and clinicaltrials.gov for randomized controlled trials assessing the use of oral antihistamines (OAH) or leukotriene receptor antagonists (LTRA) in children

Abbreviations: AE, adverse event; AR, allergic rhinitis; ARIA, the Allergic Rhinitis and its Impact on Asthma; CoE, certainty in the body of evidence; EAACI, the European Academy of Allergy and Clinical Immunology; GRADE NMA, the GRADE approach for network meta-analysis; LTRA, leukotriene receptor antagonists; MD, mean difference; NMA, network meta-analysis; OAH, oral antihistamines; PAR, perennial allergic rhinitis; PRISMA-NMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses; RCT, randomized controlled trial; RoB, risk of bias; RQLQ, the Rhinoconjunctivitis Quality-of-Life Questionnaire; RR, risk ratio; SAR, seasonal allergic rhinitis; SD, standard deviation; TNSS, the Total Nasal Symptom Score.

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(<12 years old) with seasonal or perennial allergic rhinitis. Evaluated outcomes included the Total Nasal Symptom Score (TNSS), the Total Ocular Symptom Score (TOSS), the Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ), development of adverse or serious adverse events, and withdrawals due to adverse events. We performed network meta-analysis at both class and individual treatment levels. Certainty in the body of evidence was assessed using the GRADE approach for network meta-analysis.

Results: We included eight primary studies with 906 participants. Overall, OAH were more effective against placebo in improving the TNSS (mean difference (MD) = −1.60; 95%CI = −2.25 to −0.95). On the other hand, OAH+LTRA did not demonstrate additional benefit over OAH in improving the TNSS (MD = -0.15; 95% CI = −1.18 to 0.88), and there were no important differences between individual OAH. Evidence on the TOSS was not found. No significant differences in the frequency of adverse events were observed. Certainty of evidence was low or very low for most comparisons.

Conclusions: Oral treatments for allergic rhinitis appear to be effective and safe in children. However, evidence is scarce and the quality of evidence is mostly low.

We performed a systematic review of randomised controlled trials assessing oral medications for allergic rhinitis in children and reporting results on nasal symptoms, ocular symptoms, quality of life and adverse events. Oral antihistamines (OAH) were found to be better than placebo, and OAH + oral leukotriene receptor antagonists (OLTRA) were not found to be better than OAH. We identified trivial differences between different OAH.

KEYWORDS
allergic rhinitis, children, leukotriene receptor antagonists, network meta-analysis, oral antihistamines, quality of life, systematic review

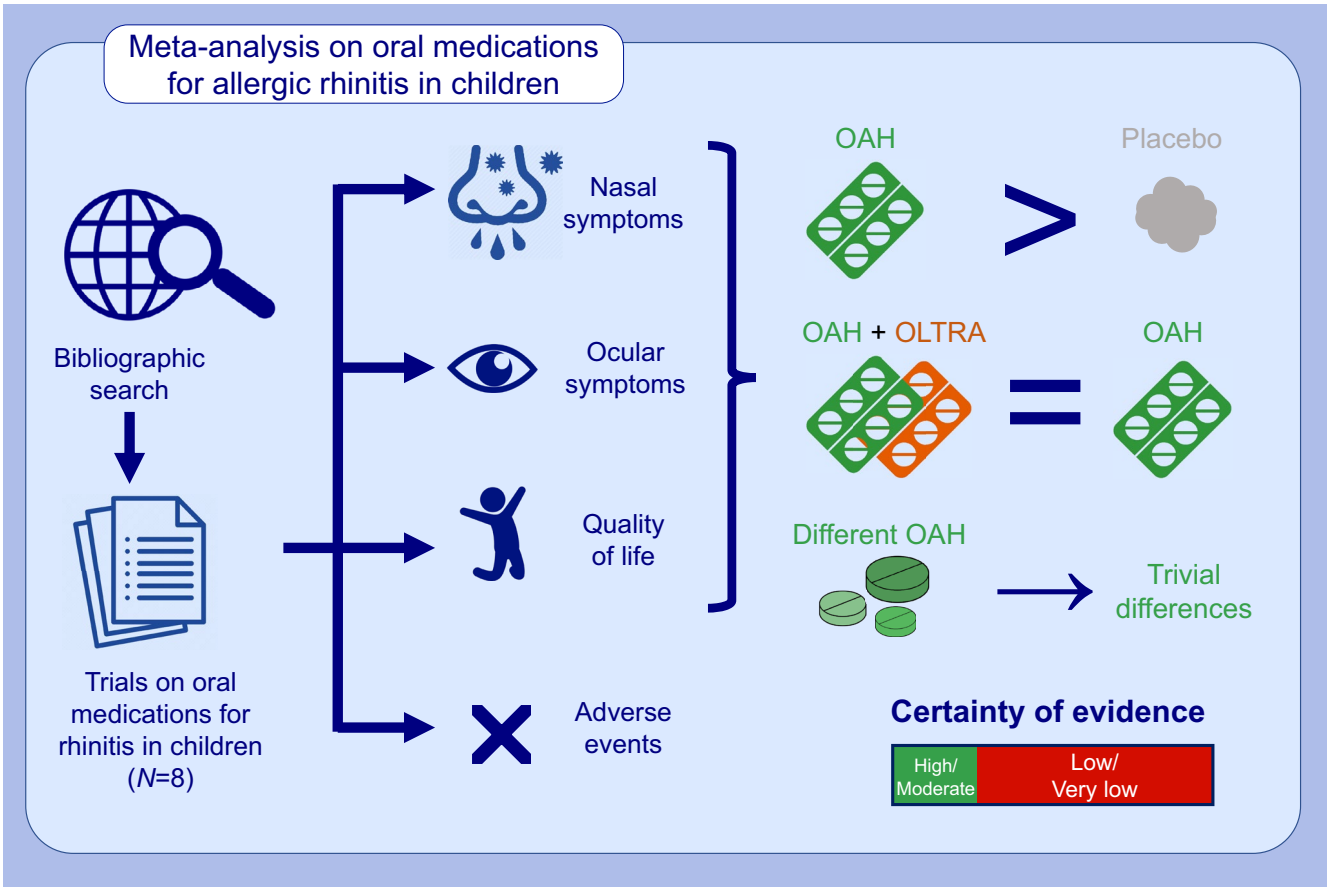
Key message

Oral treatments—in particular oral antihistamines—appear to be effective and safe for allergic rhinitis in children, while co-medication with leukotriene receptor antagonists does not seem to be associated with additional benefits. No important differences between individual oral antihistamines were found.

1 | INTRODUCTION

Allergic rhinitis (AR) is the most common chronic disease in children, having a prevalence of 20%–40% and being a risk factor for asthma.[1–3] In both children and adults, the mainstay of AR pharmacological treatment includes intranasal and oral medications. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines suggested that, compared to oral treatments, intranasal medications may be preferred for the treatment of AR due to their higher effectiveness.[4] A subsequent systematic review and meta-analysis confirmed the higher efficacy of intranasal versus oral treatments for AR.[5] However, oral treatments may be better tolerated in children[6] and patient preference should also be considered in the shared decision-making. In fact, despite the higher efficacy of intranasal corticosteroids (INCS), some children may prefer oral medications or caregivers may prefer treatments that do not include steroids. In fact, a previous study using MASK-air® mHealth data showed that, among days reported by adolescent (13–17 years) MASK-air® users, 21% concerned oral antihistamines (OAH) as monotherapy, whereas just 7% concerned INCS as monotherapy, and 5% OAH+INCS.[7] Still, information on the efficacy of specific oral medications in children is scarce and has not been systematically evaluated. This is particularly relevant as findings observed in adults may not necessarily be directly applicable to children as shown in our previous network meta-analysis (NMA) of intranasal medications for AR in children[8,9]: for example, intranasal medications are effective and safe in the treatment of AR in children, but their efficacy in improving nasal symptoms appears to be lower than that observed in adults.[8]

This systematic review and NMA aims to compare the efficacy and safety of oral medications—at both class and individual levels—in



GRAPHICAL ABSTRACT

The contents of this page will be used as part of the graphical abstract of html only. It will not be published as part of main article.

We performed a systematic review of randomised controlled trials assessing oral medications for allergic rhinitis in children and reporting results on nasal symptoms, ocular symptoms, quality of life and adverse events. Oral antihistamines (OAH) were found to be better than placebo, and OAH + oral leukotriene receptor antagonists (OLTRA) were not found to be better than OAH. We identified trivial differences between different OAH.

children with seasonal AR (SAR) or perennial AR (PAR). We will not compare oral versus intranasal interventions, as this comparison entails serious transitivity concerns: oral and intranasal placebos are different, with nasal placebo being associated with greater symptom improvements than oral placebo (work in progress based on studies performed in adults). The results of this study will inform the ARIA 2024–2025 guidelines on the treatment of AR,[7] which are endorsed by the European Academy of Allergy and Clinical Immunology (EAACI). The guidelines will give recommendations on first-line and add-on therapy decisions.

2 | METHODS

2.1 | Protocol and registration

This systematic review applies the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) checklist.[10]

The protocol of this systematic review has been registered in PROSPERO (CRD42025635590). Initially, the protocol considered performing a NMA for adults only. However, following the decision of the ARIA guideline panel to consider the subgroup of children, a similar NMA for children has been conducted. The only dissimilarity between these two NMAs concerns the age-related inclusion criterion.

2.2 | Eligibility criteria

We included only randomized controlled trials (RCTs) with a parallel design and a minimum follow-up period of (i) 2 weeks if assessing SAR or (ii) 4 weeks if assessing PAR.[11] We included studies evaluating preschool- or school-age children (<12 years old). Studies assessing patients <18 years old were included if they predominantly (>50% of the participants with adequately reported data) involved children <12 years of age. Oral antihistamines (OAH), leukotriene receptor antagonists (LTRA), and combinations of OAH+LTRA were considered eligible interventions. Both studies directly comparing oral medications and those comparing active oral medications with placebo were included. We did not adopt exclusion criteria based on publication language, date, or status. Neither inclusion of nasal treatments was an exclusion criterion, but only oral treatment arms were investigated.

2.3 | Information sources and search

We performed the search queries (Table S1) in three bibliographic databases: MEDLINE via Ovid, Web of Science, and the Cochrane Central Register of Controlled Trials. All databases were searched by BSP and RJV from inception. Additionally, a manual search was conducted in clinicaltrials.gov, with unpublished results being considered. All searches were conducted in November 2023. Searches were updated in July 2025.

2.4 | Study selection, data items and data collection

Two reviewers independently reviewed each record first by screening titles and abstracts and then by reading full texts. A pre-specified online form was used for data extraction which was conducted independently by two reviewers. The following data was retrieved from each study: (i) the assessed disease (SAR or PAR), (ii) the participants' eligibility criteria, (iii) the period and place of data collection, (iv) the follow-up period, (v) the assessed interventions (and their total daily dose), (vi) the number of randomized participants, (vii) the number of participants who completed the study, (viii) age and sex distributions of participants, and (ix) assessed outcomes. The main evaluated outcomes were the total nasal symptom score (TNSS; computed based on four symptoms[5,9]), the total ocular symptom score (TOSS; computed based on three symptoms[5,9]), and the rhinoconjunctivitis quality of life questionnaire (RQLQ). TNSS has 4 domains, each assessed on a 4-point scale (0 absence of symptoms, 1 mild, 2 moderate, and 3 severe symptoms), with a total score range from 0 (asymptomatic) to 12 (most severe symptoms).[12] RQLQ includes 23 items with 5 domains of which each is assessed on a 7-point scale (0–6; 0—not impaired at all, 6—severely impaired).[13] The minimally important difference (MID) has been reported to be 0.28 for the TNSS[14] and 0.5 for the RQLQ.[13] Secondary outcomes included the frequency of patients developing (i) at least one adverse event (AE) or (ii) at least one serious AE, and (iii) discontinuing treatment due to AE (safety outcomes). Both baseline values and post-intervention and/or change from baseline values of efficacy outcomes (TNSS, TOSS, and/or RQLQ) were collected.

Laser AI software was applied to support the screening process (https://laser.ai). Study selection, data extraction, and risk of bias (RoB) assessment was performed by teams involving the following pre-trained researchers: TT, PRS, RJV, AF, VHD, HV, AMP, RFS, HFC, MMC, JCT, MCL, ATF, NLS, JLB, EB, ES, RAC, PP, JPM, DI, AWLC, IPC, MIT, and ARR.

Disagreements between reviewers in data selection or extraction were solved by a third reviewer (either BSP or SGM).

2.5 | Risk of bias and certainty of evidence assessment

Two reviewers independently assessed the risk of bias (RoB) of each included primary study at an efficacy outcome level using the Cochrane RoB 2.[15] Disagreements were solved by a third reviewer. Certainty in the body of evidence (CoE) was assessed per outcome using the GRADE approach for network meta-analysis (GRADE NMA).[16–18]

2.6 | Data analysis

2.6.1 | Summary measures

The efficacy outcomes were continuous variables and described using mean (± standard deviation (SD)) baseline and as change-from-baseline values. Safety outcomes were dichotomous and described as absolute and relative frequencies.

2.6.2 | Meta-analysis

To compare oral medications taking into account both direct and indirect evidence we conducted a NMA for each efficacy and safety outcome. Efficacy outcomes were analyzed by a random-effects NMA of mean differences (MD) in change-from-baseline values. Safety outcomes were analyzed by a random-effects NMA of risk ratios (RR). The random effects model was as we assumed that the different studies were estimating different (even if related) intervention effects (e.g., the different studies evaluated different individual medications within the same class or different medication doses).[19] Meta-analyses have been performed separately both for (i) patients with SAR and PAR and for (ii) individual treatments and treatment classes. Analyses were conducted using the netmeta package of R (version 4.5.0).

For efficacy outcomes, we performed a complementary meta-analytical approach using Bayesian methods to compute the probability that, for each pair of interventions, differences corresponded to large, moderate, small, or trivial (no meaningful) effects (a more detailed description of the method is available elsewhere[9]). We performed a meta-analysis of standardized mean differences, considering 0.2, 0.5, and 0.8 as effect size thresholds defining small, moderate, and large effects. These thresholds were also used to support the application of GRADE NMA when judging the CoE for efficacy outcomes. For safety outcomes, we used the decision thresholds of 65 events/1000 individuals, 161/1000, and 303/1000 (computed following a previously described approach[20]).

We used the PlotDigitizer tool (https://plotdigitizer.com/) to estimate results which were provided only in graphical form. An algorithm suggested by Weir et al.[21] was used to estimate missing information on spread measures and as previously described.[9]

2.6.3 | Assessment of assumptions

We evaluated intransitivity (violation of the assumption that the divergent sets of included RCTs are indistinguishable in all principal

variables except for the comparison of interventions being made)[22] by assessing patient and study characteristics across the studies. We evaluated the coherence assumption (i.e., coherence between direct and indirect evidence) based on the *p* value for the incoherence test. Furthermore, we examined heterogeneity based on the I^2 statistic. A *p* value <0.05 and an $I^2 \geq 50\%$ were respectively considered to represent significant incoherence and substantial heterogeneity. Considering the small number of included primary studies, we were not able to perform subgroup or sensitivity analyses.

3 | RESULTS

3.1 | Study selection

We retrieved 6242 study results from our original search strategy. After duplicates removal, we obtained 3779 studies. Among those, 410 manuscripts were assessed for eligibility, of which eight[23–30] were included in our systematic review and meta-analysis (Figure 1). An additional primary study[31] was identified in the search update, resulting in the inclusion of a total of nine primary studies.

3.2 | Study characteristics

Altogether, 752 participants with PAR (six studies)[23,25–28,30] and 301 with SAR (two studies)[24,29] were included in this NMA (Table 1).

Across all included studies, participants' mean age was 4.4–12.1 years old with 39.3% female and the follow-up 2–16 weeks. Most patients had moderate–severe symptoms with the mean (SD) baseline TNSS varying between 4.0 (1.1) and 8.8 (1.6) (Table S2). We did not identify any study evaluating the TOSS.

3.3 | Meta-analytical results

3.3.1 | TNSS: PAR

Three studies reported results for TNSS in PAR (Table S2). The NMA had a heterogeneity with an $I^2 = 47.9\%$. No significant differences were found in the comparison between OAH+LTRA versus OAH (MD = -0.15; 95% CI = −1.18 to 0.88) (Table 2). The CI encompassed the MID values (−0.28 and 0.28). OAH+LTRA versus OAH had a 40.6% probability of a resulting in a clinically relevant improvement compared to OAH, while OAH had a 17.6% probability of resulting in a relevant improvement compared to OAH+LTRA. The CoE for this comparison was "Very Low" (Table 3).

Similarly, no significant differences were observed in the comparisons between OAH vs. LTRA (MD = −0.41; 95% CI = -2.10 to 1.27) or between OAH+LTRA versus LTRA (−0.56; 95%CI = −0.77 to 1.89) (Table 2). The CoE for these comparisons was "Very Low" (Table 3).

The included studies did not have any individual treatment in common, so that NMA could not be performed for. When assessing individual medications, loratadine decreased TNSS more than loratadine combined with montelukast (MD = −0.44; 95% CI = −1.61 to 0.73) and fexofenadine combined with montelukast more than fexofenadine (MD = 0.62; 95% CI = −0.32 to 1.56), but without statistical significance.

3.3.2 | TNSS: SAR

Only one study reported results for TNSS in SAR, comparing an OAH (cetirizine) to placebo (Table S2). OAH improved the TNSS more than the MID (MD = −1.60; 95% CI = −2.25 to −0.95), corresponding to a 100% probability of a relevant improvement. The CoE for this comparison was "Low" (Table 3 and Table S3).

3.3.3 | RQLQ: PAR

Four studies reported results for RQLQ in PAR, comparing OAH versus placebo (Table S2). OAH was associated with a significant improvement (MD = -0.83; 95% CI = −1.33 to −0.32) (Tables 1 and 2) with substantial heterogeneity ($I^2 = 87.8$). This difference was larger than the MID and OAH had an 82.4% probability of resulting in a clinically meaningful improvement in RQLQ (71.7% probability of this effect being moderate or large).

Heterogeneity ceased to be detected once excluding the studies for which data was inputted (MD = −1.04; 95% CI = −1.21 to −0.87), but not studies with a high risk of bias (MD = −0.78; 95% CI = −1.39 to −0.18) or data from first generation antihistamines (MD = −0.84; 95% CI = −1.35 to −0.33). The CoE for this comparison was "Moderate" (Table 3).

The NMA on individual treatments had high heterogeneity ($I^2 = 89.2\%$). Cetirizine resulted in a significant improvement compared to placebo (MD = −0.95; 95% CI = −1.58 to −0.33), as did levocetirizine (MD = −0.70; 95% CI = −1.40 to −0.01) (Table 4). No significant differences were observed between OAH. The CoE was "Very Low" for all comparisons (Table S3).

3.3.4 | RQLQ: SAR

Only one study reported results for RQLQ in SAR, comparing OAH versus placebo. The quantitative information provided was insufficient for meta-analysis to be performed.

3.3.5 | AE: PAR

Five studies of PAR provided information on development of at least one AE (Table S4). However, due to the lack of a common comparator, we were not able to perform NMA comparing different medication

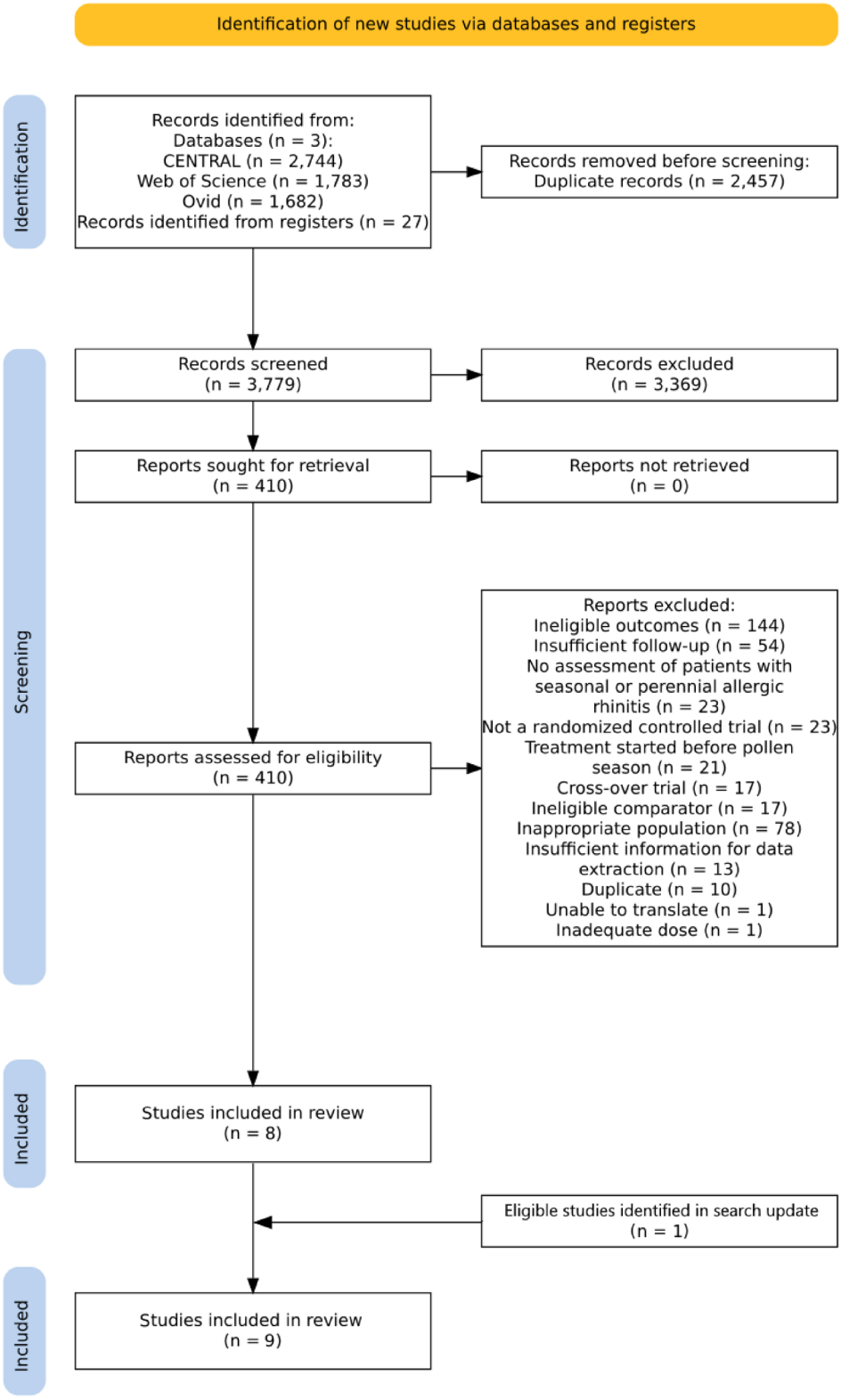


FIGURE 1 PRISMA flow diagram for primary study selection.

classes. OAH were associated with a non-significantly higher risk of developing at least one AE (RR = 1.06; 95% CI = 0.86–1.30; I^2 = 0%) (Table 2). This corresponds to 21 more events per 1000 individuals (from 49 fewer to 106 more; trivial to small difference), and a 13.8% probability of a meaningful difference. The CoE was "Moderate" (Table 3).

The NMA on individual treatments for the development of any AE had no significant differences (Table S5) and with low

TABLE 1 Characteristics of the included primary studies.

Study identification	Place and period of data collection	Treatments	OAH generation	Assessed outcomes	Follow-up	*N* Participants	*N* (%) completers	*N* (%) females	Mean [min, max] age (years)
A. Perennial allergic rhinitis									
Lai DS, 2002	–; –	Cetirizine 10 mg (QD) Oxatomide 1 mg/kg (BID) Ketotifen 1 mg (QD) Placebo	1, 2	RQLQ	3 months	80	69 (86.3)	39 (48.8)	8.1 [6, 12]
Potter PC, 2005	South Africa (24 sites); 2002 (April–September)	Levocetirizine 5 mg (QD) Placebo	2	RQLQ	4 weeks	306	297 (97.1)	120 (39.2)	9.9 [6, 12]
Chen ST, 2006	–; –	Cetirizine 5 mg (QD) Placebo	2	RQLQ	12 weeks	40	40 (100)	19 (47.5)	4.4 [2, 6]
Hung CH, 2007	Taiwan (single center); –	Loratadine 5 mg (QD) Loratadine 5 mg + Montelukast 5 mg (QD)	2	TNSS	8 weeks	22	22 (100)	11 (50.0)	8.1 [5, 14]
Lee CF, 2008	Taiwan	Cetirizine 10 mg (QD) Levocetirizine 5 mg (QD) Placebo	2	RQLQ	12 weeks	80	74 (92.5)	31 (38.8)	8.4 [6, 12]
Li AM, 2009	–; –	Fexofenadine 60 mg (<12 years) or 120 mg (≥12 years) (QD) + Montelukast 5 mg (<14 years) or 10 mg (≥14 years) (QD) Fexofenadine 60 mg (<12 years) or 120 mg (≥12 years) (QD)	2	TNSS	16 weeks	44	44 (100)	24 (54.5)	12.1 [6, 18]
Kim CK, 2024	South Korea (9 sites); 2019 (May)–2022 (June)	Montelukast 5 mg (QD) Levocetirizine 5 mg + montelukast 5 mg (QD)	2	TNSS	4 weeks	147	136 (92.5)	49 (33.3)	9.7 [6, 14]
B. Seasonal allergic rhinitis									
Masi M, 1993	Italy; 1990 (May–July)	Cetirizine 10 mg (BID) Placebo	2	TNSS	2 weeks	124	114 (91.9)	48 (38.7)	10.1 [6, 12]
de Blic J, 2005	France and Germany; 2002 (April–September)	Levocetirizine 5 mg (QD) Placebo	2	RQLQ	6 weeks	177	145 (81.9)	60 (33.9)	9.9 [6, 12]

Abbreviations: BID, twice per day; LTRA, leukotriene receptor antagonist; OAH, oral antihistamines; QD, once per day; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TNSS, Total Nasal Symptom Score.

TABLE 2 Net league tables displaying the network meta-analysis results for each outcome in perennial allergic rhinitis (top-right; in green) and in seasonal allergic rhinitis (bottom-left; in blue).

A. Total Nasal Symptom Score			
OAH	−0.41 (−2.10 to 1.27)	0.15 (−0.88 to 1.18)	–
–	**LTRA**	0.56 (−0.77 to 1.89)	–
–	–	**OAH+LTRA**	–
−1.60 (−2.25 to −0.95)	–	–	**Placebo**
B. Rhinoconjunctivitis Quality of Life Questionnaire			
OAH	–	–	**−0.83 (−1.33 to −0.32)**
–	**LTRA**	–	–
–	–	**OAH+LTRA**	–
–	–	–	**Placebo**
C. Adverse events			
OAH	–	–	1.06 (0.86–1.30)
–	**LTRA**	–	–
–	–	**OAH+LTRA**	–
1.07 (0.75 to 1.54)	–	–	**Placebo**

Note: Results are expressed (i) as mean differences [95% confidence intervals] for the TNSS and RQLQ, and (ii) as risk ratios [95% confidence intervals] for the frequency of any adverse event. Results in the table should be interpreted as the comparisons between interventions in rows versus interventions in columns. Significant results are presented in bold. TNSS ranges from 0 to 12. RQLQ ranges from 0 to 6. Negative values represent improvement in all outcomes.

Abbreviations: LTRA, leukotriene receptor antagonist; OAH, oral antihistamines.

heterogeneity (I^2 = 0%). The CoE was "Low" for all comparisons except one (Table S3).

Compared to LTRA alone, OAH+LTRA resulted in a decreased risk of AE (RR = 0.36; 95% CI = 0.12–1.06). This corresponds to 102 fewer cases per 1000 (from 141 fewer cases to 9 more cases; small to trivial difference). The CoE was "Very Low" (Table 3).

Six studies provided information on the occurrence of withdrawals due to AE. There were four withdrawals due to AE (two in a placebo group and two in an OAH group).

The low frequency precluded NMA (Table S4). No serious AEs were reported.

3.3.6 | AE: SAR

Two studies comparing OAH vs. placebo in patients with SAR provided data on AEs (Table S4). OAH resulted in a non-significantly higher risk of developing at least one AE (RR = 1.07; 95% CI = 0.75–1.54; I^2 = 0%) (Table 2). This corresponds to 19 more events per 1000 individuals (from 68 fewer to 148 more), and a 21.9% probability of a meaningful difference. The CoE was "Low" (Table 3).

No significant differences in the risk of developing at least one AE were observed when comparing individual medications (Table S5). The CoE was "Very Low" for all comparisons (Table S3).

There were four withdrawals due to AE (two in placebo groups and two in OAH groups), with the low frequency of such events precluding NMA (Table S4). No serious AEs were reported.

3.4 | Network geometry

There were two outcomes for which, when comparing treatment classes, we identified more than one comparison: TNSS in PAR, and development of at least one AE in PAR (Figure S1). However, the network was disconnected for the latter. For the remaining outcomes, we only identified one comparison, so that results only reflect direct evidence between the treatment classes that were part of these comparisons. The networks for the analyses involving individual medications (whenever there was more than one comparison) are shown in Figure S1.

3.5 | Risk of bias within studies and across studies

Figure 2 displays the results of the RoB assessment for all included studies. No study was considered to have a low risk of bias. Three studies displayed a high risk of bias (particularly because of high risk of bias associated with (i) deviations from intended intervention and (ii) selection of the reported result). All remaining studies had an unclear risk of bias, particularly reflecting the risk of bias arising from the randomization process and in the selection of the reported result.

4 | DISCUSSION

4.1 | Summary of evidence

In this study, we systematically reviewed all RCTs assessing oral medications for children with AR. We performed NMA, obtaining results for the comparisons between different interventions based on direct and indirect evidence. We found that (i) OAH may be effective against placebo, (ii) OAH+LTRA did not demonstrate additional benefit over OAH alone, although evidence was very limited and of very low certainty, and (iii) there were no important differences between individual OAH. However, in most cases, CoE was judged as "very low" and data was limited for individual treatment comparisons. Additionally, only in two studies,[25,28] OAH+LTRA were compared to OAH alone. Importantly, this systematic review demonstrates that evidence on oral interventions in children from RCTs is scarce. Data on many outcome measures, particularly in the TOSS, are lacking. Even

TABLE 3 Assessment of the certainty of evidence for the comparisons on efficacy and safety outcomes when comparing medication classes.

	Direct comparisons					Indirect comparisons		Network		
Comparison	Risk of bias	Inconsistency	Indirectness	Publication bias	Imprecision	Intransitivity	Imprecision	Incoherence	Imprecision	Final rating
Total Nasal Symptom Score: Perennial Allergic Rhinitis										
OAH+LTRA:OAH	Not serious	Not serious	Not serious	Not serious	Extremely serious	—	—	—	Extremely serious[a]	Very low
OAH+LTRA: LTRA	Very serious[b]	Very serious[c]	Not serious	Not serious	Very serious[d]	—	—	—	Very serious[d]	Very low
OAH:LTRA	—	—	—	—	—	Not serious	Extremely serious[a]	—	Extremely serious[a]	Very low
Total Nasal Symptom Score: Seasonal Allergic Rhinitis										
OAH:Placebo	Not serious	Not serious	Not serious	Not serious	Very serious[d]	—	—	—	Very serious[d]	Low
Rhinoconjunctivitis Quality of Life Questionnaire: Perennial Allergic Rhinitis										
OAH:Placebo	Not serious	Very serious	Not serious	Not serious	Serious[e]	—	—	—	Serious[e]	Very low
Development of at least one AE: Perennial Allergic Rhinitis										
OAH:Placebo	Not serious	Not serious	Not serious	Not serious	Serious[e]	—	—	—	Serious[e]	MODERATE
OAH+LTRA:LTRA	Very serious[b]	Not serious	Not serious	Not serious	Serious[e]	—	—	—	Serious[e]	VERY LOW
Development of at least one AE: Seasonal Allergic Rhinitis										
OAH:Placebo	Not serious	Not serious	Not serious	Not serious	Very serious[d]	—	—	—	Very serious	LOW

Note: For comparisons for which there was no downgrading of the certainty of evidence due to risk of bias, either the comparison did not include studies with high risk of bias or those studies did not have a relevant impact on the meta-analytical estimates and their CIs.

Abbreviations: AE, adverse event; LTRA, leukotriene receptor antagonist; OAH, oral antihistamines.

[a]The fixed-effects meta-analytical measure crosses at least three decision thresholds.

[b]All primary studies have a high risk of bias.

[c]Difference of two decision thresholds crossed between the random-effects and the fixed-effects meta-analytical measures.

[d]The fixed-effects meta-analytical measure crosses two decision thresholds.

[e]The fixed-effects meta-analytical measure crosses one decision threshold.

Cetirizine	−0.23 (−1.41; 0.95)	−0.25 (−1.07; 0.57)	0.07 (−1.09; 1.23)	−0.95 (−1.58; −0.33)
–	Ketotifen	−0.02 (−1.36; 1.31)	0.30 (−1.01; 1.61)	−0.72 (−1.91; 0.46)
–	–	Levocetirizine	0.32 (−1.00; 1.64)	**−0.70 (−1.40; −0.01)**
–	–	–	Oxatomide	−1.02 (−2.19; 0.14)
–	–	–	–	Placebo

Note: Results are expressed as mean differences (95% confidence intervals) and they concern the comparisons between interventions in rows versus interventions in columns. Significant results are presented in bold. RQLQ ranges from 0 to 6. Negative values represent an improvement.

TABLE 4 Net league table displaying the network meta-analysis results for Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) in perennial allergic rhinitis (top-right; in green) and in seasonal allergic rhinitis (bottom-left; in blue).

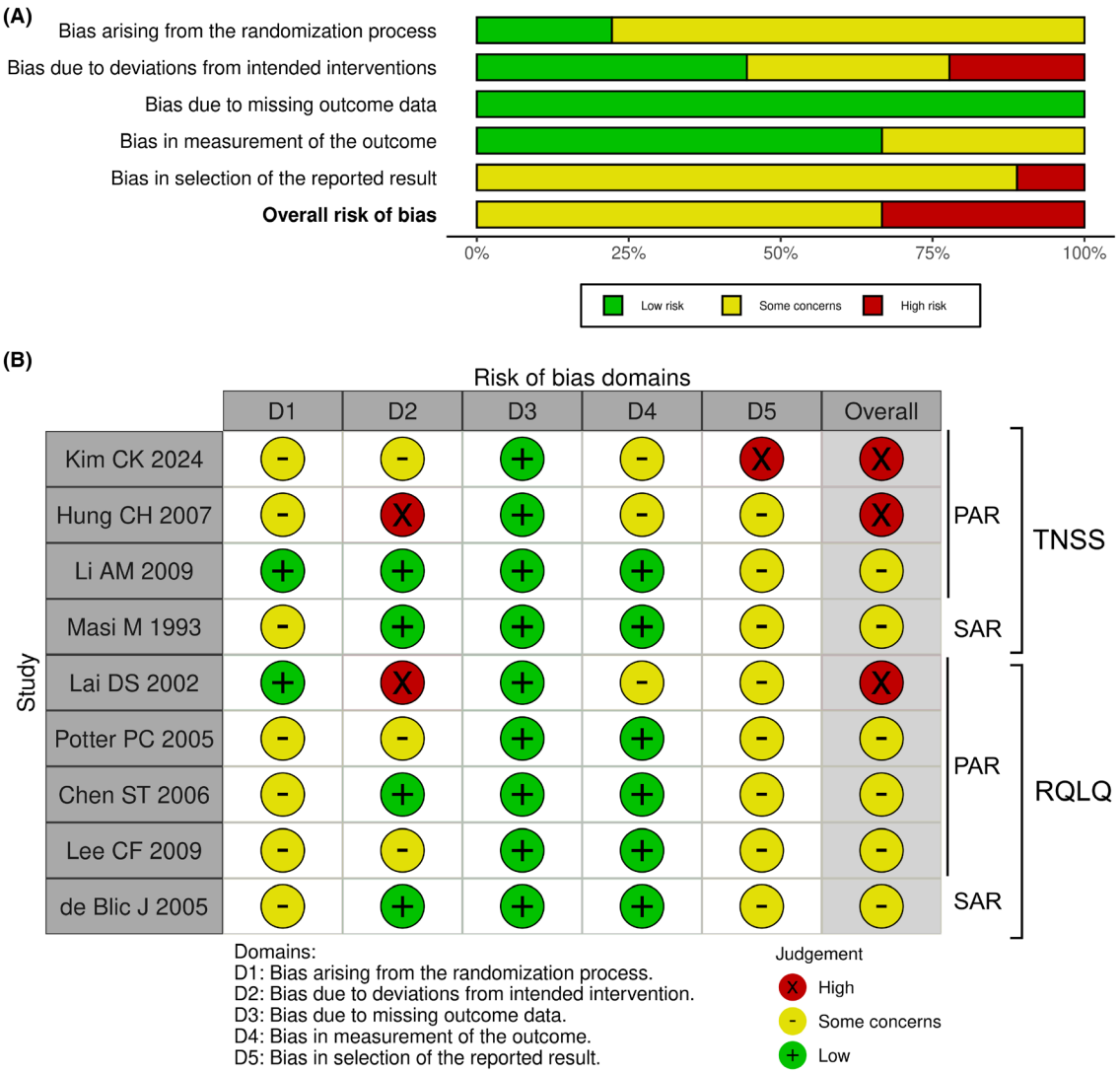


FIGURE 2 Risk of bias assessment for all included primary studies. RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TNSS, Total Nasal Symptom Score.

for outcomes for which there was information, the number of included primary studies tended to be low, resulting in (i) estimates with high imprecision, and (ii) several individual medications not having been evaluated in RCTs on children. This was particularly true for SAR. This lack of evidence is also reflected in the scarcity of observational studies on the topic. We performed a rapid evidence review in MEDLINE, Scopus and among our results excluded for not being RCTs. We only identified one observational study specifically performed in children and comparing oral medications.[32] That study[32] had different outcome measures than in our NMA but compared OAHs and found that levocetirizine and fexofenadine were the individual drugs whose reported satisfaction scores were highest for efficacy, tolerability,

satisfaction, and impact. Considering this scarceness of evidence, future studies are needed in children—such studies may include either RCTs or observational studies using a target trial emulation approach. The latter have the advantages of adequately dealing with confounding while at the same time being less resource consuming than RCTs and leveraging real word data from widely used medications in children.

Overall, oral interventions appeared to be safe. However, the follow-up period of most studies was limited, and sample sizes were small; therefore, decreasing the likelihood of detecting rare adverse events. With an assumed event rate of 1:1000, the probability of detecting at least one adverse event in the available sample was approximately 60%, indicating moderate sensitivity for detecting rare adverse events. Complementary studies using pharmacovigilance data may help to identify eventual occasional adverse events.

Most comparisons evaluated in this study were associated with "Low" or "Very Low" certainty of evidence. While this in part reflects imprecision of the estimates, these ratings were also the most common ones in a recent NMA of OAHs for allergic rhinitis in adults (Vieira RJ et al. Submitted.) in which more studies were included.

To our knowledge, there are no previous systematic reviews on oral medications of allergic rhinitis in children that (i) performed both comparisons at a class and individual level, and (ii) presented meta-results. There have been previous systematic reviews assessing OAH in children. However, such reviews were either not accompanied by a meta-analysis[33,34] and/or displayed different designs and eligibility criteria compared to ours. For example, Velentza et al. compared the efficacy and safety of newer antihistamines not only to other oral medications but also to intranasal treatments.[33] However, the authors did not evaluate OAH + LTRA combinations and did not perform meta-analysis. On the other hand, contrary to our systematic review, Zhou et al. did not perform comparisons at a class level and only focused on the evaluation of cetirizine.[35]

4.2 | Strengths and limitations

This systematic review and NMA provide comprehensive data on the efficacy and safety of oral treatments in children. We showed that OAHs may be effective alone, and there seems to be no significant symptom improvement when they are combined with LTRA. Another strength concerns the fact that, when comparing different interventions, we not only evaluated whether there were "significant" differences, but we also quantified the probability that there would be a clinically relevant difference.

This systematic review also has limitations, mostly related to primary studies. The limited number of included primary studies resulted in a scarce number of comparisons between individual treatments and treatment classes, particularly in SAR. As a result, we were not always able to conduct NMA. Adding to that, there were some medications assessed at different doses in different studies, potentially resulting in heterogeneity. One example is cetirizine, which has been evaluated at 5 and 10 mg. Studies were not only scarce but had often risk of bias concerns, particularly in domains such as deviations from intended intervention and selection of the reported result. Many treatments had missing data on outcome measures. For example, the TOSS was not reported in any included studies and therefore, ocular symptom data is missing. Of note, we have only included studies that would have computed the TNSS based on four symptoms and the TOSS based on three symptoms. Older studies may have used other ways to compute TNSS/TOSS or even to evaluate nasal or ocular symptoms. However, for comparative purposes with the other systematic reviews informing the ARIA 2024–2025 guidelines,[5,9] we opted not to broaden our eligibility criteria. Furthermore, due to the limited overall number of studies and on the subgroup (PAR vs. SAR) and outcome level, pre-school and school-aged children could not be investigated separately. This limitation also reflected the fact that, while one of the included studies[23] had only pre-school aged children, all the others had both pre-school and school-aged children without providing data separately. On the other hand, while our results concerning TNSS in children with PAR included adolescents, differences between adolescents and children <12 years old regarding this particular outcome do not seem to be relevant enough to raise concerns over bias. In fact, previously identified differences in symptoms' perception by children did not involve nasal symptoms, but rather ocular complaints and impact on daily activities.[36] Finally, heterogeneity in RQLQ PAR remained substantial both on class and individual treatment levels; the small number of included primary studies did not allow us to explore possible effect modifiers, such as differences in doses, age distributions, duration, and baseline TNSS. In addition, it did not allow the evaluation of small study effects.

5 | CONCLUSIONS

This study summarized all RCTs of oral treatments for AR in children. Overall, oral treatments—in particular OAH—appear to be effective and safe in children, while co-medication with LTRA does not seem to be associated with additional benefits. While we did not find relevant differences between individual OAH, it is important to note that evidence is scarce and CoE associated with most comparisons is low. Furthermore, longer-term (>16 weeks) evaluation of safety is needed.

AUTHOR CONTRIBUTIONS

Pau Riera-Serra: Methodology; data curation; formal analysis; writing – original draft. **Rafael José Vieira:** Investigation; writing – review and editing. **Vítor Henrique Duarte:** Investigation; writing – review and editing. **Hugo Viegas:** Investigation; writing – review and editing. **Sara Gil-Mata:** Methodology; data curation; writing – original draft; formal analysis. **João A. Fonseca:** Validation; writing – review and editing. **Tuuli Thomander:** Methodology;

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For transparency, the peer review documents associated with this article are available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/pai.70431.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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