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Allergic Rhinitis and Its Impact on Asthma (ARIA)-EAACI Guidelines—2024–2025 Revision: Part II—Guidelines on Oral and Ocular Treatments

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Abbreviations: AI, artificial intelligence; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; EAACI, European Academy of Allergy and Clinical Immunology; EtD, evidence-to-decision framework; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; INAH, intranasal antihistamine; INCS, intranasal corticosteroid; LTRA, leukotriene receptor antagonist; NMA, network meta-analysis; OAH, oral antihistamine; OcAH, ocular antihistamine; PAR, perennial allergic rhinitis; RCT, randomised controlled trial; SAR, seasonal allergic rhinitis; WHO, World Health Organisation.

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ABSTRACT

Background: Oral and ocular medications are frequently used in the treatment of allergic rhinitis (AR). As part of the update of the Allergic Rhinitis and its Impact on Asthma (ARIA)-EAACI guidelines, this manuscript presents the ARIA-EAACI 2024–2025 recommendations for oral and ocular treatments.

Methods: The ARIA-EAACI 2024–2025 guideline panel issued recommendations following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) evidence-to-decision framework. Several sources of evidence were used to inform panel judgements and recommendations, including systematic reviews, mHealth and pharmacovigilance data as well as a survey on costs.

Results: Eight guideline questions concerning oral treatments for AR and three questions concerning ocular treatments were addressed. These questions led to the recommendations. Overall, these questions concern the choice between different classes of medication. They also discuss the role of oral antihistamines (OAH), leukotriene receptor antagonists (LTRA), ocular antihistamines (OcAH) and ocular mast cell stabilisers. Four questions had not been previously evaluated in ARIA guidelines, while, for the other four, there was a change in the strength or directionality of the recommendations. Overall, these guidelines recommend using intranasal corticosteroids over OAH and using OAH over LTRA. Moreover, they suggest using OAH over OcAH and suggest being against adding LTRA to OAH. Finally, considerations for choosing between different individual OAHs are presented.

Conclusion: This ARIA-EAACI 2024–2025 article supports patients, their caregivers and healthcare professionals in choosing oral and ocular treatments for AR. Decisions on treatment should consider the clinical variability of the disease, patients' values and the affordability of medications.

1 | Introduction

Allergic rhinitis (AR) is a highly prevalent and burdensome disease [1–5]. Over the past two decades, clinical practice guidelines have supported healthcare providers and patients in managing AR effectively. Among these, the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative first published its guidelines in 2001 [6], with updates in 2008 [7], 2010 [8], 2016 [9] and 2020 [10]. These updates reflected the development of new treatments and/or methodological improvements, including the adoption of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach in 2010 and 2016 [9], and the inclusion of MASK-air mHealth data in 2020 [10].

The new revision of the ARIA guidelines (ARIA-EAACI 2024–2025) has been endorsed by the European Academy of Allergy and Clinical Immunology (EAACI). It aims to respond to emerging evidence and evolving clinical needs. In recent years, evidence from other data sources, particularly mHealth, has expanded our understanding of AR beyond traditional randomised controlled trials (RCTs) [11], enabling a more comprehensive evaluation of the acceptability of AR treatments, cost-effectiveness of the interventions and patients' values associated with AR. In particular, this has been made possible as mHealth evidence has shed light on medication use patterns and adherence [12, 13], patients' satisfaction with treatments [14], utilities associated with each treatment (Lourenço-Silva et al., under review) and the impact of AR on work productivity [3]. A comprehensive description on how mHealth data have been used to support these guidelines can be found elsewhere [15, 16].

Considering the above, the ARIA-EAACI 2024–2025 guidelines have been conceived as person-centred, digitally enabled and assisted by artificial intelligence (AI), using the GRADE approach

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[15]. This emphasis on a person-centred guideline is relevant due to inter-individual variability in (i) exposure and responses to triggers/allergens, (ii) impact of AR on daily life, (iii) values in relation to rhinitis health states and (iv) disease management. The use of AI has supported the identification of patient-centred guideline questions [17] and of potentially relevant outcomes (for a detailed discussion see [15, 16]).

The first set of recommendations from the ARIA-EAACI 2024–2025 guidelines focused on intranasal treatments for AR [18].

This report presents the recommendations on oral and ocular treatments of AR. Most recommendations concern oral H_1-antihistamines (OAH), leukotriene receptor antagonists (LTRA) and ocular H_1-antihistamines (OcAH). The target audience of these guidelines includes, among others, patients with AR, health professionals managing adults or children with AR, social workers and health policymakers.

2 | Questions Addressed by This Guideline

In ARIA-EAACI 2024–2025, 42 questions on AR management were voted by guideline panel members as "prioritised questions" [17]. Among these, nine concerned oral and ocular AR treatments and are addressed by this report. Two additional questions are addressed in this guideline as the panel judged them assufficiently important to be included: (i) should OAH vs. LTRA be used for the treatment of AR? (added because there were questions comparing OAH vs. no treatment, and LTRA vs. no treatment); and (ii) should OcAH vs. ocular mast cell stabilisers be used for the treatment of ocular symptoms in patients with AR? (added because mast cell stabilisers are widely used in low- and middle-income countries). The full list of questions is presented in Table 1, alongside their corresponding recommendations and capsule justifications.

3 | Methodology

A detailed description of the methods used to develop these recommendations is available elsewhere [16, 18], with a brief overview being provided in the online supplement.

3.1 | How to Use These Guidelines

The ARIA guidelines are not intended to impose a mandate or standard of care for individual countries, but rather to provide a basis for rational, informed decisions. Recommendations provide guidance for typical patients but cannot account for all unique individual circumstances. Thus, clinicians are encouraged to individualise their practice - considering the clinical presentation of each patient and the specificities of the local context - and to reach decisions via shared decision-making.

For each question, in accordance with GRADE, we issued either a "strong" or "conditional" recommendation (terminology clarification in Box 1). The wording of the recommendations reflects their strength, with "we recommend" implying a strong recommendation and "we suggest" implying a conditional recommendation. In each recommendation, we present information on the certainty of evidence across the different outcomes of interest (quality of the whole body of evidence, considering altogether desirable and undesirable effects; Box 1). Finally, to support panel members in formulating guideline recommendations, effect sizes were categorised as "trivial or none", "small", "moderate" or "large". This terminology will be used throughout this report and is clarified in Box 1.

In this manuscript, we provide only a summary of the evidence underlying each recommendation ("brief justification"). The full Evidence-to-Decision (EtD) frameworks for each question can be found online (links provided below alongside each question).

4 | Recommendations and Summary of Findings

Table 1 outlines the recommendations for each addressed question. In the subsequent sections, we provide the rationale for each recommendation. Of note, we do not discuss patients' values and preferences individually for each question, as these were consistent across all topics. Specifically, patients with AR generally (i) place greater importance on the efficacy of AR interventions than on their safety and (ii) consider nasal symptoms (in particular, nasal congestion) to have the greatest impact [20]. Also, please note that whenever mentioning OAH, unless otherwise specified (i.e., in recommendation 10), we are referring to "second-generation OAH". Table 2 presents, for each question, the judgement of the effect size and the certainty of the evidence for each outcome.

A. New questions in ARIA-EAACI 2024–2025

1. Should any specific individual second-generation oral H_1-antihistamines vs. other individual oral H_1-antihistamines be used for the treatment of allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_oral-01/

Context: There are several second-generation OAH available, rendering it important to provide recommendations not only at a class level but also in relation to individual OAH.

Recommendation: In patients with AR, we suggest that the choice of specific second-generation OAHs over others should be based on patients' preferences on efficacy and safety and on availability and affordability (conditional recommendation based on mostly very low certainty of evidence).

- Considerations in children, adolescents and pregnant women: In preschool- and school-age children, evidence was not sufficient to support recommending a specific second-generation OAH. In pregnant women, existing studies do not suggest a teratogenic effect of OAH and the Food and Drug Administration (FDA) considers loratadine and cetirizine generally safe in pregnancy [21].
- Implementation considerations: When selecting a second-generation OAH, several factors should be considered, including efficacy, safety (e.g., sedative potential), affordability and specific patient characteristics. Patients often value efficacy

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TABLE 1 | Recommendations of the ARIA-EAACI 2024–2025 guidelines for the prioritised questions on oral and ocular treatments.

Recommendation	Capsule justification	Subgroup considerations	Implementation considerations
(A) New questions in ARIA 2024–2025			
Should any specific OAH vs. other OAH be used for the treatment of AR?			
In patients with AR, we suggest that the choice of specific OAH over others should be based on patients' preferences on efficacy and safety and on availability and affordability. (Conditional recommendation|Very Low CoE)	Bilastine, ebastine, rupatadine and cetirizine are effective OAHs, with rupatadine acting rapidly and cetirizine being affordable yet sedating. Loratadine and fexofenadine are non-sedating and in the WHO List of Essential Medicines, albeit the latter is less effective.	In preschool- and school-aged children, evidence was not sufficient to support a specific recommendation.	Cost and availability may influence treatment choices. Bilastine and fexofenadine may be preferred in the case of renal/hepatic impairment. Locally produced medications may help reduce the environmental impact.
Should an OAH + LTRA vs. OAH be used for the treatment of AR?			
In patients with AR, we suggest using OAH over OAH + LTRA. (Conditional recommendation|Moderate CoE)	OAH + LTRA show no added clinically relevant benefit over OAH alone and result in increased costs. In addition, there are important safety concerns with LTRA (montelukast).	Recommendation applicable to preschool- and school-aged children.	In LMIC, OAH in the WHO List of Essential Medicines or locally produced generics may be considered.
Should OcAH vs. OAH be used for the treatment of ocular symptoms in patients with AR?			
In patients with AR, we suggest **against** using OcAH over OAH, except for very fast relief of ocular symptoms (Conditional recommendation|Very Low CoE)	Compared to OcAH, OAH are more efficacious and associated with higher acceptability. In addition, OAH tend to be more affordable with some being in the WHO List of Essential Medicines.	Recommendation applicable to (i) preschool- and school-aged children, and (ii) patients with allergic conjunctivitis without nasal symptoms.	In LMIC, OAH in the WHO List of Essential Medicines or locally produced generics may be considered.
Should OcAH vs. ocular mast cell stabilisers be used for the treatment of ocular symptoms in patients with AR?			
In patients with AR, we suggest using OcAH over mast cell stabilisers (Conditional recommendation|Very Low CoE)	OcAH and ocular mast cell stabilisers are similar in terms of efficacy and safety. However, OcAH are associated with a faster onset of action and fewer applications, and are probably cost-effective in a wide set of countries.	Recommendation applicable to preschool- and school-aged children.	Mast cell stabilisers may be considered in countries where ocular antihistamines are not available or are less affordable.

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TABLE 1 | (Continued)

Recommendation	Capsule justification	Subgroup considerations	Implementation considerations
(B) Questions with changed recommendation in terms of strength or directionality (compared to ARIA 2010/2016)			
Should OAH versus LTRA be used for the treatment of AR?			
In patients with AR, we recommend using OAH over LTRA. (Strong recommendation|Moderate CoE)	OAH offer only a trivial added benefit over LTRA in symptom relief, but have a more favourable safety profile. LTRA have important safety concerns, and OAH are generally more accessible.	Recommendation applicable to preschool- and school-aged children.	In LMIC, OAH in the WHO List of Essential Medicines or locally produced generics may be considered.
Should INCS versus OAH be used for the treatment of AR?			
In patients with AR, we recommend using INCS over OAH. (Strong recommendation|Moderate CoE)	INCS are more effective in improving nasal symptoms and quality of life. INCS and OAH display a similar safety profile. INCS tend to be cost-effective and are associated with higher satisfaction.	Recommendation applicable to preschool- and school-aged children. In pregnant women, triamcinolone may have teratogenic effects.	In LMIC, INCS in the WHO List of Essential Medicines or locally produced generics may be considered.
Should LTRA vs. no treatment be used for the treatment of AR?			
In patients with AR under no treatment, we suggest **against** using LTRA. (Conditional recommendation|Moderate CoE).	LTRA offer small improvements in seasonal AR, with limited evidence in perennial AR. LTRA (montelukast) have rare but important neuropsychiatric safety concerns and there are safer alternatives for patients under no treatment.	Recommendation applicable to preschool- and school-aged children.	LTRA may be considered in patients who are not well-controlled with other medications and have a strong preference for oral treatments (particularly if they have asthma).
Should OcAH versus no treatment be used for the treatment of ocular symptoms in patients with AR?			
In patients with seasonal AR, we suggest **against** using OcAH over no treatment, except for few days (7 or less) or as-needed for very fast symptom relief (Conditional recommendation|Low CoE). In patients with perennial AR, we suggest using OcAH over no treatment (Conditional recommendation|Very Low CoE).	In perennial AR, the desirable effects outweigh the risks for undesirable effects but the same does not happen in seasonal AR. In addition, OcAH are associated with moderate costs and with impacts on equity and planetary health.	Recommendation applicable to preschool- and school-aged children.	This question is not focused on adding OcAH to a previous treatment

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TABLE 1 | (Continued)

Recommendation	Capsule justification	Subgroup considerations	Implementation considerations
(C) Other questions in ARIA 2024–2025			
Should OAH versus no treatment be used for the treatment of AR?			
In patients with AR, we recommend using OAH over no treatment. (Strong recommendation|Moderate CoE)	OAH are effective in improving nasal symptoms, ocular symptoms and quality-of-life. OAH are overall safe, cost-effective and well accepted by patients.	Recommendation applicable to preschool- and school-aged children.	In LMIC, OAH in the WHO List of Essential Medicines or locally produced generics may be considered.
Should second-generation OAH versus first-generation OAH be used for the treatment of AR?			
In patients with AR, we recommend using second-generation OAH over first-generation OAH. (Strong recommendation|Very low CoE).	Evidence comparing first- and second-generation OAH is limited. Second-generation agents are safer (in particular, resulting in less sedation) and associated with better adherence and higher patient satisfaction.	Recommendation applicable to preschool- and school-aged children.	In LMIC, second-generation OAH in the WHO List of Essential Medicines or locally produced generics may be considered.
Should INAH versus OAHs be used for the treatment of AR?			
In patients with AR, we suggest either using INAH or OAH (Conditional recommendation|Moderate CoE)	INAH are more effective in improving nasal symptoms and quality of life. However, OAH are associated with a lower risk of adverse events, are more widely available and cost-effective. OAH are associated with higher treatment satisfaction and better adherence.	Recommendation applicable to preschool- and school-aged children.	None specific

Abbreviations: AR, allergic rhinitis; CoE, certainty of evidence; INAH, intranasal antihistamines; INCS, intranasal corticosteroids; LMIC, low- and middle-income countries; LTRA, leukotriene receptor antagonists; OAH, oral H_1-antihistamines; OcAH, ocular H_1-antihistamines.

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BOX 1 | Clarification of the terminology used in these guidelines.

Strength of recommendations:

- Strong recommendation
  - *For patients*: Most patients in this situation would want the recommended course of action, and only a small proportion would not.
  - *For clinicians*: Most patients should receive the intervention. Adherence to a strong recommendation could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help patients make decisions consistent with their values and preferences.
  - *For healthcare policy makers*: The recommendation can be adopted as a policy or performance measure in most situations
- Conditional recommendation
  - *For patients*: Most patients in this situation would want the suggested course of action, but many would not.
  - *For clinicians*: Recognise that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids might be useful in helping patients to make decisions consistent with their values and preferences.
  - *For healthcare policy makers*: Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g., shared) decision-making processes can serve as a performance measure.

Certainty of evidence: The certainty of evidence concerns how certain we are that the observed magnitude of desirable and undesirable anticipated effects lies on one side of a specified threshold or within a chosen range (reflecting the "quality" of available evidence). The certainty of evidence can be classified as "very low", "low", "moderate" or "high". The certainty of evidence is independent of the directionality of the recommendation and of the effect sizes of the associations.
Categorisation of the effect sizes: The magnitude of the anticipated desirable and undesirable effects ("benefits and harms") is classified by the GRADE working group as "trivial or none", "small [but meaningful]", "moderate" or "large". A trivial effect is observed when the magnitude of the effects is so small that it is not sufficiently important in terms of anticipated health consequences. Non-trivial effects can be considered "small [but meaningful]", "moderate" or "large" depending on the magnitude of effect sizes.
Of note, for continuous outcomes, effects were classified as "trivial or none", "small", "moderate" or "large" based on their meta-analytical standardised mean differences (the cutoff values of 0.2, 0.5 and 0.8 were used for decision thresholds). For dichotomous outcomes, we used as decision thresholds the values of 65, 161 and 303 events per 1000 participants (defining respectively what corresponds to a small, moderate and large effect) [19].

over safety; however, the sedative effects of some OAH can influence adherence and daily functioning, making the balance between efficacy and safety clinically relevant. Moreover, in some professions, workers cannot have medications with sedative effect. Table 3 displays a summary of implementation and safety aspects. Some highlights include:

- Cetirizine consistently ranks high in terms of efficacy and patient satisfaction. It is affordable in most countries and included in the World Health Organisation (WHO) List of Essential Medicines. Nonetheless, it has a relatively higher sedative potential compared to other second-generation OAH and may be better suited for evening use. In addition, the FDA has warned that cetirizine (and levocetirizine) can rarely result in severe itching after discontinuation.
- Loratadine offers good efficacy, is non-sedating, widely affordable, and also included in the WHO List of Essential Medicines.
- Fexofenadine, also in the WHO List of Essential Medicines, is considered non-sedating but appears to be less efficacious than other OAH.
- Bilastine, ebastine and rupatadine are among the most efficacious second-generation OAHs and are generally well-accepted by patients. Rupatadine has a rapid onset of action. However, the affordability of these medications can vary depending on the setting, potentially limiting their use in low- and middle-income countries.
- In terms of renal or hepatic impairment, bilastine and fexofenadine are preferred due to the absence of required dose adjustments. However, fexofenadine and bilastine blood levels (as well as those of rupatadine) may be reduced because of interactions with grapefruit and some other fruit juices [22], so they should be taken with water (Table 3) [23].
- In low- and middle-income countries, the choice of OAH is often shaped by local availability and cost.
- Planetary health concerns may also play a role, encouraging the selection of locally manufactured generics to minimise environmental impact.

Brief justification:

- Efficacy and safety:
  - A network meta-analysis (NMA) [24] suggested that, in seasonal AR (SAR), cetirizine, desloratadine, ebastine, loratadine, olopatadine and rupatadine were associated with a high probability of clinically meaningful improvement in nasal symptoms. Among these, cetirizine, ebastine and rupatadine had the highest probability of being the most effective. In perennial AR (PAR), all OAHs except loratadine were superior to placebo, with rupatadine showing the highest probability of being the most effective, followed by ebastine.

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TABLE 2 | Judgements on the effect sizes and certainty of evidence (CoE) assessments for each outcome in each prioritised question comparing each intervention to a comparator.

Question		Seasonal allergic rhinitis					Perennial allergic rhinitis				
		Nasal symptoms	Ocular symptoms	Quality of life	AE	Serious AE	Nasal symptoms	Ocular symptoms	Quality of life	AE	Serious AE
Should any specific OAH versus other OAH be used for the treatment of AR?	Effect size	Small	Small	Small	Trivial	—[b]	Small	—[b]	Small	Trivial	—[b]
	CoE	Very low/low[a]	Very low/low[a]	Very low[a]	Very low/low[a]	—[b]	Low/moderate[a]	—[b]	Moderate	Very low/low[a]	—[b]
Should OAH + LTRA versus OAH be used for the treatment of AR?	Effect size	Trivial	Trivial	Trivial	Trivial	Trivial	—[b]	—[b]	—[b]	—[b]	—[b]
	CoE	High	Low	High	Moderate	Moderate	—[b]	—[b]	—[b]	—[b]	—[b]
Should OcAH versus OAH be used for the treatment of ocular symptoms in AR?	Effect size	—[b]	Small	—[b]	Small	—[b]	—[b]	—[b]	—[b]	Small	—[b]
	CoE	—[b]	Very low	—[b]	Very low	—[b]	—[b]	—[b]	—[b]	Very low	—[b]
Should OcAH versus MCS be used for the treatment of ocular symptoms in AR?	Effect size	—[b]	Trivial	—[b]	Trivial	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
	CoE	—[b]	Very low	—[b]	Very low	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
Should OAH versus LTRA be used for the treatment of AR?	Effect size	Trivial	Trivial	Trivial	Trivial	Trivial	Trivial	—[b]	Trivial	—[b]	—[b]
	CoE	High	Low	High	Moderate	Moderate	Moderate	—[b]	Very low	—[b]	—[b]
Should INCS versus OAH be used for the treatment of AR?	Effect size	Small	Trivial	Moderate	Trivial	—[b]	Small	—[b]	Small	Small	—[b]
	CoE	Moderate	Moderate	Very low	High	—[b]	Moderate	—[b]	Very low	High	—[b]
Should LTRA versus no treatment be used for the treatment of AR?	Effect size	Small	Small	Small	Trivial	Trivial	Trivial	—[b]	Small	—[b]	—[b]
	CoE	Moderate	Low	Moderate	Moderate	Moderate	Moderate	—[b]	Very low	—[b]	—[b]
Should OcAH versus no treatment be used for the treatment of ocular symptoms in AR?	Effect size	—[b]	Trivial	—[b]	Trivial	—[b]	—[b]	Large	—[b]	Small	—[b]
	CoE	—[b]	Low	—[b]	Low	—[b]	—[b]	Very low	—[b]	Very low	—[b]

(Continues)

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TABLE 2 | (Continued)

Question		Seasonal allergic rhinitis					Perennial allergic rhinitis				
		Nasal symptoms	Ocular symptoms	Quality of life	AE	Serious AE	Nasal symptoms	Ocular symptoms	Quality of life	AE	Serious AE
Should OAH versus no treatment be used for the treatment of AR?	Effect size	Small	Small	Small	Trivial	Trivial	Small	—[b]	Small	Trivial	Trivial
	CoE	High	Moderate	High	Moderate	Moderate	High	—[b]	Moderate	Moderate	Moderate
Should second-generation OAH versus first-generation OAH be used for the treatment of AR?	Effect size	Small	—[b]	Trivial	Small	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
	CoE	Very low	—[b]	Low	Very low	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
Should INAH versus OAH be used for the treatment of AR?	Effect size	Small	Trivial	Small	Small	—[b]	Trivial	—[b]	Small	Small	—[b]
	CoE	Moderate	Moderate	Moderate	Low	—[b]	Moderate	—[b]	Moderate	Low	—[b]

Abbreviations: AE, adverse events; AR, allergic rhinitis; INAH, intranasal antihistamines; INCS, intranasal corticosteroids; LTRA, leukotriene receptor antagonists; MCS, mast cell stabilisers; OAH, oral H_1-antihistamines; OcAH, Ocular H1-antihistamines. Colour code: Green=High certainty of evidence; Yellow=Moderate certainty of evidence; Orange=Low certainty of evidence; Red=Very low certainty of evidence; Blue=Effect size (the darker the shade of blue, the larger the effect size).

[a]Most common CoE assessments for the considered comparisons.

[b]No available evidence.

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TABLE 3 | Considerations of affordability, adjustments and interactions of second-generation oral antihistamines.

	WHO list of essential medicines	Sedative effect	Need for adjustments		Interactions		Electrocardiographic changes described as rare AEs
			Renal impairment	Liver impairment	Fruit juices	Other medications	
Bilastine	No	No	No	No	Yes	Yes	Yes
Cetirizine	Yes	Moderate	Yes	If renal impairment	No	No	No
Desloratadine	No	Low	No	No	No	No	Yes
Ebastine	No	No	No	No	No	Yes	No
Fexofenadine	Yes	No	No	No	Yes	Yes	No
Levocetirizine	No	Moderate	Yes	If renal impairment	No	No	No
Loratadine	Yes	Low	No	Yes	No	Yes	No
Rupatadine	No	Low	Possibly	Possibly	Yes	Yes	No

Abbreviations: AE, adverse events; WHO, World Health Organisation. Colour code: Green=Desirable; Yellow=Partly undesirable; Red=Undesirable.

- In SAR, desloratadine, rupatadine, bilastine, loratadine and cetirizine were among the OAHs with the highest probability of improving ocular symptoms. All OAHs except fexofenadine showed a clinically meaningful improvement compared to placebo. Loratadine had the highest probability of being the most effective. In PAR, no studies were available on ocular symptoms.
- In terms of rhinoconjunctivitis-related quality of life (RQLQ), in SAR, desloratadine, fexofenadine, loratadine, olopatadine and rupatadine were the OAHs with the highest probability of improving quality of life. All OAHs showed significant improvement compared to placebo. Among medications assessed in more than one study, desloratadine had the highest probability of achieving a moderate improvement. In PAR, cetirizine, desloratadine, levocetirizine and rupatadine were all more effective than placebo, with levocetirizine and cetirizine showing the highest probability of a clinically meaningful benefit. Levocetirizine and desloratadine were the OAHs most likely to be the most effective in improving quality of life.
- Similar frequencies and patterns of adverse events and serious adverse events were observed with the different second-generation OAHs based on data from RCTs and pharmacovigilance.

- Resources required, cost-effectiveness and equity: A survey of ARIA experts reported that the least and most expensive OAH vary widely across countries, but that loratadine, cetirizine and levocetirizine are most frequently the least expensive OAH. We did not identify any cost-effectiveness study comparing OAH. However, the cost data from our survey, combined with EQ-5D data from MASK-air indicate that bilastine, fexofenadine, loratadine, rupatadine and desloratadine are the OAH most frequently found to be cost-effective compared to others. Cetirizine, fexofenadine and loratadine are in the WHO List of Essential Medicines.
- Acceptability and feasibility: Observational studies suggest that levocetirizine and cetirizine are associated with the highest levels of patient and physician satisfaction among OAH. Fexofenadine also performed well, particularly in paediatric populations, with high satisfaction scores from both parents and physicians. MASK-air data suggest that OAH are generally associated with similar levels of treatment satisfaction. However, desloratadine was associated with slightly higher satisfaction than bilastine, levocetirizine and loratadine. Fexofenadine and ebastine were more often used in co-medication than cetirizine, desloratadine and loratadine, suggesting possible differences in perceived effectiveness in monotherapy.
- Planetary health: No specific evidence was found in terms of comparative impact on planetary health.

2. Should a combination of a leukotriene receptor antagonist and an oral H_1-antihistamine vs. an oral H_1-antihistamine alone be used for the treatment of allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_oral-02/

Context: Patients taking OAH often resort to co-medication with LTRA, prompting a need for assessing the added value of such co-medication strategy.

Recommendation: In patients with AR, we suggest using OAH alone over combinations of OAH and LTRA (conditional recommendation based on moderate certainty of evidence).

- Considerations in children and adolescents: The recommendation is applicable to preschool and school-aged children
- Implementation considerations: In low- and middle-income countries (LMIC), OAH in the WHO List of Essential Medicines and/or locally produced generics may be preferred.

Brief justification:

- Efficacy and safety:

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- A NMA (data in the EtD link) found that, in SAR, the combined use of OAH and LTRA does not improve nasal or ocular symptoms or RQLQ compared with OAH alone. In PAR, no studies were available.
- Regarding safety, a NMA of RCTs did not find differences between OAH + LTRA versus OAH alone. Serious adverse events were rare and not treatment-related. However, observational studies and pharmacovigilance data have raised concerns about rare neuropsychiatric adverse events associated with LTRA, such as insomnia, mood changes and suicidal ideation, leading to an FDA black box warning [25].

- Resources required, cost-effectiveness and equity: OAH + LTRA are more expensive than OAH alone. We did not identify any cost-effectiveness study comparing these two interventions. Some OAH are in the WHO List of Essential Medicines (cetirizine, fexofenadine and loratadine), contrary to LTRA.
- Acceptability and feasibility: MASK-air data suggest that OAH + LTRA are associated with slightly higher adherence and greater treatment satisfaction compared to OAH alone.
- Planetary health: No specific evidence was found in terms of comparative impact on planetary health. However, the use of OAH + LTRA, compared to OAH alone, implies the use of additional resources with environmental impact.

3. Should ocular H_1-antihistamines vs. oral H_1-antihistamines be used for the treatment of ocular symptoms in patients with allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_ocular-01/

Context: OAH are frequently used not only to control nasal but also ocular symptoms. However, some patients may prefer OcAH due to their faster onset of action.

Recommendation: In patients with AR, we suggest against using OcAH over OAH except for very fast relief of ocular symptoms (conditional recommendation based on very low certainty of evidence).

- Considerations in children and adolescents: The recommendation is applicable to preschool and school-aged children.
- Implementation considerations: In LMIC, OAH in the WHO List of Essential Medicines and/or locally produced generics may be preferred.

Brief justification:

- Efficacy and safety:
  - A NMA based on previously conducted systematic reviews [26, 27] (data on the EtD link) found that, compared with OcAH, OAH are associated with a small but important improvement in ocular symptoms in patients with SAR. In PAR, no studies were available.
  - Regarding safety, a NMA of RCTs found that OcAH are associated with a higher risk of adverse events than OAH both in SAR and PAR (small but important effect). Serious adverse events were rare and not treatment-related.
- Resources required, cost-effectiveness and equity: A survey of ARIA experts reported OcAH to be more expensive than OAH in 39 out of 44 countries for which data were available. Considering the results of effectiveness studies, it is likely that OcAH are not cost-effective. Three OAH—cetirizine, fexofenadine and loratadine—are in the WHO List of Essential Medicines, but this is not the case with any OcAH. In addition, OAH are available in more countries than OcAH.
- Acceptability and feasibility: MASK-air data suggest that OAH are associated with higher adherence and lower odds of being used as co-medication (a proxy for poor rhinitis control). OAH and OcAH are associated with similar treatment satisfaction. However, OcAH displays a faster onset of action.
- Planetary health: No specific evidence comparing OAH and OcAH in terms of impact on planetary health was found. OcAH frequently come in small plastic vials with short expiry time windows—their occasional use may result in relevant waste.

4. Should ocular H_1-antihistamines vs. ocular mast cell stabilisers be used for the treatment of ocular symptoms in patients with allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_ocular-02/

Context: Ocular antihistamines and mast cell stabilisers (chromones) are two medication classes which are frequently topically used to control ocular symptoms.

Recommendation: In patients with AR, we suggest using OcAH over ocular mast cell stabilisers (conditional recommendation based on very low certainty of evidence).

- Considerations in children and adolescents: The recommendation is applicable to preschool and school-aged children.
- Implementation considerations: None

Brief justification:

- Efficacy and safety:
  - In SAR, identified studies suggested trivial differences when comparing the improvement of ocular symptoms between OcAH and ocular mast cell stabilisers. In PAR, no studies were available.
  - The identified trials in SAR suggested trivial differences in the frequency of adverse events when comparing OcAH and ocular mast cell stabilisers. Serious adverse events were not reported in the identified trials. In PAR, no studies were available.
- Resources required, cost-effectiveness and equity: A survey of ARIA experts suggested OcAH to be more expensive than ocular mast cell stabilisers in 20 out of 34 countries for which data were available. In most countries where OcAH are more expensive, they were found to be cost-effective in relation to ocular mast cell stabilisers. No OcAH or ocular mast cell stabiliser is in the WHO List of Essential Medicines.

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- Acceptability and feasibility: MASK-air data suggest that OcAH are associated with higher odds of being used as co-medication. However, compared to mast cell stabilisers, OcAH have a faster onset of action and require fewer uses per day (which can make them more acceptable to patients).
- Planetary health: No specific evidence was found in terms of comparative impact on planetary health.

B. Questions with a change in recommendation directionality and/or strength in ARIA-EAACI 2024–2025.

5. Should oral H_1-antihistamines vs. leukotriene receptor antagonists be used for the treatment of allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_oral-03/

Context: OAH and LTRA may both be used for the treatment of AR. While OAH are widely used as first-line treatment, LTRA are often used in patients with coexisting asthma or when OAH are not well tolerated.

Recommendation: In patients with AR, we recommend using OAH over LTRA (strong recommendation based on moderate certainty of evidence).

- Considerations in children and adolescents: The recommendation is applicable to preschool and school-aged children.
- Implementation considerations: In LMIC, OAH in the WHO List of Essential Medicines and/or locally produced generics may be preferred.

Change in recommendation from previous ARIA guidelines: Previous ARIA guidelines suggested using either OAH or LTRA (conditional recommendation) in patients with SAR, and suggested using OAH over LTRA (conditional recommendation) in patients with PAR.

Brief justification:

- Efficacy and safety:
  - A NMA found that OAH were associated with greater improvement in nasal symptoms compared to LTRA in both SAR and PAR (data in the EtD link). However, the differences displayed a high probability of being trivial.
  - For ocular symptoms, OAH resulted in trivial improvements compared to LTRA in SAR. No studies were available for PAR.
  - Regarding RQLQ, we found trivial differences between OAH and LTRA in either SAR or PAR.
  - We found no significant difference in the frequency of adverse events between OAH and LTRA in SAR. No evidence was available for PAR. However, observational studies and pharmacovigilance data have raised concerns about rare neuropsychiatric effects associated with LTRA, including depression, anxiety and suicidal ideation, which led to a black box warning issued by the FDA [25].
- Resources required, cost-effectiveness and equity: A survey of ARIA experts reported that OAH and LTRA are widely available. In 46 out of the 48 countries with available data, OAH are cheaper than LTRA. Limited utility data prevented cost-effectiveness analyses. LTRA are not included in the WHO List of Essential Medicines, while three OAHs (cetirizine, fexofenadine and loratadine) are.
- Acceptability and feasibility: MASK-air data suggest that satisfaction with LTRA may be higher than with OAH, though data for LTRA were sparse. Co-medication was more frequent with LTRA (83.0%) than with OAH (50.1%).
- Planetary health: No specific evidence was found in terms of comparative impact on planetary health.

6. Should intranasal corticosteroids vs. oral H_1-antihistamines be used for the treatment of allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_oral-04/

Context: Intranasal corticosteroids (INCSs) and OAHs are widely used for the treatment of AR. While INCS have been described as more effective, OAH have some advantages, including their onset of action and route of administration.

Recommendation: In patients with AR, we recommend using INCS over OAH (strong recommendation based on moderate certainty of evidence).

- Considerations in children, adolescents and pregnant women: The recommendation is applicable to preschool-aged, school-aged children and pregnant women. However, for pregnant women, there are concerns that one INCS, triamcinolone, may have teratogenic effects.
- Implementation considerations: In LMIC, INCS in the WHO List of Essential Medicines and/or locally produced generics may be preferred.

Change in recommendation from previous ARIA guidelines: Previous ARIA guidelines suggested using INCS over OAH (conditional recommendation).

Brief justification:

- Efficacy and safety:
  - A pairwise meta-analysis comparing INCS versus OAH on nasal symptoms included 15 RCTs in SAR [28]. INCS were associated with an improvement in nasal symptoms (68% probability of a meaningful difference). Consistent results were observed when INCS and OAH were compared in a NMA (data in the EtD link). For PAR, no RCTs were identified directly comparing INCS versus OAH. Indirect comparisons from a NMA indicated that INCS were associated with improved nasal symptoms compared to OAH (data in the EtD link).
  - For ocular symptoms in patients with SAR, a pairwise meta-analysis of five RCTs revealed that INCS displayed a 21% probability of a larger improvement compared to OAH [28]. Consistent results were observed in a NMA (data in the EtD link). No evidence was obtained for PAR.

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- Regarding RQLQ, a pairwise meta-analysis comparing INCS versus OAH included two RCTs in SAR [28]. INCS were associated with an improvement in RQLQ (100% probability of a meaningful difference). Consistent results were observed when INCS and OAH were compared in a NMA (data in the EtD link). For PAR, no RCTs were identified directly comparing INCS versus OAH. Indirect comparisons from a NMA indicated that INCS were associated with a greater RQLQ improvement compared to OAH, although the difference was smaller than that observed for SAR (data in the EtD link).
- Regarding safety, both a pairwise meta-analysis [28] and a NMA pointed to a trivial difference between INCS and OAH in terms of adverse events. For PAR, no RCTs were identified directly comparing INCS versus OAH. Indirect comparisons from a NMA indicated that the impact of INCS may range from a small decrease to a moderate increase in the frequency of adverse events compared to OAH (data in the EtD link).

- Resources required, cost-effectiveness and equity: A survey of ARIA experts reported that INCS and OAH are widely available. In 35 out of the 51 countries with available data, OAH are cheaper than INCS. However, based on utilities computed using MASK-air data, INCS would be cost-effective in most countries. One INCS (budesonide) and three OAHs (cetirizine, fexofenadine and loratadine) are included in the WHO List of Essential Medicines.
- Acceptability and feasibility: MASK-air data suggest that INCS are associated with higher treatment satisfaction compared to OAH [14]. However, INCS are more frequently used in co-medication than OAH. OAH have a faster onset of action compared to INCS (median of 60 min versus 720 min, respectively).
- Planetary health: No specific evidence was found in terms of comparative impact on planetary health.

7. Should leukotriene receptor antagonists vs. no treatment be used for the treatment of allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_oral-05/

Context: LTRA are sometimes used for the treatment of AR, particularly if there is comorbid asthma. However, some safety concerns have emerged.

Recommendation: In patients with AR under no treatment, we suggest against using LTRA (conditional recommendation based on moderate certainty of evidence).

- Considerations in children and adolescents: The recommendation is applicable to children and adolescents.
- Implementation considerations: LTRA may be considered in patients who are not well-controlled with other medications and have a strong preference for oral treatments (particularly if they have asthma). In patients who are not using any treatment, the ARIA guideline panel suggests against using LTRA as the starting medication.

Change in recommendation from previous ARIA guidelines: Previous ARIA guidelines suggested using LTRA over no treatment in SAR (conditional recommendation), but suggested against its use in PAR.

Brief justification: LTRA have rare but important neuropsychiatric safety concerns and there are safer alternatives for patients under no treatment. See online supplement for more details.

8. Should ocular H_1-antihistamines vs. no treatment be used for the treatment of ocular symptoms in patients with allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_ocular-03/ and https://aria.med.up.pt/etd_ocular-04/

Context: OcAH are frequently used to provide fast relief of ocular symptoms in patients with AR.

Recommendation: In patients with SAR under no ocular treatment, we suggest against starting OcAH (conditional recommendation based on low certainty of evidence) except for few days (7 or less) or as-needed for very fast symptom relief. In patients with PAR under no treatment, we suggest using OcAH (conditional recommendation based on very low certainty of evidence). This recommendation is not focused on adding OcAH to a previous treatment.

- Considerations in children and adolescents: The recommendation is applicable to children and adolescents.
- Implementation considerations: None specific

Change in recommendation from previous ARIA guidelines: Previous ARIA guidelines suggested using OcAH over no treatment (conditional recommendation) in patients with SAR.

Brief justification: In PAR, the benefits of OcAH outweigh the risks for harms, but the same does not happen in SAR. See online supplement for more details.

C. Questions with no change in recommendation directionality and/or strength in ARIA-EAACI 2024–2025.

9. Should oral H_1-antihistamines vs. no treatment be used for the treatment of allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_oral-06/

Context: OAH are one of the mainstays of the treatment of AR and are widely available.

Recommendation: In patients with AR, we recommend using OAH over no treatment. (Strong recommendation based on moderate certainty of evidence)

- Considerations in children and adolescents: The recommendation is applicable to children and adolescents.
- Implementation considerations: In LMIC, OAH in the WHO List of Essential Medicines and/or locally produced generics may be preferred.

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Brief justification: OAH are overall efficacious, safe, cost-effective and well-accepted by patients. See online supplement for details.

10. Should second-generation oral H_1-antihistamines vs. first-generation oral H_1-antihistamines be used for the treatment of allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_oral-07/

Context: First-generation OAHs are still frequently used in several countries, in part because of their low cost and over-the-counter availability. However, second-generation OAHs are associated with improved safety profiles and reduced sedation.

Recommendation: In patients with AR, we recommend using second-generation OAH over first-generation OAH (strong recommendation based on very low certainty of evidence).

- Considerations in children, adolescents and older adults: The recommendation is applicable to preschool-aged, school-aged children and older adults.
- Implementation considerations: See the implementation considerations for question number 1.

Brief justification: Second-generation OAH are safer and associated with higher patient satisfaction. See online supplement for more details.

11. Should intranasal H_1-antihistamines vs. oral H_1-antihistamines be used for the treatment of allergic rhinitis?

Link for the full EtD: https://aria.med.up.pt/etd_oral-08/

Context: While intranasal antihistamines (INAH) can have some benefits in terms of efficacy, OAH are more widely available and may have a higher acceptability.

Recommendation: In patients with AR, we suggest either using INAH or OAH (conditional recommendation based on moderate certainty of evidence).

- Considerations in children and adolescents: The recommendation is applicable to preschool and school-aged children
- Implementation considerations: None specific

Brief justification: INAH are associated with higher efficacy, but OAH present a lower risk of adverse events, higher affordability and acceptability. See online supplement for more details.

5 | Conclusions

In ARIA-EAACI 2024–2025, we formulated recommendations on eleven questions concerning oral or ocular treatments for AR. Overall, we suggest using INCS over second-generation OAH, and second-generation OAH over LTRA or OcAH. In addition, except in specific scenarios, we suggest against using LTRA or OcAH in untreated patients or as an addition to OAH. However, decisions on AR treatment should consider the clinical variability of the disease, patients' values and preferences, the affordability of treatment options, and planetary health considerations.

Questions on oral and ocular treatments had been previously addressed in past editions of the ARIA guidelines (see Box 2 and Table 4 for a comparison of recommendations of ARIA-EAACI 2024–2025 with those of the ARIA 2010/2016 guidelines). However, four questions were addressed for the first time in ARIA-EAACI 2024–2025, while, for four other questions, there was a change in the strength and/or directionality of recommendations.

Considering all recommendations, second-generation OAH are the preferred option among oral treatments for AR. Regarding individual second-generation OAH, the identified evidence did not indicate that a specific medication should be recommended over all others. Instead, we suggest a shared decision-making process considering criteria such as effectiveness, sedative effect, onset of action, affordability, availability and the patient's context and values. In these guidelines, we provide evidence on how the different second-generation OAH compare in relation to the aforementioned aspects.

By contrast, due to safety concerns and low effectiveness, LTRA should be restricted to specific situations, particularly for patients who are not well-controlled with OAH and have a strong preference for oral treatments and/or comorbid asthma. Overall, the addition of an LTRA to an OAH is discouraged. The addition of oral decongestants to OAH has not been evaluated in these guidelines, as the corresponding question has not been prioritised, and a rapid literature review by our team did not find new, relevant RCTs. ARIA 2010 recommended against using OAH + oral decongestants versus OAH alone [8] (Table 5 lists ARIA 2010 recommendations on oral treatments for which questions were not prioritised in ARIA-EAACI 2024–2025, namely oral decongestants and oral corticosteroids).

When considering intranasal versus oral treatments, we recommend INCS (but not INAH) over OAH, as the former are more effective. On the other hand, OAH may be preferred to the use of topical ocular treatments. In fact, these guidelines suggest against using topical ocular treatments except for achieving a fast relief of eye symptoms, in which case, the use of OcAH is suggested over that of mast cell stabilisers.

Based on the first ARIA guidelines [6] and on the algorithm of ARIA 2016 [29], when initiating a treatment, physicians and pharmacists often propose a short course of OAH in mild rhinitis patients or in those with corticosteroid-phobia [30, 31]. This approach does not contradict the ARIA-EAACI 2024–2025 recommendations, and a new algorithm will be proposed (and subsequently tested) in a later report of the ARIA-EAACI 2024–2025 guidelines.

Importantly, there are still knowledge gaps that would merit further research. Some of these gaps are common to those identified in the guidelines of intranasal treatments [18], including (i) lack of RCTs assessing patients with mild disease,

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TABLE 4 | Comparison of the recommendations on oral and ocular treatments of the ARIA 2024–2025 and of the ARIA 2010/2016 guidelines.

Question	Disease	Recommendation				
Should any specific OAH vs. other OAH be used for the treatment of AR?	PAR/ SAR	Strong recommendation against specific interventions	Conditional recommendation against specific interventions	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for specific interventions	Strong recommendation for specific interventions
Should OAH+LTRA vs. OAH be used for the treatment of AR?	SAR[a]	Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
Should OcAH vs. OAH be used for the treatment of ocular symptoms in patients with AR?	SAR[a]	Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
Should OcAH vs. mast cell stabilisers be used for the treatment of ocular symptoms in patients with AR?	SAR[a]	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
Should OAH vs. LTRA be used for the treatment of AR?	PAR	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
	SAR	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
Should INCS vs. OAH be used for the treatment of AR?	PAR/ SAR	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
Should LTRA vs. no treatment be used for the treatment of AR?	SAR[b]	Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
Should OcAH vs. no treatment be used for the treatment of ocular symptoms in patients with AR?	PAR	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
	SAR	Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
Should OAH vs. no treatment be used for the treatment of AR?	PAR/ SAR	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**[c]
Should second-generation OAH vs. first-generation OAH be used for the treatment of AR?	SAR[a]	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
Should INAH vs. OAH be used for the treatment of AR?	PAR/ SAR	Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention

Note: Recommendations of the ARIA 2024–2025 guidelines are highlighted by a shade in a cell; recommendations of the ARIA 2010/2016 guidelines are highlighted by a frame in a cell. Shade/frame colour code: Green = High certainty of evidence; Yellow = Moderate certainty of evidence; Orange = Low certainty of evidence; Red = Very low certainty of evidence.

Abbreviations: AR, allergic rhinitis; INAH, intranasal antihistamine; INCS, intranasal corticosteroid; LTRA, oral leukotriene receptor antagonists; OAH, oral H_1-antihistamines; OcAH, ocular H_1-antihistamines; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis.

[a]No evidence for PAR.

[b]No evidence for PAR. In ARIA 2010, the recommendation was conditional against the use of LTRA in patients with PAR.

[c]In ARIA 2010, the recommendation was strong for second-generation OAH that do not cause sedation and do not interact with cytochrome P450, and conditional for second-generation OAH that cause sedation and/or interact with cytochrome P450.

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BOX 2 | Summary of what is new in the ARIA-EAACI 2024–2025 guidelines in comparison to ARIA 2010/2016 guidelines.

New questions:

- Should any specific OAH vs. other OAH be used for the treatment of AR?
  - Recommendation: "In patients with AR, we suggest that the choice of specific OAH over others should be based on patients' preferences on efficacy and safety and on availability and affordability (conditional recommendation based on mostly very low certainty of evidence)."
- Should an OAH + LTRA vs. OAH be used for the treatment of AR?
  - Recommendation: "In patients with AR, we suggest using OAH over OAH+LTRA (conditional recommendation based on moderate certainty of evidence)." [a]
- Should OcAH vs. OAH be used for the treatment of ocular symptoms in patients with AR?
  - Recommendation: "In patients with AR, we suggest against using OcAH over OAH except for very fast relief of ocular symptoms (conditional recommendation based on very low certainty of evidence)."
- Should OcAH vs. ocular mast cell stabilisers be used for the treatment of ocular symptoms in patients with AR?
  - Recommendation: "In patients with AR, we suggest using OcAH over ocular mast cell stabilisers (conditional recommendation based on very low certainty of evidence)."

Questions with changed recommendation (in terms of directionality or strength):

- Should OAH vs. LTRA be used for the treatment of AR?
  - Recommendation changed from a *conditional recommendation in favour of either OAH or LTRA in seasonal AR* and a *conditional recommendation in favour of OAH in perennial AR* (2010/2016 guidelines) to a *strong recommendation in favour of OAH in both seasonal and perennial AR* (2024–2025 guidelines). [a]
- Should INCS vs. OAH be used for the treatment of AR?
  - Recommendation changed from a *conditional recommendation in favour of INCS* (2010/2016 guidelines) to a *strong recommendation in favour of INCS* (2024–2025 guidelines).
- Should LTRA vs. no treatment be used for the treatment of AR?
  - Recommendation changed from a *conditional recommendation in favour of LTRA in seasonal AR* and a *conditional recommendation against LTRA in perennial AR* (2010/2016 guidelines) to a *conditional recommendation against LTRA in both seasonal and perennial AR* (2024–2025 guidelines). [a]
- Should OcAH vs. no treatment be used for the treatment of ocular symptoms in patients with AR?
  - Recommendation changed from a *conditional recommendation in favour of OcAH* (2010/2016 guidelines) to a *conditional recommendation against OcAH in seasonal AR and a conditional recommendation in favour of OcAH in perennial AR*.

AR, allergic rhinitis; ARIA, allergic rhinitis and its impact on asthma; INCS, intranasal corticosteroids; LTRA, leukotriene receptor antagonists; OAH, oral H_1-antihistamines; OcAH, ocular H_1-antihistamines. [a]Recommendations suggesting against the use of LTRA reflect, in part, the risk of rare neuropsychiatric adverse events.

TABLE 5 | ARIA 2010 guideline recommendations for oral medications which have not been evaluated in ARIA-EAACI 2024–2025 guidelines (oral corticosteroids and oral decongestants).

Question	Recommendation
Should oral corticosteroids be used for treatment of AR in patients not responding to other therapy?	In patients with AR and moderate to severe nasal and/or ocular symptoms that are not controlled with other treatments, we suggest a short course of oral corticosteroids (conditional recommendation|very low-quality evidence).
Should oral decongestant be used for treatment of AR?	In patients with AR, we suggest that clinicians do **not** administer and patients do **not** use oral decongestants regularly (conditional recommendation|low-quality evidence).
Should a combination of oral decongestant and H_1-antihistamine versus oral H_1-antihistamine alone be used for treatment of AR?	In patients with AR, we suggest clinicians do **not** administer and patients do **not** use regularly a combination of oral H_1-antihistamine and an oral decongestant compared with oral H_1-antihistamine alone (conditional recommendation|moderate-quality evidence).

(ii) lack of evidence stratified according to the presence of comorbid asthma, or according to patients' age group, sex and ethnicity, and (iii) lack of cost-effectiveness studies or evidence on the planetary health of interventions. However, specific considerations should also be highlighted. In particular, there is less evidence informing recommendations on oral and ocular treatments in comparison to intranasal medications. Moreover, evidence on topical ocular treatments and on first-generation OAH tended to be of particularly low quality, with a limited number of available eligible RCTs: in the case of topical ocular treatments, most RCTs evaluate short periods of time and/or only the immediate effect after conjunctival allergen

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challenge; for first-generation OAH, most RCTs had been conducted prior to standardisation of outcome measurements. The scarce amount of evidence has resulted in downgrading the underlying certainty of evidence due to imprecision. Imprecision was also the certainty of evidence domain which was most frequently rated down in the NMA that informed the question comparing different individual OAH [24], pointing to the need for more and larger RCTs, particularly involving direct comparisons between active interventions.

As with the guidelines comparing intranasal treatments [18], we opted (i) not to present separate recommendations for SAR vs. PAR for most recommendations, and (ii) to refer to "perennial" or "seasonal AR" instead of "persistent" or "intermittent" AR (only a small amount of RCTs used the persistent/intermittent classification) [32–34]. In addition, we did not explore variations in the dosage or patterns of use (as-needed versus regular) of treatments, as these questions will be addressed in future documents of the ARIA-EAACI 2024–2025 guidelines.

These guidelines have limitations. For desirable and undesirable effects, evidence was mostly obtained from RCTs, in most cases with (i) an overrepresentation of patients with more severe AR, and (ii) a sample size and a follow-up period that are too limited to detect serious but rare adverse events. This latter aspect is particularly relevant in the evaluation of LTRA. In addition, most included RCTs do not present stratified results for several relevant variables, including the presence of comorbid asthma. Finally, for OAH, several pivotal studies have evaluated only three nasal symptoms, excluding nasal congestion. The systematic reviews informing these guidelines have not considered these studies (even though this may result in a smaller number of included primary studies per OAH), (i) as nasal congestion is valued by patients as the most important symptom [20] and (ii) in order to ensure consistency within the different parts of the ARIA 2024–2025 guidelines.

There are also important strengths associated with ARIA-EAACI 2024–2025. We have followed the GRADE approach, using EtDs to develop recommendations. In addition, we have used several approaches to formulate guideline questions and considered different data sources. The ARIA-EAACI 2024–2025 guidelines have a global scope and recommendations have implementation considerations for LMIC. In addition to these considerations, the links of the EtD display maps informing about the most affordable medications in different countries. Finally, we have conducted several systematic reviews and meta-analyses to provide updated evidence on the desirable and undesirable effects of interventions.

In conclusion, this article of the ARIA-EAACI 2024–2025 guidelines focuses on oral and ocular treatments for the management of AR. It has been developed following the GRADE approach and considering evidence from a comprehensive set of evidence from multiple sources, such as systematic reviews of RCTs, mHealth data and a survey of experts.

Author Contributions

Bernardo Sousa-Pinto, Jean Bousquet, Holger J. Schünemann and Torsten Zuberbier were responsible for the coordination of the project (as members of the ARIA 2024–2025 guidelines steering committee) and contributed to the methodology (including evidence synthesis and analysis), the discussion of the evidence and the drafting of recommendations (as members of the ARIA 2024–2025 guideline panel) and writing the manuscript. Rafael José Vieira and Antonio Bognanni contributed to the methodology (including evidence synthesis and analysis), discussion of the evidence and drafting of recommendations (as members of the ARIA 2024–2025 guideline panel) and writing the manuscript. Arunas Valiulis, Sian Williams, Anna Bedbrook, Maria Jose Torres, G. Walter Canonica, Leticia de las Vecillas, Mark S. Dykewicz, Cristina Jacomelli, Ludger Klimek, Lucas Leemann, Olga Lourenço, Nikolaos G. Papadopoulos, Ana Margarida Pereira, Marine Savouré, Sanna K. Toppila-Salmi, Maria Teresa Ventura, Juan José Yepes-Nuñez, Elena Azzolini, Gilles Louis, Elena Parmelli and Jaron Zuberbier contributed to the discussion of the evidence and drafting of recommendations (as members of the ARIA 2024–2025 guideline panel) and writing the manuscript. Rita Amaral, Sara Gil-Mata, Manuel Marques-Cruz, Ewa Borowiack, Raquel Albuquerque Costa, Henrique Pereira, Renato Ferreira-da-Silva, Despo Ierodiakonou, Justyna Litynska, Inês Ribeiro-Vaz, Ewelina Sadowska, Tuuli Thomander and João A. Fonseca contributed to the methodology (including evidence synthesis and analysis) and revising and editing the manuscript. All other authors were part of the international panel revising the recommendations, contributing to the guidelines by providing feedback to the recommendations and revising and editing the manuscript.

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Conflicts of Interest

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Data Availability Statement

The authors have nothing to report.

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