

Guidelines

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision

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Background: Allergic rhinitis (AR) affects 10% to 40% of the population. It reduces quality of life and school and work performance and is a frequent reason for office visits in general practice. Medical costs are large, but avoidable costs associated with lost work productivity are even larger than those incurred

by asthma. New evidence has accumulated since the last revision of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines in 2010, prompting its update.

Objective: We sought to provide a targeted update of the ARIA guidelines.

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Methods: The ARIA guideline panel identified new clinical questions and selected questions requiring an update. We performed systematic reviews of health effects and the evidence about patients' values and preferences and resource requirements (up to June 2016). We followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence-to-decision frameworks to develop recommendations.

Results: The 2016 revision of the ARIA guidelines provides both updated and new recommendations about the pharmacologic treatment of AR. Specifically, it addresses the relative merits of using oral H₁-antihistamines, intranasal H₁-antihistamines, intranasal corticosteroids, and leukotriene receptor antagonists either alone or in combination. The ARIA guideline panel provides specific recommendations for the choice of treatment and the rationale for the choice and discusses specific considerations that clinicians and patients might want to review to choose the management most appropriate for an individual patient.

Conclusions: Appropriate treatment of AR might improve patients' quality of life and school and work productivity. ARIA recommendations support patients, their caregivers, and health care providers in choosing the optimal treatment. (*J Allergy Clin Immunol* 2017;■■■:■■■-■■■.)

Key words: Allergic rhinitis, practice guideline

Allergic rhinitis (AR) is among the most common diseases globally and usually persists throughout life.¹ The prevalence of self-reported AR has been estimated to be approximately 2% to 25% in children² and 1% to greater than 40% in adults.^{1,3} The prevalence of confirmed AR in adults in Europe ranged from 17% to 28.5%. Recent studies show that the prevalence of AR has increased in particular in countries with initial low prevalence (for a discussion of prevalence of AR, see section 5.1-5.2 in Allergic Rhinitis and its Impact on Asthma [ARIA] 2008 Update¹). Classical symptoms of AR are nasal itching, sneezing, rhinorrhea, and nasal congestion. Ocular symptoms are also frequent; allergic rhinoconjunctivitis is associated with itching and redness of the eyes and tearing. Other symptoms include itching of the palate, postnasal drip, and cough.

AR is also frequently associated with asthma, which is found in 15% to 38% of patients with AR,^{4,5} and nasal symptoms are present in 6% to 85% of patients with asthma.⁶⁻⁹ In addition, AR is a risk factor for asthma,^{4,9} and uncontrolled moderate-to-severe AR affects asthma control.^{10,11}

Compared with other medical conditions, AR might not appear to be serious because it is not associated with severe morbidity and mortality. However, the burden and costs are substantial.¹² AR reduces the quality of life of many patients, impairing sleep quality and cognitive function and causing irritability and fatigue. AR is associated with decreased school and work performance, especially during the peak pollen season.¹ AR is a frequent reason for general practice office visits. Annual direct medical costs of AR are substantial, but indirect costs associated with lost work productivity are greater than those incurred by asthma.¹³⁻¹⁵ Appropriate treatment of AR improves symptoms, quality of life, and work and school performance.

Clinical practice guidelines for AR management were developed over the past 20 years¹⁶ and have improved the care of

Abbreviations used

AR:	Allergic rhinitis
ARIA:	Allergic Rhinitis and its Impact on Asthma
EtD:	Evidence to decision
GRADE:	Grades of Recommendation, Assessment, Development, and Evaluation
ICP:	Integrated care pathway
PAR:	Perennial allergic rhinitis
SAR:	Seasonal allergic rhinitis
SMD:	Standardized mean difference

patients with AR.¹⁷ However, transparent reporting of guidelines to facilitate understanding and acceptance are needed. The ARIA initiative was initiated during a World Health Organization workshop in 1999¹⁸ and updated in 2008.¹ The ARIA 2010 revision was the first evidence-based guideline in allergy to follow the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach¹⁹ with no influence of for-profit organizations and an explicit declaration and management of potential competing interests of panel members.²⁰ It summarized the potential benefits and harms underlying the recommendations, as well as assumptions around values and preferences that influenced the strength and direction of the recommendations. In 2014, the ARIA revision was found to rank first in the rigor of development and quality of reporting of guidelines about the management of AR,¹⁶ although recent guidelines published later were not considered.²¹

CLINICAL QUESTIONS

Since the last revision of the ARIA guidelines in 2010,²⁰ new treatments have become available, and new evidence has accumulated about selected other treatments. By using a modified Delphi process, the ARIA guideline panel selected new questions that required answering with recommendations or the existing recommendations that required an updated review of the evidence and potentially updating the recommendations themselves. Therefore this revision of the ARIA guidelines is limited in scope and addresses 6 questions about the treatment of AR:

1. Should a combination of oral H₁-antihistamine and intranasal corticosteroid versus intranasal corticosteroid alone be used for treatment of AR?
2. Should a combination of intranasal H₁-antihistamine and intranasal corticosteroid versus intranasal corticosteroid alone be used for treatment of AR?
3. Should a combination of an intranasal H₁-antihistamine and an intranasal corticosteroid versus intranasal H₁-antihistamine alone be used for treatment of AR?
4. Should a leukotriene receptor antagonist versus an oral H₁-antihistamine be used for treatment of AR?
5. Should an intranasal H₁-antihistamine versus an intranasal corticosteroid be used for treatment of AR?
6. Should an intranasal H₁-antihistamine versus an oral H₁-antihistamine be used for treatment of AR?

The target audience of these guidelines is primary care clinicians, school nurses, pharmacists, specialists in allergy and clinical immunology, general internists managing patients with AR, and pediatricians. Ear-nose-throat specialists, other health

care professionals, and health care policy makers can also benefit from these guidelines.

CLASSIFICATION OF AR

The classification of AR was revised by ARIA in 2001. A major change was the introduction of the terms “intermittent” and “persistent.”¹⁸ Before then, AR was classified, based on the time and type of exposure and symptoms, into seasonal allergic rhinitis (SAR; most often caused by outdoor allergens, such as pollens or molds), perennial allergic rhinitis (PAR; most frequently, although not necessarily, caused by indoor allergens such as house dust mites, molds, cockroaches, and animal dander), and occupational allergic rhinitis.^{22,23} With very few exceptions, published studies refer to SAR and PAR and enroll patients based on the offending allergen (pollen, house dust mites, or both), and we retained the terms SAR and PAR to enable the interpretation of published evidence.

The recommendations in the ARIA 2016 update apply directly to patients with moderate-to-severe AR. They might be less applicable to treatment of patients with mild AR who frequently do not seek medical help and manage their symptoms themselves with medications available over the counter.

RECOMMENDATIONS FOR CHILDREN

Almost all studies used to answer the questions in this update of the ARIA guidelines included exclusively adult patients. However, careful extrapolation to the pediatric population can be attempted. One can assume that the relative effects of treatment of AR are likely similar among adults and children, but adverse effects might be more or less frequent, and their perception and importance might be different (eg, bitter taste). Values and preferences for specific outcomes and treatments can also vary between adults and children.

METHODOLOGY

The full description of methods used to develop recommendations in these guidelines is described in the [Methods](#) section of the full version of the guideline document (see [Online Repository item E1](#) in this article's Online Repository at www.jacionline.org). Here we describe briefly the methodology to facilitate the interpretation of the guidelines.

Questions and outcomes of interest

The scope and questions for this update of the ARIA guidelines were identified by the ARIA guideline panel members. The guideline panel deemed the following outcomes to be important to patients: nasal and ocular symptoms, quality of life, work/school performance, and adverse effects. As for the previous revision of the ARIA guidelines, we did not formally assess the relative importance of each outcome of interest (ie, which outcomes are more and which are less important) but rather adopted the rating agreed upon by the guideline panel according to the structured discussion.²⁴ In general, combined nasal symptoms, ocular symptoms, quality of life, work/school performance, and serious adverse effects were considered critical to the decision, and individual symptoms, a composite outcome of all adverse effects and adverse effects that were not serious or did

not lead to discontinuation of treatment, were considered important but not critical (see evidence profiles in [Online Repository item E2](#) in this article's Online Repository at www.jacionline.org).

Evidence review and development of clinical recommendations

For each question, the methodology group performed a full systematic review of the literature to identify and summarize evidence about the effects of interventions on the outcomes of interest. We also searched systematically for information about patients' values and preferences and resource use (cost). We systematically searched the Medline, Embase, and Cochrane CENTRAL electronic databases. Titles and abstracts and subsequently full-text articles were screened in duplicate to assess eligibility according to prespecified criteria. Panel members were contacted to confirm completeness of the body of evidence and suggest additional articles that might have been missed in electronic searches.

To obtain the estimates of effects on each outcome of interest, we performed meta-analyses using the Cochrane Collaboration Review Manager Software, version 5.3.5.²⁵ We prepared evidence summaries (see [Online Repository item E2](#)) for each question according to the GRADE approach¹⁹ by using the GRADEpro Guideline Development Tool online application (www.gradepro.org).

When continuous outcomes (eg, symptom scores or quality of life) are measured by using different scales, the results can only be combined in meta-analysis by using the standardized mean difference (SMD), which is expressed in SD units.²⁶ Results expressed as an SMD are challenging to interpret. To facilitate understanding, we used interpretation of the effect size according to Cohen conventional criteria²⁷: an SMD of around 0.2 is considered a small effect, an SMD of around 0.5 is considered a moderate effect, and an SMD of around 0.8 or higher is considered a large effect. We used this interpretation throughout this document when we referred to effects of interventions as small, moderate, or large.

We assessed the risk of bias at the outcome level by using the Cochrane Collaboration's risk of bias tool.²⁸ Subsequently, we assessed the certainty of the body of evidence (ie, confidence in the estimated effects, which is also known as “quality of the evidence”) for each of the outcomes of interest according to the GRADE approach²⁹ based on the following criteria: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of a dose-effect relationship, and assessment of the effect of residual opposing confounding. Certainty of the evidence was categorized into 4 levels: high, moderate, low, and very low.

For each question, we summarized all information in evidence-to-decision (EtD) frameworks (see [Online Repository item E2](#)) that included concise description of desirable and undesirable health effects, certainty of the evidence about those effects, evidence and assumptions about patients' values and preferences, required resources and cost-effectiveness, potential influence on health equity, acceptability of the intervention to various stakeholders, and feasibility of implementation.³⁰ Judgments about all these factors and suggested recommendations in EtD frameworks were drafted by J.L.B., who was also a clinical expert.

EtDs for all questions were reviewed by the ARIA guideline panel members, who provided feedback by means of electronic communication and during a face-to-face meeting of Integrated Care Pathways for Airway Diseases (AIRWAYS ICPs)^{31,32} and Frailty European Innovation Partnership on Active and Healthy Ageing Reference Sites in Lisbon, Portugal on July 1, 2015.³³ All comments were addressed, and the frameworks were modified accordingly. Modified EtD frameworks that included judgments about the research evidence, additional considerations of ARIA panel members, and draft recommendations were sent to all ARIA panel members for review and approval or disapproval and comments by using the online SurveyMonkey software (www.surveymonkey.com). We recorded and addressed all agreements/disagreements, comments, and suggestions for changes. We present the final EtD frameworks in [Online Repository item E2](#).

Recommendations and their strength were decided by consensus. The ARIA guideline panel agreed on the final wording of recommendations and remarks with further qualifications for each recommendation. The final document, including the recommendations, was reviewed and approved by all members of the guideline panel.

According to the GRADE approach, the recommendations can be either “strong” or “conditional” depending on the guideline panel’s confidence that following the recommendation would bring more good than harm to patients. The wording of recommendations reflects their strength, and one can use the terms “we recommend” for strong recommendations and “we suggest” for conditional recommendations. [Box 1](#) provides suggested interpretation of strong and conditional recommendations.

Recommendations

We present all recommendations in [Table I](#). We provide the rationale for the recommendations and the consideration of all factors that influenced the recommendations: effects on all important health outcomes, certainty of the available evidence, values and preferences, acceptability by stakeholders, requirements for resources, feasibility, and any issues of health equity in the unabridged guideline document in [Online Repository item E1](#). Detailed summaries of the evidence supporting each recommendation and the guideline panel judgements are shown in [Online Repository item E2](#).

How to use these guidelines

The ARIA guidelines about treatment of AR are not intended to impose a standard of care for individual countries. They provide the basis for rational informed decisions for patients, parents, clinicians, and other health care professionals. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should not view these recommendations as dictates. Recommendations provide guidance for typical patients; no recommendation can take into account all of the often-compelling unique individual circumstances. Thus, no one charged with evaluating health care professionals’ actions should apply the recommendations from these guidelines by rote or in a blanket fashion.

Statements regarding the underlying values and preferences, as well as qualifying remarks accompanying each recommendation,

Box 1. Strength of recommendation

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 health care policy makers: The recommendation can be adopted as a policy or performance measure in most situations.

Conditional recommendation

For patients: The majority of patients in this situation would want the suggested course of action, but many would not.

For clinicians: Recognize 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 health care policy makers: Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (eg, shared) decision-making processes can serve as a performance measure.

should never be omitted when quoting or translating recommendations from these guidelines.

CONCLUSIONS

Evidence-based guidelines are at the cornerstone of integrated care pathways (ICPs),^{31,32} structured multidisciplinary care plans that promote translation of guideline recommendations into local protocols and their subsequent application in clinical practice. Usually, several guidelines are available providing advice about the management of the same condition.¹⁶ It is important to wisely choose appropriate guidelines for local adaptation and creation of ICPs because most of them have limitations because of either the development of the guideline itself or the available research evidence and its interpretation. The most common limitations of guidelines in AR are narrowness in scope (addressing only a small selection of important questions about the management of a given condition), suboptimal rigor of development and reporting, and inadequate representation of the views of patients and their caregivers.¹⁶ We acknowledge that for the ARIA 2016 update, we have not reviewed all recommendations from the ARIA 2010 guidelines. However, we updated only 3 recommendations suggested by the ARIA panel members as requiring the update, and we addressed 3 new questions. We also acknowledge that the ARIA guideline panel included allergists, ear-nose-throat specialists, pulmonologists, general practitioners, and pediatricians but did not include other health care professionals, pharmacists, and patients themselves. However, for the ARIA 2016 update, we systematically searched and reviewed the published evidence about the patients’ values and preferences regarding the outcomes and treatments for AR that to certain degree helped to overcome this limitation. We summarized the results in the section about the assumed

TABLE I. Recommendations

Recommendation	Assumed values and preferences	Explanations and other considerations
Question 1: Should a combination of an oral H1-antihistamine (OAH) and intranasal corticosteroid (INCS) vs INCS alone be used for treatment of AR?		
Recommendation 1A: In patients with SAR, we suggest either a combination of an INCS with an OAH or an INCS alone (conditional recommendation low certainty of evidence).	ARIA guideline panel acknowledged that the choice of treatment would depend mostly on patient preferences and local availability and cost of treatment. Panel members assumed that in the majority of situations, potential net benefit would not justify spending additional resources.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. In settings in which the additional cost of an OAH is not large and/or patients' values and preferences differ from those assumed by guideline panel members, a combination therapy might be a reasonable choice, especially in patients whose symptoms are not well controlled with an INCS alone, those with pronounced ocular symptoms, or those commencing treatment because of likely faster onset of treatment effects. This recommendation concerns regular use of newer and less sedative OAHs and INCSs in patients with SAR. For older OAHs with more sedative effects, the balance of desirable and undesirable effects may be different.
Recommendation 1B: In patients with PAR, we suggest an INCS alone rather than a combination of an INCS with an OAH (conditional recommendation very low certainty of evidence).	—	Currently available evidence suggests that there is no additional benefit from a combination therapy compared with INCS alone, and there might be additional undesirable effects. This recommendation is conditional because of sparse information and thus very low certainty of the estimated effects.
Question 2: Should a combination of an intranasal H₁-antihistamine (INAH) and INCS vs an INCS alone be used for treatment of AR?		
Recommendation 2A: In patients with SAR, we suggest either a combination of an INCS with an INAH or an INCS alone (conditional recommendation moderate certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. At initiation of treatment (approximately the first 2 weeks), a combination of an INCS with an INAH might act faster than an INCS alone and thus might be preferred by some patients.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. In settings in which the additional cost of combination therapy is not large and/or patients value potential benefits more than any increased risk of adverse effects, a combination therapy might be a reasonable choice.
Recommendation 2B: In patients with PAR, we suggest either a combination of an INCS with an INAH or an INCS alone (conditional recommendation very low certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.	This is a conditional recommendation because of the very low certainty of the evidence. At the initiation of treatment (approximately the first 2 weeks), combination of an INCS with an INAH might act faster than an INCS alone and thus might be preferred by some patients.
Question 3: Should a combination of an INAH and INCS vs an INAH alone be used for treatment of AR?		
Recommendation 3A: In patients with SAR, we suggest a combination of an INCS with an INAH rather than an INAH alone (conditional recommendation low certainty of evidence).	This recommendation places higher value on additional reduction of symptoms and improved quality of life with a combination therapy compared with an INAH alone. It places a lower value on avoiding additional cost (expenditure of resources).	This is a conditional recommendation, and thus different choices will be appropriate for different patients. In settings in which the additional cost of a combination therapy is large, an alternative choice (ie, an INAH alone) might be equally reasonable. One panel member thought that the recommendation should be conditional for either the intervention or comparison.
Question 4: Should a leukotriene receptor antagonist (LTRA) vs an OAH be used for treatment of AR?		
Recommendation 4A: In patients with SAR, we suggest either an LTRA or an OAH (conditional recommendation moderate certainty of evidence).	Panel members acknowledged that the choice of an LTRA or OAH will mostly depend on patient preferences and local availability and cost of specific medications. In many settings an OAH might still be more cost-effective, but this will largely depend on availability of generic LTRAs and the local cost of various newer-generation OAHs and LTRAs.	Some patients with AR who have concomitant asthma, especially exercise-induced and/or aspirin-exacerbated respiratory disease, might benefit from an LTRA more than from an OAH. However, this recommendation applies to treatment of AR but not to treatment of asthma. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.

(Continued)

TABLE I. (Continued)

Recommendation	Assumed values and preferences	Explanations and other considerations
Recommendation 4B: In patients with PAR, we suggest an OAH rather than a LTRA (conditional recommendation low certainty of evidence).	This recommendation places a higher value on possibly larger improvement of symptoms and quality of life with an OAH compared with an LTRA. It places a lower value on possible increased risk of somnolence.	This is a conditional recommendation, and thus different choices will be appropriate for different patients based on their preferences for reduction of symptoms vs avoiding the risk of adverse effects. This might be more important for patients with PAR than those with SAR because they might use those medications for longer periods of time. Some patients with AR and concomitant asthma, especially exercise-induced and/or aspirin-exacerbated respiratory disease, might benefit from an LTRA more than from an OAH. However, this recommendation applies to treatment of AR but not to treatment of asthma. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.
Question 5: Should an INAH vs an INCS be used for treatment of AR?		
Recommendation 5A: In patients with SAR, we suggest an INCS rather than an INAH (conditional recommendation moderate certainty of evidence).	This recommendation places a higher value on likely small but greater reduction of symptoms and improvement of quality of life with an INCS compared with an INAH and a lower value on avoiding larger cost of treatment with an INCS in many jurisdictions.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. Clinicians must help each patient to arrive at a decision consistent with her or his values and preferences, considering local availability and costs.
Recommendation 5B: In patients with PAR, we suggest an INCS rather than an INAH (conditional recommendation low certainty of evidence).	This recommendation places a higher value on probably greater reduction of nasal symptoms with an INCS compared with an INAH, although the overall difference is likely small. It places a lower value on avoiding larger cost of treatment with an INCS in many jurisdictions.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. Clinicians must help each patient to arrive at a decision consistent with her or his values and preferences, considering local availability and costs.
Question 6: Should an INAH vs an OAH be used for treatment of AR?		
Recommendation 6A: In patients with SAR, we suggest either an INAH or OAH (conditional recommendation low certainty of evidence).	The panel members acknowledged that the choice of treatment will depend mostly on patient preferences and local availability and cost of treatment.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. Clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.
Recommendation 6B: In patients with PAR, we suggest either an INAH or OAH (conditional recommendation very low certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. Clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.

INAH, Intranasal H₁-antihistamine; INCS, intranasal corticosteroid; LTRA, leukotriene receptor antagonist; OAH, oral H₁-antihistamine.

values and preferences in the full text of the ARIA 2016 update (see [Online Repository item E1](#)) and in the relevant sections of EtD tables (see [Online Repository item E2](#)).

The available evidence has important limitations: (1) selective measurement and reporting of outcomes (eg, few studies properly measure and report quality of life, which is the most important outcome in patients with AR), (2) selection of patients for clinical trials that might not represent appropriately the patients seen in primary care,³⁴ and (3) not distinguishing between patients with different age or severity of symptoms (lack of proper stratification),³⁵ thus limiting the applicability and generalizability of the research findings. Given these limitations, clinical practice guidelines, especially those with international audience, should emphasize rigorous systematic review of the health effects and explicit and detailed description of the assumed values and

preferences and considerations of cost, feasibility, acceptability, and health equity issues because it is currently following the GRADE EtD frameworks.³⁶⁻³⁸ Such detailed, explicit, and transparent reporting of guidelines facilitates local adaptation of recommendations and their translation into ICPs. Systematic and transparent summaries of the evidence clearly identifying gaps in available research evidence are needed to direct the research agenda and to avoid unnecessary expenditure of resources for further clinical research when it is not necessary.³⁹

Implementation of guidelines in different settings and countries depends on the availability of health interventions (eg, medical tests, medications, and equipment), availability of resources, and cultural differences, among others. Thus local adaptation of recommendations can be required, and ICPs need to be developed at the national, regional, or local level. However,

they should always be based on systematically reviewed evidence of desirable and undesirable consequences. The ARIA 2016 revision will be used to develop the ICPs proposed by the European Innovation Partnership on Active and Healthy Ageing^{31,32,40} by using MASK (MACVIA-ARIA Sentinel Network). ARIA is developing a novel implementation strategy using mobile technology^{41,42} and a clinical decision support system⁴¹ that is deployed in 21 countries.⁴³ The ARIA 2016 revision will be embedded in the clinical decision support system for real-time patient stratification by using mobile technology.

Most of the recommendations are based on low- or very low-certainty evidence, mainly because of the imprecision of the estimated effects due to few patients being studied. For those questions, there is a need for more well-designed and executed randomized controlled trials that would measure and properly report all important outcomes.

Clinical implications: The 2016 revision of the ARIA guidelines offers updated advice for clinicians and patients about the most commonly used treatments for AR.

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Online Repository 1: Unabridged full text of the guideline document

Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines – 2016 Revision (unabridged full text)

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Introduction

Since the last revision of the ARIA guidelines in 2010 ¹ new treatments became available and new evidence accumulated about selected other treatments. The ARIA guideline panel determined new questions that required answering with recommendations or the existing recommendations that required updated review of the evidence and potentially updating the recommendations themselves.

Clinical practice guidelines for AR management were developed over the past 20 years ² and have improved the care of patients with AR ³. Transparent reporting of guidelines to facilitate understanding and acceptance are however needed. The ARIA (Allergic Rhinitis and its Impact on Asthma) initiative was initiated during a WHO workshop in 1999 ⁴. It was updated in 2008 ⁵. The ARIA 2010 Revision was the first chronic respiratory disease evidence-based guideline to follow the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach ⁶ with no influence of for-profit organizations and an explicit declaration and management of potential competing interests of panel members ¹. It summarized the potential benefits and harms underlying the recommendations as well as assumptions around values and preferences that influenced the strength and direction of the recommendations. In 2014, the ARIA 2010 Revision was found to rank first in the rigor of development and quality of reporting of guidelines about the management of AR ² although recent guidelines published later were not considered ⁷.

Allergic rhinitis

Allergic rhinitis (AR) is defined clinically by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to an offending allergen. Symptoms of rhinitis include rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip that are reversible spontaneously or with treatment. Allergic rhino-conjunctivitis often accompanies AR.

Allergic rhinitis (AR) is among the most common diseases globally and usually persists throughout life ⁵. The prevalence of AR has been estimated to be approximately 2 to 25% in children⁸ and 1 to over 40% in adults^{5, 9}. The prevalence of confirmed AR in adults in Europe ranged from 17% to 28.5%. Recent studies show that the prevalence of AR has increased, in particular in countries with initial low prevalence (for a discussion of prevalence of AR see section 5.1.–5.2. in ARIA 2008 Update⁵). Classical symptoms of AR are nasal itching, sneezing, rhinorrhea, and nasal congestion. Ocular symptoms are also frequent; allergic rhino-conjunctivitis is associated with itching and redness of the eyes and tearing. Other symptoms include itching of the palate, postnasal drip and cough. AR is also frequently associated with asthma which is found in 15% to 38% of patients with allergic rhinitis^{10, 11} and that nasal symptoms are present in 6% to 85% patients with asthma¹²⁻¹⁵. In

addition AR is a risk factor for asthma^{10, 15} and uncontrolled moderate/severe AR impacts asthma control^{16, 17}.

Compared to other medical conditions, AR may appear not to be serious because it is not associated with a high morbidity and mortality. However, the burden and costs are still substantial¹⁸. AR symptoms are associated with decreased quality of life, sleep quality, energy levels, and ability to focus (see sections 5.3 to 5.7 in the ARIA 2008 Update)⁵. The prevalence of AR has been estimated to be approximately 10 to 20% in the population (see sections 5.1 and 5.2 in the ARIA 2008 Update). AR is one of the main reasons for general practice office visits. Annual direct medical costs of AR in the United States alone have been estimated at from \$0.8 billion in 1987 to \$4.5 billion in 1997¹⁹⁻²². Indirect costs associated with AR, including days missed from work or school and decreased productivity at work, were estimated to range from \$2.4 billion to \$4.6 billion in 1995²³. Annual indirect costs associated with lost work productivity may be greater than those incurred by asthma²⁴⁻²⁶. An appropriate treatment of AR improves symptoms, quality of life, and work and school performance.

Classification of allergic rhinitis

The classification of AR was revised by ARIA in 2001⁴. A major change was the introduction of the terms "intermittent" and "persistent". Currently ARIA classifies allergic rhinitis according to:

1. Duration of symptoms:

Intermittent – symptoms are present less than 4 days a week or for less than 4 weeks.

Persistent – symptoms are present at least 4 days a week and for at least 4 weeks.

2. Severity of symptoms (sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, and troublesome symptoms):

Mild – none of the above is present.

Moderate-severe – at least one of the above is present.

A modification of the ARIA severity classification has been proposed.²⁷

The recommendations in the ARIA 2016 update apply directly to patients with moderate-severe AR. They may be less applicable to treatment of patients with mild AR who frequently do not seek medical help and manage their symptoms themselves with medications available over-the-counter.

Allergic rhinitis has been traditionally subdivided into *seasonal*, *perennial*, and *occupational* rhinitis²⁸.²⁹ *Seasonal allergic rhinitis* (SAR) is most often caused by outdoor allergens such as pollens or molds. *Perennial allergic rhinitis* (PAR) is most frequently, although not necessarily, caused by indoor allergens such as house dust mites, molds, cockroaches, and animal dander.

With very few exceptions published studies refer to *seasonal* and *perennial* allergic rhinitis and enroll patients based on the offending allergen rather than based on the severity of symptoms. In this

document, as in the previous editions of ARIA guidelines ^{1, 4, 5}, **we retained the terms *seasonal* and *perennial* allergic rhinitis to enable the interpretation of published evidence.**

Approval of medications for specific indications

The ARIA guidelines represent international effort and are meant to help patients and health care professionals worldwide. Thus, we explicitly decided not to take into consideration the approval status of individual medications in specific countries. We encourage health care professionals and local organizations to consider those issues and, when needed, perform explicit adaptation of the ARIA guidelines to country-specific circumstances, local costs and community values and preferences (see section on Adaptation at the end of this document).

Scope and purpose

The purpose of this document is to provide guidance about the management of adults and children with allergic rhinitis. The recommendations in this document do not apply to treatment of other types of rhinitis (i.e. non-allergic) or complications of allergic rhinitis (e.g. sinusitis).

This targeted revision of the ARIA guidelines is an update of the ARIA Revision 2010 ¹ and is limited in scope. It addresses only 6 questions related to treatment of AR that were identified by the ARIA guideline panel. These questions either have not been asked in ARIA 2010 or the panel determined that they required updating owing to new evidence being available:

1. Should a combination of oral H1-antihistamine (OAH) and intranasal corticosteroid (INCS) vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?
2. Should a combination of intranasal H1-antihistamine (INAH) and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?
3. Should a combination of an intranasal H1-antihistamine and an intranasal corticosteroid vs. intranasal H1-antihistamine alone be used for treatment of allergic rhinitis?
4. Should a leukotriene receptor antagonist (LTRA) vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?
5. Should an intranasal H1-antihistamine vs. an intranasal corticosteroid be used for treatment of allergic rhinitis?
6. Should an intranasal H1-antihistamine vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?

Target audience

The target audience of these guidelines is primary care clinicians, school nurses, pharmacists, and specialists in allergy and clinical immunology. General internists managing patients with allergic rhinitis, pediatricians, ear-nose-throat specialists, other health care professionals, and health care

policy makers may also benefit from these guidelines. This document may also serve as the basis for local adaptation and implementation (see Adaptation section at the end of this document).

Methods

Panel composition

This guideline was developed by a multidisciplinary panel that consisted of 44 members including allergists, ENT specialists, pulmonologists, general practitioners and pediatricians. The committee worked with the methodology group with experience in evidence synthesis and guideline development from McMaster University in Hamilton, Ontario, Canada.

The ARIA guideline panel members were: Ioana Agache, Claus Bachert, Sinthia Bosnic-Anticevich, Jean Bousquet (Chair), Jan Brożek (non-voting member), Giorgio Walter Canonica, Thomas Casale, Niels Chavannes, Jaime Correia da Sousa, Alvaro Cruz, Pascal Demoly, Mark Dykewicz, Wytke Fokkens, Joao Fonseca, Peter Hellings, Ludger Klimek, Piotr Kuna, Désirée Larenas Linnemann, Karin Lødrup Carlsen, PJ Manning, Eli Meltzer, Joaquim Mullol, Antonella Muraro, Robyn O’Hehir, Ken Ohta, Petr Panzner, Nikolaos Papadopoulos, Hae-Sim Park, Gianni Passalacqua, Ruby Pawankar, David Price, Dermot Ryan, Boleslaw Samolinski, Peter Schmid-Grendelmeier, Holger Schünemann (non-voting member), Aziz Sheikh, Alkis Togias, Antonio Valero, Arunas Valiulis, Erkka Valovirta, Dana Wallace, Suzan Wasserman, Magnus Wickman, Luo Zhang, Mihaela Zidarn, and Torsten Zuberbier.

Conflict of interest declaration and management

Committee members disclosed all potential conflicts of interest according to the World Health Organization policies. The declarations were reviewed and classified as no potential conflict or the interest is irrelevant or insignificant, manageable conflicts of interest, or disqualifying conflict of interest. One guideline panel member was excused from participation in the process owing to disqualifying conflict. Summary of the declarations of actual, potential or perceived conflicts of interest are provided at the end of this document. Members of the methodology group did not participate in the decision-making process and JLB and HJS were non-voting members of the panel, but they suggested the initial direction of the recommendation based on established criteria. The ARIA initiative provided US\$40,000 of financial support to McMaster University to perform all systematic reviews. The views and interests of any commercial entity that might have provided external funding for ARIA initiative had no influence on the final recommendations and their names have not been revealed to the methodologists.

Clinical questions and outcomes of interest

The scope and questions for this targeted update of the ARIA guidelines were identified by the ARIA guideline panel members. The guideline panel deemed the following outcomes to be

important to patients: nasal and ocular symptoms, quality of life, work/school performance, and adverse effects. As for the previous revision of the ARIA guidelines we did not formally assess the relative importance of each outcome of interest (i.e. which outcomes are more and which are less important) but rather adopted the rating agreed upon by the guideline panel following the structured discussion³⁰. In general, combined nasal symptoms, ocular symptoms, quality of life, work/school performance, and serious adverse effects were considered to be critical to the decision, and individual symptoms, a composite outcome of any adverse effects, adverse effects that were not serious or did not lead to discontinuation of treatment were considered important but not critical (see evidence profiles in Online Repository 2).

Evidence review and development of clinical recommendations

For each question the methodology group performed a full systematic review of the literature to identify and summarize the evidence about the effects of interventions on the outcomes of interest. We also systematically searched for the information about patients' values and preferences, and resource use (cost). We systematically searched Medline, Embase and Cochrane CENTRAL electronic databases. Titles and abstracts, and subsequently full-text articles were screened in duplicate to assess eligibility according to pre-specified criteria. Panel members were contacted to confirm completeness of the body of evidence and suggest additional articles that might have been missed in electronic searches.

To obtain the estimates of effects on each outcome of interest we performed meta-analyses using the Cochrane Collaboration Review Manager Software, version 5.3.5.³¹ We prepared evidence summaries (Online Repository 2) for each question following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach⁶ using GRADEpro Guideline Development Tool online application (www.grade-pro.org).

When continuous outcomes (e.g. symptoms scores or quality of life) are measured using different scales, the results may only be combined in meta-analysis using standardized mean difference (SMD) which is expressed in standard deviation (SD) units. Results expressed as a SMD are challenging to interpret. To facilitate understanding we used interpretation of the effect size following Cohen's conventional criteria³²: an SMD of around 0.2 is considered a small effect, around 0.5 – a moderate effect, and around 0.8 or higher – a large effect. We used this interpretation throughout this document whenever we referred to effects of interventions as small, moderate or large.

We assessed the risk of bias at the outcome level using the Cochrane Collaboration's risk of bias tool³³. Subsequently, we assessed the certainty of the body of evidence (i.e. confidence in the estimated effects, also known as "quality of the evidence") for each of the outcomes of interest following the GRADE approach³⁴ based on the following criteria: risk of bias in primary studies, precision,

consistency, and magnitude of the estimates of effects, directness of the evidence, risk of publications bias, presence of dose–effect relationship, and an assessment of the effect of residual, opposing confounding. Certainty of the evidence was categorized into 4 levels: high, moderate, low and very low.

For each question we summarized all information in Evidence-to-Decision (EtD) frameworks (Online Repository 2) that included concise description of desirable and undesirable health effects, certainty of the evidence about those effects, evidence and assumptions about patients' values and preferences, required resources and cost-effectiveness, potential influence on health equity, acceptability of the intervention to various stakeholders, and feasibility of implementation³⁵. Judgments about all these factors and suggested recommendation in EtD frameworks were drafted by JLB who was also a clinical expert. EtDs for all questions were reviewed by ARIA guideline panel members who provided feedback by electronic communication and during a face-to-face meeting of Integrated Care Pathways for Airway Diseases (AIRWAYS ICPs) and Frailty European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) Reference Sites in Lisbon, Portugal on July 1st, 2015. All comments were addressed and the frameworks were modified accordingly. Modified EtD frameworks that included judgments about the research evidence, additional considerations of ARIA panel members and draft recommendations were sent to all ARIA panel members for review and approval or disapproval and comments using the online SurveyMonkey software (www.surveymonkey.com). We recorded and addressed all agreements/disagreements, comments and suggestions for changes. We present the final EtD frameworks in Online Repository 2. Following draft proposals by the methodologists, the final recommendations and their strength were decided by consensus. The ARIA guideline panel agreed on the final wording of recommendations and remarks with further qualifications for each recommendation. The final document including recommendations was reviewed and approved by all members of the guideline panel.

We labeled the recommendations as either “strong” or “conditional” according to the GRADE approach. We used the words “we recommend” for strong recommendations and “we suggest” for conditional recommendations. Table e1 provides suggested interpretation of strong and conditional recommendations.

Document review

Each member of the ARIA guideline panel reviewed the final draft and approved the document, which was then submitted for peer review with a condition that no recommendation may be changed at this stage, unless an error of fact or missing evidence is identified. The document was revised to incorporate the pertinent comments suggested by the external reviewers.

Use of indirect evidence

Pathophysiology of SAR and PAR is similar. When data for some outcomes were available only for SAR, we assumed that the evidence about the treatment effects in SAR would provide an indirect evidence about corresponding effects in PAR. The main difference is the usually long-term use of medications in PAR compared to mostly short-term or as needed use in SAR. Specifically, the adverse effects of treatments in PAR are likely to be similar to those in SAR, but there would be more concern about the long-term safety. In this document we explicitly stated whenever indirect evidence from SAR was used to inform recommendations for PAR.

Most patients recruited into randomized controlled trials have moderate-severe AR, thus, it is uncertain whether or not the available evidence directly applies to patients with mild AR.

Table e1: Interpretation of strong and conditional (weak) recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize 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 may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g. shared) decision-making processes can serve as performance measure.

How to use these guidelines

The ARIA guidelines about treatment of allergic rhinitis are not intended to impose a standard of care for individual countries. They provide the basis for rational, informed decisions for patients, parents, clinicians, and other health care professionals. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should not view these recommendations as dictates. Recommendations provide guidance for typical patients – no recommendation can take into account all of the often-compelling unique individual circumstances. Thus, no one charged with evaluating health care professionals' actions should apply the recommendations from these guidelines by rote or in a blanket fashion.

Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation should never be omitted when quoting or translating recommendations from these guidelines. They are integral to the recommendations and serve to facilitate more accurate interpretation.

General issues necessary for correct interpretation and implementation of recommendations

Assumed values and preferences of patients with SAR and PAR

Outcomes

Our systematic search for studies of values and preferences revealed 2 studies that reported utilities associated with different severity of AR (i.e. measures of the desirability of various outcomes to a patient; the value or utility of the present health state is placed on a continuum between 0 that typically corresponds to death and 1 that typically corresponds to a perfect health). A study using time trade-off technique³⁶ found utilities 0.96 associated with mild AR, 0.94 for moderate, 0.89 for severe and 0.83 for severest AR³⁷. The same study used visual analog scale (VAS) to estimate health status (values between 0 – worst and 1 – best) and found it to be 0.82 for mild, 0.71 for moderate, 0.56 for severe, and 0.43 for severest AR. Another study used standard gamble technique³⁸ and found utilities ranging 0.61 to 0.69 for severe individual symptoms, and 0.44 to 0.64 for multiple coexisting moderate to severe symptoms³⁹.

Several studies assessed the relative importance of individual symptoms. One study used VAS to assess impairment associated with individual symptoms and found largest impairment associated with nasal congestion (0.70), followed by nasal itching (0.79), sneezing (0.80), and ocular itching (0.88)⁴⁰. A survey of 1001 patients with AR in Canada showed the following symptoms were considered extremely bothersome: stuffed nose (26%), itchy eyes (21%), runny nose (17%), headache (17%), watering eyes (16%) and sneezing (14%)⁴¹. In a sample of 83 Japanese patients nasal obstruction and limitation in outdoor activities were identified as the most important factors influencing patient satisfaction from treatment⁴².

There is some uncertainty about how generalizable are the results from these studies because there are differences in preference rating with the same instrument among populations in different countries and cultures⁴³.

Treatments

A cross-sectional study of 170 patients with AR examined the preferences in view of treatment and fear of side effects of the most common treatment options; 30% preferred a nasal spray, 25% preferred oral treatment and 16% preferred combination treatment, whereas 15% preferred injection therapy. Additionally, 48% expressed concern regarding the side effects of INCS compared to other

treatments, 33% feared side effects of oral antihistamines, and 20% were concerned about adverse effects for LTRAs ⁴⁴. A study in Turkey found similar results with 36% of 100 patients with AR perceiving INCS as being dangerous and 47% would use them if prescribed ⁴⁵. Two studies found that patients prefer treatment options with no smell or taste ^{46, 47}.

Recommendations for children

Almost all studies used to answer the questions in this update of the ARIA guidelines exclusively included adult patients. However, careful extrapolation to pediatric population may be attempted. One may assume that the relative effects of treatment of AR are likely similar among adults and children but adverse effects may be more or less frequent and their perception and importance may be different, e.g. that of a bitter taste. Values and preferences for specific outcomes and treatments may also vary between adults and children.

Coexisting conditions

A recent systematic review of the prevalence of allergic rhinitis, asthma and eczema found 31 studies among over 1.4 million children in 102 countries. The calculated worldwide prevalence was 12.7% for allergic rhinitis, 12.00% for asthma, and 7.88% for eczema. All 3 conditions coexisted in 1.17% of children but the risk of having all three diseases was 9.8 times higher than could be expected by chance. For children with allergic rhinitis the calculated risk ratio of having the other two disorders was 6.20 (95% CI: 5.30-7.27) ⁴⁸.

Allergic rhinitis and asthma frequently coexist – epidemiological studies suggest that asthma is found in as many as 15% to 38% of patients with allergic rhinitis ^{10, 49-51}. Some studies estimate that nasal symptoms are present in at least 75% of patients with asthma, but these estimates vary widely from 6% to 85% depending on the study ^{13-15, 50, 52}. Asthma is also common in the older patients and strongly associated with rhinitis. The risk of asthma is especially high in persistent and severe ARIA classification rhinitis types ⁴⁹.

Recommendations for specific treatment questions

We present all recommendations in Table e2. Below, we provide the complete rationale for each recommendation and the consideration of all factors that influenced the recommendations (effects on all important health outcomes, certainty of the available evidence, values and preferences, acceptability by stakeholders, requirements for resources, feasibility, and any issues of health equity). Detailed summaries of the evidence supporting each recommendation and the actual guideline panel judgments are in the Online Repository 2.

Table e2. Recommendations

Recommendation	Assumed values and preferences	Explanations and other considerations
Question 1: Should a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?		
Recommendation 1A In patients with seasonal allergic rhinitis, we suggest either a combination of an intranasal corticosteroid with an oral H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation low certainty of evidence)	ARIA guideline panel acknowledged that the choice of treatment would mostly depend on patient preferences and local availability and cost of treatment. Panel members assumed that in majority of situations, potential net benefit would not justify spending additional resources.	This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of OAH is not large and/or patient values and preferences differ from those assumed by guideline panel members a combination therapy may be a reasonable choice, especially in patients not well controlled with INCS alone, those with pronounced ocular symptoms or those commencing treatment because of likely faster onset of treatment effects. This recommendation concerns regular use of newer, less sedative OAH and INCS in seasonal AR. For older OAHs with more sedative effects the balance of desirable and undesirable effects may be different.
Recommendation 1B In patients with perennial allergic rhinitis, we suggest an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H1-antihistamine (conditional recommendation very low certainty of evidence)	–	Currently available evidence suggests that there is no additional benefit from a combination therapy compared to INCS alone and there may be additional undesirable effects. This recommendation is conditional because of sparse information, thus, very low certainty of the estimated effects.
Question 2: Should a combination of intranasal H1-antihistamine (INAH) and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?		
Recommendation 2A In patients with seasonal AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation moderate certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. At the initiation of treatment (~ first 2 weeks) a combination of INCS with INAH may act faster than INCS alone and, thus, may be preferred by some patients.	This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of combination therapy is not large and/or patients value potential benefits more than any increased risk of adverse effects, a combination therapy may be a reasonable choice.
Recommendation 2B In patients with perennial AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation very low certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.	This is a conditional recommendation because of the very low certainty of the evidence. At the initiation of treatment (~ first 2 weeks) a combination of INCS with INAH may act faster than INCS alone, thus, may be preferred by some patients.
Question 3: Should a combination of an intranasal H1-antihistamine and an intranasal corticosteroid vs. intranasal H1-antihistamine alone be used for treatment of allergic rhinitis?		
Recommendation 3A In patients with seasonal AR, we suggest a combination of an intranasal corticosteroid with an intranasal H1-antihistamine rather than an intranasal H1-antihistamine alone (conditional recommendation low certainty of evidence)	This recommendation places higher value on additional reduction of symptoms and improved quality of life with a combination therapy, compared to INAH alone. It places a lower value on avoiding additional cost (expenditure of resources).	This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of a combination therapy is large, an alternative choice, i.e. INAH alone, may be equally reasonable. One panel member thought that the recommendation should be conditional for either the intervention or the comparison.
Question 4: Should a leukotriene receptor antagonist (LTRA) vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?		

Recommendation 4A In patients with seasonal AR, we suggest either a leukotriene receptor antagonist or an oral H1-antihistamine (conditional recommendation moderate certainty of evidence)	Panel members acknowledged that the choice of LTRA or OAH will mostly depend on patient preferences and local availability and cost of specific medications. In many settings OAH may still be more cost-effective but this will largely depend on availability of generic LTRA and the local cost of various newer-generation OAH and LTRA.	Some patients with AR who have concomitant asthma, especially exercise-induced and/or aspirin exacerbated respiratory disease, may benefit from LTRA more than from OAH. However, this recommendation applies to treatment of AR not to treatment of asthma. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.
Recommendation 4B In patients with perennial AR, we suggest an oral H1-antihistamine rather than a leukotriene receptor antagonist (conditional recommendation low certainty of evidence)	This recommendation places a higher value on possibly larger improvement of symptoms and quality of life with OAH, compared to LTRA. It places a lower value on possible increased risk of somnolence.	This is a conditional recommendation, thus different choices will be appropriate for different patients based on their preferences for reduction of symptoms versus avoiding the risk of adverse effects – this may be more important for patients with PAR than with SAR as they might use those medications for longer periods of time. Some patients with AR and concomitant asthma, especially exercise-induced and/or aspirin exacerbated respiratory disease, may benefit from LTRA more than from OAH. However, this recommendation applies to treatment of AR not to treatment of asthma. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.
Question 5: Should an intranasal H1-antihistamine vs. an intranasal corticosteroid be used for treatment of allergic rhinitis?		
Recommendation 5A In patients with seasonal AR, we suggest an intranasal corticosteroid rather than an intranasal H1-antihistamine (conditional recommendation moderate certainty of evidence).	This recommendation places a higher value on likely small but greater reduction of symptoms and improvement of quality of life with INCS, compared to INAH, and a lower value on avoiding larger cost of treatment with INCS in many jurisdictions.	This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs.
Recommendation 5B In patients with perennial AR, we suggest an intranasal corticosteroid rather than intranasal H1-antihistamine (conditional recommendation low certainty of evidence).	This recommendation places a higher value on probably greater reduction of nasal symptoms with INCS, compared to INAH, although the overall difference is likely small. It places a lower value on avoiding larger cost of treatment with INCS in many jurisdictions.	This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs.
Question 6: Should an intranasal H1-antihistamine vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?		
Recommendation 6A In patients with SAR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation low certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.	This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.
Recommendation 6B In patients with perennial AR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation very low certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.	This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.

Question 1. Should a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?

Intranasal corticosteroids (INCS) and oral H1-antihistamines (OAH) are the classes of medications most often used by patients with AR. A combination of INCS with OAH may have an advantage over monotherapy as their mechanisms of action are different. Their effects may be additive and each has specific advantages and disadvantages.

Summary of the evidence

We found 8 randomized controlled trials (RCTs) that compared a combined use of INCS and OAH with INCS alone in patients with SAR ⁵³⁻⁶⁰ and 2 RCTs in patients with PAR ^{61, 62}. All studies in SAR included adults (1 quasi-RCT included 78 teenagers ⁵⁷). Studies used a variety of INCS (mometasone, fluticasone and beclomethasone) and newer H1-antihistamines (loratadine, cetirizine and levocetirizine). Treatment duration in all studies was 2 weeks or longer. One study in PAR used mometasone and levocetirizine in adults for 1 month ⁶². The other study used ciclesonide and levocetirizine in adults for 3–5 weeks ⁶¹. However, only 70% patients had PAR and the remaining patients had SAR.

Evidence profiles for question 1A (seasonal AR) and 1B (perennial AR) are in the Online Repository 2.

Benefits

In patients with SAR the additional reduction in nasal (SMD 0.13 SD lower, 95% CI: 0.25 lower to 0) and ocular symptoms (SMD 0.19 lower, 95% CI: 0.33 to 0.05 lower) with OAH + INCS, compared to INCS alone, is small and most likely would not be noticed by most patients (assuming that an SMD of 0.2 is a small effect and 0.5 a moderate effect). The improvement in quality of life may be large but available evidence does not allow to estimate it precisely enough to exclude a possibility of no effect or even small harm (SMD 0.61 lower, 95% CI: 1.44 lower to 0.23 higher; lower score indicates better quality of life). There was no evidence of that combination therapy might affect one the nasal symptoms more than the others (see exploratory analysis in evidence profile for question 1A in Online Repository 2).

In patients with PAR there was no observed benefit from adding OAH to INCS, compared to INCS alone, in nasal symptoms (mean difference 0.2 points on a 12-point scale favoring INCS alone) and in ocular symptoms (mean difference 0.1 points on a 9-point scale favoring INCS alone).

Harms and burden

There were no serious adverse effects reported in any of the studies in SAR and PAR. There was also no evidence of a difference in the risk of adverse effects leading to discontinuation of therapy (relative risk: 0.65, but the low total number of events did not allow to estimate it precisely and the confidence interval does not exclude harm with either treatment option – 95% CI: 0.13 to 3.23). Similarly there were too few events of sedation or epistaxis to precisely estimate the difference between the treatments (see evidence profile for question 1A in Online Repository 2).

In patients with PAR there was no difference in quality of life scores between the groups but the results did not exclude a possibility of importantly reduced quality of life with combination therapy, compared to INCS alone (mean RQLQ score was 0.2 points lower with combination therapy; 95% CI: 0.53 lower to 0.13 higher). There was no evidence of more adverse effects with any of the treatments.

All studies in SAR and PAR investigated new generation OAH. Older generation OAH, that are usually more sedating, will have more adverse effects than observed in these studies.⁶³

Decision criteria and additional considerations

ARIA panel members noted that some patients beginning treatment may prefer the combination therapy because of faster onset of action of OAH compared to INCS alone. This, however, may be less important in patients with PAR than with SAR. Adherence to treatment may be lower with an increase in the number of medications.

We found two studies that compared the cost of INCS alone to their combination with OAH –a retrospective database analysis using pharmacy and medical claims data from a US health plan that compared medical and pharmacy cost of different treatments for rhinitis ⁶⁴ and a Swedish population-based questionnaire study that estimated an annual cost of treatment with OAH and INCS ⁶⁵. The cost per patient varied with the ARIA classification of the severity of symptoms and was higher for persons with moderate to severe persistent allergic rhinitis compared to mild persistent disease. Panel members thought that unit costs assumed in both analyses do not reflect current costs in most settings and, thus, relying on those analyses could be misleading. Panel members agreed that additional resources required for combination therapy might be a concern in settings where OAH are currently more expensive but not in settings where their relative cost is not high. From the patient perspective, increased cost of treatment with OAH + INCS, compared to INCS alone, may be particularly important in settings where OAH are available other-the-counter and not covered by drug plans. The cost of adding OAH might therefore be relatively high, particularly to those individuals with limited resources.

Conclusions and research needs

We found little additional benefit from a combination of OAH+INCS, compared to INCS alone in patients with SAR. However, there may be some patients, particularly at the beginning of treatment that might benefit from likely faster relief of symptoms.

ARIA guideline panel acknowledged that the choice of treatment would mostly depend on patient preferences and local availability and cost of treatment. Panel members felt that in majority of situations, where a combination therapy is considerably more expensive than INCS alone, any potential net benefit would not justify spending additional resources.

There is no currently available direct evidence from experimental studies about the effects in subgroups based on severity of individual symptoms. However, based on indirect evidence it is possible that selected patients may benefit more from a combination therapy (e.g. those not well controlled with INCS alone, those with pronounced ocular symptoms or those at the beginning of treatment because of likely faster onset of treatment effect).

All evidence is available only for new generation OAHs; for older OAHs with more sedative effects the balance of desirable and undesirable effects may be different.

We found no additional benefit of a combination of OAH and INCS, compared to INCS alone, in patients with PAR.

Further research of a combination of OAH with INCS as a step-up therapy in patients with not well controlled with INCS alone is warranted. Additional information about the effects of INCS + OAH, compared to INCS alone, in subpopulation of patients with pronounced ocular symptoms or those in whom rhinorrhea rather than congestion is the main symptom may be beneficial. Studies of real life effects of the combination therapy used as needed, rather than regularly, may also be warranted. If done, studies should measure not only nasal symptoms but also quality of life and properly report adverse effects. Further research to identify subgroups of patient with PAR more likely to benefit from H1-antihistamine added to INCS may be warranted.

What others are saying

The American Academy of Otolaryngology – Head and Neck Surgery guidelines offer an option: “clinicians may offer combination pharmacologic therapy in patients with AR who have inadequate response to pharmacologic monotherapy” but state that “when patients have no response to INCS or incomplete control of nasal symptoms with an INCS, OAH should not be routinely used as additive therapy” ⁷.

The American Academy of Family Physicians suggests a combination of “INCS plus OAH for severe, persistent symptoms” but “INCS alone for the initial treatment for AR with symptoms affecting quality of life”. It also states that “although most patients should be treated with just one

medication at a time, combination therapy is an option for patients with severe or persistent symptoms”⁶⁶.

The Diagnosis and Management of Rhinitis: An Updated Practice Parameter developed by the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) and the Joint Council of Allergy, Asthma and Immunology does not make explicit recommendations for practice but provides statements about specific treatments. It states that a “combination of OAH and INCS may be considered, although supporting studies are limited and many studies unsupportive of additive benefit of adding OAH to INCS”⁶⁷. Note that this Practice Parameter was developed in 2008 when much less information was available.

University of Michigan guidelines do not mention combination therapy with OAH and INCS⁶⁸.

Recommendation 1A

In patients with seasonal allergic rhinitis, we suggest either a combination of an intranasal corticosteroid with an oral H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation | low certainty of evidence)

Values and preferences

The ARIA guideline panel acknowledged that the choice of treatment would mostly depend on patient preferences and local availability and cost of treatment. Panel members assumed that in the majority of situations, potential net benefit would not justify spending additional resources.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of OAH is not large and/or patient values and preferences differ from those assumed by guideline panel members a combination therapy may be a reasonable choice, especially in patients not well controlled with INCS alone, those with pronounced ocular symptoms or those commencing treatment because of likely faster onset of treatment effects. This recommendation concerns *regular* use of newer, less sedative OAH and INCS in seasonal AR. For older OAHs with more sedative effects the balance of desirable and undesirable effects may be different.

Recommendation 1B

In patients with perennial allergic rhinitis, we suggest an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H1-antihistamine (conditional recommendation | very low certainty of evidence)

Explanations and other considerations

Currently available evidence suggests that there is no additional benefit from combination therapy compared to INCS alone and there may be additional undesirable effects. This recommendation is conditional because of sparse information, thus, very low certainty of the estimated effects.

Question 2. Should a combination of intranasal H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?

A combination of INCS with INAH may have an advantage over INCS alone as their mechanisms of action are different. The antihistaminic effect of INAH could be additive to anti-inflammatory effects of INCS.

Summary of the evidence

We found 5 RCTs that compared a combination of INAH with INCS with INCS alone in patients with SAR. Three studies were reported together in one journal article⁶⁹. Some results from one of these 3 studies were published in an additional separate article⁷⁰. Of the remaining 2 studies one was published in 2 separate articles^{71, 72} and the last one was published in 1 article⁷³.

Four out of 5 studies used a combination drug in one container and one study used INCS and INAH as separate sprays⁷³. There is some uncertainty whether the desirable and undesirable effects of these different formulations would be the same owing to no available evidence about possible interactions of the two separate solutions. All 5 studies included adult patients and used fluticasone and azelastine nasal sprays for 2 weeks.

We found 1 RCT (results published in 2 separate articles) that investigated a combination of fluticasone and azelastine, compared to fluticasone alone, for 52 weeks in adults with PAR^{74, 75}.

All 6 studies in SAR and in PAR were funded by a single manufacturer of the combination drug in one container. Evidence profiles for question 2A (seasonal AR) and 2B (perennial AR) are in the Online Repository 2.

We also found 6 studies that examined the time to onset of action in patients with SAR. Two studies presented the results only as graphs with no reported variability in results and showed that the difference between a combination of INAH+INCS vs. INCS alone was achieved already by day 2-3 of treatment^{71, 73}. Three studies assessed nasal symptoms 4 hours after drug administration and found total nasal symptom score (TNSS) being reduced by 0.5 point more (95% CI: 0.07 to 0.93; scale 0 to 24) with combination therapy compared to INCS alone⁶⁹. In the best case scenario a difference of 0.93 point on a 24-point scale would be unlikely to be noticed by majority of patients (we assumed that a difference of around 1.1 to 1.3 points on a 24-point TNSS scale would be the minimal

important difference [MID] based on a study in SAR⁷⁶ and on an empirical observation that a difference of around 0.5 point on a 7-point scale is frequently an MID in respiratory diseases including AR⁷⁷, asthma⁷⁸⁻⁸¹ and COPD⁸²). However, in these studies patients reached 50% reduction of symptoms up to 3 days earlier with combination therapy compared to INCS alone. One study using an allergen challenge found better improvement of symptoms with INAH+INCS compared to INCS alone over 2-4 hours after drug administration (mean difference 1.36 point on a 12-point scale; 95% CI: 0.87 to 1.85)⁸³.

In studies that used combination therapy in one spray, one showed benefit with combination therapy⁷¹ and the other did not show the difference⁶⁹. Indirect evidence from bioavailability study suggests that a combination of azelastine and fluticasone acts faster than fluticasone alone⁸⁴. This observation is consistent with clinical observations of some ARIA panel members.

Benefits

In patients with SAR, a combination of INAH with INCS, compared to INCS alone improved nasal symptoms (mean difference 0.77 point lower on a 24-point scale; 95% CI: 0.3 to 1.24 lower), ocular symptoms (SMD 0.2 SD lower, 95% CI: 0.07 to 0.33 lower), and most likely also quality of life (mean difference 0.13 points in RQLQ higher, 95% CI: 0.01 to 0.24 higher). However, all effects were small and confidence intervals did not exclude almost no difference. A combination of azelastine and fluticasone acts faster than fluticasone alone.

In patients with PAR, use of combination of INAH with INCS may improve nasal symptoms (mean score 0.27 points lower on a 24-point scale, 95% CI: 0.56 lower to 0.02 higher) although any difference would be small, compared to INCS alone. Combination therapy most likely increased number of symptom-free days by an average of 24 days during 52 weeks of treatment (95% CI: 48 more to 0.24 fewer). Although there is no direct evidence about ocular symptoms and quality of life from studies in patients with PAR, indirect evidence from studies in patients with SAR suggest that the effect might be trivial, if any.

Harms and burden

There were no serious adverse effects among 1801 in 4 studies of patients with SAR. There is no evidence that combined therapy led to more discontinuation of treatment but confidence interval does not exclude an important increase of this risk (from 2 fewer to 25 more per 1000 patients). There were more “any adverse effects” in the combined treatment group (risk difference: 41 more per 1000 patients, 95% CI: 12 to 81 more). All studies used azelastine as INAH and bitter taste was reported by some patients in combination therapy group (risk difference 26 more per 1000 patients, 95% CI: 8 to 72 more).

There were 4 serious adverse effects in the study of patients with PAR but all were very unlikely related to treatment (Dengue fever, pyrexia, appendicitis, and gastroenteritis). There was no evidence that combination treatment would lead to more discontinuation of treatment owing to adverse effects. Azelastine was used as INAH and bitter taste was reported by some patients in combination therapy group (risk difference: 20 more per 1000 patients, 95% CI: from 2 fewer to 187 more).

Decision criteria and additional considerations

Panel members noted that some patients beginning treatment may prefer the combination therapy because of quicker onset of action of a combination of INCS with INAH, compared to INCS alone.

We found one retrospective cohort study of adult patients with AR in the United States that examined the cost of INCS monotherapy, INAH monotherapy, or their combination ⁸⁵. Panel members thought that unit costs assumed in this study do not reflect the current costs in most settings and relying on those estimates could be misleading. Some panel members thought that a combination is not cost effective compared to INCS alone, because of little – if any – additional benefit from a combination therapy. This may be particularly important in settings where the combination therapy is more expensive than INCS alone. Some panel members thought that the combination therapy may not be acceptable to third party payers because of cost-effectiveness.

Conclusions and research needs

In SAR, the additional reduction in symptoms with combination therapy is small and unlikely to be noticed by majority of patients. There is currently no available direct evidence from experimental studies about subgroups based on severity of individual symptoms of SAR. However, based on indirect evidence it is possible that selected patients with SAR may benefit more from a combination therapy (e.g. those not well controlled with INCS alone or those in whom rhinorrhea rather than congestion is the main complaint).

Based on limited evidence in treatment of PAR, any additional reduction in symptoms with combination therapy, if existing, would likely be small and unlikely to be noticed by majority of patients.

Panel members thought that in the majority of situations, both in SAR and in PAR, where a combination therapy is more expensive than INCS alone, any possible net benefit would not justify spending additional resources.

Further research of a combination of INAH with INCS as a step-up therapy in patients with SAR not well controlled with INCS alone is warranted. A pragmatic trial in real-life setting measuring cost-effectiveness may also be warranted. The only INAH used in these studies was azelastine and the only INCS was fluticasone – studies of other INAH and INCS may provide important insight. Further research of a combination of INAH with INCS in patients with PAR may also be justified. However, indirect evidence from SAR suggests that any potential benefit from combination therapy is likely to be trivial. Thus, further research specifically in PAR may not be cost-effective.

What others are saying

The American Academy of Otolaryngology – Head and Neck Surgery guidelines offer an option: “clinicians may offer combination pharmacologic therapy in patients with AR who have inadequate response to pharmacologic monotherapy” and state that “in patients who tolerate INCS or INAH spray and have inadequate control of AR symptoms with a single agent, combined INCS + INAH is an effective option” ⁷.

The American Academy of Family Physicians suggests a combination of “INCS plus INAH for severe, persistent symptoms” but “INCS alone for the initial treatment for AR with symptoms affecting quality of life”. It also states that “although most patients should be treated with just one medication at a time, combination therapy is an option for patients with severe or persistent symptoms” ⁶⁶.

The most recent AAAAI/ACAAI Practice Parameter from 2008 does not make explicit recommendations for practice but states that a “combination may be considered based on limited data” particularly “for mixed rhinitis, there may be significant added benefit to the combination of INAH with INCS” ⁶⁷. Note, that this Practice Parameter was developed in 2008 when less information was available.

University of Michigan guidelines make no specific recommendations but state that “more recent evidence suggests that combination of intranasal antihistamines and intranasal corticosteroids are synergistic and provide greater benefit than monotherapy in the treatment of seasonal allergic rhinitis” ⁶⁸.

Recommendation 2A

In patients with seasonal AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation | moderate certainty of evidence).

Values and preferences

The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. At the initiation of treatment (~ first 2 weeks)

a combination of INCS with INAH may act faster than INCS alone and, thus, may be preferred by some patients.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of combination therapy is not large and/or patients value potential benefits more than any increased risk of adverse effects, a combination therapy may be a reasonable choice.

Recommendation 2B

In patients with perennial AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation | very low certainty of evidence).

Values and preferences

The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.

Explanations and other considerations

This is a conditional recommendation because of the very low certainty of the evidence. At the initiation of treatment (~ first 2 weeks) a combination of INCS with INAH may act faster than INCS alone, thus, may be preferred by some patients.

Question 3. Should a combination of an intranasal H1-antihistamine and an intranasal corticosteroid vs. intranasal H1-antihistamine alone be used for treatment of allergic rhinitis?

A combination of INCS with INAH may have an advantage over INAH alone as their mechanisms of action are different. Their effects may be additive and each has specific advantages and disadvantages.

Summary of the evidence

The same 5 RCTs in patients with SAR that compared a combination of INAH with INCS with INCS alone, described in question 2, used INAH alone as a second comparison group^{69, 71, 73}. Four out of 5 studies used a combination drug in one container and one study used INCS and INAH as separate sprays⁷³. There also is uncertainty whether the desirable and undesirable effects of one solution compared to 2 separate containers would be the same owing to no available evidence about possible interactions of the two separate solutions. All 5 studies included adult patients and used fluticasone

and azelastine nasal sprays for 2 weeks. All were funded by a single manufacturer of the combination drug in one container. Evidence profile for question 3 is in the Online Repository 2.

We did not find any study that investigated a combination of INCS with INAH, compared to INAH alone, in patients with PAR.

Benefits

There are small to moderate benefits from combined therapy. A combination of INAH with INCS, compared to INAH alone, reduced nasal symptoms (mean difference: 1.4 points on a 24-point scale lower, 95% CI: 0.98 to 1.82 lower), ocular symptoms (SMD: 0.33 SD lower, 95% CI: 0.02 to 0.65 lower), and improved quality of life (mean difference: 0.53 points in RQLQ lower, 95% CI: 0.06 to 1.01 lower, scale 1 to 7 and lower values indicate improvement). However, the effects could not be estimated precisely enough to exclude at least a moderate benefit or no difference.

Harms and burden

There were no serious adverse effects in those studies. There was no evidence of an increased risk of any adverse effect with the combination therapy, compared to INAH alone. All studies used azelastine and bitter taste was reported by some patients in both groups.

Decision criteria and additional considerations

We found one retrospective cohort study of adult patients with AR in the United States that examined the cost of INAH monotherapy and a combination of INAH and INCS⁸⁵. Panel members thought that unit costs assumed in this study do not reflect the current costs in most settings and relying on the estimates from this study could be misleading. Panel members noted that the choice of therapy will highly depend on the local health system owing to large variability in cost and coverage: public or private insurance plans, co-payment models and patient out of the pocket expenses. Some panel members thought that, a combination therapy may not be cost effective compared to INAH alone.

Conclusions and research needs

There is a small improvement in symptoms and quality of life with a combination of INAH with INCS, compared to INAH alone. Mean estimates of improvement of symptoms are close to minimal important difference (MID) and an estimate of mean improvement in QoL is larger than MID – it is therefore likely that the difference would be noticed by many patients.

Further research may be warranted to better estimate the effect of a combination of INAH with INCS on quality of life. The only INAH used in these studies was azelastine and the only INCS was fluticasone – studies of other INAH and INCS may be warranted.

What others are saying

The American Academy of Otolaryngology—Head and Neck Surgery guidelines offer an option: “clinicians may offer combination pharmacologic therapy in patients with AR who have inadequate response to pharmacologic monotherapy” and state that “in patients who tolerate INCS or INAH spray and have inadequate control of AR symptoms with a single agent, combined INCS + INAH is an effective option” ⁷.

The American Academy of Family Physicians suggests a combination of “INCS plus INAH for severe, persistent symptoms” but “INAH as needed for mild intermittent symptoms” and adds that “because INAH are more expensive, less effective, and have more adverse effects than INCS, they are not recommended as first-line therapy for AR” ⁶⁶. It also states that “although most patients should be treated with just one medication at a time, combination therapy is an option for patients with severe or persistent symptoms”.

The AAAAI/ACAAI Practice Parameter does not make explicit recommendations for practice but states that a “combination may be considered based on limited data” particularly “for mixed rhinitis, there may be significant added benefit to the combination of INAH with INCS” ⁶⁷. Note that this Practice Parameter was developed in 2008 when much less information was available.

University of Michigan guidelines make no specific recommendations but state that “more recent evidence suggests that combination of intranasal antihistamines and intranasal corticosteroids are synergistic and provide greater benefit than monotherapy in the treatment of seasonal allergic rhinitis” ⁶⁸.

Recommendation 3

In patients with seasonal AR, we suggest a combination of an intranasal corticosteroid with an intranasal H1-antihistamine rather than an intranasal H1-antihistamine alone (conditional recommendation | low certainty of evidence)

Values and preferences

This recommendation places higher value on additional reduction of symptoms and improved quality of life with a combination therapy, compared to INAH alone. It places a lower value on avoiding additional cost (expenditure of resources).

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of a combination therapy is large, an alternative choice, i.e. INAH alone, may be equally reasonable.

One panel member thought that the recommendation should be conditional for either the intervention or the comparison.

Question 4. Should a leukotriene receptor antagonist (LTRA) vs. an oral H1-antihistamine (OAH) be used for treatment of allergic rhinitis?

Oral H1-antihistamines and leukotriene receptor antagonists (LTRA) are used for the treatment of AR. LTRA may have an advantage over OAH as they may cause less somnolence attributed to OAH. Both medications have different mechanisms of action and each may have specific advantages. In the 2010 revision of the ARIA guidelines we recommended OAH rather than LTRA based on lower cost of OAH. With the generic LTRA available since late 2012 the ARIA guideline panel decided that this recommendation should be revisited.

Summary of the evidence

We found 11 RCTs described in 10 articles that compared LTRA to OAH in adult patients with SAR⁸⁶⁻⁹⁵. No study included children. In 7 studies some or all patients had concomitant asthma. Montelukast was used in all studies except for one that used pranlukast⁹². Studies used loratadine in the control group except for one that used cetirizine⁸⁶, another that used levocetirizine⁸⁷, and one that used fexofenadine⁹². Follow-up was between 2 and 6 weeks. All studies were funded by Merck, manufacturer of montelukast, except for one that was independently funded by an academic institution and possibly also 2 that failed to report the source of funding.

We identified one additional RCT of LTRA vs. OAH in patients with SAR but the LTRA used was ibudilast which is not commonly used for treatment of AR⁹⁶. We did not include this study in further analyses.

We also found 7 RCTs of LTRA compared to OAH in patients with PAR. Five included adults⁹⁷⁻¹⁰¹ and 2 included children^{102, 103}. Five studies used montelukast and 3 used zafirlukast. Cetirizine was used as the control medication in 5 studies and levocetirizine, loratadine and desloratadine were used in one study each. All studies followed patients for 4 to 12 weeks, except for one that followed patients only for 2 weeks¹⁰⁰. However, its results were consistent with those of other studies, thus, we included it in the analyses.

Evidence profiles for question 4A (seasonal AR) and 4B (perennial AR) are in the Online Repository 2.

Benefits

There is high certainty evidence showing that the health effects of LTRA in patients with SAR are similar to those of newer generation OAH: nasal symptoms (SMD: 0.06 higher, 95% CI: 0.01 lower to 0.13 higher), ocular symptoms (SMD: 0.06 higher, 95% CI: 0.04 lower to 0.16 higher), and quality of life (mean difference in RQLQ score: 0.04 higher, 95% CI: 0.04 lower to 0.13 higher).

In patients with PAR, the effects could not be precisely estimated owing to small number of patients and the evidence is of low certainty. OAH possibly reduce nasal symptoms more than LTRA (SMD: 0.26 higher with LTRA, 95% CI: 0.45 lower to 0.97 higher) but the confidence interval does not exclude a moderate benefit from LTRA or a large benefit from OAH. The effect on ocular symptoms seemed to differ between adults (mean difference: 0.19 point lower on a 4-point scale, 95% CI: 1.03 lower to 0.65 higher) and children (mean difference: 0.29 point higher on a 3-point scale, 95% CI: 0.04 lower to 0.62 higher). Similarly, quality of life seemed to improve more in adults (mean difference: 0.17 point lower RQLQ score, 95% CI: 0.98 lower to 0.58 higher) than in children (mean difference: 12 points higher in a 138-point PRQLQ score, 95% CI: 1.66 lower to 25.66 higher). However, studies were very small and the differences were not large, thus, any dissimilarities in the effects between children and adults may be spurious.

Harms and burden

There were no serious adverse effects in any of the studies of SAR and PAR. There is also no evidence that more patients might discontinue treatment owing to adverse effects with either medication. There was no difference in any adverse effects observed in patients with SAR and somnolence was not reported in any of the studies of SAR.

In patients with PAR, fewer any adverse effects were observed (14 events fewer per 100 patients over 6 weeks, 95% CI: 5 to 23 fewer) and less somnolence (5 fewer per 100 patients, 95% CI: 3 to 5 fewer) with LTRA compared to OAH. However, there is low confidence that the observed results reflect true effects owing to limitations in study designs (see evidence profile for question 4B in Online Repository 2).

Decision criteria and additional considerations

We found one retrospective analysis of an insurance claim database in the United States that analyzed costs of treatment with montelukast compared with oral, branded second-generation

antihistamines¹⁰⁴. We also found descriptions of two economic models that compared various OAH and montelukast¹⁰⁵¹⁰⁶. However, all analyses were based on historical prices from 2000s and panel members thought they were not applicable today. The ARIA panel members noted that the cost of LTRA will frequently be higher compared to OAH but the cost of various OAH is also highly variable across countries and health care systems. Cost may be a more important factor for patients with PAR since they might use medications for longer periods of time. In settings where generic LTRA are available, cost of treatment may be lower compared to branded LTRA. When choosing the optimal treatment option clinicians need to consider the local availability and costs of LTRA and various OAH. Panel members also noted that many clinicians currently start therapy of AR from OAH rather than LTRA, most likely based on actual or perceived cost effectiveness.

Panel members also noted that in some countries LTRA are currently available only for treatment of asthma which may be a barrier to implementation for treatment of AR.

Conclusions and research needs

There seems to be no clear difference in health outcomes between LTRA and OAH in patients with SAR, thus, the panel members concluded that the choice of treatment will largely depend on patient preferences and local availability and cost of medications.

In patients with PAR, there is low certainty about the differences in health outcomes between LTRA and OAH – OAH may reduce symptoms and improve quality of life more but the risk of somnolence is possibly higher. Any true differences are likely to be small.

Studies investigating the comparative effects of LTRA and OAH in patients with AR and specific subgroups defined by type of concomitant asthma may be warranted.

What others are saying

The American Academy of Otolaryngology—Head and Neck Surgery guidelines not make a specific recommendation for the choice of OAH or LTRA but make a separate strong recommendation to use “second generation/less sedating OAH for patients with AR and primary complaints of sneezing and itching” and a recommendation against the use of LTRA: “clinicians should not offer oral LTRA as primary therapy for patients with AR”⁷. The rationale provided was “to reduce the use of a more expensive, less effective agent as first-line treatment of AR”.

The American Academy of Family Physicians makes no specific recommendation for the use of LTRA versus OAH but states that “montelukast is comparable to OAH but is less effective than INCS” and that “it may be particularly useful in patients with coexistent asthma”⁶⁶.

The AAAAI/ACAAI Practice Parameter does not make explicit recommendations for practice but states that there is “no significant difference in efficacy between LTRA and OAH” and that LTRA may be considered in patients who have both AR and asthma and has minimal side effects⁶⁷. Note that this Practice Parameter was developed in 2008 when less information was available.

University of Michigan guidelines make no specific recommendations but state that OAH are the first or second and LTRA are a second or third option to add in the treatment of allergic rhinitis”⁶⁸.

Recommendation 4A

In patients with seasonal AR, we suggest either a leukotriene receptor antagonist or an oral H1-antihistamine (conditional recommendation | moderate certainty of evidence)

Values and preferences

Panel members acknowledged that the choice of LTRA or OAH will mostly depend on patient preferences for the affected outcomes and local availability and cost of specific medications. In many settings OAH may still be more cost-effective but this will largely depend on availability of generic LTRA and the local cost of various newer-generation OAH and LTRA.

Explanations and other considerations

Some patients with AR who have concomitant asthma, especially exercise-induced and/or aspirin exacerbated respiratory disease, may benefit from LTRA more than from OAH. However, *this recommendation applies to treatment of AR not to treatment of asthma*. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.

Recommendation 4B

In patients with perennial AR, we suggest an oral H1-antihistamine rather than a leukotriene receptor antagonist (conditional recommendation | low certainty of evidence)

Values and preferences

This recommendation places a higher value on possibly greater improvement of symptoms and quality of life with OAH, compared to LTRA. It places a lower value on possible increased risk of somnolence.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients based on their preferences for reduction of symptoms versus avoiding the risk of adverse effects – this may be more important for patients with PAR than with SAR as they might use those medications for longer periods of time.

Some patients with AR and concomitant asthma, especially exercise-induced and/or aspirin exacerbated respiratory disease, may benefit from LTRA more than from OAH. However, *this recommendation applies to treatment of AR not to treatment of asthma*. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.

Question 5. Should an intranasal H1-antihistamine vs. an intranasal corticosteroid be used for treatment of allergic rhinitis?

INAH and INCS are two most effective intranasal therapies for AR. INAH may have an advantage over INCS in their faster onset of symptom relief as their mechanisms of action are different. In the 2010 revision of the ARIA guidelines we recommended INCS rather than INAH. However, no well done systematic review was available at that time and new studies have been performed and published that might change the recommendation. The ARIA guideline panel decided that this recommendation should be reviewed.

Summary of the evidence

We identified 15 RCTs that compared INAH to INCS in patients with SAR^{69, 71-73, 107-116} and 4 RCTs in patients with PAR¹¹⁷⁻¹²⁰. All studies included adult patients and none included children. Studies in patients with SAR used various INCS (beclomethasone, budesonide, flunisolide, fluticasone, and mometasone) and various INAH (azelastine, levocabastine and olopatadine) for 2 to 6 weeks. For those studies that have not reported numerical results and/or variability in the results we used numbers provided in two previous systematic reviews^{121, 122}. We performed sensitivity analyses and the combined results were similar with and without those studies.

We found some differences among different INAH and daily doses of INAH but they were not consistent across outcomes and there is not enough information to allow any conclusions about specific INAH or INCS.

Evidence profiles for question 5A (seasonal AR) and 5B (perennial AR) are in the Online Repository 2.

Benefits

There seem be no desirable effects of INAH when compared to INCS in SAR and in PAR.

There was no evidence of a difference in ocular symptoms in patients with SAR (SMD: 0.08 SD higher, 95% CI: 0.11 lower to 0.26 higher) and with PAR (mean difference: 0.29 point higher on a 5-point scale, 95% CI: 0.39 lower to 0.97 higher).

Eight studies examined the time to onset of action in patients with SAR. Results were most often reported as graphs with no variability and showed inconsistent results: 2 studies ^{110, 112} showed that INAH may relieve symptoms faster over the first 2-4 days with INCS being more effective from day 4 onwards, two additional studies showed no difference ^{71, 73} and 4 studies showed quicker relief of symptoms in the INCS group ^{69, 111}. One study using an allergen challenge found better improvement of symptoms with INAH compared to INCS over the first 2-4 hours after drug administration ⁸³.

Harms and burden

In patients with SAR, effects of INAH were smaller compared to INCS on nasal symptoms (SMD: 0.17 SD higher, 95% CI: 0.07 to 0.28 higher) and quality of life (mean difference in RQLQ score: 0.26 points higher, 95% CI: 0.09 to 0.43 higher). However, confidence intervals around the estimated effects do not exclude the possibility that this difference may not be large enough to be perceived by a substantial proportion of patients.

In patients with PAR, there is some evidence, albeit of low certainty, that INAH do not relieve nasal symptoms as well as INCS (mean difference: 1.08 points higher on a 10-point scale, 95% CI: 0.36 to 1.8 higher). There is no information about quality-of-life in patients with PAR. However, assuming that symptoms are a good surrogate for quality of life, it is very likely that it would also be improved more with INCS.

There were no serious adverse effects in any of the studies in SAR and in PAR. There was no evidence of higher risk of discontinuation of treatment owing to adverse effects with either medication. There were more any adverse effects with INAH compared to INCS in studies of SAR (risk difference: 35 more per 1000 patients, 95% CI: 4 to 77 more). As expected, bitter taste was more frequent with INAH than with INCS. Increased risk of somnolence was higher in patients with PAR (risk difference: 170 more per 1000 patients, 95% CI: 1 fewer to 330 more) than in SAR (risk difference: 3 more per 1000 patients, 95% CI: 0 to 17 more), but the confidence intervals did not exclude the possibility of no difference between the groups. There was no evidence of a difference in the risk of epistaxis.

Decision criteria and additional considerations

Panel members noted that relative effects of INAH and INCS may be different when used continuously (as in these studies) vs. as need (not investigated in clinical trials).

We found one retrospective cohort study of adult patients with AR in the United States that examined the cost of INAH and INCS ⁸⁵. Panel members thought that unit costs assumed in this study do not reflect the current costs in most settings and relying on the estimates from this study could be misleading. Panel members noted that the choice of therapy will likely highly depend on the local health system owing to large variability in cost and coverage among countries, healthcare systems, public and private insurance plans, co-payment models, and patient out of the pocket expenses.

Conclusions and research needs

There seem be no desirable effects of INAH when compared to INCS in SAR and PAR. There is some evidence that INCS relieve nasal symptoms better and have fewer adverse effects. However, the differences in the effects are small and adverse effects mild, thus, the choice may primarily depend on availability and cost of particular medications, and patient's values and preferences.

Further research of an effect of INAH compared with INCS on quality of life in patients with PAR may be warranted. The only INAH used in these 3 studies was azelastine – studies of other INAH may also be beneficial.

What others are saying

The American Academy of Otolaryngology—Head and Neck Surgery guidelines do not make a specific recommendation for the choice of INAH or INCS but make a separate strong recommendation to use INCS “for patients with a clinical diagnosis of AR whose symptoms affect their quality of life” and give an option to use of INAH: “clinicians may offer INAH for patients with seasonal, perennial, or episodic AR” ⁷.

The American Academy of Family Physicians suggests “INCS alone for the initial treatment for AR with symptoms affecting quality of life” and “INAH as needed for mild intermittent symptoms” and adds that “because INAH are more expensive, less effective, and have more adverse effects than INCS, they are not recommended as first-line therapy for AR” ⁶⁶.

The AAAAI/ACAAI Practice Parameter does not make explicit recommendations for practice but states that INAH is “effective for SAR and PAR” but “less effective than INS” ⁶⁷. Note that this Practice Parameter was developed in 2008 when less information was available.

University of Michigan guidelines make no specific recommendations but state that INCS are the first and INAH are the fourth option to add in the treatment of seasonal allergic rhinitis” ⁶⁸.

Recommendation 5A

In patients with seasonal AR, we suggest an intranasal corticosteroid rather than an intranasal H1-antihistamine (conditional recommendation | moderate certainty of evidence).

Values and preferences

This recommendation places a higher value on greater reduction of symptoms and improvement of quality of life with INCS, compared to INAH, but and a lower value on avoiding larger cost of treatment with INCS in many jurisdictions.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs.

Recommendation 5B

In patients with perennial AR, we suggest an intranasal corticosteroid rather than intranasal H1-antihistamine (conditional recommendation | low certainty of evidence).

Values and preferences

This recommendation places a higher value on probably greater reduction of nasal symptoms with INCS, compared to INAH, although the overall difference is likely small. It places a lower value on avoiding larger cost of treatment with INCS in many jurisdictions.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs.

Question 6. Should a intranasal H1-antihistamine (INAH) vs. an oral H1-antihistamine (OAH) be used for treatment of allergic rhinitis?

Theoretically the major advantage of INAH is the delivery directly into the nose and possible avoidance or reduction in severity of systemic side effects of OAH. In 2010 revision of the ARIA guidelines we suggested that for majority of patients OAH would be a better choice, but the recommendation was mainly based on indirect evidence of the likely higher patient preference for an oral versus intranasal route of administration.

Summary of the evidence

We found 9 RCTs that investigated the effects of INAH compared to OAH in patients with SAR ¹²³⁻¹³⁴ and 4 studies in patients with PAR ¹³⁵⁻¹³⁸. All studies in SAR and 3 studies in PAR included only adult patients; only one study in PAR included older children and teenagers ¹³⁵. All studies in SAR and PAR used newer OAH except for 2 studies in SAR that used chlorpheniramine ^{131, 134}. Most studies used azelastine as INAH but one study in SAR and 2 studies in PAR used levocabastine. Studies in SAR followed patients for 2 to 6 weeks whereas only one study in PAR followed patient for at least 4 weeks ¹³⁸ that is recommended for studies in PAR ^{139, 140}.

Evidence profiles for questions 6A (seasonal AR) and 6B (perennial AR) are in the Online Repository 2.

Benefits

There seem to be differences in the effects among different INAH and OAH on nasal symptoms. There is moderate certainty evidence that azelastine has a smaller effect on nasal symptoms compared to cetirizine (SMD 0.21 SD higher, 95% CI: 0.06 to 0.36 higher). There is low certainty evidence that azelastine (in either dose) improves nasal symptoms more than chlorpheniramine (SMD 0.48 SD lower, 95% CI: 0.08 to 0.87 lower). However, in both cases confidence intervals do not exclude almost no effect. For all other comparisons there is no evidence that either INAH or OAH better relieve nasal symptoms (SMD 0 SD, 95% CI: 0.19 lower to 0.19 higher). In one study that measured this outcome, azelastine improved quality of life more than cetirizine (mean difference 0.3 point in RQLQ lower, 95% CI: 0.03 to 0.57 lower).

Panel members commented that there is a belief among researchers that INAH have a larger effect on nasal congestion, compared to OAH. We were not able to prove this effect in the 5 studies in SAR that reported congestion. Two studies reported end-of-study values (SMD: 0.01; 95% CI: 0.21 lower to 0.23 higher) and 3 studies reported changes from baseline (SMD: 0.08; 95% CI: 0.10 lower to 0.26 higher). This observation remained almost unchanged when we included only 2 studies that used larger doses of INAH (SMD: 0.13; 95% CI: 0.07 lower to 0.33 higher).

In patients with PAR, there was no evidence of a difference between INAH and OAH in nasal symptoms (SMD 0.13 higher, 95% CI: 0.12 lower to 0.39 higher) and in ocular symptoms (SMD 0.03 higher, 95% CI: 0.23 lower to 0.28 higher). No study in PAR measured quality of life.

Panel members noted that nasal congestion is an important persistent symptom of PAR. However, none of the studies in PAR reported the symptoms separately.

Harms and burden

There were no serious adverse effects in any of the trials in SAR or PAR. There was also no evidence of a difference in all adverse effects taken together.

Patients receiving INAH, compared to OAH, were more likely to discontinue treatment owing to adverse effect in studies of SAR (12 more per 1000 patients, 95% CI: from 1 fewer to 41 more) but not PAR (2 fewer per 1000 patients, 95% CI: from 20 fewer to 248 more). Patients receiving INAH, compared to OAH, were less likely to experience somnolence in studies of SAR (37 fewer per 1000 patients, 95% CI: 16 to 51 fewer) and PAR (24 fewer per 1000 patients, 95% CI: from 39 fewer to 67 more). We have not seen any inconsistency in comparative sedating effects in 8 studies of SAR irrespective of the newer or older OAH being used). Bitter taste was the most common adverse effect of INAH (120 more per 1000 patients, 95% CI: 60 to 190 more).

Decision criteria and additional considerations

We found no studies comparing cost of treatment with INAH and OAH. However, as with other treatment of AR, cost of treatment will very much depend on local availability and cost of branded and generic OAH and INAH. Generic OAH or INAH, if available, may be more cost-effective. Panel members noted that the availability of OAH and/or INAH other-the-counter in many countries may have an impact on the choice of treatment because patients' access to one or the other medication may be different based on their ability to cover out of the pocket expenses.

Conclusions and research needs

There is no consistent evidence showing better health outcomes with INAH or OAH in SAR and in PAR. However the evidence is of low or very low certainty. Choice of treatment will likely depend on patient's preferences for relief of specific symptoms and aversion to adverse effects – increased somnolence with OAH and increased bitter or perverted taste with INAH.

Additional RCTs of individual INAH vs. individual OAH that properly measure and report symptoms and quality of life may be warranted in SAR and in PAR. Specifically, the studies that measure real life effects of continuous or as-needed use of INAH and OAH that also measure patient preference for the route of administration may be beneficial.

What others are saying

The American Academy of Otolaryngology—Head and Neck Surgery guidelines do not make a specific recommendation for the choice of INAH or OAH but make a separate strong recommendation to use “second generation/less sedating OAH for patients with AR and primary

complaints of sneezing and itching” and give an option to use of INAH: “clinicians may offer INAH for patients with seasonal, perennial, or episodic AR” ⁷.

The American Academy of Family Physicians suggests either “OAH or INAH as needed for mild intermittent symptoms” and adds that “although INAH are an option if symptoms do not improve with nonsedating OAH, their use as first- or second-line therapy is limited by adverse effects, twice daily dosing, cost, and decreased effectiveness compared with INCS” ⁶⁶.

The AAAAI/ACAAI Practice Parameter does not make explicit recommendations for practice but states that the effectiveness of INAH for AR is equal or superior to second-generation OAH ⁶⁷. Note that this Practice Parameter was developed in 2008 when less information was available.

University of Michigan guidelines make no specific recommendations but state that OAH are the first and INAH are the fourth option to add in the treatment of allergic rhinitis” ⁶⁸.

Recommendation 6A

In patients with SAR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation | low certainty of evidence).

Values and preferences

The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.

Recommendation 6B

In patients with perennial AR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation | very low certainty of evidence).

Values and preferences

The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.

Plans for updating these guidelines

Guidelines are living products. To remain useful, they need to be updated regularly as new information accumulates. A revision of this document will be needed, because there was limited evidence for many clinical questions. This document will be updated when major new research is published. The need for update will be determined not later than in 2020.

Updating or adapting recommendations locally

The methods used to develop these guidelines are transparent. The recommendations have been developed to be as specific and detailed as possible without losing sight of the simplicity of the document. Since ARIA are meant as international guidelines, the guideline panel encourages feedback on all its aspects including applicability of recommendations in individual countries.¹⁴¹ This feedback will be considered with the next revision of ARIA guidelines.

Adaptation of ARIA guidelines will be necessary in many circumstances and we suggest that responsible parties use the GRADE-Adolopment process, a combination of adoption, adaptation of de novo creation of recommendations, with collaboration of the authors of this document.

Depending on when such a process takes place, the following steps are part of that process:

- Appointing a guideline committee comprising clinicians and methodologists
- Determining the scope of the local guidelines
- Defining the relevant clinical questions to be addressed in local guidelines
- Updating the evidence profiles and Evidence-to-Decision tables, if necessary
- Reviewing the recommendations in the ARIA guidelines (the recommendations may need to be modified at a local level, depending on the local values and preferences, availability of medications, costs, etc.)

Conclusions

Evidence-based guidelines are at the cornerstone of integrated care pathways (ICPs)^{142, 143}, structured multidisciplinary care plans that promote translation of guideline recommendations into local protocols and their subsequent application in clinical practice. Usually several guidelines are available providing advice about the management of the same condition². It is important to wisely choose appropriate guidelines for local adaptation and creation of ICPs, because most of them have limitations owing to either the development of the guideline itself or the available research evidence and its interpretation. The most common limitations of guidelines in AR are narrow scope (addressing only a small selection of important questions about the management of a given condition), suboptimal rigor of development and reporting, and inadequate representation of the views of patients and their caregivers². We acknowledge, that for the ARIA 2016 update we have

not reviewed all recommendations from the ARIA 2010 but we updated only 3 recommendations suggested by the ARIA panel members as requiring the update and we addressed 3 new questions. We also acknowledge that the ARIA guideline panel included allergists, ENT specialists, pulmonologists, general practitioners and pediatricians but did not include other health care professionals, pharmacists and patients themselves. However, for the ARIA 2016 update we systematically searched and reviewed the published evidence about the patient values and preferences regarding the outcomes and treatments for AR that to certain degree helped to overcome this limitation. We summarized the results in the section about the assumed values and preferences above and in the relevant sections of evidence-to-decision tables (Online Repository 2).

The available evidence has important limitations: 1) selective measurement and reporting of outcomes (e.g. few studies properly measure and report quality of life which is the most important outcome in AR), 2) selection of patients for clinical trials that may not represent appropriately the patients seen in primary care ¹⁴⁴ as well as 3) not distinguishing between patients with different age or severity of symptoms (lack of proper stratification) ¹⁴⁵, thus, limiting the applicability and generalizability of the research findings. Given these limitations, clinical practice guidelines – especially those with international audience – should emphasize rigorous systematic review of the health effects and explicit and detailed description of the assumed values and preferences and considerations of cost, feasibility, acceptability and health equity issues, as it is currently following the GRADE evidence-to-decision frameworks ¹⁴⁶⁻¹⁴⁸. Such detailed, explicit and transparent reporting of guidelines facilitates local adaptation of recommendations and their translation into ICPs. Systematic and transparent summaries of the evidence clearly identifying gaps in available research evidence are needed to direct research agenda and to avoid unnecessary expenditure of resources for further clinical research when it is not necessary ¹⁴⁹.

Implementation of guidelines in different settings and countries depends on the availability of health interventions (e.g. medical tests, medications, equipment, etc.), availability of resources, and cultural differences, among others. Thus, local adaptation of recommendations may be required and ICPs need to be developed at national, regional or local level. However, they always should be based on systematically reviewed evidence of desirable and undesirable consequences. The ARIA 2016 revision will be used to develop the ICPs proposed by the European Innovation Partnership on Active and Healthy Ageing ^{142, 143, 150} using MASK (MACVIA-ARIA Sentinel Network). ARIA is developing a novel implementation strategy using mobile technology ^{151, 152} and a clinical decision support system (CDSS) ¹⁵¹ and deployed in 21 countries ¹⁵³. The ARIA 2016 revision will be embedded in the CDSS for real-time patient stratification using mobile technology.

Most of the recommendations are based on low or very low certainty evidence mainly because the imprecision of the estimated effects owing to few patients being studied. For those questions there is a need for more well designed and executed randomized controlled trials that would measure and properly report all important outcomes.

Disclosure of potential conflict of interest

All ARIA panel members declared their actual, potential or perceived competing interests within the past 4 years related to the subject matter of these guidelines following the standard procedure of the World Health Organization.

Claus Bachert received honoraria for speaking and/or serving on advisory board from Meda, ALK, and Stallergenes; he is a member of guideline committee of the German Allergy Society (DGAKI).

Sinthia Bosnic-Anticevich is leading the update of the Pharmacy ARIA guidelines.

Jean Bousquet received honoraria for speaking and/or serving on scientific or advisory board from Almirall, AstraZeneca, Chiesi, GSK, Meda, Menarini, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach.

Jan Brozek together with Holger Schünemann received US\$40,000 from the ARIA Initiative to support performing systematic reviews for these guidelines that have been deposited to McMaster University research account (it was used to support research assistants involved in this work; the majority of funding for the systematic reviews was contributed by McMaster University internal research funds); he has no other competing interests.

Giorgio Walter Canonica received honoraria for speaking and/or serving on scientific or advisory board, and research support from Alk-Abello', Almirall, Allergy Therapeutics, Anallergo, AstraZeneca, Boehringer Ingelheim, Boston Scientific, Bruschettini, Chiesi Farmaceutici, Circassia, Danone, Faes, Glaxo Smith Kline, Lab.Guidotti, Lallemand, Lofarma, Malesci, Meda Pharmaceuticals, Menarini, Mundifarma, Novartis, Pfizer, Roche, Sanofi, Stallergenes, Thermo Fisher, Uriach, Teva and Valeas.

Thomas Casale received honoraria for consultation from Sanofi Regeneron, Ora, Circassia and Capnia.

Alvaro Cruz received honoraria for serving on advisory board from AstraZeneca, Boehringer Ingelheim, GSK, Meda Pharmaceuticals, and Roche; he also received research grants and travel support from GSK, AstraZeneca, and MSD.

Pascal Demoly received honoraria for consultation and/or speaking for Allergopharma, AllergyTherapeutics, ALK-Abello, AstraZeneca, Chiesi, Circassia, GlaxoSmithKline, Meda Pharmaceuticals, Merck, Menarini, Stallergenes-Greer, and ThermoFisherScientific.

Mark Dykewicz received honoraria for consultation from Merck; he also served as consultant for U.S. FDA about allergen immunotherapy and is a co-author of the American Academy of Otolaryngology-Head Neck Surgery Clinical Practice Guideline on Allergic Rhinitis and currently being updated U.S. Joint Task Force (AAAAI/ACAAI) Rhinitis Practice Parameter.

Wyske Fokkens reported receiving support from Allergopharma, GSK, Meda Pharmaceuticals and Stallergenes, paid to her institution.

Joao Fonseca received honoraria for consultation from Novartis and for speaking from Menarini, Lab Vitoria, and Novartis and research support from MSD; he is a secretary general of the Portuguese Society of Allergy and Clinical Immunology (SPAIC).

Ludger Klimek received honoraria for consultation and/or speaking for ALK-Abelló, Allergopharma, HAL, Allergy Therapeutics/Bencard, Meda Pharmaceuticals, and Leti; he also received research support from ALK-Abelló, Allergopharma, Stallergenes, HAL, Allergy Therapeutics/Bencard, Lofarma, MEDA, Novartis, Leti, ROXALL, and Cytos.

Piotr Kuna received honoraria for speaking from Adamed, Allergopharma, AstraZeneca, Berlin Chemie, Meda, Boehringer Ingelheim, Chiesi, FAES, GSK, MSD, Novartis, Pfizer, Stallergenes, and Teva.

Désirée Larenas Linnemann received honoraria for consultation and/or speaking from AstraZeneca, Glenmark, MEDA, Mit-pharma, MSD, Novartis, Pfizer, Sanofi, and TEVA; she also received research support from MEDA, MSD, AstraZeneca, Novartis, GSK, TEVA, Senosiain, Carnot, Sanofi, Pfizer and travel support from MEDA, MSD, Sanofi, Novartis, Stallergenes, UCB, Pfizer, ALK-Abelló.

Eli Meltzer received honoraria for consultation and/or speaking from AstraZeneca, Boehringer Ingelheim, Church & Dwight, Circassia, Meda, Merck, Regeneron-Sanofi and Teva; he is a co-author of the currently being updated U.S. Joint Task Force (AAAAI/ACAAI) Rhinitis Practice Parameter.

Joaquim Mullol received honoraria for speaking from UCB Pharma, Uriach Group, GSK, Hartington Pharmaceuticals, Menarini, Hyphens, Novartis, MSD, MEDA Pharma, and Sanofi-Aventis and research support from Uriach Group, Meda Pharmaceuticals, GSK, MSD, and FAES.

Petr Panzner received honoraria for speaking from Stallergenes, AstraZeneca, MEDA, and MSD.

Nikos Papadopoulos received research support from Menarini and Merck and for speaking for several undisclosed companies; he is the past president of EAACI and a member of the board of the Global Allergy and Asthma European Network (GA²LEN).

David Price received honoraria for speaking, research and travel support from Meda Pharmaceuticals.

Dermot Ryan received honoraria for speaking and/or serving on advisory board from Uriach, Stallergenes, and MEDA; he is chairing the Primary Care Interest Group in EAACI.

Boleslaw Samolinski received honoraria for speaking from Nexter-Allergopharma, Meda, Adamed, Polpharma and Teva.

Peter Schmid-Grendelmeier received honoraria for consulting from ALK ABello, Novartis and Thermo Fisher.

Holger Schünemann together with Jan Brozek received US\$40,000 from the ARIA Initiative to support performing systematic reviews for these guidelines that have been deposited to McMaster University research account (it was used to support research assistants involved in this work; the majority of funding for the systematic reviews was contributed by McMaster University internal research funds); he has no other competing interests.

Aziz Sheikh declared that his institution received research support from Asthma UK (charitable funder), the Scottish Government, EAACI and unrestricted industry funding from a multiple

companies to run the Scottish Allergy and Respiratory Academy (SARA); he is involved in guideline initiatives of EAACI, BTS/SIGN, WAO and the Resuscitation Council (UK).

Antonio Valero received honoraria from Novartis, Sanofi, GSK, Chiesi, Boehringer, FAES, Meda, Orion Pharma, Stallergenes, and Leti and research support from Novartis, Uriach, FAES, and Leti.

Dana Wallace received honoraria for consultation, speaking and serving on advisory board from MEDA Pharmaceuticals; she is a co-author of the American Academy of Otolaryngology-Head Neck Surgery Clinical Practice Guideline on Allergic Rhinitis and currently being updated U.S. Joint Task Force (AAAAI/ACAAI) Rhinitis Practice Parameter.

Susan Wasserman received honoraria for speaking, serving on advisory board and/or travel support from Merck, Meda Pharmaceuticals, Stallergens, Pfizer, and Pediapharm.

Magnus Wickman received honoraria for speaking and/or serving on advisory board from ALK, Meda Pharmaceuticals, Thermofischer Scientific and Stallergens

Torsten Zuberbier received institutional funding for research and/or honoraria for lectures and/or consulting from AstraZeneca, AbbVie, ALK, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES, HAL, Henkel, Kryolan, Leti, L'Oreal, Meda Pharmaceuticals, Menarini, Merck, MSD, Novartis, Pfizer, Sanofi, Stallergenes, Takeda, Teva and UCB. In addition, he is a member of the German Society for Allergy and Clinical Immunology (DGAKI), the European Centre for Allergy Research Foundation (ECARF), the Global Allergy and Asthma European Network (GA²LEN), and the World Allergy Organization (WAO).

Other authors: Ioana Agache, Niels Chavannes, Jaime Correia de Sousa, Peter Hellings, Pat Manning, Robyn O'Hehir, Ken Ohta, Giovanni Passalacqua, Arunas Valiulis, Erkkä Valovirta, Luo Zhang, and Mihaela Zidarn declared that they had no competing interests related to these guidelines.

Members of the methodology team who participated in systematic review of the literature (Romina Brignardello-Petersen, Carlos A. Cuello-Garcia, Itziar Etxeandia Ikobaltzeta, Iván Florez, Sergio Kowalski, Kaja-Triin Laisaar, John Riva, Yetiani Roldán, Behnam Sadeghirad, Matthew Ventresca, Wojtek Wiercioch, Juan José Yepes-Nuñez, Yuan Zhang) also declared that they had no competing interests related to these guidelines.

All ARIA panel members and methodology team members declared no relationship with any entity directly or indirectly involved in the production, distribution or sale of tobacco or tobacco products.

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ARIA 2016 Update

Online Repository 2

Evidence-to-Decisions frameworks

Question 1A

Should a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of seasonal allergic rhinitis?

POPULATION:	Patients with seasonal AR	BACKGROUND: A combination of INCS with OAH may have an advantage over INCS alone as their mechanisms of action are different. Their effects may be additive and each has specific advantages and disadvantages.
INTERVENTION:	a combination of OAH and INCS	
COMPARISON:	INCS alone	
MAIN OUTCOMES:	symptoms, quality of life, adverse effects	
SETTING:	primary care	
PERSPECTIVE:	individual patient	

Assessment

	JUDGMENT	RESEARCH EVIDENCE				ADDITIONAL CONSIDERATIONS																																	
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).																																					
	How substantial are the desirable anticipated effects? ☐ Trivial ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	<table><thead><tr><th>Outcome</th><th>Ns of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr></thead><tbody><tr><td>Nasal symptoms</td><td>1193 (5 RCTs)</td><td>-</td><td>SMD 0.13 lower (0.25 lower to 0)</td></tr><tr><td>Ocular symptoms</td><td>754 (2 RCTs)</td><td>-</td><td>SMD 0.19 lower (0.33 lower to 0.05 lower)</td></tr><tr><td>Quality of life</td><td>354 (2 RCTs)</td><td>-</td><td>SMD 0.61 lower (1.44 lower to 0.23 higher)</td></tr><tr><td>Serious adverse effects (SAE)</td><td>739 (4 RCTs)</td><td>not estimable</td><td>0 fewer per 1000 (10 fewer to 10 more)</td></tr></tbody></table>	Outcome	Ns of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms	1193 (5 RCTs)	-	SMD 0.13 lower (0.25 lower to 0)	Ocular symptoms	754 (2 RCTs)	-	SMD 0.19 lower (0.33 lower to 0.05 lower)	Quality of life	354 (2 RCTs)	-	SMD 0.61 lower (1.44 lower to 0.23 higher)	Serious adverse effects (SAE)	739 (4 RCTs)	not estimable	0 fewer per 1000 (10 fewer to 10 more)	<table><tbody><tr><td>Withdrawal owing to an adverse event</td><td>754 (2 RCTs)</td><td>RR 0.65 (0.13 to 3.23)</td><td>20 fewer per 1000 (51 fewer to 130 more)</td></tr><tr><td>Any adverse effect</td><td>414 (3 RCTs)</td><td>RR 1.21 (0.29 to 5.01)</td><td>42 more per 1000 (141 fewer to 794 more)</td></tr><tr><td>Sedation/somnolence</td><td>1213 (5 RCTs)</td><td>RR 1.55 (0.39 to 6.13)</td><td>15 more per 1000 (17 fewer to 143 more)</td></tr><tr><td>Epistaxis</td><td>1153 (4 RCTs)</td><td>RR 1.77 (0.86 to 3.63)</td><td>15 more per 1000 (3 fewer to 50 more)</td></tr></tbody></table>	Withdrawal owing to an adverse event	754 (2 RCTs)	RR 0.65 (0.13 to 3.23)	20 fewer per 1000 (51 fewer to 130 more)	Any adverse effect	414 (3 RCTs)	RR 1.21 (0.29 to 5.01)	42 more per 1000 (141 fewer to 794 more)	Sedation/somnolence	1213 (5 RCTs)	RR 1.55 (0.39 to 6.13)	15 more per 1000 (17 fewer to 143 more)	Epistaxis	1153 (4 RCTs)	RR 1.77 (0.86 to 3.63)	15 more per 1000 (3 fewer to 50 more)
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UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ☐ Large ☐ Moderate ☒ Small ☐ Trivial ☐ Varies ☐ Don't know	All studies investigated new generation OAH. Older generation OAH that are usually more sedating, may have more adverse effects.																																					

CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? ☐ High ☒ Moderate ☐ Low ☐ Very low ☐ No included studies	<table><tr><th>Outcome</th><th>Quality</th><th>Importance</th></tr><tr><td>Nasal symptoms</td><td>HIGH</td><td>Critical</td></tr><tr><td>Ocular symptoms</td><td>MODERATE</td><td>Critical</td></tr><tr><td>Quality of life</td><td>LOW</td><td>Critical</td></tr><tr><td>Serious adverse effect</td><td>HIGH</td><td>Critical</td></tr><tr><td>Withdrawal owing to adverse event</td><td>MODERATE</td><td>Critical</td></tr><tr><td>Any adverse effect</td><td>VERY LOW</td><td>Important</td></tr><tr><td>Sedation/somnolence</td><td>LOW</td><td>Important</td></tr><tr><td>Epistaxis</td><td>MODERATE</td><td>Important</td></tr></table>	Outcome	Quality	Importance	Nasal symptoms	HIGH	Critical	Ocular symptoms	MODERATE	Critical	Quality of life	LOW	Critical	Serious adverse effect	HIGH	Critical	Withdrawal owing to adverse event	MODERATE	Critical	Any adverse effect	VERY LOW	Important	Sedation/somnolence	LOW	Important	Epistaxis	MODERATE	Important	
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VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability	Values and Preferences: Outcomes One systematic review identified 7 cross-sectional studies (Burstrom 2011, Revicki 1998, Revicki 2011, Gold 1998, Demoly 2013, Senti 2007, Tamayama 2009) on utility/value associated with AR. With 0 indicating death and 1 indicating perfect health, the overall range of utility/value based on generic measurements was 0.63-0.91 for allergic rhinitis (HUI-2: 0.83, EQ-5D: 0.85-0.91, VAS: 0.63). Two studies (Lo 2006, Tamayama 2009) reported utility for different severity of allergic rhinitis, one using rating scale and time trade off (Tamayama 2009), another one using disease specific rhinitis symptom utility index (RSUI) (Lo 2006). The utilities based on time trade off were 0.96, 0.94, 0.89, 0.83 for mild, moderate, severe and very severe AR, respectively. The utilities based on rating scale were 0.82, 0.71, 0.56 and 0.43 for mild, moderate, severe and very severe AR, respectively. The disease specific RSUI suggested the utilities were 0.83, 0.69 and 0.50 for mild, moderate, and severe allergic rhinitis. One RCT (Poole 2014) studied the disutility in relation to a unit change in symptom score and medication score. This study suggested the disabilities were 0.17 and 0.13 for one unit increase in daily rhinoconjunctivitis symptom score and daily medication score, respectively. In a small sample of 83 Japanese patients, regarding clinical symptoms, nasal obstruction was identified as the most important symptom influencing patient satisfaction. (Ogino 2006) Values and Preferences: Treatments A cross-sectional study of 170 patients with AR examined the preferences in view of treatment and fear of side effects of the most common treatment options; 30% (52/170) preferred a nasal spray, 25% (42/170) preferred oral treatment and 16% (30/170) preferred combination treatment, whereas 15% (27/170) preferred injection treatment. Additionally, 48% (81/170) expressed concern regarding the side effects of INCS sprays compared to other treatments (Hellings 2012). A cross-sectional study of 503 patients with AR and an RCT in Indonesia found that patients prefer treatment options with no smell or taste (Kaliner 2001, Bunnag 2003). Populations in Spain identified that positive formulation attributes were correct texture, appearance, color, size and rapid dissolution (reported by 95% of patients (57/60) and 91% of physicians (75/82)). (Roger 2006)	Panel members noted that some patients beginning treatment may prefer the combination therapy because of faster onset of action of OAH and slower onset of action for INCS. Panel members also noted that adherence to treatment may be lower with increased number of medications.																											
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☒ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ Don't know	<table><tr><th>Outcome</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr><tr><td>Nasal symptoms</td><td>-</td><td>SMD 0.13 lower (0.25 lower to 0)</td></tr><tr><td>Ocular symptoms</td><td>-</td><td>SMD 0.19 lower (0.33 lower to 0.05 lower)</td></tr><tr><td>Quality of life</td><td>-</td><td>SMD 0.61 lower (1.44 lower to 0.23 higher)</td></tr><tr><td>Serious adverse effects (SAE)</td><td>not estimable</td><td>0 fewer per 1000 (10 fewer to 10 more)</td></tr><tr><td>Withdrawal owing to an adverse event</td><td>RR 0.65 (0.13 to 3.23)</td><td>20 fewer per 1000 (51 fewer to 130 more)</td></tr></table>	Outcome	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms	-	SMD 0.13 lower (0.25 lower to 0)	Ocular symptoms	-	SMD 0.19 lower (0.33 lower to 0.05 lower)	Quality of life	-	SMD 0.61 lower (1.44 lower to 0.23 higher)	Serious adverse effects (SAE)	not estimable	0 fewer per 1000 (10 fewer to 10 more)	Withdrawal owing to an adverse event	RR 0.65 (0.13 to 3.23)	20 fewer per 1000 (51 fewer to 130 more)	All evidence is available only for new generation OAH; for older OAH with more sedative effects the balance of desirable and undesirable effects may be different.									
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RESOURCES REQUIRED	How large are the resource requirements (costs)? ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	A retrospective database analysis using pharmacy and medical claims data from a US health plan compared medical and pharmacy cost of different treatments for rhinitis (Dalai 2008). Prescription cost of INCS alone was estimated to be US\$188 ±173 per person per year. Cost of a combination therapy with INCS and an antihistamine (authors have not reported whether these were oral or intranasal antihistamines; we assumed they were oral) was estimated to be US\$253 ±169 plus US\$186 ±169 per person per year. A Swedish population-based questionnaire study (Cardell 2016) found a mean annual cost of treatment with OAH to be €35.4 per person and the cost of INCS – €32.4 per person. The cost per patient varied with the ARIA classification of the severity of symptoms and was higher for persons with moderate to severe persistent allergic rhinitis compared to mild persistent disease	Some panel members thought that resources would be a concern in settings where those medications are currently more expensive (e.g. the USA) and not in settings where their relative cost is not high (e.g. in EU).
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	No research evidence was identified.	Judgment was based on one retrospective cohort, one cross-sectional survey, and unsystematic observations in panel members practice.
COST-EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☒ Varies ☐ No included studies	No research evidence was identified.	Some panel members thought that a combination is not cost effective compared to INCS alone, because of little, if any, additional benefit and nontrivial additional cost of a combination therapy.
EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced ☒ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	No research evidence was identified.	Apart from the availability of resources, combined intervention compared to INCS alone would likely have no impact on health equity. From the patient perspective, increased cost of the combined treatment compared to INCS alone may be particularly important in settings where OAH are available over the counter and not covered by drug plans. With a minimum co-pay for INCS and no coverage for OAH, the cost of adding OAH is often high, particularly to those individuals with limited resources.
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	

FEASIBILITY	Is the intervention feasible to implement?	No research evidence was identified.	
	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know		

Summary of Judgments

	JUDGMENT							IMPLICATIONS
PROBLEM	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
DESIRABLE EFFECTS	Don't know	Varies	No known desirable effects	Trivial	Small	Moderate	Large	Favors OAH+INCS
UNDESIRABLE EFFECTS	Don't know	Varies	No known undesirable effects	Large	Moderate	Small	Trivial	Favors INCS alone
CERTAINTY OF EVIDENCE	No included studies			Very low	Low	Moderate	High	Favors neither intervention
VALUES				Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	Favors neither intervention
BALANCE OF EFFECTS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors OAH+INCS
RESOURCES REQUIRED	Don't know	Varies	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Favors INCS alone
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies			Very low	Low	Moderate	High	Favors INCS alone
COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INCS alone
EQUITY	Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Favors neither intervention
ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of seasonal allergic rhinitis?

TYPE OF RECOMMENDATION	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
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	☐	☐	☒	☐	☐
RECOMMENDATION	In patients with seasonal AR, we suggest either a combination of an intranasal corticosteroid with an oral H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation low certainty of evidence)				
JUSTIFICATION	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. The additional reduction in severity of nasal and ocular symptoms with a combination therapy is small and unlikely to be noticed by majority of patients. The beneficial impact on quality of life is uncertain, as is the magnitude of increase in adverse effects. Panel members felt that in majority of situations, where a combination therapy is considerably more expensive than INCS alone, any potential net benefit would not justify spending additional resources. This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of OAH is not large and/or patient values and preferences differ from those assumed by guideline panel members a combination therapy may be a reasonable choice, especially in the subgroups of patients identified below. This recommendation concerns regular use of OAH and INCS in seasonal AR. All evidence is available only for new generation OAH; for older OAH with more sedative effects the balance of desirable and undesirable effects may be different.				
SUBGROUP CONSIDERATIONS	There is no currently available direct evidence from experimental studies about subgroups based on severity of individual symptoms. However, based on indirect evidence it is possible that selected patients may benefit more from a combination therapy (e.g. those not well controlled with INCS alone, those with pronounced ocular symptoms or those at the beginning of treatment for faster onset of treatment effect).				
IMPLEMENTATION CONSIDERATIONS	–				
MONITORING AND EVALUATION	–				
RESEARCH PRIORITIES	Further research of a combination of OAH with INCS as a step-up therapy in patients not well controlled with INCS alone is warranted. Additional information is needed about the effects of combination therapy relative to INCS alone in subpopulation of patients with pronounced ocular symptoms or those in whom rhinorrhea rather than congestion is the main symptom. Studies of real life effects of the combination therapy compared to monotherapy used as needed, rather than regularly, may also be warranted. If done, studies should measure not only nasal symptoms but also quality of life and properly report adverse effects.				

Question 1B

Should a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of perennial allergic rhinitis?

POPULATION:	Patients with perennial AR	BACKGROUND: A combination of INCS with OAH may have an advantage over INCS alone as their mechanisms of action are different. Their effects may be additive and each has specific advantages and disadvantages.
INTERVENTION:	a combination of OAH and INCS	
COMPARISON:	INCS alone	
MAIN OUTCOMES:	symptoms, quality of life, adverse effects	
SETTING:	primary care	
PERSPECTIVE:	individual patient	

Assessment

	JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																				
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).																					
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ☒ No desirable effects ☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	<table border="1"> <thead> <tr> <th>Outcome</th><th>N₂ of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr> </thead> <tbody> <tr> <td>Nasal symptoms (all patients had PAR)</td><td>117 (1 RCT)</td><td>–</td><td>MD 0.2 points in TNSS higher (not reported)</td></tr> <tr> <td>Nasal symptoms (70% patients with PAR)</td><td>170 (1 RCT)</td><td>–</td><td>MD 0 points in TNSS lower (0.73 lower to 0.73 higher)</td></tr> <tr> <td>Ocular symptoms (70% patients with PAR)</td><td>170 (1 RCT)</td><td>–</td><td>MD 0.1 points in TOSS higher (0.38 lower to 0.58 higher)</td></tr> <tr> <td>Quality of life (70% patients with PAR)</td><td>170 (1 RCT)</td><td>–</td><td>MD 0.2 points in RQLQ lower (0.53 lower to 0.13 higher)</td></tr> </tbody> </table>	Outcome	N ₂ of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms (all patients had PAR)	117 (1 RCT)	–	MD 0.2 points in TNSS higher (not reported)	Nasal symptoms (70% patients with PAR)	170 (1 RCT)	–	MD 0 points in TNSS lower (0.73 lower to 0.73 higher)	Ocular symptoms (70% patients with PAR)	170 (1 RCT)	–	MD 0.1 points in TOSS higher (0.38 lower to 0.58 higher)	Quality of life (70% patients with PAR)	170 (1 RCT)	–	MD 0.2 points in RQLQ lower (0.53 lower to 0.13 higher)	
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UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ☐ Large ☐ Moderate ☒ Small ☐ Trivial ☐ Varies ☐ Don't know	<table border="1"> <tbody> <tr> <td>Any adverse effect (70% patients with PAR)</td><td>170 (1 RCT)</td><td>RR 5.36 (0.64 to 44.94)</td><td>49 more per 1000 (4 fewer to 494 more)</td></tr> <tr> <td>Serious adverse effect (70% patients with PAR)</td><td>170 (1 RCT)</td><td>not estimable</td><td>0 more per 1000 (22 fewer to 23 more)</td></tr> </tbody> </table>	Any adverse effect (70% patients with PAR)	170 (1 RCT)	RR 5.36 (0.64 to 44.94)	49 more per 1000 (4 fewer to 494 more)	Serious adverse effect (70% patients with PAR)	170 (1 RCT)	not estimable	0 more per 1000 (22 fewer to 23 more)	Levocetirizine was used in both studies. Older generation OAH that are usually more sedating, may have more adverse effects.												
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CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	<table><tr><th>Outcome</th><th>Quality</th><th>Importance</th></tr><tr><td>Nasal symptoms</td><td>LOW</td><td>Critical</td></tr><tr><td>Ocular symptoms</td><td>LOW</td><td>Critical</td></tr><tr><td>Quality of life</td><td>VERY LOW</td><td>Critical</td></tr><tr><td>Serious adverse effect</td><td>MODERATE</td><td>Critical</td></tr><tr><td>Any adverse effect</td><td>VERY LOW</td><td>Important</td></tr></table>	Outcome	Quality	Importance	Nasal symptoms	LOW	Critical	Ocular symptoms	LOW	Critical	Quality of life	VERY LOW	Critical	Serious adverse effect	MODERATE	Critical	Any adverse effect	VERY LOW	Important				
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VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability	Values and Preferences: Outcomes One systematic review identified 7 cross-sectional studies (Burstrom 2011, Revicki 1998, Revicki 2011, Gold 1998, Demoly 2013, Senti 2007, Tamayama 2009) on utility/value associated with AR. With 0 indicating death and 1 indicating perfect health, the overall range of utility/value based on generic measurements was 0.63-0.91 for allergic rhinitis (HUI-2: 0.83, EQ-5D: 0.85-0.91, VAS: 0.63). Two studies (Lo 2006, Tamayama 2009) reported utility for different severity of allergic rhinitis, one using rating scale and time trade off (Tamayama 2009), another one using disease specific rhinitis symptom utility index (RSUI) (Lo 2006). The utilities based on time trade off were 0.96, 0.94, 0.89, 0.83 for mild, moderate, severe and very severe AR, respectively. The utilities based on rating scale were 0.82, 0.71, 0.56 and 0.43 for mild, moderate, severe and very severe AR, respectively. The disease specific RSUI suggested the utilities were 0.83, 0.69 and 0.50 for mild, moderate, and severe allergic rhinitis. One RCT (Poole 2014) studied the disutility in relation to a unit change in symptom score and medication score. This study suggested the disabilities were 0.17 and 0.13 for one unit increase in daily rhinoconjunctivitis symptom score and daily medication score, respectively. In a small sample of 83 Japanese patients, regarding clinical symptoms, nasal obstruction was identified as the most important symptom influencing patient satisfaction. (Ogino 2006) Values and Preferences: Treatments A cross-sectional study of 170 patients with AR examined the preferences in view of treatment and fear of side effects of the most common treatment options; 30% (52/170) preferred a nasal spray, 25% (42/170) preferred oral treatment and 16% (30/170) preferred combination treatment, whereas 15% (27/170) preferred injection treatment. Additionally, 48% (81/170) expressed concern regarding the side effects of INCS sprays compared to other treatments (Hellings 2012). A cross-sectional study of 503 patients with AR and an RCT in Indonesia found that patients prefer treatment options with no smell or taste (Kalinier 2001, Bunnag 2003). Populations in Spain identified that positive formulation attributes were correct texture, appearance, color, size and rapid dissolution (reported by 95% of patients (57/60) and 91% of physicians (75/82)). (Roger 2006)	Panel members noted that some patients beginning treatment may prefer the combination therapy because of faster onset of action of OAH and slower onset of action for INCS. This may be less important in PAR than in SAR.																					
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ☒ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ Don't know	<table><tr><th>Outcome</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr><tr><td>Nasal symptoms (all PAR)</td><td>–</td><td>MD 0.2 higher (–)</td></tr><tr><td>Nasal symptoms (70% with PAR)</td><td>–</td><td>MD 0 lower (0.73 lower to 0.73 higher)</td></tr><tr><td>Ocular symptoms (70% with PAR)</td><td>–</td><td>MD 0.1 higher (0.38 lower to 0.58 higher)</td></tr><tr><td>Quality of life (70% with PAR)</td><td>–</td><td>MD 0.2 lower (0.53 lower to 0.13 higher)</td></tr><tr><td>Any adverse effect (70% with PAR)</td><td>RR 5.36 (0.64 to 44.94)</td><td>49 more per 1000 (4 fewer to 494 more)</td></tr><tr><td>Serious adverse effect (70% with PAR)</td><td>not estimable</td><td>0 more per 1000 (22 fewer to 23 more)</td></tr></table>	Outcome	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms (all PAR)	–	MD 0.2 higher (–)	Nasal symptoms (70% with PAR)	–	MD 0 lower (0.73 lower to 0.73 higher)	Ocular symptoms (70% with PAR)	–	MD 0.1 higher (0.38 lower to 0.58 higher)	Quality of life (70% with PAR)	–	MD 0.2 lower (0.53 lower to 0.13 higher)	Any adverse effect (70% with PAR)	RR 5.36 (0.64 to 44.94)	49 more per 1000 (4 fewer to 494 more)	Serious adverse effect (70% with PAR)	not estimable	0 more per 1000 (22 fewer to 23 more)	
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RESOURCES REQUIRED	How large are the resource requirements (costs)? ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	A retrospective database analysis using pharmacy and medical claims data from a US health plan compared medical and pharmacy cost of different treatments for rhinitis (Dalai 2008). Prescription cost of INCS alone was estimated to be US\$188 ±173 per person per year. Cost of a combination therapy with INCS and an antihistamine (authors have not reported whether these were oral or intranasal antihistamines; we assumed they were oral) was estimated to be US\$253 ±169 plus US\$186 ±169 per person per year. A Swedish population-based questionnaire study (Cardell 2016) found a mean annual cost of treatment with OAH to be €35.4 per person and the cost of INCS – €32.4 per person. The cost per patient varied with the ARIA classification of the severity of symptoms and was higher for persons with moderate to severe persistent allergic rhinitis compared to mild persistent disease.	Some panel members thought that resources would be a concern in settings where those medications are currently more expensive (e.g. the USA) and not in settings where their relative cost is not high (e.g. in EU).
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	No research evidence was identified.	Judgment was based on one retrospective cohort, one cross-sectional survey, and unsystematic observations in panel members practice.
COST-EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ☒ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ No included studies	No research evidence was identified.	Panel members decided that a combination is not cost effective compared to INCS alone, because of no evidence of additional benefit.
EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced ☒ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	No research evidence was identified.	Apart from the availability of resources, combined intervention compared to INCS alone would likely have no impact on health equity. From the patient perspective, increased cost of the combined treatment compared to INCS alone may be particularly important in settings where OAH are available over the counter and not covered by drug plans. With a minimum co-pay for INCS and no coverage for OAH, the cost of adding OAH is often high, particularly to those individuals with limited resources.
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	

FEASIBILITY	Is the intervention feasible to implement?	No research evidence was identified.	
	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know		

Summary of Judgments

	JUDGMENT							IMPLICATIONS
PROBLEM	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
DESIRABLE EFFECTS	Don't know	Varies	No known desirable effects	Trivial	Small	Moderate	Large	Favors INCS alone
UNDESIRABLE EFFECTS	Don't know	Varies	No known undesirable effects	Large	Moderate	Small	Trivial	Favors INCS alone
CERTAINTY OF EVIDENCE	No included studies			Very low	Low	Moderate	High	Favors neither intervention
VALUES				Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	Favors neither intervention
BALANCE OF EFFECTS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INCS alone
RESOURCES REQUIRED	Don't know	Varies	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Favors INCS alone
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies			Very low	Low	Moderate	High	Favors INCS alone
COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INCS alone
EQUITY	Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Favors neither intervention
ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of perennial allergic rhinitis?

TYPE OF RECOMMENDATION	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 ☐
RECOMMENDATION	In patients with perennial AR, we suggest an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H1-antihistamine (conditional recommendation very low certainty of evidence)				
JUSTIFICATION	Currently available evidence suggests that there is no additional benefit from a combination therapy compared to INCS alone and there may be additional undesirable effects. This recommendation is conditional because of very low certainty of the estimated effects.				
SUBGROUP CONSIDERATIONS	–				
IMPLEMENTATION CONSIDERATIONS	–				
MONITORING AND EVALUATION	–				
RESEARCH PRIORITIES	Further research to identify subgroups of patient more likely to benefit from H1-antihistamine added to INCS may be warranted.				

Question 2A

Should a combination of **intranasal H1-antihistamine and intranasal corticosteroid** vs. **intranasal corticosteroid alone** be used for treatment of **seasonal allergic rhinitis**?

POPULATION:	Patients with seasonal AR	BACKGROUND: A combination of INCS with INAH may have an advantage over INCS alone as their mechanisms of action are different. Their effects may be additive and each has specific advantages and disadvantages.
INTERVENTION:	a combination of INAH and INCS	
COMPARISON:	INCS alone	
MAIN OUTCOMES:	symptoms, quality of life, adverse effects	
SETTING:	primary care	
PERSPECTIVE:	individual patient	

Assessment

	JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																												
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).																													
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ☒ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	<table> <tr> <th>Outcome</th><th>N_e of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr> <tr> <td>Nasal symptoms (TNSS; scale 0-24)</td><td>2100 (5 RCTs)</td><td>–</td><td>MD 0.77 lower (1.24 lower to 0.3 lower)</td></tr> <tr> <td>Ocular symptoms (different scales)</td><td>2100 (5 RCTs)</td><td>–</td><td>SMD 0.2 lower (0.33 lower to 0.07 lower)</td></tr> <tr> <td>Quality of life (RQLQ; scale 1-7)</td><td>2100 (5 RCTs)</td><td>–</td><td>MD 0.13 higher (0.01 higher to 0.24 higher)</td></tr> <tr> <td>Serious adverse effect</td><td>1801 (4 RCTs)</td><td>not estimable (no events)</td><td>2 fewer per 1000 (from 3 fewer to 7 fewer)</td></tr> <tr> <td>Withdrawal owing to adverse effect</td><td>1699 (3 RCTs)</td><td>RR 1.94 (0.59 to 6.36)</td><td>4 more per 1000 (from 2 fewer to 25 more)</td></tr> <tr> <td>Any adverse effect</td><td>1699 (3 RCTs)</td><td>RR 1.66 (1.19 to 2.31)</td><td>41 more per 1000 (from 12 more to 81 more)</td></tr> </table>	Outcome	N _e of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms (TNSS; scale 0-24)	2100 (5 RCTs)	–	MD 0.77 lower (1.24 lower to 0.3 lower)	Ocular symptoms (different scales)	2100 (5 RCTs)	–	SMD 0.2 lower (0.33 lower to 0.07 lower)	Quality of life (RQLQ; scale 1-7)	2100 (5 RCTs)	–	MD 0.13 higher (0.01 higher to 0.24 higher)	Serious adverse effect	1801 (4 RCTs)	not estimable (no events)	2 fewer per 1000 (from 3 fewer to 7 fewer)	Withdrawal owing to adverse effect	1699 (3 RCTs)	RR 1.94 (0.59 to 6.36)	4 more per 1000 (from 2 fewer to 25 more)	Any adverse effect	1699 (3 RCTs)	RR 1.66 (1.19 to 2.31)	41 more per 1000 (from 12 more to 81 more)	There are small additional benefits from combined therapy. In studies that used combination therapy in one spray, one showed benefit with combination therapy (Hampel 2010) and the other did not show the difference (Carr 2012). Indirect evidence from bioavailability study (Derendorf 2012) suggests that a combination of azelastine and fluticasone acts faster than fluticasone alone. This is consistent with clinical observations of some panel members. Five of 36 panel members considered desirable effects to be small to moderate.
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BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ☐ Favors the comparison ☐ Probably favors the comparison ☒ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ Don't know	<table><thead><tr><th>Outcome</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr></thead><tbody><tr><td>Nasal symptoms (TNSS)</td><td>–</td><td>MD 0.77 lower (1.24 lower to 0.3 lower)</td></tr><tr><td>Ocular symptoms</td><td>–</td><td>SMD 0.2 lower (0.33 lower to 0.07 lower)</td></tr><tr><td>Quality of life (RQLQ)</td><td>–</td><td>MD 0.13 higher (0.01 higher to 0.24 higher)</td></tr><tr><td>Serious adverse effects</td><td>not estimable</td><td>2 fewer per 1000 (from 3 fewer to 7 fewer)</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>RR 1.94 (0.59 to 6.36)</td><td>4 more per 1000 (from 2 fewer to 25 more)</td></tr><tr><td>Any adverse effect</td><td>RR 1.66 (1.19 to 2.31)</td><td>41 more per 1000 (from 12 more to 81 more)</td></tr><tr><td>Bitter taste</td><td>RR 6.46 (2.58 to 16.20)</td><td>26 more per 1000 (8 more to 72 more)</td></tr><tr><td>Epistaxis</td><td>RR 1.01 (0.53 to 1.92)</td><td>0 fewer per 1000 (from 9 fewer to 17 more)</td></tr><tr><td>Somnolence</td><td>RR 3.19 (0.28 to 36.26)</td><td>2 more per 1000 (from 1 fewer to 35 more)</td></tr></tbody></table>	Outcome	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms (TNSS)	–	MD 0.77 lower (1.24 lower to 0.3 lower)	Ocular symptoms	–	SMD 0.2 lower (0.33 lower to 0.07 lower)	Quality of life (RQLQ)	–	MD 0.13 higher (0.01 higher to 0.24 higher)	Serious adverse effects	not estimable	2 fewer per 1000 (from 3 fewer to 7 fewer)	Withdrawal owing to adverse effect	RR 1.94 (0.59 to 6.36)	4 more per 1000 (from 2 fewer to 25 more)	Any adverse effect	RR 1.66 (1.19 to 2.31)	41 more per 1000 (from 12 more to 81 more)	Bitter taste	RR 6.46 (2.58 to 16.20)	26 more per 1000 (8 more to 72 more)	Epistaxis	RR 1.01 (0.53 to 1.92)	0 fewer per 1000 (from 9 fewer to 17 more)	Somnolence	RR 3.19 (0.28 to 36.26)	2 more per 1000 (from 1 fewer to 35 more)	
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RESOURCES REQUIRED	How large are the resource requirements (costs)? ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	A retrospective cohort study of allergic rhinitis patients aged >16 examined the cost of intranasal steroid monotherapy, intranasal antihistamine monotherapy, or their combination. It was found that the average cost of AR intranasal medication(s) for 1-year of follow-up was highest for the combination therapy (\$378.56), followed by the intranasal corticosteroids (\$177.42) and then the intranasal antihistamine (\$130.06) (Fairchild 2011).																															
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	No research evidence was identified.	Judgment was based on one retrospective cohort and unsystematic observations in panel members practice.																														
COST-EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ☐ Favors the comparison ☒ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ No included studies	No research evidence was identified.	Some panel members thought that a combination is not cost effective compared to INCS alone, because of little – if any – additional benefit from a combination therapy. This may be particularly important in settings where the combination therapy is much more expensive than INCS alone (e.g. currently in the USA)																														
EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced ☒ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	No research evidence was identified.	Apart from the availability of resources, combined intervention compared to INCS alone would likely have no impact on health equity. Two of the 36 panel members thought that the equity would be reduced owing to much larger cost of the combination therapy.																														

ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	Some panel members thought that the combination therapy will probably not be acceptable to third party payers because of cost-effectiveness.
FEASIBILITY	Is the intervention feasible to implement? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	

Summary of Judgments

	JUDGMENT							IMPLICATIONS
PROBLEM	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
DESIRABLE EFFECTS	Don't know	Varies	No known desirable effects	Trivial	Small	Moderate	Large	Favors INAH+HNCs
UNDESIRABLE EFFECTS	Don't know	Varies	No known undesirable effects	Large	Moderate	Small	Trivial	Favors INCS alone
CERTAINTY OF EVIDENCE	No included studies			Very low	Low	Moderate	High	Favors neither intervention
VALUES				Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	Favors neither intervention
BALANCE OF EFFECTS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INAH+HNCs
RESOURCES REQUIRED	Don't know	Varies	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Favors INCS alone
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies			Very low	Low	Moderate	High	Favors INCS alone
COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INCS alone
EQUITY	Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Favors neither intervention
ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should a combination of intranasal H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of seasonal allergic rhinitis?					
TYPE OF RECOMMENDATION	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 ☐
RECOMMENDATION	In patients with seasonal AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation moderate certainty of evidence)				
JUSTIFICATION	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. The additional reduction in symptoms with combination therapy is small and unlikely to be noticed by majority of patients. Panel members decided that in majority of situations, where a combination therapy is considerably more expensive than INCS alone, any possible net benefit would not justify spending additional resources. This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of combination therapy is not large and/or patients value potential benefits more than an increased risk of adverse effects a combination therapy may be a reasonable choice. At the initiation of treatment a combination of INAH+INCS may act faster than INCS alone and, thus, may be preferred by some patients.				
SUBGROUP CONSIDERATIONS	There is no currently available direct evidence from experimental studies about subgroups based on severity of individual symptoms. However, based on indirect evidence it is possible that selected patients may benefit more from a combination therapy (e.g. those not well controlled with INCS alone or those in whom rhinorrhea rather than congestion is the main complaint).				
IMPLEMENTATION CONSIDERATIONS	–				
MONITORING AND EVALUATION	–				
RESEARCH PRIORITIES	Further research of a combination of INAH with INCS as a step-up therapy in patients not well controlled with INCS alone is warranted. A pragmatic trial in real-life setting measuring cost-effectiveness may also be warranted. The only INAH used in these studies was azelastine and the only INCS was fluticasone – studies of other INAH and INCS may be beneficial.				

Question 2B

Should a combination of **intranasal H1-antihistamine and intranasal corticosteroid** vs. **intranasal corticosteroid alone** be used for treatment of **perennial allergic rhinitis**?

POPULATION:	Patients with perennial AR	BACKGROUND: A combination of INCS with INAH may have an advantage over INCS alone as their mechanisms of action are different. Their effects may be additive and each has specific advantages and disadvantages.
INTERVENTION:	a combination of INAH and INCS	
COMPARISON:	INCS alone	
MAIN OUTCOMES:	symptoms, quality of life, adverse effects	
SETTING:	primary care	
PERSPECTIVE:	individual patient	

Assessment

	JUDGMENT	RESEARCH EVIDENCE				ADDITIONAL CONSIDERATIONS																																												
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).																																																
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ☒ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	<table><thead><tr><th>Outcome</th><th>N_e of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr></thead><tbody><tr><td>Nasal symptoms (TNSS; 0-24 pts)</td><td>611 (1 RCT)</td><td>–</td><td>mean 0.27 points lower (0.56 lower to 0.02 higher)</td></tr><tr><td>Ocular symptoms - not measured</td><td>–</td><td>–</td><td>–</td></tr><tr><td>Quality of life - not measured</td><td>–</td><td>–</td><td>–</td></tr><tr><td>Symptom-free days</td><td>405 (1 RCT)</td><td>–</td><td>mean 23.9 days higher (0.24 lower to 48 higher)</td></tr><tr><td>Serious Adverse Effects</td><td>611 (1 RCT)</td><td>RR 1.54 (0.16 to 14.69)</td><td>3 more per 1000 (4 fewer to 66 more)</td></tr><tr><td>Withdrawal owing to adverse event</td><td>611 (1 RCT)</td><td>RR 0.94 (0.35 to 2.50)</td><td>2 fewer per 1000 (19 fewer to 43 more)</td></tr><tr><td>Any adverse effect</td><td>611 (1 RCT)</td><td>RR 1.05 (0.87 to 1.26)</td><td>22 more per 1000 (58 fewer to 116 more)</td></tr><tr><td>Epistaxis</td><td>611 (1 RCT)</td><td>RR 2.56 (0.30 to 21.79)</td><td>8 more per 1000 (3 fewer to 100 more)</td></tr><tr><td>Distortion of taste</td><td>611 (1 RCT)</td><td>RR 5.12 (0.66 to 39.75)</td><td>20 more per 1000 (2 fewer to 187 more)</td></tr></tbody></table> See appendix for full evidence profile.	Outcome	N _e of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms (TNSS; 0-24 pts)	611 (1 RCT)	–	mean 0.27 points lower (0.56 lower to 0.02 higher)	Ocular symptoms - not measured	–	–	–	Quality of life - not measured	–	–	–	Symptom-free days	405 (1 RCT)	–	mean 23.9 days higher (0.24 lower to 48 higher)	Serious Adverse Effects	611 (1 RCT)	RR 1.54 (0.16 to 14.69)	3 more per 1000 (4 fewer to 66 more)	Withdrawal owing to adverse event	611 (1 RCT)	RR 0.94 (0.35 to 2.50)	2 fewer per 1000 (19 fewer to 43 more)	Any adverse effect	611 (1 RCT)	RR 1.05 (0.87 to 1.26)	22 more per 1000 (58 fewer to 116 more)	Epistaxis	611 (1 RCT)	RR 2.56 (0.30 to 21.79)	8 more per 1000 (3 fewer to 100 more)	Distortion of taste	611 (1 RCT)	RR 5.12 (0.66 to 39.75)	20 more per 1000 (2 fewer to 187 more)	Despite there is no direct evidence about ocular symptoms and quality of life from studies in patients with PAR, indirect evidence from studies in patients with SAR suggest that the effect would be trivial, if any: <table><thead><tr><th>Outcome</th><th>Effect (95% CI)</th></tr></thead><tbody><tr><td>Ocular symptoms</td><td>SMD 0.2 lower (0.33 to 0.07 lower)</td></tr><tr><td>Quality of life (RQLQ)</td><td>MD 0.13 higher (0.01 to 0.24 higher)</td></tr></tbody></table>		Outcome	Effect (95% CI)	Ocular symptoms	SMD 0.2 lower (0.33 to 0.07 lower)	Quality of life (RQLQ)	MD 0.13 higher (0.01 to 0.24 higher)
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UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ☐ Large ☐ Moderate ☒ Small ☐ Trivial ☐ Varies ☐ Don't know	There were 4 serious adverse effects in this study but all were very unlikely related to treatment (Dengue fever, pyrexia, appendicitis, gastroenteritis). All studies used azelastine – bitter taste was reported by some patients in combination therapy group.																																																

CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	<table><tr><th>Outcome</th><th>Quality</th><th>Importance</th></tr><tr><td>Nasal symptoms</td><td>VERY LOW</td><td>Critical</td></tr><tr><td>Ocular symptoms</td><td>Not measured</td><td>Critical</td></tr><tr><td>Quality of life</td><td>Not measured</td><td>Critical</td></tr><tr><td>Symptom-free days</td><td>LOW</td><td>Critical</td></tr><tr><td>Serious adverse effect</td><td>LOW</td><td>Critical</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>VERY LOW</td><td>Critical</td></tr><tr><td>Any adverse effect</td><td>VERY LOW</td><td>Important</td></tr><tr><td>Epistaxis</td><td>LOW</td><td>Important</td></tr><tr><td>Distortion of taste</td><td>LOW</td><td>Important</td></tr></table>	Outcome	Quality	Importance	Nasal symptoms	VERY LOW	Critical	Ocular symptoms	Not measured	Critical	Quality of life	Not measured	Critical	Symptom-free days	LOW	Critical	Serious adverse effect	LOW	Critical	Withdrawal owing to adverse effect	VERY LOW	Critical	Any adverse effect	VERY LOW	Important	Epistaxis	LOW	Important	Distortion of taste	LOW	Important	Study used a combination drug in one container whereas INCS and INAH could also be used as separate sprays. There is some uncertainty whether the desirable and undesirable effects would be the same owing to no available evidence about possible interactions of the two separate solutions.
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VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability	Values and Preferences: Outcomes One systematic review identified 7 cross-sectional studies (Burstrom 2011, Revicki 1998, Revicki 2011, Gold 1998, Demoly 2013, Senti 2007, Tamayama 2009) on utility/value associated with AR. With 0 indicating death and 1 indicating perfect health, the overall range of utility/value based on generic measurements was 0.63-0.91 for allergic rhinitis (HUI-2: 0.83, EQ-5D: 0.85-0.91, VAS: 0.63). Two studies (Lo 2006, Tamayama 2009) reported utility for different severity of allergic rhinitis, one using rating scale and time trade off (Tamayama 2009), another one using disease specific rhinitis symptom utility index (RSUI) (Lo 2006). The utilities based on time trade off were 0.96, 0.94, 0.89, 0.83 for mild, moderate, severe and very severe AR, respectively. The utilities based on rating scale were 0.82, 0.71, 0.56 and 0.43 for mild, moderate, severe and very severe AR, respectively. The disease specific RSUI suggested the utilities were 0.83, 0.69 and 0.50 for mild, moderate, and severe allergic rhinitis. In a small sample of 83 Japanese patients, regarding clinical symptoms, nasal obstruction was identified as the most important symptom influencing patient satisfaction. (Ogino 2006) Values and Preferences: Treatments A cross-sectional study of 170 patients with AR examined the preferences in view of treatment and fear of side effects of the most common treatment options; 30% (52/170) preferred a nasal spray, 25% (42/170) preferred oral treatment and 16% (30/170) preferred combination treatment, whereas 15% (27/170) preferred injection treatment. Additionally, 48% (81/170) expressed concern regarding the side effects of INCS sprays compared to other treatments (Hellings 2012). A cross-sectional study of 503 patients with AR and an RCT in Indonesia found that patients prefer treatment options with no smell or taste (Kaliner 2001, Bunnag 2003). Populations in Spain identified that positive formulation attributes were correct texture, appearance, color, size and rapid dissolution (reported by 95% of patients (57/60) and 91% of physicians (75/82)). (Roger 2006)	Panel members noted that some patients may prefer the combination therapy because of quick onset of action, however, this may be less important in patients with persistent symptoms.																														
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EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced ☒ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	No research evidence was identified.	Apart from the availability of resources, combined intervention compared to INCS alone would likely have no impact on health equity.
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	

Summary of Judgments

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RESOURCES REQUIRED	Don't know	Varies	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Favors INCS alone
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies			Very low	Low	Moderate	High	Favors INCS alone
COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INCS alone
EQUITY	Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Favors neither intervention
ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should a combination of intranasal H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of perennial allergic rhinitis?					
TYPE OF RECOMMENDATION	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 ☐
RECOMMENDATION	In patients with perennial AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation very low certainty of evidence)				
JUSTIFICATION	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. Based on limited evidence, any additional reduction in symptoms with combination therapy, if present, would likely be small and unlikely to be noticed by majority of patients. Panel members decided that in majority of situations, where a combination therapy is more expensive than INCS alone, any possible net benefit would not justify spending additional resources. This is a conditional recommendation because of the very low certainty of the evidence. At the initiation of treatment a combination of INAH+INCS may act faster than INCS alone, thus, may be preferred by some patients.				
SUBGROUP CONSIDERATIONS	There is no currently available direct evidence from experimental studies about subgroups based on severity of individual symptoms. However, based on indirect evidence it is possible that selected				

	patients may benefit more from a combination therapy (e.g. those not well controlled with INCS alone or those in whom rhinorrhea rather than congestion is the main complaint).
IMPLEMENTATION CONSIDERATIONS	–
MONITORING AND EVALUATION	–
RESEARCH PRIORITIES	Further research of a combination of INAH with INCS in patients with persistent/perennial AR may be warranted. However, indirect evidence from SAR suggests that any potential benefit from combination therapy is likely to be trivial. Thus, further research specifically in PAR may not be cost-effective.

Question 3

Should a combination of an **intranasal H1-antihistamine and an intranasal corticosteroid** vs. **intranasal H1-antihistamine alone** be used for treatment of **seasonal allergic rhinitis**?

POPULATION:	Patients with seasonal AR	BACKGROUND: A combination of INCS with INAH may have an advantage over INAH alone as their mechanisms of action are different. Their effects may be additive and each has specific advantages and disadvantages.
INTERVENTION:	a combination of INAH and INCS	
COMPARISON:	INAH alone	
MAIN OUTCOMES:	symptoms, quality of life, adverse effects	
SETTING:	primary care	
PERSPECTIVE:	individual patient	

Assessment

	JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS												
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).													
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ☐ Trivial ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	<table> <tr> <th>Outcome</th><th>N_e of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr> <tr> <td>Nasal symptoms (TNSS; scale 0-24)</td><td>2101 (5 RCTs)</td><td>-</td><td>MD 1.4 points lower (1.82 lower to 0.98 lower)</td></tr> <tr> <td>Ocular symptoms</td><td>2100 (5 RCTs)</td><td>-</td><td>SMD 0.33 SD lower (0.65 lower to 0.02 lower)</td></tr> </table>	Outcome	N _e of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms (TNSS; scale 0-24)	2101 (5 RCTs)	-	MD 1.4 points lower (1.82 lower to 0.98 lower)	Ocular symptoms	2100 (5 RCTs)	-	SMD 0.33 SD lower (0.65 lower to 0.02 lower)	There are small benefits from combined therapy. However, the effects have not been estimated precisely enough to exclude at least a moderate benefit or no difference.
Outcome	N _e of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)												
Nasal symptoms (TNSS; scale 0-24)	2101 (5 RCTs)	-	MD 1.4 points lower (1.82 lower to 0.98 lower)												
Ocular symptoms	2100 (5 RCTs)	-	SMD 0.33 SD lower (0.65 lower to 0.02 lower)												

UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ☐ Large ☐ Moderate ☐ Small ☒ Trivial ☐ Varies ☐ Don't know	<table><tr><td>Quality of life (RQLQ; scale 1-7)</td><td>2100 (5 RCTs)</td><td>-</td><td>MD 0.53 points lower (1.01 lower to 0.06 lower)</td></tr><tr><td>Serious adverse effect</td><td>2106 (5 RCTs)</td><td>not estimable</td><td>0 fewer per 1000 (0 fewer to 0 fewer)</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>2006 (4 RCTs)</td><td>RR 1.19 (0.41 to 3.42)</td><td>2 more per 1000 (5 fewer to 22 more)</td></tr><tr><td>Any adverse effect</td><td>2005 (4 RCTs)</td><td>RR 1.15 (0.73 to 1.81)</td><td>16 more per 1000 (28 fewer to 84 more)</td></tr><tr><td>Bitter taste</td><td>2106 (5 RCTs)</td><td>RR 0.98 (0.48 to 2.00)</td><td>1 fewer per 1000 (25 fewer to 49 more)</td></tr><tr><td>Epistaxis</td><td>2005 (4 RCTs)</td><td>RR 1.19 (0.61 to 2.33)</td><td>3 more per 1000 (6 fewer to 21 more)</td></tr><tr><td>Somnolence</td><td>2005 (4 RCTs)</td><td>RR 1.95 (0.48 to 7.96)</td><td>3 more per 1000 (2 fewer to 21 more)</td></tr></table> See appendix for full evidence profile.	Quality of life (RQLQ; scale 1-7)	2100 (5 RCTs)	-	MD 0.53 points lower (1.01 lower to 0.06 lower)	Serious adverse effect	2106 (5 RCTs)	not estimable	0 fewer per 1000 (0 fewer to 0 fewer)	Withdrawal owing to adverse effect	2006 (4 RCTs)	RR 1.19 (0.41 to 3.42)	2 more per 1000 (5 fewer to 22 more)	Any adverse effect	2005 (4 RCTs)	RR 1.15 (0.73 to 1.81)	16 more per 1000 (28 fewer to 84 more)	Bitter taste	2106 (5 RCTs)	RR 0.98 (0.48 to 2.00)	1 fewer per 1000 (25 fewer to 49 more)	Epistaxis	2005 (4 RCTs)	RR 1.19 (0.61 to 2.33)	3 more per 1000 (6 fewer to 21 more)	Somnolence	2005 (4 RCTs)	RR 1.95 (0.48 to 7.96)	3 more per 1000 (2 fewer to 21 more)	There were no serious adverse effects in those studies. All studies used azelastine – bitter taste was reported by some patients in combination therapy group.		
	Quality of life (RQLQ; scale 1-7)	2100 (5 RCTs)	-	MD 0.53 points lower (1.01 lower to 0.06 lower)																													
Serious adverse effect	2106 (5 RCTs)	not estimable	0 fewer per 1000 (0 fewer to 0 fewer)																														
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CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? ☐ High ☐ Moderate ☒ Low ☐ Very low ☐ No included studies	<table><tr><th>Outcome</th><th>Quality</th><th>Importance</th></tr><tr><td>Nasal symptoms</td><td>HIGH</td><td>Critical</td></tr><tr><td>Ocular symptoms</td><td>MODERATE</td><td>Critical</td></tr><tr><td>Quality of life</td><td>LOW</td><td>Critical</td></tr><tr><td>Serious adverse effect</td><td>HIGH</td><td>Critical</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>MODERATE</td><td>Critical</td></tr><tr><td>Any adverse effect</td><td>LOW</td><td>Important</td></tr><tr><td>Distortion of taste</td><td>HIGH</td><td>Important</td></tr><tr><td>Epistaxis</td><td>MODERATE</td><td>Important</td></tr><tr><td>Somnolence</td><td>MODERATE</td><td>Important</td></tr></table>	Outcome	Quality	Importance	Nasal symptoms	HIGH	Critical	Ocular symptoms	MODERATE	Critical	Quality of life	LOW	Critical	Serious adverse effect	HIGH	Critical	Withdrawal owing to adverse effect	MODERATE	Critical	Any adverse effect	LOW	Important	Distortion of taste	HIGH	Important	Epistaxis	MODERATE	Important	Somnolence	MODERATE	Important	Four out of 5 studies used a combination drug in one container whereas INCS and INAH could also be used as separate sprays. There is some uncertainty whether the desirable and undesirable effects would be the same owing to no available evidence about possible interactions of the two separate solutions. Overall certainty is low because of inconsistency and imprecision of estimate of QoL – there is a possibility that it substantially improves with combination therapy compared to INAH alone, which is important considering estimated modest improvement in symptom scores.
Outcome	Quality	Importance																															
Nasal symptoms	HIGH	Critical																															
Ocular symptoms	MODERATE	Critical																															
Quality of life	LOW	Critical																															
Serious adverse effect	HIGH	Critical																															
Withdrawal owing to adverse effect	MODERATE	Critical																															
Any adverse effect	LOW	Important																															
Distortion of taste	HIGH	Important																															
Epistaxis	MODERATE	Important																															
Somnolence	MODERATE	Important																															
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability	Values and Preferences: Outcomes One systematic review identified 7 cross-sectional studies (Burstrom 2011, Revicki 1998, Revicki 2011, Gold 1998, Demoly 2013, Senti 2007, Tamayama 2009) on utility/value associated with AR. With 0 indicating death and 1 indicating perfect health, the overall range of utility/value based on generic measurements was 0.63-0.91 for allergic rhinitis (HUI-2: 0.83, EQ-5D: 0.85-0.91, VAS: 0.63). Two studies (Lo 2006, Tamayama 2009) reported utility for different severity of allergic rhinitis, one using rating scale and time trade off (Tamayama 2009), another one using disease specific rhinitis symptom utility index (RSUI) (Lo 2006). The utilities based on time trade off were 0.96, 0.94, 0.89, 0.83 for mild, moderate, severe and very severe AR, respectively. The utilities based on rating scale were 0.82, 0.71, 0.56 and 0.43 for mild, moderate, severe and very severe AR, respectively. The disease specific RSUI suggested the utilities were 0.83, 0.69 and 0.50 for mild, moderate, and severe allergic rhinitis. In a small sample of 83 Japanese patients, regarding clinical symptoms, nasal obstruction was identified as the most important symptom influencing patient satisfaction. (Ogino 2006) Values and Preferences: Treatments A cross-sectional study of 170 patients with AR examined the preferences in view of treatment and fear of side effects of the most common treatment options; 30% (52/170) preferred a nasal spray, 25% (42/170) preferred oral treatment and 16% (30/170) preferred combination treatment, whereas 15% (27/170) preferred injection treatment. Additionally, 48% (81/170) expressed concern regarding the side effects of INCS sprays compared to other treatments (Helling 2012). A cross-sectional study of 503 patients with AR and an RCT in Indonesia found that patients prefer treatment options with no smell or taste (Kaliner 2001, Bunnag 2003).																															

BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☒ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ Don't know	<table><tr><th>Outcome</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr><tr><td>Nasal symptoms (TNSS)</td><td>-</td><td>MD 1.4 points lower (1.82 lower to 0.98 lower)</td></tr><tr><td>Ocular symptoms</td><td>-</td><td>SMD 0.33 SD lower (0.65 lower to 0.02 lower)</td></tr><tr><td>Quality of life (RQLQ)</td><td>-</td><td>MD 0.53 points lower (1.01 lower to 0.06 lower)</td></tr><tr><td>Serious adverse effect</td><td>not estimable</td><td>0 fewer per 1000 (0 fewer to 0 fewer)</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>RR 1.19 (0.41 to 3.42)</td><td>2 more per 1000 (5 fewer to 22 more)</td></tr><tr><td>Any adverse effect</td><td>RR 1.15 (0.73 to 1.81)</td><td>16 more per 1000 (28 fewer to 84 more)</td></tr></table>	Outcome	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms (TNSS)	-	MD 1.4 points lower (1.82 lower to 0.98 lower)	Ocular symptoms	-	SMD 0.33 SD lower (0.65 lower to 0.02 lower)	Quality of life (RQLQ)	-	MD 0.53 points lower (1.01 lower to 0.06 lower)	Serious adverse effect	not estimable	0 fewer per 1000 (0 fewer to 0 fewer)	Withdrawal owing to adverse effect	RR 1.19 (0.41 to 3.42)	2 more per 1000 (5 fewer to 22 more)	Any adverse effect	RR 1.15 (0.73 to 1.81)	16 more per 1000 (28 fewer to 84 more)	Panel members decided that the balance probably favored the combination therapy because of imprecision in the estimates of effects.
Outcome	Relative effect (95% CI)	Absolute effect (95% CI)																						
Nasal symptoms (TNSS)	-	MD 1.4 points lower (1.82 lower to 0.98 lower)																						
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RESOURCES REQUIRED	How large are the resource requirements (costs)? ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	A retrospective cohort study of allergic rhinitis patients aged >16 examined the cost of intranasal steroid monotherapy, intranasal antihistamine monotherapy, or their combination. It was found that the average cost of AR intranasal medication(s) for 1-year of follow-up was highest for the combination therapy (\$378.56), followed by the intranasal corticosteroids (\$177.42) and then the intranasal antihistamine (\$130.06) (Fairchild 2011).	Panel members noted that the answer will highly depend on the local health system owing to large variability in cost and coverage: public or private insurance plans, co-payment models and patient out of the pocket expenses.																					
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	No research evidence was identified.	Judgment was based on one retrospective cohort and unsystematic observations in panel members practice.																					
COST-EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ☐ Favors the comparison ☒ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ No included studies	No research evidence was identified.	Some panel members thought that a combination may not be cost effective compared to INAH alone, particularly in settings where the combination therapy is much more expensive than INAH alone.																					
EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced ☒ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	No research evidence was identified.	Apart from the availability of resources, combined intervention compared to INCS alone would likely have no impact on health equity.																					

ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	

Summary of Judgments

	JUDGMENT							IMPLICATIONS
PROBLEM	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
DESIRABLE EFFECTS	Don't know	Varies	No known desirable effects	Trivial	Small	Moderate	Large	Favors INAH+HNCS
UNDESIRABLE EFFECTS	Don't know	Varies	No known undesirable effects	Large	Moderate	Small	Trivial	Favors neither intervention
CERTAINTY OF EVIDENCE	No included studies			Very low	Low	Moderate	High	Favors neither intervention
VALUES				Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	Favors neither intervention
BALANCE OF EFFECTS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INAH+HNCS
RESOURCES REQUIRED	Don't know	Varies	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Favors INAH alone
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies			Very low	Low	Moderate	High	Favors INAH alone
COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INAH alone
EQUITY	Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Favors neither intervention
ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should a combination of intranasal H1-antihistamine and intranasal corticosteroid vs. intranasal H1-antihistamine alone be used for treatment of seasonal allergic rhinitis?					
TYPE OF RECOMMENDATION	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 ☐
RECOMMENDATION	In patients with seasonal AR, we suggest a combination of an intranasal corticosteroid with an intranasal H1-antihistamine rather than an intranasal H1-antihistamine alone (conditional recommendation low certainty of evidence)				
JUSTIFICATION	There is a small improvement in symptoms and quality of life with a combination of INAH with INCS compared to INAH alone. Mean estimates of improvement of symptoms are close to minimal important difference and an estimate of mean improvement in QoL is larger than MID – it is therefore likely that the difference would be noticed by many patients. One of 36 panel members thought that the recommendation should be conditional for either the intervention or the comparison. This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of a combination therapy is large, an alternative choice, i.e. INAH alone, may be equally reasonable.				
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS	Four out of 5 studies used a combination drug in one container whereas INCS and INAH could also be used as separate sprays. There is some uncertainty whether the desirable and undesirable effects would be the same owing to no available evidence about possible interactions of the two separate solutions.				
MONITORING AND EVALUATION	–				
RESEARCH PRIORITIES	Further research may be warranted to better estimate the effect of a combination of INAH with INCS on quality of life. The only INAH used in these studies was azelastine and the only INCS was fluticasone – studies of other INAH and INCS may be warranted.				

Question 4A

Should a **leukotriene receptor antagonist (LTRA)** vs. an **oral H1-antihistamine (OAH)** be used for treatment of **seasonal allergic rhinitis**?

POPULATION:	Patients with seasonal AR	BACKGROUND: LTRA may have an advantage over OAH as they may cause less somnolence attributed to OAH. They have different mechanisms of action. Each has specific advantages and disadvantages.
INTERVENTION:	LTRA	
COMPARISON:	OAH	
MAIN OUTCOMES:	symptoms, quality of life, adverse effects	
SETTING:	primary care	
PERSPECTIVE:	individual patient	

Assessment

	JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).																																	
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ☒ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ No evidence of desirable effects ☐ Don't know	<table> <tr> <th>Outcome</th><th>N_e of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr> <tr> <td>Nasal symptoms</td><td>3605 (8 RCTs)</td><td>–</td><td>SMD 0.06 higher (0.01 lower to 0.13 higher)</td></tr> <tr> <td>Ocular symptoms</td><td>3605 (8 RCTs)</td><td>–</td><td>SMD 0.06 higher (0.04 lower to 0.16 higher)</td></tr> <tr> <td>Quality of life (RQLQ)</td><td>2914 (5 RCTs)</td><td>–</td><td>MD 0.04 higher (0.04 lower to 0.13 higher)</td></tr> <tr> <td>Serious adverse effect</td><td>1015 (5 RCTs)</td><td>not estimable</td><td>1 fewer per 1000 (from 6 fewer to 9 more)</td></tr> <tr> <td>Withdrawal owing to adverse effect</td><td>2980 (9 RCTs)</td><td>RR 1.22 (0.47 to 3.16)</td><td>2 more per 1000 (from 4 fewer to 18 more)</td></tr> <tr> <td>Any adverse effect</td><td>2350 (6 RCTs)</td><td>RR 0.95 (0.78 to 1.16)</td><td>9 fewer per 1000 (from 28 more to 39 fewer)</td></tr> <tr> <td>Somnolence (not reported)</td><td>–</td><td>–</td><td>–</td></tr> </table> See appendix for full evidence profile.	Outcome	N _e of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms	3605 (8 RCTs)	–	SMD 0.06 higher (0.01 lower to 0.13 higher)	Ocular symptoms	3605 (8 RCTs)	–	SMD 0.06 higher (0.04 lower to 0.16 higher)	Quality of life (RQLQ)	2914 (5 RCTs)	–	MD 0.04 higher (0.04 lower to 0.13 higher)	Serious adverse effect	1015 (5 RCTs)	not estimable	1 fewer per 1000 (from 6 fewer to 9 more)	Withdrawal owing to adverse effect	2980 (9 RCTs)	RR 1.22 (0.47 to 3.16)	2 more per 1000 (from 4 fewer to 18 more)	Any adverse effect	2350 (6 RCTs)	RR 0.95 (0.78 to 1.16)	9 fewer per 1000 (from 28 more to 39 fewer)	Somnolence (not reported)	–	–	–	
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Somnolence (not reported)	–	–	–																																
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ☐ Large ☐ Moderate ☐ Small ☒ Trivial ☐ Varies ☐ No evidence of undesirable effects ☐ Don't know																																		

CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? ☒ High ☐ Moderate ☐ Low ☐ Very low ☐ No included studies	<table><tr><th>Outcome</th><th>Quality</th><th>Importance</th></tr><tr><td>Nasal symptoms</td><td>HIGH</td><td>Critical</td></tr><tr><td>Ocular symptoms</td><td>HIGH</td><td>Critical</td></tr><tr><td>Quality of life</td><td>HIGH</td><td>Critical</td></tr><tr><td>Serious adverse effect</td><td>HIGH</td><td>Critical</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>HIGH</td><td>Critical</td></tr><tr><td>Any adverse effect</td><td>LOW</td><td>Important</td></tr></table>	Outcome	Quality	Importance	Nasal symptoms	HIGH	Critical	Ocular symptoms	HIGH	Critical	Quality of life	HIGH	Critical	Serious adverse effect	HIGH	Critical	Withdrawal owing to adverse effect	HIGH	Critical	Any adverse effect	LOW	Important	
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Quality of life	HIGH	Critical																						
Serious adverse effect	HIGH	Critical																						
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Any adverse effect	LOW	Important																						
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability	Values and Preferences: Outcomes One systematic review identified 7 cross-sectional studies (Burstrom 2011, Revicki 1998, Revicki 2011, Gold 1998, Demoly 2013, Senti 2007, Tamayama 2009) on utility/value associated with AR. With 0 indicating death and 1 indicating perfect health, the overall range of utility/value based on generic measurements was 0.63-0.91 for allergic rhinitis (HUI-2: 0.83, EQ-5D: 0.85-0.91, VAS: 0.63). Two studies (Lo 2006, Tamayama 2009) reported utility for different severity of allergic rhinitis, one using rating scale and time trade off (Tamayama 2009), another one using disease specific rhinitis symptom utility index (RSUI) (Lo 2006). The utilities based on time trade off were 0.96, 0.94, 0.89, 0.83 for mild, moderate, severe and very severe AR, respectively. The utilities based on rating scale were 0.82, 0.71, 0.56 and 0.43 for mild, moderate, severe and very severe AR, respectively. The disease specific RSUI suggested the utilities were 0.83, 0.69 and 0.50 for mild, moderate, and severe allergic rhinitis. In a small sample of 83 Japanese patients, regarding clinical symptoms, nasal obstruction was identified as the most important symptom influencing patient satisfaction. (Ogino 2006) Values and Preferences: Treatments A cross-sectional study of 170 patients with AR examined the preferences in view of treatment and fear of side effects of the most common treatment options; 30% (52/170) preferred a nasal spray, 25% (42/170) preferred oral treatment and 16% (30/170) preferred combination treatment, whereas 15% (27/170) preferred injection treatment. Additionally, 48% (81/170) expressed concern regarding the side effects of INCS sprays compared to other treatments (Hellings 2012). A cross-sectional study of 503 patients with AR and an RCT in Indonesia found that patients prefer treatment options with no smell or taste (Kalinier 2001, Bunnag 2003).																						
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ☐ Favors the comparison ☐ Probably favors the comparison ☒ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ Don't know	<table><tr><th>Outcome</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr><tr><td>Nasal symptoms</td><td>-</td><td>SMD 0.06 higher (0.01 lower to 0.13 higher)</td></tr><tr><td>Ocular symptoms</td><td>-</td><td>SMD 0.06 higher (0.04 lower to 0.16 higher)</td></tr><tr><td>Quality of life (RQLQ)</td><td>-</td><td>MD 0.04 higher (0.04 lower to 0.13 higher)</td></tr><tr><td>Serious adverse effect</td><td>not estimable</td><td>1 fewer per 1000 (from 6 fewer to 9 more)</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>RR 1.22 (0.47 to 3.16)</td><td>2 more per 1000 (from 4 fewer to 18 more)</td></tr><tr><td>Any adverse effect</td><td>RR 0.95 (0.78 to 1.16)</td><td>9 fewer per 1000 (from 28 more to 39 fewer)</td></tr></table>	Outcome	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms	-	SMD 0.06 higher (0.01 lower to 0.13 higher)	Ocular symptoms	-	SMD 0.06 higher (0.04 lower to 0.16 higher)	Quality of life (RQLQ)	-	MD 0.04 higher (0.04 lower to 0.13 higher)	Serious adverse effect	not estimable	1 fewer per 1000 (from 6 fewer to 9 more)	Withdrawal owing to adverse effect	RR 1.22 (0.47 to 3.16)	2 more per 1000 (from 4 fewer to 18 more)	Any adverse effect	RR 0.95 (0.78 to 1.16)	9 fewer per 1000 (from 28 more to 39 fewer)	
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RESOURCES REQUIRED	How large are the resource requirements (costs)? ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	Retrospective analysis of an insurance claim database found that patients receiving montelukast experienced higher total medical costs (\$1,542 versus \$989), drug costs (\$714 versus \$477), AR drug costs (\$474 versus \$298), and outpatient visit costs (\$480 versus \$277) compared with oral, branded second-generation antihistamines (Hay 2009).	Cost of LTRA will be higher compared to some OAH and comparable with other OAH. In settings where generic LTRAs are available total costs of using them may be lower. Costs of various OAH is also very variable. It is important to consider the local availability and costs of LTRAs and various OAH.																					

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	No research evidence was identified.	
COST-EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ☐ Favors the comparison ☒ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ No included studies	An economic model created by Goodman (2008) found that, compared with levocetirizine, ICERs for an additional significant symptom improvement were \$2107 for desloratadine, \$205 for fexofenadine (generic), \$1658 for fexofenadine (brand) and \$2335 for montelukast. Another economic model found that montelukast has been shown to be less efficacious than intranasal steroids and no more effective than less-sedating antihistamines, but it cost more relative to the other products (Lee 2004).	Panel members noted that, likely based on cost effectiveness, many clinicians currently start therapy from OAH rather than LTRA.
EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced ☒ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	No research evidence was identified.	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	In some countries LTRAs are currently available only for treatment of asthma which may be a barrier to implementation.

Summary of Judgments

	JUDGMENT							IMPLICATIONS
PROBLEM	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
DESIRABLE EFFECTS	Don't know	Varies	No evidence of desirable effects	Trivial	Small	Moderate	Large	Favors neither intervention
UNDESIRABLE EFFECTS	Don't know	Varies	No evidence of undesirable effects	Large	Moderate	Small	Trivial	Favors neither intervention
CERTAINTY OF EVIDENCE	No included studies			Very low	Low	Moderate	High	Favors neither intervention
VALUES				Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	Favors neither intervention
BALANCE OF EFFECTS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors neither intervention
RESOURCES REQUIRED	Don't know	Varies	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Favors OAH
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies			Very low	Low	Moderate	High	Favors neither intervention
COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors OAH
EQUITY	Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Favors neither intervention
ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should a leukotriene receptor antagonist vs. oral H1-antihistamine be used for treatment of seasonal allergic rhinitis?					
TYPE OF RECOMMENDATION	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 ☐
RECOMMENDATION	In patients with seasonal AR, we suggest either an oral H1-antihistamine or a leukotriene receptor antagonist (conditional recommendation moderate certainty of evidence)				
JUSTIFICATION	There seems to be no clear difference in health outcomes between LTRA and OAH in patients with SAR, thus, the panel members concluded that the choice of treatment will largely depend on patient preferences and local availability and cost of medications. OAH may be more cost effective but this will largely depend on local availability of generic LTRAs and the cost of various OAHs and LTRAs. This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences.				
SUBGROUP CONSIDERATIONS	Some patients with allergic rhinitis who have concomitant asthma, especially exercise-induced, and aspirin exacerbated respiratory disease may benefit from LTRA more than from OAH.				

	Note: this recommendation applies to treatment of AR not to treatment of asthma. Patients with asthma, who have concomitant AR, should receive an appropriate treatment according to the guidelines for the treatment of asthma.
IMPLEMENTATION CONSIDERATIONS	In some countries LTRAs are currently available only for treatment of asthma which may be a barrier to implementation.
MONITORING AND EVALUATION	–
RESEARCH PRIORITIES	Studies investigating the comparative effects of LTRA and OAH in patients with AR and specific subgroups defined by type of concomitant asthma may be warranted.

Question 4B

Should a **leukotriene receptor antagonist (LTRA)** vs. an **oral H1-antihistamine (OAH)** be used for treatment of **perennial allergic rhinitis**?

POPULATION:	Patients with perennial AR	BACKGROUND: LTRA may have an advantage over OAH as they may cause less somnolence attributed to OAH. They have different mechanisms of action. Each has specific advantages and disadvantages.
INTERVENTION:	LTRA	
COMPARISON:	OAH	
MAIN OUTCOMES:	symptoms, quality of life, adverse effects	
SETTING:	primary care	
PERSPECTIVE:	individual patient	

Assessment

	JUDGMENT	RESEARCH EVIDENCE				ADDITIONAL CONSIDERATIONS																																					
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).																																									
	How substantial are the desirable anticipated effects? ☐ Trivial ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ No evidence of desirable effects ☐ Don't know	<table><thead><tr><th>Outcome</th><th>N₂ of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr></thead><tbody><tr><td>Nasal symptoms</td><td>792 (2 RCTs)</td><td>–</td><td>SMD 0.26 higher (0.45 lower to 0.97 higher)</td></tr><tr><td>Ocular symptoms [adults]</td><td>40 (2 RCTs)</td><td>–</td><td>MD 0.19 lower (1.03 lower to 0.65 higher)</td></tr><tr><td>Ocular symptoms [children]</td><td>40 (1 RCT)</td><td>–</td><td>MD 0.29 higher (0.04 lower to 0.62 higher)</td></tr><tr><td>Quality of life [adults] (RQLQ; 0-6)</td><td>40 (2 RCTs)</td><td>–</td><td>MD 0.17 lower (0.93 lower to 0.58 higher)</td></tr><tr><td>Quality of life [children] (PRQLQ; 0-138)</td><td>40 (1 RCT)</td><td>–</td><td>MD 12 higher (1.66 lower to 25.66 higher)</td></tr><tr><td>Serious adverse effect</td><td>912 (5 RCTs)</td><td>not estimable</td><td>3 fewer per 1000 (from 17 fewer to 8 more)</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>914 (5 RCTs)</td><td>RR 1.40 (0.50 to 3.92)</td><td>8 more per 1000 (10 fewer to 58 more)</td></tr><tr><td>Any adverse effect</td><td>1794 (2 RCTs)</td><td>Rate ratio 0.64 (0.50 to 0.81)</td><td>140 events fewer per 1000 patients over 6 weeks (from 230 fewer to 50 fewer)</td></tr><tr><td>Somnolence</td><td>1834 (3 RCTs)</td><td>RR 0.12 (0.03 to 0.38)</td><td>49 fewer per 1000 (54 fewer to 34 fewer)</td></tr></tbody></table> <i>See appendix for full evidence profile.</i>	Outcome	N ₂ of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms	792 (2 RCTs)	–	SMD 0.26 higher (0.45 lower to 0.97 higher)	Ocular symptoms [adults]	40 (2 RCTs)	–	MD 0.19 lower (1.03 lower to 0.65 higher)	Ocular symptoms [children]	40 (1 RCT)	–	MD 0.29 higher (0.04 lower to 0.62 higher)	Quality of life [adults] (RQLQ; 0-6)	40 (2 RCTs)	–	MD 0.17 lower (0.93 lower to 0.58 higher)	Quality of life [children] (PRQLQ; 0-138)	40 (1 RCT)	–	MD 12 higher (1.66 lower to 25.66 higher)	Serious adverse effect	912 (5 RCTs)	not estimable	3 fewer per 1000 (from 17 fewer to 8 more)	Withdrawal owing to adverse effect	914 (5 RCTs)	RR 1.40 (0.50 to 3.92)	8 more per 1000 (10 fewer to 58 more)	Any adverse effect	1794 (2 RCTs)	Rate ratio 0.64 (0.50 to 0.81)	140 events fewer per 1000 patients over 6 weeks (from 230 fewer to 50 fewer)	Somnolence	1834 (3 RCTs)	RR 0.12 (0.03 to 0.38)	49 fewer per 1000 (54 fewer to 34 fewer)	Studies were very small and the differences are not large, thus, any differences in the effects between children and adults may be spurious. There may be fewer adverse effects with LTRA.
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UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ☐ Large ☐ Moderate ☒ Small ☐ Trivial ☐ Varies ☐ No evidence of undesirable effects ☐ Don't know					Symptoms may be less controlled with LTRA compared to OAH, especially in children. However there is low confidence that the observed results reflect true effects.																																					

CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? ☐ High ☐ Moderate ☒ Low ☐ Very low ☐ No included studies	<table><tr><th>Outcome</th><th>Quality</th><th>Importance</th></tr><tr><td>Nasal symptoms</td><td>LOW</td><td>Critical</td></tr><tr><td>Ocular symptoms</td><td>LOW</td><td>Critical</td></tr><tr><td>Quality of life</td><td>LOW</td><td>Critical</td></tr><tr><td>Serious adverse effect</td><td>HIGH</td><td>Critical</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>MODERATE</td><td>Critical</td></tr><tr><td>Any adverse effect</td><td>LOW</td><td>Important</td></tr><tr><td>Somnolence</td><td>LOW</td><td>Important</td></tr></table>	Outcome	Quality	Importance	Nasal symptoms	LOW	Critical	Ocular symptoms	LOW	Critical	Quality of life	LOW	Critical	Serious adverse effect	HIGH	Critical	Withdrawal owing to adverse effect	MODERATE	Critical	Any adverse effect	LOW	Important	Somnolence	LOW	Important							
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COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors OAH
EQUITY	Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Favors neither intervention
ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should a leukotriene receptor antagonist vs. oral H1-antihistamine be used for treatment of perennial allergic rhinitis?					
TYPE OF RECOMMENDATION	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 ☐
RECOMMENDATION	In patients with perennial AR, we suggest an oral H1-antihistamine rather than a leukotriene receptor antagonist (conditional recommendation low certainty of evidence)				
JUSTIFICATION	There is low certainty about any differences in health outcomes between LTRA and OAH in patients with PAR – OAH may reduce symptoms and improve QoL better but the risk of somnolence is higher. Any differences are likely to be small. OAH may be more cost effective but this will largely depend on local availability of generic LTRAs and the cost of various OAHs and LTRAs. This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences. This will be more important for patients with PAR than in SAR as they might use those medication for longer periods of time.				
SUBGROUP CONSIDERATIONS	Patients with allergic rhinitis who have concomitant asthma, especially exercise-induced, and aspirin exacerbated respiratory disease may benefit from LTRA more than from OAH.				

IMPLEMENTATION CONSIDERATIONS	–
MONITORING AND EVALUATION	–
RESEARCH PRIORITIES	Well designed, powered to confirm or refute a difference, and well executed RCTs that properly measure and report all patient-important outcomes may be warranted. Studies that investigate factors associated with better response to LTRA and OAH may also be beneficial.

Question 5A

Should an **intranasal H1-antihistamine** vs. an **intranasal corticosteroid** be used for treatment of **seasonal allergic rhinitis**?

POPULATION:	Patients with seasonal AR	BACKGROUND: INAH may have an advantage over INCS in its faster onset of symptom relief as their mechanisms of action are different. Each has specific advantages and disadvantages.
INTERVENTION:	INAH	
COMPARISON:	INCS	
MAIN OUTCOMES:	symptoms, quality of life, adverse effects	
SETTING:	primary care	
PERSPECTIVE:	individual patient	

Assessment

	JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).																	
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ No evidence of desirable effects ☐ Don't know	<table> <tr> <th>Outcome</th><th>N_e of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr> <tr> <td>Nasal symptoms (TNSS)</td><td>2618 (13 RCTs)</td><td>-</td><td>SMD 0.17 SD higher (0.07 higher to 0.28 higher)</td></tr> <tr> <td>Ocular symptoms</td><td>2554 (8 RCTs)</td><td>-</td><td>SMD 0.08 SD higher (0.11 lower to 0.26 higher)</td></tr> <tr> <td>Quality of life (RQLQ)</td><td>400 (2 RCTs)</td><td>-</td><td>MD 0.26 points higher (0.09 higher to 0.43 higher)</td></tr> </table>	Outcome	N _e of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms (TNSS)	2618 (13 RCTs)	-	SMD 0.17 SD higher (0.07 higher to 0.28 higher)	Ocular symptoms	2554 (8 RCTs)	-	SMD 0.08 SD higher (0.11 lower to 0.26 higher)	Quality of life (RQLQ)	400 (2 RCTs)	-	MD 0.26 points higher (0.09 higher to 0.43 higher)	Relative effects of INAH vs. INCS may be different when used continuously vs. as need. This, however, has not been investigated in clinical trials. Effects of INCS on symptoms and quality of life are larger, compared to INAH. However, imprecision of the estimated effects does not exclude the possibility that this difference may not be large enough to be perceived by a substantial proportion of patients.
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UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ☐ Large ☐ Moderate ☒ Small ☐ Trivial ☐ Varies ☐ No evidence of undesirable effects ☐ Don't know	<table><tr><td>Serious adverse effect</td><td>2385 (10 RCTs)</td><td>not estimable</td><td>0 fewer per 1000 (4 fewer to 4 more)</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>2463 (9 RCTs)</td><td>RR 1.36 (0.53 to 3.51)</td><td>2 more per 1000 (3 fewer to 14 more)</td></tr><tr><td>Any adverse effect</td><td>2690 (11 RCTs)</td><td>RR 1.39 (1.04 to 1.86)</td><td>35 more per 1000 (4 more to 77 more)</td></tr><tr><td>Bitter taste</td><td>2433 (8 RCTs)</td><td>RR 7.18 (3.24 to 15.90)</td><td>25 more per 1000 (9 more to 61 more)</td></tr><tr><td>Epistaxis</td><td>2379 (7 RCTs)</td><td>RR 0.94 (0.52 to 1.69)</td><td>1 fewer per 1000 (9 fewer to 13 more)</td></tr><tr><td>Somnolence</td><td>2379 (7 RCTs)</td><td>RR 2.90 (0.76 to 11.08)</td><td>3 more per 1000 (0 fewer to 17 more)</td></tr></table> See appendix for full evidence profile. 10 studies examined the time to onset of action. Results were most often reported as graphs with no variability and showed inconsistent results: 2 studies (Kaliner 2009 and Newson-Smith 1997) showed that INAH may relieve symptoms better over the first 2-4 days with INCS being more effective from day4 onwards, 2 studies showed no difference (Hampel 2010, Ratner 2008) and 4 showed quicker relief in INCS group (Lange 2005, Carr 2012ABC). One study using an allergen challenge found better improvement of symptoms with INAH compared to INCS over 2-4h after drug administration (Murdoch 2015).	Serious adverse effect	2385 (10 RCTs)	not estimable	0 fewer per 1000 (4 fewer to 4 more)	Withdrawal owing to adverse effect	2463 (9 RCTs)	RR 1.36 (0.53 to 3.51)	2 more per 1000 (3 fewer to 14 more)	Any adverse effect	2690 (11 RCTs)	RR 1.39 (1.04 to 1.86)	35 more per 1000 (4 more to 77 more)	Bitter taste	2433 (8 RCTs)	RR 7.18 (3.24 to 15.90)	25 more per 1000 (9 more to 61 more)	Epistaxis	2379 (7 RCTs)	RR 0.94 (0.52 to 1.69)	1 fewer per 1000 (9 fewer to 13 more)	Somnolence	2379 (7 RCTs)	RR 2.90 (0.76 to 11.08)	3 more per 1000 (0 fewer to 17 more)							
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VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability	Values and Preferences: Outcomes One systematic review identified 7 cross-sectional studies (Burstrom 2011, Revicki 1998, Revicki 2011, Gold 1998, Demoly 2013, Senti 2007, Tamayama 2009) on utility/value associated with AR. With 0 indicating death and 1 indicating perfect health, the overall range of utility/value based on generic measurements was 0.63-0.91 for allergic rhinitis (HUI-2: 0.83, EQ-5D: 0.85-0.91, VAS: 0.63). Two studies (Lo 2006, Tamayama 2009) reported utility for different severity of allergic rhinitis, one using rating scale and time trade off (Tamayama 2009), another one using disease specific rhinitis symptom utility index (RSUI) (Lo 2006). The utilities based on time trade off were 0.96, 0.94, 0.89, 0.83 for mild, moderate, severe and very severe AR, respectively. The utilities based on rating scale were 0.82, 0.71, 0.56 and 0.43 for mild, moderate, severe and very severe AR, respectively. The disease specific RSUI suggested the utilities were 0.83, 0.69 and 0.50 for mild, moderate, and severe allergic rhinitis. In a small sample of 83 Japanese patients, regarding clinical symptoms, nasal obstruction was identified as the most important symptom influencing patient satisfaction. (Ogino 2006) Values and Preferences: Treatments A cross-sectional study of 170 patients with AR examined the preferences in view of treatment and fear of side effects of the most common treatment options; 30% (52/170) preferred a nasal spray, 25% (42/170) preferred oral treatment and 16% (30/170) preferred combination treatment, whereas 15% (27/170) preferred injection treatment. Additionally, 48% (81/170) expressed concern regarding the side effects of INCS sprays compared to other treatments (Hellings 2012). A cross-sectional study of 503 patients with AR and an RCT in Indonesia found that patients prefer treatment options with no smell or taste (Kaliner 2001, Bunnag 2003).	Patients might prefer the treatment with faster onset of action, however, there is no evidence that either treatment is superior in this respect.																														

BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ☐ Favors the comparison ☒ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ Don't know	<table><tr><th>Outcome</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr><tr><td>Nasal symptoms (TNSS)</td><td>-</td><td>SMD 0.17 SD higher (0.07 higher to 0.28 higher)</td></tr><tr><td>Ocular symptoms</td><td>-</td><td>SMD 0.08 SD higher (0.11 lower to 0.26 higher)</td></tr><tr><td>Quality of life (RQLQ)</td><td>-</td><td>MD 0.26 points higher (0.09 higher to 0.43 higher)</td></tr><tr><td>Serious adverse effect</td><td>not estimable</td><td>0 fewer per 1000 (4 fewer to 4 more)</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>RR 1.36 (0.53 to 3.51)</td><td>2 more per 1000 (3 fewer to 14 more)</td></tr><tr><td>Any adverse effect</td><td>RR 1.39 (1.04 to 1.86)</td><td>35 more per 1000 (4 more to 77 more)</td></tr></table>	Outcome	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms (TNSS)	-	SMD 0.17 SD higher (0.07 higher to 0.28 higher)	Ocular symptoms	-	SMD 0.08 SD higher (0.11 lower to 0.26 higher)	Quality of life (RQLQ)	-	MD 0.26 points higher (0.09 higher to 0.43 higher)	Serious adverse effect	not estimable	0 fewer per 1000 (4 fewer to 4 more)	Withdrawal owing to adverse effect	RR 1.36 (0.53 to 3.51)	2 more per 1000 (3 fewer to 14 more)	Any adverse effect	RR 1.39 (1.04 to 1.86)	35 more per 1000 (4 more to 77 more)	
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RESOURCES REQUIRED	How large are the resource requirements (costs)? ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	A retrospective cohort study of allergic rhinitis patients aged >16 examined the cost of intranasal steroid monotherapy and intranasal antihistamine monotherapy. It was found that the average cost of AR intranasal medication(s) for 1-year of follow-up was higher for intranasal corticosteroids (\$177.42) compared with intranasal antihistamine (\$130.06) (Fairchild 2011).	Panel members noted that the answer will highly depend on the local health system owing to large variability in cost and coverage of both the INAH and INCS: availability of lower cost generic formulations, public or private insurance plans, copayment models and patient out of the pocket expenses. In many countries INAH are more costly than INCS.																					
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	No research evidence was identified.	Judgment was based on one retrospective cohort and unsystematic observations in panel members practice.																					
COST-EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ☐ Favors the comparison ☒ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ No included studies	No research evidence was identified.																						
EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced ☒ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	No research evidence was identified.																						

ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	

Summary of Judgments

	JUDGMENT							IMPLICATIONS
PROBLEM	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
DESIRABLE EFFECTS	Don't know	Varies	No evidence of desirable effects	Trivial	Small	Moderate	Large	Favors INCS
UNDESIRABLE EFFECTS	Don't know	Varies	No evidence of undesirable effects	Large	Moderate	Small	Trivial	Favors INCS
CERTAINTY OF EVIDENCE	No included studies			Very low	Low	Moderate	High	Favors neither intervention
VALUES				Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	Favors neither intervention
BALANCE OF EFFECTS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INCS
RESOURCES REQUIRED	Don't know	Varies	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Favors neither intervention
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies			Very low	Low	Moderate	High	Favors neither intervention
COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INCS
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ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should a intranasal H1-antihistamine vs. intranasal corticosteroid be used for treatment of seasonal allergic rhinitis?					
TYPE OF RECOMMENDATION	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 ☐
RECOMMENDATION	In patients with seasonal AR, we suggest an intranasal corticosteroid rather than an intranasal H1-antihistamine (conditional recommendation moderate certainty of evidence)				
JUSTIFICATION	There seem be no desirable effects of INAH when compared to INCS in seasonal AR. There is some evidence that INCS relieve nasal symptoms better and have fewer adverse effects. However, the differences in the effects are small and adverse effects mild, thus, the choice may primarily depend on availability and cost of particular medications, and patient's values and preferences. This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs.				
SUBGROUP CONSIDERATIONS	–				
IMPLEMENTATION CONSIDERATIONS	–				
MONITORING AND EVALUATION	–				
RESEARCH PRIORITIES	–				

Question 5B

Should an **intranasal H1-antihistamine** vs. an **intranasal corticosteroid** be used for treatment of **perennial allergic rhinitis**?

POPULATION:	Patients with perennial AR	BACKGROUND: INAH may have an advantage over INCS in its faster onset of symptom relief as their mechanisms of action are different. Each has specific advantages and disadvantages.
INTERVENTION:	INAH	
COMPARISON:	INCS	
MAIN OUTCOMES:	symptoms, quality of life, adverse effects	
SETTING:	primary care	
PERSPECTIVE:	individual patient	

Assessment

	JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																				
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).																					
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ No evidence of desirable effects ☐ Don't know	<table border="1"> <thead> <tr> <th>Outcome</th><th>N_e of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr> </thead> <tbody> <tr> <td>Nasal symptoms</td><td>96 (1 RCT)</td><td>-</td><td>MD 1.08 higher (0.36 higher to 1.8 higher)</td></tr> <tr> <td>Ocular symptoms</td><td>38 (1 RCT)</td><td>-</td><td>MD 0.29 higher (0.39 lower to 0.97 higher)</td></tr> <tr> <td>Quality of life</td><td>-</td><td>-</td><td>-</td></tr> <tr> <td>Serious adverse effect</td><td>264 (3 RCTs)</td><td>not estimable</td><td>0 fewer per 1000 (20 fewer to 20 more)</td></tr> </tbody> </table>	Outcome	N _e of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms	96 (1 RCT)	-	MD 1.08 higher (0.36 higher to 1.8 higher)	Ocular symptoms	38 (1 RCT)	-	MD 0.29 higher (0.39 lower to 0.97 higher)	Quality of life	-	-	-	Serious adverse effect	264 (3 RCTs)	not estimable	0 fewer per 1000 (20 fewer to 20 more)	There seem be no desirable effects of INAH when compared to INCS in perennial AR. There is some evidence that INCS better relieve nasal symptoms, albeit the evidence is of low certainty. There is no information about quality-of-life, but assuming that symptoms are a good surrogate for it call mom it is very likely that Quality of life would also be improved more with INCS.
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Somnolence	VERY LOW	Important																												
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability	Values and Preferences: Outcomes One systematic review identified 7 cross-sectional studies (Burstrom 2011, Revicki 1998, Revicki 2011, Gold 1998, Demoly 2013, Senti 2007, Tamayama 2009) on utility/value associated with AR. With 0 indicating death and 1 indicating perfect health, the overall range of utility/value based on generic measurements was 0.63-0.91 for allergic rhinitis (HUI-2: 0.83, EQ-5D: 0.85-0.91, VAS: 0.63). Two studies (Lo 2006, Tamayama 2009) reported utility for different severity of allergic rhinitis, one using rating scale and time trade off (Tamayama 2009), another one using disease specific rhinitis symptom utility index (RSUI) (Lo 2006). The utilities based on time trade off were 0.96, 0.94, 0.89, 0.83 for mild, moderate, severe and very severe AR, respectively. The utilities based on rating scale were 0.82, 0.71, 0.56 and 0.43 for mild, moderate, severe and very severe AR, respectively. The disease specific RSUI suggested the utilities were 0.83, 0.69 and 0.50 for mild, moderate, and severe allergic rhinitis. In a small sample of 83 Japanese patients nasal obstruction was the most important symptom. (Ogino 2006) Values and Preferences: Treatments A cross-sectional study of 170 patients with AR examined the preferences in view of treatment and fear of side effects of the most common treatment options; 30% (52/170) preferred a nasal spray, 25% (42/170) preferred oral treatment and 16% (30/170) preferred combination treatment, whereas 15% (27/170) preferred injection treatment. Additionally, 48% (81/170) expressed concern regarding the side effects of INCS sprays compared to other treatments (Hellings 2012). A cross-sectional study of 503 patients with AR and an RCT in Indonesia found that patients prefer treatment options with no smell or taste (Kalinier 2001, Bunnag 2003).																												
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ☐ Favors the comparison ☒ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ Don't know	<table><tr><th>Outcome</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr><tr><td>Nasal symptoms</td><td>-</td><td>MD 1.08 higher (0.36 higher to 1.8 higher)</td></tr><tr><td>Ocular symptoms</td><td>-</td><td>MD 0.29 higher (0.39 lower to 0.97 higher)</td></tr><tr><td>Quality of life</td><td>-</td><td>–</td></tr><tr><td>Serious adverse effect</td><td>not estimable</td><td>0 fewer per 1000 (20 fewer to 20 fewer)</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>RR 1.46 (0.62 to 3.41)</td><td>28 more per 1000 (23 fewer to 148 more)</td></tr><tr><td>Bitter taste</td><td>RR 5.50 (2.06 to 14.68)</td><td>277 more per 1000 (65 more to 842 more)</td></tr><tr><td>Epistaxis</td><td>RR 0.69 (0.36 to 1.31)</td><td>76 fewer per 1000 (158 fewer to 76 more)</td></tr><tr><td>Somnolence</td><td>RR 7.56 (0.43 to 132.48)</td><td>170 more per 1000 (1 fewer to 330 more)</td></tr></table>	Outcome	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms	-	MD 1.08 higher (0.36 higher to 1.8 higher)	Ocular symptoms	-	MD 0.29 higher (0.39 lower to 0.97 higher)	Quality of life	-	–	Serious adverse effect	not estimable	0 fewer per 1000 (20 fewer to 20 fewer)	Withdrawal owing to adverse effect	RR 1.46 (0.62 to 3.41)	28 more per 1000 (23 fewer to 148 more)	Bitter taste	RR 5.50 (2.06 to 14.68)	277 more per 1000 (65 more to 842 more)	Epistaxis	RR 0.69 (0.36 to 1.31)	76 fewer per 1000 (158 fewer to 76 more)	Somnolence	RR 7.56 (0.43 to 132.48)	170 more per 1000 (1 fewer to 330 more)	
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RESOURCES REQUIRED	How large are the resource requirements (costs)? ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	A retrospective cohort study of allergic rhinitis patients aged >16 examined the cost of intranasal steroid monotherapy and intranasal antihistamine monotherapy. It was found that the average cost of AR intranasal medication(s) for 1-year of follow-up was higher for intranasal corticosteroids (\$177.42) compared with intranasal antihistamine (\$130.06) (Fairchild 2011).	Panel members noted that the answer will highly depend on the local health system owing to large variability in cost and coverage of both the INAH and INCS: availability of lower cost generic formulations, public or private insurance plans, copayment models and patient out of the pocket expenses. In many countries INAH are more costly than INCS.																											

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	No research evidence was identified.	Judgment was based on one retrospective cohort and unsystematic observations in panel members practice.
COST-EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ☐ Favors the comparison ☒ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ No included studies	No research evidence was identified.	
EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced ☒ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	No research evidence was identified.	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	

Summary of Judgments

	JUDGMENT							IMPLICATIONS
PROBLEM	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
DESIRABLE EFFECTS	Don't know	Varies	No evidence of desirable effects	Trivial	Small	Moderate	Large	Favors INCS
UNDESIRABLE EFFECTS	Don't know	Varies	No evidence of undesirable effects	Large	Moderate	Small	Trivial	Favors INCS
CERTAINTY OF EVIDENCE	No included studies			Very low	Low	Moderate	High	Favors neither intervention
VALUES				Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	Favors neither intervention
BALANCE OF EFFECTS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INCS
RESOURCES REQUIRED	Don't know	Varies	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Favors neither intervention
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies			Very low	Low	Moderate	High	Favors neither intervention
COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors INCS
EQUITY	Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Favors neither intervention
ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should an intranasal H1-antihistamine vs. an intranasal corticosteroid be used for treatment of perennial allergic rhinitis?					
TYPE OF RECOMMENDATION	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 ☐
RECOMMENDATION	In patients with perennial AR, we suggest an intranasal corticosteroid rather than intranasal H1-antihistamine (conditional recommendation low certainty of evidence)				
JUSTIFICATION	There seem be no desirable effects of INAH when compared to INCS in perennial as well as seasonal AR. There is some evidence that INCS better relieve nasal symptoms, albeit the evidence is of low certainty. This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs.				
SUBGROUP CONSIDERATIONS	–				

IMPLEMENTATION CONSIDERATIONS	–
MONITORING AND EVALUATION	–
RESEARCH PRIORITIES	Further research of an effect of INAH compared with INCS on quality of life may be warranted. The only INAH used in these 3 studies was azelastine – studies of other INAH may be warranted.

Question 6

Should an **intranasal H1-antihistamine (INAH)** vs. an **oral H1-antihistamine (OAH)** be used for treatment of **seasonal allergic rhinitis**?

POPULATION: Patients with seasonal or intermittent AR

INTERVENTION: INAH

COMPARISON: OAH

MAIN OUTCOMES: symptoms, quality of life, adverse effects

SETTING: primary care

PERSPECTIVE: individual patient

BACKGROUND:

Assessment

	JUDGMENT	RESEARCH EVIDENCE				ADDITIONAL CONSIDERATIONS																													
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).																																	
	How substantial are the desirable anticipated effects? ☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ No evidence of desirable effects ☐ Don't know	<table><tr><th>Outcome</th><th>N_e of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr><tr><td>Nasal symptoms (<i>azelastine</i> vs. <i>cetirizine</i>)</td><td>660 (2 RCTs)</td><td>–</td><td>SMD 0.21 higher (0.06 higher to 0.36 higher)</td></tr><tr><td>Nasal symptoms (<i>azelastine</i> vs. <i>chlorpheniramine</i>)</td><td>600 (2 RCTs)</td><td>–</td><td>SMD 0.48 lower (0.87 lower to 0.08 lower)</td></tr><tr><td>Nasal symptoms (<i>azelastine</i> or <i>levocabastine</i> vs. <i>loratadine</i> or <i>ebastine</i>)</td><td>414 (3 RCTs)</td><td>–</td><td>SMD 0 (0.19 lower to 0.19 higher)</td></tr><tr><td>Ocular symptoms</td><td>197 (2 RCTs)</td><td>–</td><td>SMD 0.01 more (0.27 fewer to 0.29 more)</td></tr><tr><td>Quality of life (RQLQ)</td><td>306 (1 RCT)</td><td>–</td><td>MD 0.3 lower (0.03 lower to 0.57 lower)</td></tr><tr><td>Serious adverse effect</td><td>1510 (9 RCTs)</td><td>not estimable</td><td>0 fewer per 1000 (from 7 fewer to 6 more)</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>1499 (9 RCTs)</td><td>RR 1.99 (0.92 to 4.29)</td><td>12 more per 1000 (1 fewer to 41 more)</td></tr></table>	Outcome	N _e of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms (<i>azelastine</i> vs. <i>cetirizine</i>)	660 (2 RCTs)	–	SMD 0.21 higher (0.06 higher to 0.36 higher)	Nasal symptoms (<i>azelastine</i> vs. <i>chlorpheniramine</i>)	600 (2 RCTs)	–	SMD 0.48 lower (0.87 lower to 0.08 lower)	Nasal symptoms (<i>azelastine</i> or <i>levocabastine</i> vs. <i>loratadine</i> or <i>ebastine</i>)	414 (3 RCTs)	–	SMD 0 (0.19 lower to 0.19 higher)	Ocular symptoms	197 (2 RCTs)	–	SMD 0.01 more (0.27 fewer to 0.29 more)	Quality of life (RQLQ)	306 (1 RCT)	–	MD 0.3 lower (0.03 lower to 0.57 lower)	Serious adverse effect	1510 (9 RCTs)	not estimable	0 fewer per 1000 (from 7 fewer to 6 more)	Withdrawal owing to adverse effect	1499 (9 RCTs)	RR 1.99 (0.92 to 4.29)	12 more per 1000 (1 fewer to 41 more)	There seems to be a difference among different comparators. There is moderate certainty evidence that cetirizine has a larger beneficial effect on nasal symptoms compared to azelastine. There is low certainty that azelastine is better than chlorpheniramine. For all other comparisons there is no evidence that either INAH or OAH better relieve nasal symptoms. Panel members commented that there is a belief among researchers that INAH have a larger effect on nasal congestion, compared to OAH. However, we were unable to prove this effect in the 5 studies that reported congestion. Two studies reported end-of-study values (SMD: 0.01; 95% CI: -0.21 to 0.23) and 3 studies reported changes from baseline (SMD: 0.08; 95% CI: -0.10 to 0.26; favoring INAH). This observation remained almost unchanged when we included only 2 studies that used larger doses of INAH (SMD: 0.13; 95% CI: -0.07 to 0.33).
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RESOURCES REQUIRED	How large are the resource requirements (costs)? ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	No research evidence was identified.	Cost of treatment will very much depend on local availability and cost of branded and generic OAH and INAH.																																	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	No research evidence was identified.																																		
COST-EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ☐ Favors the comparison ☐ Probably favors the comparison ☒ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ No included studies	No research evidence was identified.	Generic OAH or INAH, if available, may be more cost-effective.																																	
EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced ☒ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	No research evidence was identified.																																		

ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	

Summary of Judgments

	JUDGMENT							IMPLICATIONS
PROBLEM	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
DESIRABLE EFFECTS	Don't know	Varies	No evidence of desirable effects	Trivial	Small	Moderate	Large	Favors neither intervention
UNDESIRABLE EFFECTS	Don't know	Varies	No evidence of undesirable effects	Large	Moderate	Small	Trivial	Favors neither intervention
CERTAINTY OF EVIDENCE	No included studies			Very low	Low	Moderate	High	Favors neither intervention
VALUES				Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	Favors neither intervention
BALANCE OF EFFECTS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors neither intervention
RESOURCES REQUIRED	Don't know	Varies	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Favors neither intervention
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies			Very low	Low	Moderate	High	Favors neither intervention
COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors neither intervention
EQUITY	Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Favors neither intervention
ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should an intranasal H1-antihistamine vs. oral H1-antihistamine be used for treatment of seasonal allergic rhinitis?					
TYPE OF RECOMMENDATION	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 ☐
RECOMMENDATION	In patients with seasonal AR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation low certainty of evidence)				
JUSTIFICATION	There is no consistent evidence showing better health outcomes with INAH or OAH. Choice of treatment will likely depend on patient's preferences for relief of specific symptoms and aversion to adverse effects: increased somnolence with OAH and increased bitter or perverted taste with INAH. This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, local availability of INAH and OAH, and costs.				
SUBGROUP CONSIDERATIONS	–				
IMPLEMENTATION CONSIDERATIONS	–				
MONITORING AND EVALUATION	–				
RESEARCH PRIORITIES	Additional RCTs of individual INAH vs. individual OAH that properly measure and report symptoms and quality of life may be warranted. Specifically, the studies that measure real life effects of continuous or as-needed use of INAH and OAH that also measure patient preference for the route of administration may be beneficial.				

Question 6

Should an **intranasal H1-antihistamine (INAH)** vs. an **oral H1-antihistamine (OAH)** be used for treatment of **persistent allergic rhinitis**?

POPULATION:	Patients with persistent or perennial AR	BACKGROUND: Theoretically the major advantage of intranasal antihistamines is the delivery directly into the nose and possible avoidance or reduction in severity of systemic side effects of oral antihistamines. In previous version ARIA guidelines suggested that for majority of patients OAH would be a better choice, but the recommendation was mainly based on the evidence about the likely higher patient preference for an oral versus intranasal route of administration.
INTERVENTION:	INAH	
COMPARISON:	OAH	
MAIN OUTCOMES:	symptoms, quality of life, adverse effects	
SETTING:	primary care	
PERSPECTIVE:	individual patient	

Assessment

	JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																				
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Allergic rhinitis (AR) is an important health problem because of its high prevalence and its impact on patients' social life, school performance, and work productivity. Most individuals develop AR during childhood. The overall prevalence of AR is 14.6% (range 1.0 to 45%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). It is probably higher in younger generations as the prevalence is increasing. Prevalence of AR depends on geographical region: Africa: 7-54%, Asia: 2-47%, Australia: 12-41%, Europe: 23-30%, Middle East: 7-45%, North America: 12-30% and South America: 6-45% (Katelaris 2011). The distribution of seasonal vs. perennial or intermittent vs. persistent AR is more difficult to estimate because it varies widely among studies and geographical regions. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).																					
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ☒ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ No evidence of desirable effects ☐ Don't know	<table> <tr> <th>Outcome</th><th>N_e of participants (studies)</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr> <tr> <td>Nasal symptoms</td><td>237 (2 RCTs)</td><td>–</td><td>SMD 0.13 higher (0.12 lower to 0.39 higher)</td></tr> <tr> <td>Ocular symptoms</td><td>237 (2 RCTs)</td><td>–</td><td>SMD 0.03 higher (0.23 lower to 0.28 higher)</td></tr> <tr> <td>Quality of life – not measured</td><td>–</td><td>–</td><td>–</td></tr> <tr> <td>Serious adverse effect</td><td>126 (3 RCTs)</td><td>not estimable</td><td>1 more per 1000 (from 49 fewer to 51 more)</td></tr> </table>	Outcome	N _e of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms	237 (2 RCTs)	–	SMD 0.13 higher (0.12 lower to 0.39 higher)	Ocular symptoms	237 (2 RCTs)	–	SMD 0.03 higher (0.23 lower to 0.28 higher)	Quality of life – not measured	–	–	–	Serious adverse effect	126 (3 RCTs)	not estimable	1 more per 1000 (from 49 fewer to 51 more)	Panel members noted that nasal congestion is an important persistent symptoms of perennial rhinitis. However, none of the studies in PAR reported the symptoms separately.
Outcome	N _e of participants (studies)	Relative effect (95% CI)	Absolute effect (95% CI)																				
Nasal symptoms	237 (2 RCTs)	–	SMD 0.13 higher (0.12 lower to 0.39 higher)																				
Ocular symptoms	237 (2 RCTs)	–	SMD 0.03 higher (0.23 lower to 0.28 higher)																				
Quality of life – not measured	–	–	–																				
Serious adverse effect	126 (3 RCTs)	not estimable	1 more per 1000 (from 49 fewer to 51 more)																				
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ☐ Large ☐ Moderate ☐ Small ☒ Trivial ☐ Varies ☐ No evidence of undesirable effects ☐ Don't know	<table> <tr> <td>Withdrawal owing to adverse effect</td><td>277 (3 RCTs)</td><td>RR 0.92 (0.07 to 12.48)</td><td>2 fewer per 1000 (20 fewer to 248 more)</td></tr> <tr> <td>Any adverse effect</td><td>333 (4 RCTs)</td><td>RR 0.84 (0.31 to 2.26)</td><td>30 fewer per 1000 (128 fewer to 234 more)</td></tr> <tr> <td>Somnolence</td><td>333 (4 RCTs)</td><td>RR 0.43 (0.07 to 2.60)</td><td>24 fewer per 1000 (39 fewer to 67 more)</td></tr> </table> See appendix for full evidence profile.	Withdrawal owing to adverse effect	277 (3 RCTs)	RR 0.92 (0.07 to 12.48)	2 fewer per 1000 (20 fewer to 248 more)	Any adverse effect	333 (4 RCTs)	RR 0.84 (0.31 to 2.26)	30 fewer per 1000 (128 fewer to 234 more)	Somnolence	333 (4 RCTs)	RR 0.43 (0.07 to 2.60)	24 fewer per 1000 (39 fewer to 67 more)	Studies compared OAH: cetirizine and loratadine to INAH (levocabastine and azelastine). The use of older generation, more sedating OAH may be associated with more adverse effects than observed in these studies.								
Withdrawal owing to adverse effect	277 (3 RCTs)	RR 0.92 (0.07 to 12.48)	2 fewer per 1000 (20 fewer to 248 more)																				
Any adverse effect	333 (4 RCTs)	RR 0.84 (0.31 to 2.26)	30 fewer per 1000 (128 fewer to 234 more)																				
Somnolence	333 (4 RCTs)	RR 0.43 (0.07 to 2.60)	24 fewer per 1000 (39 fewer to 67 more)																				

CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	<table><tr><th>Outcome</th><th>Quality</th><th>Importance</th></tr><tr><td>Nasal symptoms</td><td>VERY LOW</td><td>Critical</td></tr><tr><td>Ocular symptoms</td><td>VERY LOW</td><td>Critical</td></tr><tr><td>Quality of life</td><td>-</td><td>Critical</td></tr><tr><td>Serious adverse effect</td><td>HIGH</td><td>Critical</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>VERY LOW</td><td>Critical</td></tr><tr><td>Any adverse effect</td><td>VERY LOW</td><td>Important</td></tr><tr><td>Somnolence</td><td>VERY LOW</td><td>Important</td></tr></table>	Outcome	Quality	Importance	Nasal symptoms	VERY LOW	Critical	Ocular symptoms	VERY LOW	Critical	Quality of life	-	Critical	Serious adverse effect	HIGH	Critical	Withdrawal owing to adverse effect	VERY LOW	Critical	Any adverse effect	VERY LOW	Important	Somnolence	VERY LOW	Important	
Outcome	Quality	Importance																									
Nasal symptoms	VERY LOW	Critical																									
Ocular symptoms	VERY LOW	Critical																									
Quality of life	-	Critical																									
Serious adverse effect	HIGH	Critical																									
Withdrawal owing to adverse effect	VERY LOW	Critical																									
Any adverse effect	VERY LOW	Important																									
Somnolence	VERY LOW	Important																									
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? ☐ Important uncertainty or variability ☒ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability	Values and Preferences: Outcomes One systematic review identified 7 cross-sectional studies (Burstrom 2011, Revicki 1998, Revicki 2011, Gold 1998, Demoly 2013, Senti 2007, Tamayama 2009) on utility/value associated with AR. With 0 indicating death and 1 indicating perfect health, the overall range of utility/value based on generic measurements was 0.63-0.91 for allergic rhinitis (HUI-2: 0.83, EQ-5D: 0.85-0.91, VAS: 0.63). Two studies (Lo 2006, Tamayama 2009) reported utility for different severity of allergic rhinitis, one using rating scale and time trade off (Tamayama 2009), another one using disease specific rhinitis symptom utility index (RSUI) (Lo 2006). The utilities based on time trade off were 0.96, 0.94, 0.89, 0.83 for mild, moderate, severe and very severe AR, respectively. The utilities based on rating scale were 0.82, 0.71, 0.56 and 0.43 for mild, moderate, severe and very severe AR, respectively. The disease specific RSUI suggested the utilities were 0.83, 0.69 and 0.50 for mild, moderate, and severe allergic rhinitis. In a small sample of 83 Japanese patients, regarding clinical symptoms, nasal obstruction was identified as the most important symptom influencing patient satisfaction. (Ogino 2006) Values and Preferences: Treatments A cross-sectional study of 170 patients with AR examined the preferences in view of treatment and fear of side effects of the most common treatment options; 30% (52/170) preferred a nasal spray, 25% (42/170) preferred oral treatment and 16% (30/170) preferred combination treatment, whereas 15% (27/170) preferred injection treatment. Additionally, 48% (81/170) expressed concern regarding the side effects of INCS sprays compared to other treatments (Hellings 2012). A cross-sectional study of 503 patients with AR and an RCT in Indonesia found that patients prefer treatment options with no smell or taste (Kalinier 2001, Bunnag 2003).																									
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ☐ Favors the comparison ☐ Probably favors the comparison ☒ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ Don't know	<table><tr><th>Outcome</th><th>Relative effect (95% CI)</th><th>Absolute effect (95% CI)</th></tr><tr><td>Nasal symptoms</td><td>–</td><td>SMD 0.13 (0.12 lower to 0.39 higher)</td></tr><tr><td>Ocular symptoms</td><td>–</td><td>SMD 0.03 higher (0.23 lower to 0.28 higher)</td></tr><tr><td>Quality of life – not measured</td><td>–</td><td>–</td></tr><tr><td>Serious adverse effect</td><td>not estimable</td><td>1 more per 1000 (from 49 fewer to 51 more)</td></tr><tr><td>Withdrawal owing to adverse effect</td><td>RR 0.92 (0.07 to 12.48)</td><td>2 fewer per 1000 (20 fewer to 248 more)</td></tr><tr><td>Any adverse effect</td><td>RR 0.84 (0.31 to 2.26)</td><td>30 fewer per 1000 (128 fewer to 234 more)</td></tr><tr><td>Somnolence</td><td>RR 0.43 (0.07 to 2.60)</td><td>24 fewer per 1000 (39 fewer to 67 more)</td></tr></table>	Outcome	Relative effect (95% CI)	Absolute effect (95% CI)	Nasal symptoms	–	SMD 0.13 (0.12 lower to 0.39 higher)	Ocular symptoms	–	SMD 0.03 higher (0.23 lower to 0.28 higher)	Quality of life – not measured	–	–	Serious adverse effect	not estimable	1 more per 1000 (from 49 fewer to 51 more)	Withdrawal owing to adverse effect	RR 0.92 (0.07 to 12.48)	2 fewer per 1000 (20 fewer to 248 more)	Any adverse effect	RR 0.84 (0.31 to 2.26)	30 fewer per 1000 (128 fewer to 234 more)	Somnolence	RR 0.43 (0.07 to 2.60)	24 fewer per 1000 (39 fewer to 67 more)	
Outcome	Relative effect (95% CI)	Absolute effect (95% CI)																									
Nasal symptoms	–	SMD 0.13 (0.12 lower to 0.39 higher)																									
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Somnolence	RR 0.43 (0.07 to 2.60)	24 fewer per 1000 (39 fewer to 67 more)																									
RESOURCES REQUIRED	How large are the resource requirements (costs)? ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	No research evidence was identified.	Cost of treatment will very much depend on local availability and cost of branded and generic OAH and INAH.																								

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ☐ High ☐ Moderate ☐ Low ☒ Very low ☐ No included studies	No research evidence was identified.	
COST-EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ☐ Favors the comparison ☐ Probably favors the comparison ☒ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ No included studies	No research evidence was identified.	Generic OAH or INAH, if available, may be more cost-effective.
EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced ☒ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	No research evidence was identified.	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	No research evidence was identified.	Availability of OAH or INAH other the counter may have an impact on implementation as the patients' access to one or the other may be different.

Summary of Judgments

	JUDGMENT							IMPLICATIONS
PROBLEM	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
DESIRABLE EFFECTS	Don't know	Varies	No evidence of desirable effects	Trivial	Small	Moderate	Large	Favors neither intervention

UNDESIRABLE EFFECTS	Don't know	Varies	No evidence of undesirable effects	Large	Moderate	Small	Trivial	Favors neither intervention
CERTAINTY OF EVIDENCE	No included studies			Very low	Low	Moderate	High	Favors neither intervention
VALUES				Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	Favors neither intervention
BALANCE OF EFFECTS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors neither intervention
RESOURCES REQUIRED	Don't know	Varies	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Favors neither intervention
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies			Very low	Low	Moderate	High	Favors neither intervention
COST-EFFECTIVENESS	Don't know	Varies	Favors the comparison	Probably favors the comparison	Favors neither the intervention nor the comparison	Probably favors the intervention	Favors the intervention	Favors neither intervention
EQUITY	Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Favors neither intervention
ACCEPTABILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention
FEASIBILITY	Don't know	Varies		No	Probably no	Probably yes	Yes	Favors neither intervention

Conclusions

Should an intranasal H1-antihistamine vs. oral H1-antihistamine be used for treatment of perennial allergic rhinitis?					
TYPE OF RECOMMENDATION	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 ☐
RECOMMENDATION	In patients with perennial AR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation low certainty of evidence)				
JUSTIFICATION	Very low certainty evidence does not show a clear larger benefit from either INAH or OAH. Choice of treatment will likely depend on patient's preferences for relief of specific symptoms and aversion to adverse effects: increased somnolence with OAH and increased bitter or perverted taste with INAH. This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences considering local availability of INAH and OAH, and costs.				
SUBGROUP CONSIDERATIONS	–				
IMPLEMENTATION CONSIDERATIONS	–				
MONITORING AND EVALUATION	–				
RESEARCH PRIORITIES	Additional RCTs of individual INAH vs. individual OAH that properly measure and report all important outcomes may be warranted. Specifically, pragmatic trials investigating the real-life impact of having to use a nasal spray and the adverse effects of oral antihistamines used both continuously and as needed may be warranted.				

ARIA 2016 Update

Appendix 3

Evidence Profiles

Author(s): JB
 Date: 2015-08-31
 Question: OAH+INCS compared to INCS alone for seasonal AR
 Setting: primary care
 Bibliography: see references below

Quality assessment							N _o of patients		Effect		Quality	Importance
N _o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OAH+INCS	INCS alone	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (measured with: Total Nasal Symptom Score, TNSS; follow-up: range 2 to 8 weeks)												
5	randomised trials	not serious ¹	not serious	not serious	not serious	none	593	600	-	SMD 0.13 lower (0.25 lower to 0)	HIGH	CRITICAL
Ocular symptoms (measured with: Total Ocular Symptom Score, TOSS; follow-up: 2 weeks)												
2	randomised trials	not serious ¹	not serious	not serious	serious ²	none	377	377	-	SMD 0.19 lower (0.33 lower to 0.05 lower)	MODERATE	CRITICAL
Quality of life (measured with: Rhinoconjunctivitis Quality of Life Questionnaire and mini-RQLQ; ; follow-up: 2 weeks)												
2	randomised trials	not serious ¹	not serious	not serious	very serious ⁶	none	177	177	-	SMD 0.61 lower (1.44 lower to 0.23 higher)	LOW	CRITICAL
Serious adverse effects (SAE; follow-up: range 2 to 6 weeks)												
4	randomised trials	not serious ¹	not serious	not serious	not serious	none	0/366 (0.0%)	0/373 (0.0%)	not estimable	0 fewer per 1000 (from 10 more to 10 fewer)	HIGH	CRITICAL
Withdrawal owing to adverse event (follow-up: 2 weeks and 8 weeks)												
2	randomised trials	not serious ¹	not serious	not serious	serious ³	none	19/377 (5.0%)	22/377 (5.8%)	RR 0.65 (0.13 to 3.23)	20 fewer per 1000 (from 51 fewer to 130 more)	MODERATE	CRITICAL
Any adverse effect (follow-up: range 2 to 4 weeks)												
3	randomised trials	not serious ¹	serious ⁴	serious ⁵	serious ⁶	none	42/207 (20.3%)	41/207 (19.8%)	RR 1.21 (0.29 to 5.01)	42 more per 1000 (from 141 fewer to 794 more)	VERY LOW	IMPORTANT
Sedation/somnolence (follow-up: range 2 to 8 weeks)												
5	randomised trials	not serious ¹	serious ⁷	not serious	serious ⁸	none	33/603 (5.5%)	17/610 (2.8%)	RR 1.55 (0.39 to 6.13)	15 more per 1000 (from 17 fewer to 143 more)	LOW	IMPORTANT
Epistaxis (follow-up: range 2 to 8 weeks)												
4	randomised trials	not serious ¹	not serious	not serious	serious ⁹	none	20/573 (3.5%)	11/580 (1.9%)	RR 1.77 (0.86 to 3.63)	15 more per 1000 (from 3 fewer to 50 more)	MODERATE	IMPORTANT

MD – mean difference, RR – relative risk

1. There is some uncertainty about the risk of bias as most important information has not been reported
2. Confidence interval does not exclude a small benefit or no difference.
3. Only 41 events; confidence interval does not exclude an appreciable benefit or an appreciable harm with either treatment.
4. CIs do not overlap for 1 of 3 studies; we could not explain this difference
5. This is a composite of all adverse effects including more and less important to patients
6. Confidence interval does not exclude an appreciable benefit or an appreciable harm with either treatment.
7. Large difference among studies with CIs barely overlapping
8. Only 50 events; confidence interval does not exclude an appreciable benefit or an appreciable harm with either treatment.
9. Only 31 events; confidence interval does not exclude an appreciable harm with combination treatment or no difference.

Exploratory analysis of individual nasal symptoms

4 studies, 366 patients in INCS+OAH groups and 373 patients in groups that received INCS alone

Outcome	Standardized Mean Difference (SMD) (95% CI)
Rhinorrhea	0.08 lower (0.27 lower to 0.12 higher)
Congestion	0 lower (0.19 lower to 0.2 higher)
Itching	0.01 higher (0.19 lower to 0.21 higher)
Sneezing	0.02 higher (0.18 lower to 0.21 higher)

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Author(s): JB (August 2015)

Date: 2015-09-01

Question: A combination of OAH and INCS compared to INCS alone in patients with PAR

Setting: primary care

Bibliography: Kim 2015¹ (Comparison of intranasal ciclesonide, oral levocetirizine, and combination treatment for allergic rhinitis. Allergy, asthma & immunology research, 2015;7:158-166), Tartar 2013 (The effect of combined medical treatment on quality of life in persistent allergic rhinitis. Indian journal of otolaryngology and head and neck surgery: official publication of the Association of Otolaryngologists of India, 2013;65:333-337)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a combination of OAH and INCS	INCS alone	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (all patients had PAR) (follow up: mean 16 days; assessed with: TNSS; scale 0 to 12 points)												
1	randomised trials	serious ²	not serious	serious ³	not serious ⁴	none	58	59	-	MD 0.2 points in TNSS higher ^{5,6}	LOW	CRITICAL
Nasal symptoms (70% patients with PAR) (follow up: mean 16 days; assessed with: change from baseline in Total Nasal Symptom Score (TNSS); Scale from: 0 to 12)												
1	randomised trials	serious ²	not serious	serious ⁷	not serious ⁸	none	82	88	-	MD 0 points in TNSS (0.73 lower to 0.73 higher)	LOW	IMPORTANT
Ocular symptoms (70% patients with PAR) (follow up: mean 16 days; assessed with: Total ocular symptom score (TOSS); Scale from: 0 to 9)												
1	randomised trials	serious ²	not serious	serious ⁷	not serious ⁸	none	82	88	-	MD 0.1 points in TOSS higher (0.38 lower to 0.58 higher)	LOW	CRITICAL
Quality of life (70% patients with PAR) (follow up: mean 16 days; assessed with: RQLQ; Scale from: 0 to 6)												
1	randomised trials	serious ²	not serious	serious ⁹	serious ⁹	none	82	88	-	MD 0.2 points in RQLQ lower (0.53 lower to 0.13 higher) ⁵	VERY LOW	CRITICAL
Any adverse effect (70% patients with PAR) (follow up: mean 16 days)												
1	randomised trials	serious ²	not serious	serious ⁷	serious ¹⁰	none	5/83 (6.0%) ¹¹	1/89 (1.1%) ¹²	RR 5.36 (0.64 to 44.94)	49 more per 1000 (from 4 fewer to 494 more)	VERY LOW	IMPORTANT
Serious adverse effect (70% patients with PAR) (follow up: mean 16 days)												
1	randomised trials	not serious	not serious	serious ⁷	not serious	none	0/83 (0.0%)	0/89 (0.0%)	not estimable	0 fewer per 1000 (from 22 fewer to 23 fewer)	MODERATE	CRITICAL

MD – mean difference, RR – relative risk

- Study used ciclesonide and oral levocetirizine
- There was no blinding in this study.
- Study assessed efficacy after 16 days but current requirement for the optimal duration of clinical trials to assess drug efficacy in perennial AR is minimum 4 weeks
- We did not lower confidence in the estimated effect because of imprecision despite only 117 patients, because the confidence interval excludes an appreciable benefit with either intervention (assuming a minimal important difference being 0.8 point on a 12-point scale)
- Another study measured this outcome and reported numerically larger improvement with combination therapy, compared with INCS alone. However, this study reported its results in graphs only with no measure of variability, thus, it was not possible to combine the results of both studies (Tatar 2013).
- There was a mean difference of 0.2 points in TNSS favouring INCS alone. Variability in the estimates was not reported so confidence intervals were not calculated
- Study assessed efficacy after 16 days but current requirement for the optimal duration of clinical trials to assess drug efficacy in perennial AR is minimum 4 weeks; included are patients with SAR (70%) and PAR (30%) together
- We did not lower confidence in the estimated effect because of imprecision despite only 170 patients, because the confidence interval excludes an appreciable benefit with either intervention (assuming a minimal important difference being 0.6 point on a 9-point scale)
- Only 170 patients; confidence interval does not exclude an appreciable benefit with combination therapy or no difference (assuming a minimal important difference being 0.5 point in RQLQ)
- Only 6 events; there is a possibility that there is an increased risk of AEs with a combination therapy
- There was 1 person with dry mouth, 1 - sleepiness, 1 - dizziness and 1 - dry nose.
- One person experienced nasal pain

Author(s): JB (August 2015)

Date: 2015-09-04

Question: A combination of INCS with INAH compared to INCS alone in patients with SAR

Setting: primary care

Bibliography: Carr 2012 (3 studies), Hampel 2010, Ratner 2008 (see below)

Quality assessment							N _e of patients		Effect		Quality	Importance
N _e of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INCS+INAH	INCS alone	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (follow up: 2 weeks; assessed with: Total Nasal Symptom Score (TNSS); Scale from: 0 to 24)												
5	randomised trials	not serious	not serious	not serious	not serious ¹	none	1053	1047	-	MD 0.77 lower (1.24 lower to 0.3 lower)	HIGH	CRITICAL
Ocular symptoms (follow up: 2 weeks; assessed with: various ocular symptom scores)												
5	randomised trials	not serious	not serious	not serious	serious ²	none	1053	1047	-	SMD 0.2 lower (0.33 lower to 0.07 lower)	MODERATE	CRITICAL
Quality of life (follow up: 2 weeks; assessed with: RQLQ [MID = 0.5 pt]; Scale from: 0 to 6)												
5	randomised trials	not serious	not serious	not serious	not serious ³	none	1053	1047	-	MD 0.13 higher (0.01 higher to 0.24 higher)	HIGH	CRITICAL
Serious adverse effect (follow up: 2 weeks)												
4	randomised trials	not serious	not serious	not serious	not serious	none	2/905 (0.2%)	0/896 (0.0%)	not estimable	2 fewer per 1000 (from 3 fewer to 7 fewer) ¹⁰	HIGH	CRITICAL
Withdrawal owing to adverse effects (follow up: 2 weeks)												
3	randomised trials	not serious	not serious	not serious	serious ⁴	none	10/853 (1.2%)	4/846 (0.5%)	RR 1.94 (0.59 to 6.36)	4 more per 1000 (from 2 fewer to 25 more)	MODERATE	CRITICAL
Adverse effects (any) (follow up: 2 weeks)												
3	randomised trials	not serious	not serious	serious ⁵	serious ⁶	none	87/853 (10.2%)	52/846 (6.1%)	RR 1.66 (1.19 to 2.31)	41 more per 1000 (from 12 more to 81 more)	LOW	IMPORTANT
Bitter taste (follow up: 2 weeks)												
5	randomised trials	not serious	not serious	not serious	serious ⁶	none	48/1058 (4.5%)	5/1049 (0.5%)	RR 6.46 (2.58 to 16.20)	26 more per 1000 (from 8 more to 72 more)	MODERATE	IMPORTANT
Epistaxis (follow up: 2 weeks)												
4	randomised trials	not serious	not serious	not serious	serious ⁷	none	19/1006 (1.9%)	19/999 (1.9%)	RR 1.01 (0.53 to 1.92)	0 fewer per 1000 (from 9 fewer to 17 more)	MODERATE	IMPORTANT
Somnolence (follow up: 2 weeks)												
4	randomised trials	not serious	not serious	not serious	serious ^{8,9}	none	6/1006 (0.6%)	1/999 (0.1%)	RR 3.19 (0.28 to 36.26)	2 more per 1000 (from 1 fewer to 35 more)	MODERATE	IMPORTANT
Exploratory analysis of individual symptoms												
Congestion (follow up: 2 weeks; assessed with: single domain of TNSS; Scale from: 0 to 6)												
5	randomised trials	not serious	not serious	not serious	not serious ⁹	none	1053	1047	-	MD 0.21 lower (0.36 lower to 0.06 lower)	HIGH	IMPORTANT
Rhinorrhoea (follow up: 2 weeks; assessed with: single domain of TNSS; Scale from: 0 to 6)												
5	randomised trials	not serious	not serious	not serious	not serious ⁹	none	1053	1047	-	MD 0.17 lower (0.29 lower to 0.04 lower)	HIGH	IMPORTANT
Itching (follow up: 2 weeks; assessed with: single domain of TNSS; Scale from: 0 to 6)												
5	randomised trials	not serious	not serious	not serious	not serious ⁹	none	1053	1047	-	MD 0.18 lower (0.3 lower to 0.06 lower)	HIGH	IMPORTANT
Sneezing (follow up: 2 weeks; assessed with: single domain of TNSS; Scale from: 0 to 6)												
5	randomised trials	not serious	not serious	not serious	not serious ⁹	none	1053	1047	-	MD 0.28 lower (0.44 lower to 0.13 lower)	HIGH	IMPORTANT

MD – mean difference, RR – relative risk

1. We assumed that a minimal important difference on a scale from 0 to 24 would be around 2 points. Confidence interval excludes MID.
2. A typical interpretation of effect size (SMD) as suggested by Cohen is: around 0.2 - small effect, around 0.5 – moderate effect, around 0.8 or higher – large effect. Confidence interval does not exclude a small beneficial effect with combination therapy.
3. Confidence interval excludes MID.
4. Only 14 events. Confidence interval around the absolute effect for this outcome and for other measures of adverse effects seems not to exclude an appreciable increase in the risk of AEs with combination therapy.
5. This composite outcome likely includes AEs that are more and less important to patients.
6. Confidence interval does not exclude an increased risk of adverse effects with combination therapy.
7. Only 38 events.
8. Only 7 events.
9. We assumed that a minimal important difference on a scale from 0 to 6 would be around 0.5 points. Confidence interval excludes MID.
10. Based on risk difference meta-analysis.

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Author(s): JB

Date: 2015-09-03

Question: A combination of INCS with INAH compared to INCS alone in patients with PAR

Setting: primary care

Bibliography: Price 2013 (see below)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	INCS+HNAH	INCS alone	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (follow up: 52 weeks; assessed with: Total Nasal Symptom Score; Scale from: 0 to 12)												
1	randomised trials	serious ¹	not serious	serious ²	serious	none	404	207	-	mean 0.27 points lower (0.56 lower to 0.02 higher)	VERY LOW	CRITICAL
Ocular symptoms - not measured												
-	-	-	-	-	-	-	-	-	-	—	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	—	-	CRITICAL
Symptom-free days (follow up: 52 weeks)												
1	randomised trials	serious ¹	not serious	not serious ³	serious ⁴	none	265	140	-	mean 23.9 days higher (0.24 lower to 48 higher)	LOW	CRITICAL
Serious Adverse Effects (follow up: 52 weeks)												
1	randomised trials	serious ¹	not serious	not serious	serious ⁵	none	3/404 (0.7%)	1/207 (0.5%)	RR 1.54 (0.16 to 14.69)	3 more per 1000 (from 4 fewer to 66 more)	LOW	CRITICAL
Withdrawal owing to adverse event (follow up: 52 weeks)												
1	randomised trials	serious ¹	not serious	serious ⁶	serious ^{7,8}	none	11/404 (2.7%)	6/207 (2.9%)	RR 0.94 (0.35 to 2.50)	2 fewer per 1000 (from 19 fewer to 43 more)	VERY LOW	CRITICAL
Any adverse effect (follow up: 52 weeks)												
1	randomised trials	serious ¹	not serious	serious ⁶	serious ⁷	none	188/404 (46.5%)	92/207 (44.4%)	RR 1.05 (0.87 to 1.26)	22 more per 1000 (from 58 fewer to 116 more)	VERY LOW	IMPORTANT
Epistaxis (follow up: 52 weeks)												
1	randomised trials	serious ¹	not serious	not serious	serious ^{7,8}	none	5/404 (1.2%)	1/207 (0.5%)	RR 2.56 (0.30 to 21.79)	8 more per 1000 (from 3 fewer to 100 more)	LOW	IMPORTANT
Dysgeusia (distortion of the sense of taste) (follow up: 52 weeks)												
1	randomised trials	serious ¹	not serious	not serious	serious ^{5,8}	none	10/404 (2.5%)	1/207 (0.5%)	RR 5.12 (0.66 to 39.75)	20 more per 1000 (from 2 fewer to 187 more)	LOW	IMPORTANT

MD – mean difference; RR – relative risk

- Study was not blinded and 10% were lost to follow-up.
- Only 70% had allergic rhinitis; others had other type of chronic rhinitis (vasomotor)
- This was a subgroup of patients with PAR; we did not downgrade the certainty for additional risk of bias because the difference between the groups was not different in total population
- Confidence interval does not exclude an appreciable benefit or no difference.
- Confidence interval does not exclude an appreciable harm with combination therapy or no difference.
- There were many adverse effects some of which may have been more important to patients than the others.
- Confidence interval does not exclude an appreciable harm with either intervention.
- Very few events

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Author(s): JB

Date: 2015-09-07

Question: Combination of an intranasal H1-antihistamine with an intranasal corticosteroid vs. intranasal H1-antihistamine alone for Seasonal Allergic Rhinitis

Setting: primary care

Bibliography: Carr 2012 (3 studies), Hampel 2010, Ratner 2008 (see below)

Quality assessment						Nº of patients			Effect		Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INCS+INAH	INCS alone	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (follow up: 2 weeks; assessed with: Total Nasal Symptom Score (TNSS); Scale from: 0 to 24)												
5	randomised trials	not serious	not serious	not serious	not serious ¹	none	1053	1048	-	MD 1.4 points lower (1.82 lower to 0.98 lower)	HIGH	CRITICAL
Ocular symptoms (follow up: 2 weeks; assessed with: various ocular symptom scores)												
5	randomised trials	not serious	not serious	not serious	serious ²	none	1053	1047	-	SMD 0.33 SD lower (0.65 lower to 0.02 lower)	MODERATE	CRITICAL
Quality of life (follow up: 2 weeks; assessed with: RQLQ [MD = 0.5 pt]; Scale from: 0 to 6)												
3	randomised trials	not serious	serious ^{3,4}	not serious	serious ²	none	1053	1046	-	MD 0.53 points lower (1.01 lower to 0.06 lower) ³	LOW	CRITICAL
Serious adverse effect (follow up: 2 weeks)												
5	randomised trials	not serious	not serious	not serious	not serious	none	2/1058 (0.2%)	0/1048 (0.0%)	not estimable	2 fewer per 1000 (from 6 fewer to 3 fewer)	HIGH	CRITICAL
Withdrawal owing to adverse effects (follow up: 2 weeks)												
4	randomised trials	not serious	not serious	not serious	serious ⁵	none	11/1006 (1.1%)	9/1000 (0.9%)	RR 1.19 (0.41 to 3.42)	2 more per 1000 (from 5 fewer to 22 more)	MODERATE	CRITICAL
Adverse effects (any) (follow up: 2 weeks)												
4	randomised trials	not serious	serious ⁶	serious ⁷	not serious ⁸	none	119/1006 (11.8%)	104/999 (10.4%)	RR 1.15 (0.73 to 1.81)	16 more per 1000 (from 28 fewer to 84 more)	LOW	IMPORTANT
Bitter taste (follow up: 2 weeks)												
5	randomised trials	not serious	not serious	not serious	not serious ⁹	none	48/1058 (4.5%)	51/1048 (4.9%)	RR 0.98 (0.48 to 2.00)	1 fewer per 1000 (from 25 fewer to 49 more)	HIGH	IMPORTANT
Epistaxis (follow up: 2 weeks)												
4	randomised trials	not serious	not serious	not serious	serious ¹⁰	none	19/1006 (1.9%)	16/999 (1.6%)	RR 1.19 (0.61 to 2.33)	3 more per 1000 (from 6 fewer to 21 more)	MODERATE	IMPORTANT
Somnolence (follow up: 2 weeks)												
4	randomised trials	not serious	not serious	not serious	serious ¹¹	none	6/1006 (0.6%)	3/999 (0.3%)	RR 1.95 (0.48 to 7.96)	3 more per 1000 (from 2 fewer to 21 more)	MODERATE	IMPORTANT
Exploratory analysis of individual symptoms												
Congestion (follow up: 2 weeks; assessed with: single domain of TNSS; Scale from: 0 to 6)												
5	randomised trials	not serious	not serious	not serious	not serious ¹²	none	1053	1048	-	MD 0.3 points lower (0.42 lower to 0.18 lower)	HIGH	IMPORTANT
Rhinorrhea (follow up: 2 weeks; assessed with: single domain of TNSS; Scale from: 0 to 6)												
5	randomised trials	not serious	not serious	not serious	not serious ¹²	none	1053	1048	-	MD 0.33 points lower (0.46 lower to 0.2 lower)	HIGH	IMPORTANT
Itching (follow up: 2 weeks; assessed with: single domain of TNSS; Scale from: 0 to 6)												
5	randomised trials	not serious	not serious	not serious	not serious ¹²	none	1053	1048	-	MD 0.3 points lower (0.45 lower to 0.15 lower)	HIGH	IMPORTANT
Sneezing (follow up: 2 weeks; assessed with: single domain of TNSS; Scale from: 0 to 6)												
5	randomised trials	not serious	not serious	not serious	not serious ¹²	none	1053	1048	-	MD 0.36 points lower (0.49 lower to 0.22 lower)	HIGH	IMPORTANT

MD – mean difference, RR – relative risk

1. We assumed that a minimal important difference on a scale from 0 to 24 would be around 2 points. Confidence interval excludes MID.
2. Confidence interval does not exclude an appreciable benefit from combination therapy or no difference.
3. We assumed that the results reported by Carr 2012 were combined across 3 studies they described. If data were not pooled for all 3 studies but just from Meltzer 2012 then MD -0.56 (-0.94 to -0.17).
4. Three studies (Carr 2012) showed substantially lower impact on QoL than the other 2 studies. Confidence intervals barely overlapped. This could not be explained.
5. Only 20 events. Confidence interval does not exclude a small benefit or a small harm from combination therapy.
6. There was large statistical heterogeneity and confidence intervals of 2 studies did not overlap. This could be explained by one study (showing the largest harm: RR 2.27 [1.26 to 4.08]) using azelastine and fluticasone from separate sprays rather than as one combination drug. Risk of any adverse effect in studies using combination drug was RR 0.96 (0.72 to 1.28). However, the number of patients who withdrew owing to adverse effects did not differ suggesting that observed inconsistency may have been owing to different definitions of AEs.
7. This composite outcome likely includes AEs that are more and less important to patients.
8. We have not downgraded the confidence in the final estimate because of imprecision, as we already downgraded for inconsistency and they are closely related in this case.
9. Only 99 events. Point estimate suggests no difference and there is no reason to believe that there would be difference as both intervention and control used the same azelastine preparation.
10. Only 35 events. Confidence interval does not exclude a small harm with combination therapy or no important difference.
11. Only 9 events. Only 99 events. There is no reason to believe that there would be difference as both interventions used the same azelastine preparation and there is little concern about somnolence with INCS.
12. We assumed that a minimal important difference on a scale from 0 to 6 would be around 0.5 points. Confidence interval excludes MID.

References

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Author(s): JB

Date: 2015-11-13

Question: Leukotriene receptor antagonist (LTRA) compared to oral H1-antihistamine (OAH) for seasonal allergic rhinitis (SAR)?

Setting: primary care

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTRA	OAH	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (follow up: range 2 to 6 weeks; assessed with: change in symptoms from baseline (various symptom scales))												
8 ¹	randomised trials	not serious	not serious	not serious	not serious ²	none	1886	1719	-	SMD 0.06 higher (0.01 lower to 0.13 higher)	HIGH	CRITICAL
Ocular symptoms (follow up: range 2 to 6 weeks; assessed with: change in symptoms from baseline (various symptom scales))												
6 ³	randomised trials	not serious	not serious ⁴	not serious	not serious ²	none	1669	1438	-	SMD 0.06 higher (0.04 lower to 0.16 higher)	HIGH	CRITICAL
Quality of life (follow up: range 2 to 6 weeks; assessed with: change in RQLQ score from baseline; MD ~0.5 point; Scale from: 0 [best] to 6 [worst])												
5	randomised trials	not serious	not serious	not serious	not serious ²	none	1568	1346	-	MD 0.04 more (0.04 fewer to 0.13 more)	HIGH	CRITICAL
Serious adverse effects (follow up: range 2 to 6 weeks)												
5	randomised trials	not serious ⁵	not serious	not serious	not serious	none	0/397 (0.0%)	0/618 (0.0%)	not estimable	1 fewer per 1000 (from 6 fewer to 9 more)	HIGH	CRITICAL
Withdrawal owing to AE (follow up: range 2 to 6 weeks)												
9	randomised trials	not serious	not serious	not serious	not serious ⁶	none	18/1392 (1.3%)	13/1588 (0.8%)	RR 1.22 (0.47 to 3.16)	2 more per 1000 (from 4 fewer to 18 more)	HIGH	CRITICAL
Any adverse effect (follow up: range 2 to 6 weeks)												
6	randomised trials	serious ⁷	not serious	serious ⁸	not serious ⁹	none	186/1147 (16.2%)	212/1203 (17.6%)	RR 0.95 (0.78 to 1.16)	9 fewer per 1000 (from 28 more to 39 fewer)	LOW	IMPORTANT
Somnolence - not measured												
-	-	-	-	-	-	-	-	see comment	not estimable	see comment	-	IMPORTANT

MD – mean difference, RR – relative risk, SMD – standardized mean difference

1. One additional study measured nasal symptoms but did not report variability in results and, thus, could not be included in analysis (Kuroski 2004). Point estimates favored OAH.
2. 95% CI excludes an appreciable additional benefit with either treatment.
3. Two additional studies (64 patients total) measured final scores only. One was consistent with other studies and one showed probably larger effect with LTRA (the only study comparing pranlukast to fexofenadine in patients already receiving mequitazine [Sagara 2009]).
4. There was some inconsistency but not serious enough to lower confidence in the final estimate.
5. Only 5 out of 10 studies reported this outcome. There is possible some residual reporting bias.
6. Despite only 31 events and wide CI around relative effect, a CI around absolute effect is narrow. We did not reduce confidence in this effect although we recognize that for some uncertainty may be large enough to justify downgrading.
7. Adverse effects were reported in 6/10 studies and usually in a way that precluded meaningful interpretation.
8. Many adverse effects with different importance to patients were reported together.
9. Results are not precise but we did not downgrade because of imprecision as risk of bias and indirectness already reduced our confidence to low.

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Author(s): JB

Date: 2015-11-13

Question: Leukotriene receptor antagonist (LTRA) compared to oral H1-antihistamine (OAH) for persistent/perennial allergic rhinitis (PAR)?

Setting: primary care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTRA	OAH	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (follow up: range 2 to 12 weeks; assessed with: change from baseline in symptoms (various scales)) ¹												
2 ²	randomised trials	not serious	serious ³	not serious	serious ⁴	none	650	142	-	SMD 0.26 higher (0.45 lower to 0.97 higher)	LOW	CRITICAL
Ocular symptoms [children] (follow up: 12 weeks; assessed with: change from baseline in symptoms; Scale from: 0 [better] to 3 [worse])												
1 ⁵	randomised trials	not serious	not serious	not serious	very serious ^{4 6}	none	20	20	-	MD 0.29 higher (0.04 lower to 0.62 higher)	LOW	IMPORTANT ¹⁶
Ocular symptoms [adults] (follow up: 6 weeks; assessed with: change from baseline in symptoms; Scale from: 0 [better] to 4 [worse])												
2	randomised trials	not serious ⁷	not serious	not serious	very serious ^{4 6}	none	20	20	-	MD 0.19 lower (1.03 lower to 0.65 higher)	LOW	IMPORTANT ¹⁶
Quality of life [children] (follow up: 12 weeks; Pediatric RQLQ [0-138 scale])												
1 ⁸	randomised trials	not serious	not serious	not serious	very serious ^{6 9}	none	20	20	-	MD 12 higher (1.66 lower to 25.66 higher)	LOW	CRITICAL
Quality of life [adults]] (follow up: 6 weeks; RQLQ, 0-6 scale)												
2 ¹⁰	randomised trials	not serious	not serious	not serious	very serious ^{4 6}	none	20	20	-	MD 0.17 lower (0.93 lower to 0.58 higher)	LOW	CRITICAL
Serious adverse effects (follow up: range 4 to 12 weeks)												
5	randomised trials	not serious	not serious	not serious	not serious	none	0/710 (0.0%)	0/202 (0.0%)	not estimable	3 fewer per 1000 (from 17 fewer to 8 more)	HIGH	CRITICAL
Withdrawal owing to AE (follow up: range 4 to 12 weeks)												
5	randomised trials	not serious	not serious	not serious	serious ^{9 11}	none	29/711 (4.1%)	4/203 (2.0%)	RR 1.40 (0.50 to 3.92)	8 more per 1000 (from 10 fewer to 58 more)	MODERATE	CRITICAL
Any adverse effect (follow up: 6 weeks)												
2	randomised trials	serious ¹²	not serious	serious ¹³	not serious	none	392/1652	47/142	Rate ratio 0.64 (0.50 to 0.81)	140 events fewer per 1000 patients over 6 weeks (from 230 fewer to 50 fewer)	LOW	IMPORTANT
Somnolence (follow up: range 4 to 12 weeks)												
3	randomised trials	serious ¹⁴	not serious	not serious	serious ¹⁵	none	5/1672 (0.3%)	9/162 (5.6%)	RR 0.12 (0.03 to 0.38)	49 fewer per 1000 (from 34 fewer to 54 fewer)	LOW	IMPORTANT

MD – mean difference, RR – relative risk, SMD – standardized mean difference

- Only 1 study followed patients for 2 weeks only, but its results were consistent with other studies. All other studies followed patients for 4 to 12 weeks.
- There were 5 additional studies (188 patients total) that reported final scores and found SMD -0.08 fewer (95% CI: -0.40 fewer to 0.24 more). The certainty about the effects from that body of evidence was also low owing to risk of bias and imprecision. We chose to present the results from 2 studies as they included more patients and the final estimate was more conservative (wider CI).
- Study in children showed larger effect with OAH compared to LTRA than the study in adults. However, CIs overlapped and both studies were not different from remaining 5 studies.
- Confidence interval does not exclude an appreciable larger benefit from either intervention or no difference.
- Another study in children only stated that "Both cetirizine and montelukast improved eye symptoms compared to placebo."
- Only 40 patients.
- 4 other studies did not report this outcome.
- Another trial in children only stated that "Cetirizine and montelukast significantly reduced the mean PRQLQ compared with placebo."
- Confidence interval does not exclude an appreciable larger benefit from OAH or no difference.
- In one additional study "RQLQ was improved with montelukast compared to placebo by 0.13 points (0 to 0.25). There was "no significant improvement with cetirizine compared with placebo" but numbers were not reported. On a graph of individual domains difference between montelukast and cetirizine was lower than MID.
- Only 33 events.

12. Only 2 studies reported this obvious outcome.
13. Many different events of different importance to patients were counted together.
14. In one study (Philip 2007) authors pooled the results for montelukast group from this and another large study (that investigated only montelukast vs. placebo).
15. Only 14 events make the results very fragile.
16. We considered this outcome only important in the context of perennial AR.

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Author(s): JB

Date: 2015-11-11

Question: Intranasal H1-antihistamine (INAH) compared to intranasal corticosteroid (INCS) for seasonal allergic rhinitis (SAR)?

Setting: primary care

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INAH	INCS	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (follow up: range 2 weeks to 6 weeks; assessed with: Total nasal symptom score – TNSS; various scales)												
13	randomised trials	not serious ¹	not serious ²	not serious	not serious	none	1306	1312	-	SMD 0.17 higher (0.07 higher to 0.28 higher)	HIGH	CRITICAL
Ocular symptoms (follow up: range 2 to 6 weeks; assessed with: Total ocular symptom score – TOSS; various scales)												
8	randomised trials	not serious ³	serious ⁴	not serious	not serious	none	1276	1278	-	SMD 0.08 higher (0.11 lower to 0.26 higher)	MODERATE	CRITICAL
Quality of life (follow up: range 2 to 6 weeks; assessed with: Rhinoconjunctivitis quality of life questionnaire – RQLQ; MID ~0.5 point; better QoL indicated by lower scores; Scale from 0 to 6)												
2	randomised trials	serious ⁵	not serious	not serious	not serious ⁶	none	201	199	-	MD 0.26 points higher (0.09 higher to 0.43 higher)	MODERATE	CRITICAL
Serious adverse effects (follow up: range 2 to 6 weeks)												
10	randomised trials	not serious ⁷	not serious	not serious	not serious	none	0/1191	0/1194	not estimable	0 fewer per 1000 (from 4 fewer to 4 more)	HIGH	CRITICAL
Withdrawal owing to adverse effect (follow up: range 2 to 6 weeks)												
9	randomised trials	not serious	not serious	not serious	serious ⁸	none	10/1233 (0.8%)	7/1230 (0.6%)	RR 1.36 (0.53 to 3.51)	2 more per 1000 (from 3 fewer to 14 more)	MODERATE	CRITICAL
Adverse effect (any) (follow up: range 2 to 6 weeks)												
11	randomised trials	not serious ⁷	not serious	not serious ⁹	serious ¹⁰	none	166/1343 (12.4%)	121/1347 (9.0%)	RR 1.39 (1.04 to 1.86)	35 more per 1000 (from 4 more to 77 more)	MODERATE	IMPORTANT
Bitter taste (follow up: range 2 to 6 weeks)												
8	randomised trials	not serious ¹¹	not serious	not serious	not serious ^{12,13}	none ¹²	60/1218 (4.9%)	5/1215 (0.4%)	RR 7.18 (3.24 to 15.90)	25 more per 1000 (from 9 more to 61 more)	HIGH	IMPORTANT
Epistaxis (follow up: range 2 to 6 weeks)												
7	randomised trials	not serious ¹⁴	not serious	not serious	serious ¹⁵	none	23/1191 (1.9%)	23/1188 (1.9%)	RR 0.94 (0.52 to 1.69)	1 fewer per 1000 (from 9 fewer to 13 more)	MODERATE	IMPORTANT
Somnolence (follow up: range 2 to 6 weeks)												
7	randomised trials	not serious ¹⁴	not serious	not serious	serious ¹⁶	none	8/1191 (0.7%)	2/1188 (0.2%)	RR 2.90 (0.76 to 11.08)	3 more per 1000 (from 0 fewer to 17 more)	MODERATE	IMPORTANT

MD – mean difference, RR – relative risk, SMD – standardized mean difference

1. Three studies were not blinded but their exclusion from analysis did not change overall results. All but 2 studies did not report allocation concealment.
2. There was some statistical inconsistency but CIs overlapped and exclusion of any outlying study from analysis did not change overall estimate.
3. Two studies were not blinded but their exclusion from analysis did not change overall results. All but 2 studies did not report allocation concealment.
4. There was unexplained inconsistency among studies using the same formulation and dose of medications.
5. Only 2 studies measured and reported this outcome that is obviously important to patients suggesting selective reporting bias.
6. Despite 95% CI excludes the MID it seems that an appreciable proportion of patients might have reached reduction of symptoms larger than MID. Only 2 studies with 400 patients reported this outcome.
7. Two studies were not blinded and one study had unclear randomization but their exclusion from analysis did not change overall results. All but 2 studies did not report allocation concealment.
8. Only 17 events and CI does not exclude an appreciable benefit from using INCS.
9. There were many adverse effects reported of various importance to patients.
10. CI does not exclude an appreciable benefit from INCS or no difference.
11. One study had unclear randomization but its exclusion from analysis did not change overall results. All but 1 study did not report allocation concealment.
12. There is a large effect favoring INCS but we did not upgrade the quality of evidence because of imprecision owing to few events.
13. Only 65 events but most of them in INAH group which is consistent with the observation from their comparisons with other treatments.
14. One study was not blinded.

15. Only 46 events and CI does not exclude small benefit from either intervention.
16. Only 10 events and CI does not exclude an appreciable benefit from INCS.

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Date: 2015-11-11

Question: INAH compared to INCS for PAR

Setting: primary care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INAH	INCS	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (follow up: 6 weeks; assessed with: Total nasal symptom score – TNSS; Scale from: 0 [no symptoms] to 9 [severe symptoms])												
1	randomised trial	serious ¹	not serious	not serious	serious ²	none	46	50	-	MD 1.08 higher (0.36 higher to 1.8 higher)	LOW	CRITICAL
Ocular symptoms (follow up: 4 weeks; assessed with: ocular symptom score; Scale from: 0 [no symptoms] to 4 [severe symptoms])												
1	randomised trial	serious ⁷	not serious	not serious	serious ⁸	none	19	19	-	MD 0.29 higher (0.39 lower to 0.97 higher)	LOW	CRITICAL
Quality of life - not measured												
–	-	-	-	-	-	-	-	-	-	–	-	CRITICAL
Serious adverse effects (follow up: range 4 to 6 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	0/134 (0.0%)	0/130 (0.0%)	not estimable	0 fewer per 1000 (from 20 more to 20 fewer)	HIGH	CRITICAL
Withdrawal due to AEs (various) (follow up: range 4 to 6 weeks)												
3	randomised trials	not serious	not serious	not serious	serious ⁹	none	14/134 (10.4%)	8/130 (6.2%)	RR 1.46 (0.62 to 3.41)	28 more per 1000 (from 23 fewer to 148 more)	MODERATE	CRITICAL
Taste perversion (follow up: range 4 to 6 weeks)												
2	randomised trials	serious ¹⁰	not serious	not serious	not serious ¹¹	none	22/69 (31.9%)	4/65 (6.2%)	RR 5.50 (2.06 to 14.68)	277 more per 1000 (from 65 more to 842 more)	MODERATE	IMPORTANT
Epistaxis (follow up: range 4 to 6 weeks)												
2	randomised trials	serious ¹⁰	serious	not serious	serious ⁸	none	11/69 (15.9%)	16/65 (24.6%)	RR 0.69 (0.36 to 1.31)	76 fewer per 1000 (from 76 more to 158 fewer)	VERY LOW	IMPORTANT
Sedation (withdrawal due to) (follow up: range 4 to 6 weeks)												
1	randomised trial	serious ¹²	not serious	not serious	very serious ^{8,13}	none	4/24 (16.7%)	0/20 (0.0%)	RR 7.56 (0.43 to 132.48)	170 more per 1000 (from 0 fewer to 330 more)	VERY LOW	IMPORTANT
Exploratory outcomes												
Daytime somnolence (improvement from baseline) (follow up: 4 weeks; Scale from: 0 [no improvement] to 4 [large improvement])												
1	randomised trial	serious ¹²	not serious	not serious	serious ^{8,14}	none	19	19	-	MD 0.2 lower (1.08 lower to 0.68 higher)	LOW	IMPORTANT
Congestion (follow up: range 4 weeks to 6 weeks)												
2 ³	randomised trials	serious ⁴	not serious	not serious	serious ⁵	none	110	114	-	SMD 0.34 higher (0 to 0.68 higher)	LOW	IMPORTANT
Rhinorrhea (follow up: range 4 to 6 weeks)												
2 ³	randomised trials	serious ⁴	not serious	not serious	very serious ⁶	none	110	114	-	SMD 0.21 higher (0.27 lower to 0.69 higher)	VERY LOW	IMPORTANT
Sneezing (follow up: range 4 to 6 weeks)												
2 ³	randomised trials	serious ⁴	not serious	not serious	serious ⁵	none	110	114	-	SMD 0.47 higher (0.13 higher to 0.81 higher)	LOW	IMPORTANT
Itching (follow up: 4 weeks; assessed with: nasal symptom score; Scale from: 0 [no symptoms] to 4 [severe symptoms])												
1 ³	randomised trial	serious ⁷	not serious	not serious	very serious ⁸	none	64	64	-	MD 0.2 higher (0.55 lower to 0.94 higher)	VERY LOW	IMPORTANT

MD – mean difference, RR – relative risk, SMD – standardized mean difference

1. 26% discontinued treatment and were excluded from analysis.
2. Only 96 patients; CI does not exclude an appreciable benefit from INCS or no difference (assuming MID -0.65 on a 9-point scale)
3. There was another study that showed better outcome with INCS but did not provide variability in the results
4. One study was not blinded and all 3 studies excluded 14-26% from analysis
5. CI does not exclude a moderate benefit from INCS or no difference
6. CI does not exclude a moderate benefit from INCS, no difference or a small benefit from INAH
7. 14% were excluded from analysis
8. CI does not exclude an appreciable benefit from either intervention or no difference
9. Only 22 events; CI does not exclude an appreciable benefit from INCS or no difference
10. Only one of the 3 studies fully reported this outcome despite all mentioned measuring it.
11. Only 26 events; we did not rate down quality of evidence because this finding is consistent with findings of other studies of INAH.
12. Only 1 study reported this outcome that seems natural to be measured in this context.
13. Only 4 events
14. Only 38 patients.

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Author(s): JB

Date: 2015-11-16

Question: Intranasal H1-antihistamine (INAH) compared to oral H1-antihistamine (OAH) for intermittent/seasonal allergic rhinitis (SAR).

Setting: primary care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INAH	OAH	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (azelastine vs. cetirizine) (follow up: 2 weeks; assessed with: change in nasal symptoms)												
2 ¹	randomised trials	not serious	not serious	not serious	serious ²	none	330	330	-	SMD 0.21 higher (0.06 higher to 0.36 higher)	MODERATE	CRITICAL
Nasal symptoms (azelastine vs. chlorpheniramine) (follow up: 2 weeks; assessed with: final nasal symptom score)												
2 ³	randomised trials	serious ³	not serious	not serious	serious ⁴	none	328	272	-	SMD 0.48 lower (0.87 lower to 0.08 lower)	LOW	CRITICAL
Nasal symptoms (azelastine or levocabastine vs. loratadine or ebastine) (follow up: range 2 to 5 weeks; assessed with: final nasal symptom score)												
3 ⁵	randomised trials	not serious	not serious	not serious ⁶	serious ⁷	none	204	210	-	SMD 0 (0.19 lower to 0.19 higher)	MODERATE	CRITICAL
Ocular symptoms (final score) (follow up: range 2 to 5 weeks; assessed with: various ocular symptom scores)												
2 ⁸	randomised trials	serious ⁹	not serious	not serious	serious ⁷	none	98	99	-	SMD 0.01 more (0.27 fewer to 0.29 more)	LOW	CRITICAL
Quality of life (change from baseline; azelastine vs. cetirizine) (follow up: 2 weeks; assessed with: RQLQ; Scale from: 0 [better] to 6 [worse])												
1 ¹⁰	randomised trials	serious ¹⁰	not serious	not serious ¹¹	serious ⁴	none	151	155	-	MD 0.3 lower (0.03 lower to 0.57 lower)	LOW	CRITICAL
Serious adverse effect (follow up: 2 to 5 weeks)												
9	randomised trials	not serious	not serious	not serious	not serious	none	0/786 (0.0%)	0/724 (0.0%)	not estimable	0 fewer per 1000 (from 7 fewer to 6 more)	HIGH	CRITICAL
Withdrawal owing to adverse effect (follow up: 2 to 5 weeks)												
9	randomised trials	not serious	not serious	not serious	not serious	none	21/778 (2.7%)	9/721 (1.2%)	RR 1.99 (0.92 to 4.29)	12 more per 1000 (from 1 fewer to 41 more)	HIGH	CRITICAL
Any adverse effect (follow up: 2 to 5 weeks)												
6	randomised trials	not serious	not serious	serious ¹²	serious ⁷	none	274/347 (79.0%)	180/283 (63.6%)	RR 1.21 (0.69 to 2.13)	134 more per 1000 (from 197 fewer to 719 more)	LOW	IMPORTANT
Somnolence (follow up: 2 to 5 weeks)												
8	randomised trials	not serious ¹³	not serious	not serious	not serious	none	29/684 (4.2%)	42/563 (7.5%)	RR 0.50 (0.31 to 0.79)	37 fewer per 1000 (from 16 fewer to 51 fewer)	HIGH	IMPORTANT
Bitter taste (follow up: 2 to 5 weeks)												
7	randomised trials	not serious	not serious	not serious	not serious	very strong association	98/781 (12.5%)	0/654 (0.0%)	RR 17.90 (6.13 to 52.27)	120 more per 1000 (60 more to 190 more)	HIGH	IMPORTANT

MD – mean difference, RR – relative risk, SMD – standardized mean difference

- There was one additional study of azelastine vs. cetirizine but it did not report variability in results; point estimates also favored cetirizine.
- Confidence interval does not exclude a small additional benefit with cetirizine or no difference.
- There were 2 more studies of azelastine vs. chlorpheniramine (197 patients total) but they reported the results for the azelastine group only.
- Confidence interval does not exclude a small additional benefit with azelastine or no difference.
- There were 2 more studies of azelastine vs. loratadine or ebastine (90 patients total) that did not report variability in results; point estimate in both showed no numerical difference between the groups.
- Different INAH and OAH are considered together but all OAH are newer generation.
- Confidence interval does not exclude a small additional benefit with either intervention.
- Three more studies assessed this outcome (200 patients total) but did not report variability in results.
- One study was not blinded and it is not clear how randomization was done.
- Only two studies measured this outcome, of which one did not report variability in results and the other did not report denominator in the control group: actual denominator was smaller as QoL was assessed only in those 18 years and older (not reported how many patients were younger)
- Both studies used cetirizine as comparator (results direct for cetirizine but not for other OAH)
- Many outcomes of various importance to patients were reported together.
- Two studies were not blinded and 2 lost large proportion to follow-up but their results were consistent with those with low risk of bias.

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Author(s): JB

Date: 2015-11-16

Question: Intranasal H1-antihistamine (INAH) compared to oral H1-antihistamine (OAH) for persistent/perennial allergic rhinitis (SAR).

Setting: primary care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INAH	OAH	Relative (95% CI)	Absolute (95% CI)		
Nasal symptoms (follow up: 2 weeks; assessed with: various nasal symptom scores)												
2 ¹	randomised trials	serious ²	not serious ³	serious ⁴	serious ⁵	none	118	119	-	SMD 0.13 higher (0.12 lower to 0.39 higher)	VERY LOW	CRITICAL
Ocular symptoms (follow up: 2 weeks; assessed with: various symptom scores)												
2	randomised trials	serious ²	not serious	serious ⁴	serious ⁵	none	118	119	-	SMD 0.03 more (0.23 fewer to 0.28 more)	VERY LOW	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Serious adverse effect (follow up: range 2 to 8 weeks)												
3	randomised trials	not serious	not serious	not serious ⁶	not serious	none	0/61 (0.0%)	0/65 (0.0%)	not estimable	1 more per 1000 (from 49 fewer to 51 more)	HIGH	CRITICAL
Withdrawal owing to adverse effect (follow up: range 2 to 8 weeks)												
3	randomised trials	serious ²	not serious	serious ⁴	serious ^{5,7}	none	3/138 (2.2%)	3/139 (2.2%)	RR 0.92 (0.07 to 12.48)	2 fewer per 1000 (from 20 fewer to 248 more)	VERY LOW	CRITICAL
Any adverse effect (follow up: range 2 to 8 weeks)												
4	randomised trials	serious ²	not serious	serious ⁸	serious ^{5,9}	none	31/166 (18.7%)	31/167 (18.6%)	RR 0.84 (0.31 to 2.26)	30 fewer per 1000 (from 128 fewer to 234 more)	VERY LOW	IMPORTANT
Somnolence (follow up: range 2 to 8 weeks)												
4	randomised trials	serious ²	not serious	serious ¹⁰	serious ^{5,11}	none	2/166 (1.2%)	7/167 (4.2%)	RR 0.43 (0.07 to 2.60)	24 fewer per 1000 (from 39 fewer to 67 more)	VERY LOW	IMPORTANT

MD – mean difference, RR – relative risk, SMD – standardized mean difference

- There was one additional study (37 patients) that reported this outcome but did not report variability in results. Point estimates favoured INAH.
- Two studies were not blinded.
- One additional study that did not report variability favoured INAH (other studies favored OAH). We did not lower certainty because of inconsistency for we already lowered it for imprecision and both are dependent.
- Treatment lasted only for 2 weeks (minimum treatment duration in PAR suggested by FDA and EMA is 4 weeks).
- Results do not exclude a small benefit with either intervention.
- We did not downgrade the quality of evidence for SAE because the results are consistent with all other studies of oral and intranasal treatments for PAR.
- Only 6 events.
- Many AEs with different importance to patients were reported together. In 3 of 4 studies treatment was given only for 2 weeks (minimum suggested by FDA and EMA is 4 weeks).
- Only 62 events.
- In 3 of 4 studies treatment was given only for 2 weeks.
- Only 9 events.

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Table e1: Interpretation of strong and conditional (weak) recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize 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 may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g. shared) decision-making processes can serve as performance measure.

Table e2. Recommendations

Recommendation	Assumed values and preferences	Explanations and other considerations
Question 1: Should a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?		
Recommendation 1A In patients with seasonal allergic rhinitis, we suggest either a combination of an intranasal corticosteroid with an oral H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation low certainty of evidence)	ARIA guideline panel acknowledged that the choice of treatment would mostly depend on patient preferences and local availability and cost of treatment. Panel members assumed that in majority of situations, potential net benefit would not justify spending additional resources.	This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of OAH is not large and/or patient values and preferences differ from those assumed by guideline panel members a combination therapy may be a reasonable choice, especially in patients not well controlled with INCS alone, those with pronounced ocular symptoms or those commencing treatment because of likely faster onset of treatment effects. This recommendation concerns regular use of newer, less sedative OAH and INCS in seasonal AR. For older OAHs with more sedative effects the balance of desirable and undesirable effects may be different.
Recommendation 1B In patients with perennial allergic rhinitis, we suggest an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H1-antihistamine (conditional recommendation very low certainty of evidence)	–	Currently available evidence suggests that there is no additional benefit from a combination therapy compared to INCS alone and there may be additional undesirable effects. This recommendation is conditional because of sparse information, thus, very low certainty of the estimated effects.
Question 2: Should a combination of intranasal H1-antihistamine (INAH) and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?		
Recommendation 2A In patients with seasonal AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation moderate certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. At the initiation of treatment (~ first 2 weeks) a combination of INCS with INAH may act faster than INCS alone and, thus, may be preferred by some patients.	This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of combination therapy is not large and/or patients value potential benefits more than any increased risk of adverse effects, a combination therapy may be a reasonable choice.
Recommendation 2B In patients with perennial AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation very low certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.	This is a conditional recommendation because of the very low certainty of the evidence. At the initiation of treatment (~ first 2 weeks) a combination of INCS with INAH may act faster than INCS alone, thus, may be preferred by some patients.
Question 3: Should a combination of an intranasal H1-antihistamine and an intranasal corticosteroid vs. intranasal H1-antihistamine alone be used for treatment of allergic rhinitis?		
Recommendation 3A In patients with seasonal AR, we suggest a combination of an intranasal corticosteroid with an intranasal H1-antihistamine rather than an intranasal H1-antihistamine alone (conditional recommendation low certainty of evidence)	This recommendation places higher value on additional reduction of symptoms and improved quality of life with a combination therapy, compared to INAH alone. It places a lower value on avoiding additional cost (expenditure of resources).	This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of a combination therapy is large, an alternative choice, i.e. INAH alone, may be equally reasonable. One panel member thought that the recommendation should be conditional for either the intervention or the comparison.
Question 4: Should a leukotriene receptor antagonist (LTRA) vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?		

Recommendation 4A In patients with seasonal AR, we suggest either a leukotriene receptor antagonist or an oral H1-antihistamine (conditional recommendation moderate certainty of evidence)	Panel members acknowledged that the choice of LTRA or OAH will mostly depend on patient preferences and local availability and cost of specific medications. In many settings OAH may still be more cost-effective but this will largely depend on availability of generic LTRA and the local cost of various newer-generation OAH and LTRA.	Some patients with AR who have concomitant asthma, especially exercise-induced and/or aspirin exacerbated respiratory disease, may benefit from LTRA more than from OAH. However, this recommendation applies to treatment of AR not to treatment of asthma. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.
Recommendation 4B In patients with perennial AR, we suggest an oral H1-antihistamine rather than a leukotriene receptor antagonist (conditional recommendation low certainty of evidence)	This recommendation places a higher value on possibly larger improvement of symptoms and quality of life with OAH, compared to LTRA. It places a lower value on possible increased risk of somnolence.	This is a conditional recommendation, thus different choices will be appropriate for different patients based on their preferences for reduction of symptoms versus avoiding the risk of adverse effects – this may be more important for patients with PAR than with SAR as they might use those medications for longer periods of time. Some patients with AR and concomitant asthma, especially exercise-induced and/or aspirin exacerbated respiratory disease, may benefit from LTRA more than from OAH. However, this recommendation applies to treatment of AR not to treatment of asthma. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.
Question 5: Should an intranasal H1-antihistamine vs. an intranasal corticosteroid be used for treatment of allergic rhinitis?		
Recommendation 5A In patients with seasonal AR, we suggest an intranasal corticosteroid rather than an intranasal H1-antihistamine (conditional recommendation moderate certainty of evidence).	This recommendation places a higher value on likely small but greater reduction of symptoms and improvement of quality of life with INCS, compared to INAH, and a lower value on avoiding larger cost of treatment with INCS in many jurisdictions.	This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs.
Recommendation 5B In patients with perennial AR, we suggest an intranasal corticosteroid rather than intranasal H1-antihistamine (conditional recommendation low certainty of evidence).	This recommendation places a higher value on probably greater reduction of nasal symptoms with INCS, compared to INAH, although the overall difference is likely small. It places a lower value on avoiding larger cost of treatment with INCS in many jurisdictions.	This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs.
Question 6: Should an intranasal H1-antihistamine vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?		
Recommendation 6A In patients with SAR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation low certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.	This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.
Recommendation 6B In patients with perennial AR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation very low certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.	This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.