Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision

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Executive summary

Introduction

Allergic rhinitis represents a global health problem affecting 10 to 20% of the population. In theory, evidence-based guidelines are the ideal way to inform and guide clinical decision makers. This document presents a revision of the clinical recommendations of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines developed in collaboration with the World Health Organization in 2001 (1) and recently updated in 2008 (2). This revision, however, differs from these previous guidelines. It results from a complete re-review of the underlying evidence based on systematic and transparent assessments of the quality of this evidence in evidence profiles. Furthermore, we have used a new process for developing recommendations following the GRADE approach. An evidence-based way of making health care decisions acknowledges that evidence alone is insufficient, and that values and preferences, clinical circumstances as well as clinical expertise inevitably influence decisions (3). The GRADE system builds on the previous grading systems and combines their advantages (4). The GRADE approach is recommended by the ~~–~~Guidelines for WHO guidelines" (5) and is being used increasingly by many organizations, including the World Health Organization (WHO), American Thoracic Society, American College of Chest Physicians

and the UK National Institute of Health and Clinical Excellence, and other organizations around the world (6).

Allergic rhinitis is defined clinically by the symptoms caused by immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to offending allergens. Symptoms of allergic rhinitis include rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip that reverse spontaneously or after treatment. Allergic conjunctivitis often accompanies allergic rhinitis.

Following ARIA guidance we classified allergic rhinitis as ―intermittent" or ―persistent" according to the duration of symptoms, and as ―mild" or ―moderate-severe" depending on its severity.

Methodology

We briefly describe the methodology used to develop and grade recommendations and the quality of the supporting evidence to facilitate the interpretation of the guidelines. For the more detailed description see the section on methods.

We assessed the evidence according to the system described by the GRADE working group.

Quality of evidence is classified as either ―high", ―moderate", ―low" or ―very low" based on methodological characteristics of the available evidence for a specific health care problem. The GRADE definitions of each category are:

- High: Further research is very unlikely to change confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
- Low: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
- Very low: Any estimate of effect is very uncertain.

According to the GRADE system, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (Table 1). Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision making.

How to use these guidelines

The ARIA guidelines provide clinicians and their patients with a basis for rational decisions in the management of allergic rhinitis. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No recommendation can take into account all of the often-compelling unique features of individual clinical circumstances. Therefore, nobody charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines as rote or in a blanket fashion.

Key questions

The clinical questions covered by this document were developed in consultation with the ARIA guideline panel. The key questions are:

- Should allergen avoidance methods be used by parents to prevent development of allergy in children?
- Should occupational allergen avoidance methods be used?
- Should patients with allergic rhinitis and/or conjunctivitis use H1-antihistamines, glucocorticosteroids, antileukotrienes, chromones, decongestants, or ipratropium bromide? What is the relative effect of these medications?
- Should allergen specific immunotherapy be used in patients with allergic rhinitis? What is the effect of subcutaneous, intranasal, and sublingual specific immunotherapy?
- Should complementary and alternative treatments be used for allergic rhinitis?
- Should medications for allergic rhinitis be used in patients with concomitant asthma for the treatment of symptoms of asthma?

Recommendations

I. Prevention of allergy

Recommendation 1: We suggest exclusive breastfeeding for at least first three months for all infants irrespective of their family history of atopy (conditional recommendation | low quality evidence).

Values and preferences

This recommendation places a relatively high value on the prevention of allergy and asthma, and a relatively low value on challenges or burden of breastfeeding in certain situations.

Remarks

The evidence, that exclusive breastfeeding for at least the first three months reduces the risk of allergy or asthma, is not convincing and, therefore, the recommendation to exclusively breastfeed is conditional. This recommendation applies to situations in which other reasons do not suggest harm from breastfeeding (e.g. classic galactosemia, active untreated tuberculosis or human immunodeficiency virus infection in mother, antimetabolites or chemotherapeutic agents or radioactive isotopes being used in the mother for diagnostic or therapeutic purposes until they clear from the milk, and bacterial or viral infection of a breast).

Recommendation 2: For pregnant or breastfeeding women, we suggest no antigen avoidance diet to prevent development of allergy in children (conditional recommendation | very low quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on adequate nourishment of mothers and children, and a relatively low value on very uncertain effects on the prevention of allergy and asthma in this setting.

Recommendation 3: In children and pregnant women, we recommend total avoidance of environmental tobacco smoke (i.e. passive smoking) (strong recommendation | very low quality evidence).

Remarks

Smoking and exposure to second-hand smoke are common health problems around the world causing a substantial burden of disease for children and adults. While it is very rare to make a strong recommendation based on low or very low quality evidence, the ARIA guideline panel felt that in the absence of important adverse effects associated with smoking cessation or reducing the exposure to second-hand smoke, the balance between the desirable and undesirable effects is clear.

Recommendation 4: In infants and preschool children, we suggest multifaceted interventions to reduce early life exposure to house dust mite (conditional recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively low value on the burden and cost of using multiple preventive measures (*e.g.* encasings to parental and child's bed, washing bedding and soft toys at temperature exceeding 55°C [131°F], use of acaricide, smooth flooring without carpets, etc.), and relatively high value on an uncertain small reduction of the risk of developing wheeze or asthma. For some children at lower risk of developing asthma and in certain circumstances an alternative choice will be equally reasonable.
Remarks
Children at high risk of developing asthma are those with at least one parent or sibling with asthma or other allergic disease.

Recommendation 5: In infants and preschool children, we suggest no special avoidance of exposure to pets at home (conditional recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on possible psychosocial downsides of not having a pet, and relatively low value on potential reduction in the uncertain risk of developing allergy and/or asthma.
Remarks
Clinicians and patients may reasonably choose an alternative action, considering circumstances that include other sensitized family members.

Recommendation 6: For individuals exposed to occupational agents, we recommend specific prevention measures eliminating or reducing occupational allergen exposure (strong recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on reducing the risk of sensitisation to occupational allergens and developing occupational rhinitis and/or asthma with the subsequent adverse consequences, and a relatively low value on the feasibility and cost of specific strategies aimed at reducing occupational allergen exposure.
Remarks
Total allergen avoidance, if possible, seems to be the most effective primary prevention measure.

II. Treatment of allergic rhinitis
Reducing allergen exposure

Recommendation 7: In patients with allergic rhinitis and/or asthma sensitive to house dust mite allergens, we recommend that clinicians do not administer and patients do not use currently available single chemical or physical preventive methods aimed at reducing exposure to house dust mites (strong recommendation | low quality evidence) or their combination (conditional recommendation | very low quality evidence), unless this is done in the context of formal clinical research.
We suggest multifaceted environmental control programmes be used in inner-city homes to improve symptoms of asthma in children (conditional recommendation | very low quality evidence).
Underlying values and preferences
The recommendation to use multifaceted environmental control programmes in inner-city homes places a relatively high value on possible reduction in the symptoms of asthma in children, and relatively low value on the cost of such programmes.

Recommendation 8: In patients allergic to indoor moulds, we suggest avoiding exposure to these allergens at home (conditional recommendation | very low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on possible reduction in the symptoms of rhinitis and asthma, and a relatively low value on the burden and cost of interventions aimed at reducing exposure to household moulds.

Recommendation 9: In patients with allergic rhinitis due to animal dander, we recommend avoiding exposure to these allergens at home (strong recommendation | very low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on potential reduction of symptoms of allergic rhinitis, and a relatively low value on psychosocial downsides of not having a pet or the inconvenience and cost of environmental control measures.
Remarks
Based on biological rationale, there is little doubt that total avoidance of animal allergens at home, and probably also marked reduction in their concentration, can improve symptoms, despite paucity of published data to substantiate this statement.

Recommendation 10: In patients with occupational asthma, we recommend immediate and total cessation of exposure to occupational allergen (strong recommendation | very low quality evidence). When total cessation of exposure is not possible, we suggest specific strategies aimed at minimizing occupational allergen exposure (conditional recommendation | very low quality evidence).
Underlying values and preferences
The recommendation to immediately and totally cease the exposure to occupational allergen places a relatively high value on reducing the symptoms of asthma and deterioration of lung function, and a relatively low value on the potential socioeconomic downsides (e.g. unemployment).

Pharmacological treatment of allergic rhinitis

Recommendation 11: In patients with allergic rhinitis, we recommend new generation oral H1-antihistamines that do not cause sedation and do not interact with cytochrome P450 (strong recommendation | low quality evidence). In patients with allergic rhinitis, we suggest new generation oral H1-antihistamines that cause some sedation and/or interact with cytochrome P450 (conditional recommendation | low quality evidence).
Underlying values and preferences
The recommendation to use new generation oral H1-antihistamines that cause some sedation and/or interact with cytochrome P450 places a relatively high value on a reduction of symptoms of allergic rhinitis, and a relatively low value on side effects of these medications.
Remarks
Astemizole and terfenadine were removed from the market due to cardiotoxic side effects.
See recommendation 12 referring to the comparison of new generation versus old generation agents for the choice of one over the other.

Recommendation 12: In patients with allergic rhinitis, we recommend new generation over old generation oral H1-antihistamines (strong recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on the reduction of adverse effects, and a relatively low value on an uncertain comparative efficacy of new versus old generation oral H1-antihistamines.

Recommendation 13: In infants with atopic dermatitis and/or family history of allergy or asthma (at high risk of developing asthma), we suggest clinicians do not administer and parents do not use oral H1-antihistamines for the prevention of wheezing or asthma (conditional recommendation | very low quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding side effects of oral H1-antihistamines in infants, and a lower value on the very uncertain reduction in the risk of developing asthma or wheezing.

Remarks

The recommendation not to use oral H1-antihistamines in these infants refers only to prevention of asthma or wheezing. The guideline panel did not consider other conditions in which these medications may be commonly used (e.g. urticaria).

Recommendation 14: We suggest intranasal H1-antihistamines in adults with seasonal allergic rhinitis (conditional recommendation| low quality evidence) and in children with seasonal allergic rhinitis (conditional recommendation | very low quality evidence). In adults and children with perennial/persistent allergic rhinitis, we suggest that clinicians do not administer and patients do not use intranasal H1-antihistamines until more data on their relative efficacy and safety is available (conditional recommendation | very low quality evidence).

Underlying values and preferences

The recommendation to use intranasal H1-antihistamines in patients with seasonal allergic rhinitis places a relatively high value on reduction of symptoms, and a relatively low value on the risk of rare or mild side effects. The recommendation not to use intranasal H1-antihistamines in patients with perennial/persistent allergic rhinitis places a relatively high value on their uncertain efficacy and possible side effects, and a relatively low value on possible small reduction in symptoms.

Recommendation 15: We suggest new generation oral H1-antihistamines rather than intranasal H1-antihistamines in adults with seasonal allergic rhinitis (conditional recommendation | moderate quality evidence) and in adults with perennial/persistent allergic rhinitis (conditional recommendation | very low quality evidence). In children with intermittent or persistent allergic rhinitis we also suggest new generation oral H1-antihistamines rather than intranasal H1-antihistamines (conditional recommendation | very low quality evidence).

Underlying values and preferences

These recommendations place a relatively high value on probable higher patient preference for oral versus intranasal route of administration as well as avoiding bitter taste of some intranasal H1-antihistamines, and relatively low value on increased somnolence with some new generation oral H1-antihistamines. In many patients with different values and preferences or those who experience adverse effects of new generation oral H1-antihistamines an alternative choice may be equally reasonable.

Recommendation 16: We suggest oral leukotriene receptor antagonists in adults and children with seasonal allergic rhinitis (conditional recommendation | high quality evidence) and in preschool children with perennial allergic rhinitis (conditional recommendation | low quality evidence). In adults with perennial allergic rhinitis we suggest that clinicians do not administer and patients do not use oral leukotriene receptor antagonists (conditional recommendation | high quality evidence).

Underlying values and preferences

The recommendation to use oral leukotriene receptor antagonists in adults and children with seasonal allergic rhinitis and in preschool children with perennial allergic rhinitis places a relatively high value on their safety and tolerability, and relatively low value on their limited efficacy and high cost.

The recommendation not to use oral leukotriene receptor antagonists in adults with perennial allergic rhinitis places a relatively high value on their very limited efficacy and high cost, and relatively low value on potential small benefit in few patients.

Remarks

Evidence is available only for montelukast. This recommendation refers to the treatment of rhinitis, not to the treatment of asthma in patients with concomitant allergic rhinitis (see recommendation 45).

Recommendation 17: We suggest oral H1-antihistamines over oral leukotriene receptor antagonists in patients with seasonal allergic rhinitis (conditional recommendation | moderate quality evidence) and in preschool children with perennial allergic rhinitis (conditional recommendation | low quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding resource expenditure.

Recommendation 18: We recommend intranasal glucocorticosteroids for treatment of allergic rhinitis in adults (strong recommendation | high quality evidence) and suggest intranasal glucocorticosteroids in children with allergic rhinitis (conditional recommendation | moderate quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on the efficacy of intranasal glucocorticosteroids, and a relatively low value on avoiding their possible adverse effects.

Recommendation 19: In patients with seasonal allergic rhinitis, we suggest intranasal glucocorticosteroids over oral H1-antihistamines in adults (conditional recommendation | low quality evidence) and in children (conditional recommendation | very low quality evidence). In patients with perennial/persistent allergic rhinitis, we suggest intranasal glucocorticosteroids over oral H1-antihistamines in adults (conditional recommendation | moderate quality evidence) and in children (conditional recommendation | low quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on the likely higher efficacy of intranasal glucocorticosteroids. In many patients with strong preference for oral versus intranasal route of administration an alternative choice may be reasonable.

Recommendation 20: In patients with allergic rhinitis, we recommend intranasal glucocorticosteroids rather than intranasal H1-antihistamines (strong recommendation | high quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on efficacy of intranasal glucocorticosteroids, and a relatively low value on their rare adverse effects.

Recommendation 21: In patients with seasonal allergic rhinitis we recommend intranasal glucocorticosteroids over oral leukotriene receptor antagonists (strong recommendation | low quality evidence).

Underlying values and preferences

This recommendation places a high value on the efficacy of intranasal glucocorticosteroids.

Remarks

Evidence is available for montelukast only.

Recommendation 22: In patients with allergic rhinitis and moderate to severe nasal and/or ocular symptoms that are not controlled with other treatments, we suggest short course of oral glucocorticosteroids (conditional recommendation | very low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on possible relief of severe symptoms, and a relatively low value on avoiding possible side effects of a short course of oral glucocorticosteroids.
Remarks
Systemic glucocorticosteroids should not be considered as a first line of treatment for allergic rhinitis. They can be used for few days as a last resort of treatment when combinations of other medications are ineffective. Oral glucocorticosteroids should be avoided in children, pregnant women, and patients with known contraindications.

Recommendation 23: In patients with allergic rhinitis, we recommend that clinicians do not administer intramuscular glucocorticosteroids (strong recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on avoiding possible side effects of a single or multiple injections of intramuscular glucocorticosteroids, and relatively low value on their efficacy and convenience of use.
Remarks
Possible side effects of intramuscular glucocorticosteroids may be far more serious than the condition they are supposed to treat (*i.e.* allergic rhinitis).

Recommendation 24: In patients with allergic rhinitis, we suggest intranasal chromones (conditional recommendation | moderate quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on excellent safety and tolerability of intranasal chromones, and relatively low value on their limited efficacy and on limiting resource expenditure.
Remarks
The need for administration 4 times daily is likely to reduce patient adherence and reduce efficacy.

Recommendation 25: In patients with allergic rhinitis, we suggest intranasal H1-antihistamines over intranasal chromones (conditional recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on possibly higher efficacy of intranasal H1-antihistamines, and relatively low value on safety and tolerability of intranasal chromones.
Remarks
Chromones require administration 4 times daily that may limit patient adherence to treatment and reduce efficacy.

Recommendation 26: In patients with perennial allergic rhinitis, we suggest intranasal ipratropium bromide for treatment of rhinorrhea (conditional recommendation | moderate quality evidence).
Remarks
Intranasal ipratropium bromide is effective for rhinorrhea. It is unlikely to be beneficial for other symptoms of allergic rhinitis.

Recommendation 27: In adults with allergic rhinitis and severe nasal obstruction, we suggest very short course (not longer than five days and preferably shorter) of intranasal decongestant while co-administering other drugs (conditional recommendation | very low quality evidence). We suggest that clinicians do not administer and parents do not use intranasal decongestants in preschool children (conditional recommendation | very low quality evidence).
Underlying values and preferences

The recommendation for use of a very short course of an intranasal decongestant in adults with allergic rhinitis places a relatively high value on the prompt relief of nasal obstruction, and relatively low value on avoiding the risk of adverse effects with a prolonged use of intranasal decongestant.
The recommendation against the use of an intranasal decongestant in children and against long-term use in adults places a relatively high value on avoiding the risk of serious adverse effects, and relatively low value on a possible benefit from a reduced nasal blockage.

Recommendation 28: In patients with allergic rhinitis, we suggest that clinicians do not administer and patients do not use oral decongestants regularly (conditional recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on avoiding adverse effects of oral decongestants, and a relatively low value on possible small reduction in symptoms of rhinitis.
Remarks
Oral decongestants may be of benefit for some patients as a rescue or ~~"a~~s needed" medication.

Recommendation 29: In patients with allergic rhinitis, we suggest clinicians do not administer and patients do not use regularly a combination of oral H1-antihistamine and an oral decongestant, compared to oral H1-antihistamine alone (conditional recommendation | moderate quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on avoiding adverse effects of oral decongestant, and a relatively low value on small additional reduction in symptoms of rhinitis.
Remarks
In adults with symptoms not controlled with oral H1-antihistamine alone who are less averse to side effects of oral decongestants an alternative choice may be equally reasonable. Administration of a combined treatment as a rescue medication may also be beneficial to some patients.

Recommendation 30: In patients with allergic rhinitis and symptoms of conjunctivitis, we suggest intraocular H1-antihistamines (conditional recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on consistent effectiveness of intraocular H1-antihistamines, and relatively low value on their side effects and uncertain effectiveness in patients already using other medications for allergic rhinitis.
Remarks
Only one study was done in children.

Recommendation 31: In patients with allergic rhinitis and symptoms of conjunctivitis, we suggest intraocular chromones (conditional recommendation | very low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on excellent safety and tolerability of intraocular chromones and relatively low value on their limited effectiveness.
Remarks
In adults and children with limited ocular symptoms, chromones may be tried first because of their excellent safety and tolerability. Chromones require administration 4 times daily that may limit patient compliance with treatment and reduce efficacy.

Recommendation 32: We suggest subcutaneous allergen specific immunotherapy in adults with seasonal (conditional recommendation | moderate quality evidence) and perennial allergic rhinitis due to house dust mites (conditional recommendation | low quality evidence).

Underlying values and preferences
This recommendation places a relatively high value on relieving the symptoms of allergic rhinitis, and a relatively low value on avoiding adverse effects and on resource expenditure.

Recommendation 33: In children with allergic rhinitis, we suggest subcutaneous specific immunotherapy (conditional recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on probable reduction in symptoms of allergic rhinitis and the potential prevention of the development of asthma, and relatively low value on avoiding adverse effects in children and resource expenditure.

Recommendation 34: We suggest sublingual allergen specific immunotherapy in adults with rhinitis due to pollen (conditional recommendation | moderate quality evidence) or house dust mites (conditional recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on alleviating the symptoms of rhinitis, and relatively low value on avoiding adverse effects and resource expenditure.
Remarks
Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable, if patients' values or preferences differ from those described here.

Recommendation 35: In children with allergic rhinitis due to pollens, we suggest sublingual allergen-specific immunotherapy (conditional recommendation | moderate quality evidence). In children with allergic rhinitis due to house dust mites, we suggest that clinicians do not administer sublingual immunotherapy outside rigorously designed clinical trials (conditional recommendation | very low quality evidence).
Underlying values and preferences
The recommendation to use sublingual immunotherapy in children with seasonal allergic rhinitis places a relatively high value on small reduction in nasal symptoms, and relatively low value on avoiding adverse effects in children and resource expenditure. The recommendation to use sublingual immunotherapy in children with perennial allergic rhinitis only in the context of clinical research places a relatively high value on avoiding adverse effects and resource expenditure, and relatively low value on possible small reduction in nasal symptoms.
Remark
Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable, if patients' values or preferences differ from those described here.

Recommendation 36: We suggest intranasal allergen specific immunotherapy in adults (conditional recommendation | low quality evidence) and in children with allergic rhinitis due to pollens (conditional recommendation | very low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on the reduction of symptoms of allergic rhinitis during pollen season, and a relatively low value on avoiding local side effects and cost. An alternative choice may be equally reasonable.

Alternative and complementary treatment for allergic rhinitis

Recommendation 37: In patients with allergic rhinitis, we suggest that clinicians do not administer and patients do not use homeopathy (conditional recommendation | very low quality evidence).
Underlying values and preferences

This recommendation places a relatively high value on avoiding possible adverse effects and resource expenditure, and a relatively low value on any possible, but unproven, benefit of these treatments in allergic rhinitis.

Recommendation 38: In patients with allergic rhinitis, we suggest clinicians do not administer and patients do not use acupuncture (conditional recommendation | very low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on avoiding the potential complications of acupuncture, and a relatively low value on uncertain reduction in symptoms of rhinitis.
Remarks
In patients who choose to be treated with acupuncture ONLY disposable needles should be used.

Recommendation 39: In patients with allergic rhinitis, we suggest clinicians do not administer and patients do not use butterbur (conditional recommendation | very low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on avoiding the uncertain adverse effects of butterbur, and a relatively low value on equally uncertain reduction in symptoms of rhinitis.
Remarks
In patients who are less risk averse an alternative may be equally reasonable. However, if one chooses to use butterbur one should consider only commercial preparations in which butterbur extract does not contain toxic pyrrolizidine alkaloids.

Recommendation 40: In patients with allergic rhinitis, we suggest clinicians do not administer and patients do not use herbal medicines (conditional recommendation | very low quality evidence).
Underlying values and preferences
The recommendation places a relatively high value on avoiding possible serious adverse events and drug interactions, and a relatively low value on possible reduction in symptoms of rhinitis.

Recommendation 41: In patients with allergic rhinitis, we suggest that clinicians do not administer and patients do not use phototherapy or other physical techniques (conditional recommendation | very low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on avoiding potential adverse effects of these therapies, and a relatively low value on their very uncertain effect on symptoms of rhinitis.

III. Treatment of asthma in patients with allergic rhinitis and asthma

Recommendation 42: In patients (both children and adults) with allergic rhinitis and asthma, we suggest clinicians do not administer and patients do not use oral H1-antihistamines for the treatment of asthma (conditional recommendation | very low quality evidence).
Underlying values and preferences
The recommendation not to use oral H1-antihistamines in adults with allergic rhinitis and asthma for the treatment of asthma places a relatively high value on avoiding their adverse effects, and a relatively low value on their very uncertain effect on symptoms of asthma.
The recommendation not to use oral H1-antihistamines in children with allergic rhinitis for the treatment of asthma or wheeze, despite the evidence of efficacy of ketotifen when used alone in children with mild to moderate asthma, places a relatively high value on avoiding its side effects, and a relatively low value on its unknown efficacy in children already using inhaled corticosteroids, since inhaled corticosteroids are currently considered medications of first choice in treatment of chronic asthma.
Remarks

This recommendation suggests that oral H1-antihistamines should not be used to treat symptoms of asthma, but they may still be used in patients with asthma and rhinitis for treatment of rhinitis (recommendations 11, 12, 15, and 17).

Recommendation 43: In patients with allergic rhinitis and asthma, we suggest clinicians do not administer and patients do not use a combination of oral H1-antihistamine and oral decongestant for treatment of asthma (conditional recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on avoiding adverse effects of combination of oral H1-antihistamine and oral decongestant, and a relatively low value on possible small reduction in asthma symptoms of uncertain clinical significance.

Recommendation 44: In patients with allergic rhinitis and asthma, we suggest that clinicians do not administer and patients do not use intranasal glucocorticosteroids for treatment of asthma (conditional recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on avoiding adverse effects, burden, and cost of intranasal glucocorticosteroids, and a relatively low value on unlikely clinical benefit.
Remarks
This recommendation suggests that intranasal glucocorticosteroids are not used to treat symptoms of asthma, but they may still be used in patients with asthma and rhinitis for treatment of rhinitis (see recommendations 18, 19, 20, and 21).

Recommendation 45: In patients with allergic rhinitis and asthma, we recommend inhaled glucocorticosteroids over oral leukotriene receptor antagonists as a single controlling medication for asthma (strong recommendation | moderate quality evidence).
In patients with allergic rhinitis and asthma who prefer not to use or cannot use inhaled glucocorticosteroids or in children whose parents do not agree to use inhaled glucocorticosteroids, we suggest oral leukotriene receptor antagonists for treatment of asthma (conditional recommendation | moderate quality evidence).
Underlying values and preferences
These recommendations place a relatively high value on a limited efficacy of LTRA and additional cost of treatment. The suggestion to use oral LTRA in patients who do not use inhaled glucocorticosteroids places relatively high value on small reduction in symptoms of asthma and improvement in quality of life, and a relatively low value on limiting the cost of treatment.
Remarks
These recommendations do not apply to the treatment of rhinitis (see recommendation 16, 17, 21).

Recommendation 46: In patients with allergic rhinitis and asthma, we suggest subcutaneous specific immunotherapy for treatment of asthma (conditional recommendation | moderate quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on reducing the symptoms of asthma, and a relatively low value on avoiding adverse effects and limiting the cost of subcutaneous specific immunotherapy. In patients who are more averse to the side effects of subcutaneous specific immunotherapy an alternative choice may be equally reasonable.
Remarks
Subcutaneous specific immunotherapy may also be used in patients with asthma and concomitant allergic rhinitis for treatment of rhinitis (see recommendations 32 and 33). Resource limitations will have stronger implications for the implementation of this recommendation.

Recommendation 47: In patients with allergic rhinitis and asthma, we suggest sublingual specific immunotherapy for treatment of asthma (conditional recommendation | low quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on possible reduction of asthma symptoms, and a relatively low value on avoiding adverse effects and limiting the cost of sublingual specific immunotherapy.
Remarks
Sublingual specific immunotherapy may also be used in patients with asthma and concomitant allergic rhinitis for treatment of rhinitis (see recommendations 34 and 35). Resource limitations will have stronger implications for the implementation of this recommendation.

Recommendation 48: In patients with allergic rhinitis and asthma with a clear IgE-dependent allergic component, uncontrolled despite optimal pharmacologic treatment and appropriate allergen avoidance, we suggest monoclonal antibody against IgE for treatment of asthma (conditional recommendation | moderate quality evidence).
Underlying values and preferences
This recommendation places a relatively high value on reduction of symptoms of asthma and exacerbations in patients with severe asthma, and a relatively low value on avoiding the burden of subcutaneous injections, cost of treatment, small risk of anaphylaxis and some uncertainty about the risk of malignancy.

Introduction and background

This document presents a revision of the Recommendations of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines developed in collaboration with the World Health Organization in 2001 (1) and recently updated in 2008 (2). This revision, however, differs from these previous guidelines. It results from a complete re-review of the underlying evidence based on systematic and transparent assessments of the quality of this evidence in evidence profiles. Furthermore, we have used a new process for developing recommendations following the GRADE approach.
An evidence-based approach to make health care decisions acknowledges that evidence alone is insufficient, and that values and preferences, clinical circumstances as well as clinical expertise inevitably influence decisions (3). GRADE has advantages over previous rating systems (4). Other systems share some of these advantages, but none, other than GRADE, combines them all (7). The GRADE approach is recommended by the "Guidelines for WHO guidelines" (5) and is being used increasingly by many organizations, including the World Health Organization (WHO), American Thoracic Society, American College of Chest Physicians and the UK National Institute of Health and Clinical Excellence and other organizations around the globe (6).

Allergic rhinitis

Allergic rhinitis 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 under treatment. Allergic conjunctivitis often accompanies allergic rhinitis.

We classified allergic rhinitis as "intermittent" or "persistent" according to the duration of symptoms, and as "mild" or "moderate-severe" according to the severity.

Classification of allergic rhinitis

Duration

- **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.

Severity

- **Mild** – none of the following is present.
- **Moderate-severe** – at least one of the following is present.
    - Sleep disturbance
    - Impairment of daily activities, leisure and/or sport
    - Impairment of school or work
    - Troublesome symptoms

Allergic rhinitis has been traditionally subdivided into seasonal, perennial, and occupational rhinitis. Perennial allergic rhinitis is most frequently, although not necessarily, caused by indoor allergens such as house dust mites, moulds, cockroaches, and animal dander. Seasonal allergic rhinitis is most often caused by outdoor allergens such as pollens or moulds. As in a previous edition of ARIA guidelines as in this document we retained the terms "seasonal" and "perennial" to enable the interpretation of published studies.

Allergic rhinitis represents a global health problem affecting 10 to 20% of the population (section 5.1.–5.2. in ARIA 2008 Update (2)). This is probably an underestimate, since many patients do not recognise rhinitis as a disease and the prevalence is increasing (8-12). Although allergic rhinitis is not usually a severe disease, it affects patients' social life, school performance, and work productivity (section 5.3.–5.7. in ARIA 2008 Update (2)).

Allergic rhinitis and asthma are linked by epidemiological, pathological, and physiological characteristics and by a common therapeutic approach (13-17). They frequently coexist – epidemiological studies suggest that asthma is found in as many as 15% to 38% of patients with allergic rhinitis (13, 18, 19). 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, 20-23).

For specific treatment of asthma, complications of allergic rhinitis or non-allergic rhinitis(e.g. infectious rhinitis, chronic sinusitis, otitis media, and nasal polyps)clinicians should consult clinical practice guidelines focusing on those diseases.

Several other conditions can cause symptoms similar to allergic rhinitis: viral and bacterial infections, hormonal imbalance, exposure to physical agents, and other causes. Rhinitis may also be a side effect of some drugs. Therefore, a detailed and correct diagnosis should be made before selecting optimal treatment. These guidelines do not address the issues related to diagnosis of allergic rhinitis and it is assumed that the correct diagnosis had been established before commencing treatment.

How to use these guidelines

The ARIA guidelines are not intended to impose a standard of care for individual countries. They should, as any guideline, provide a basis for rational decisions in the management of allergic rhinitis to clinicians and their patients. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. Strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to **all** patients in **all** circumstances. No guidelines or recommendations can take into account all of the often-compelling unique features of individual clinical circumstances. Therefore, nobody charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines as rote or in a blanket fashion.

Scope

The target audience of these guidelines is principally primary care clinicians and specialists managing patients with allergic rhinitis, but it includes other health care professionals and health care policy makers. It has been shown that a guideline-based treatment of allergic rhinitis is more effective than an unsystematic and variable treatment administered by both primary care physician (24) or a specialist. National programmes and treatment guideline groups may also wish to use this document as the basis for implementation or development of locally adapted guidelines (see Adaptation of guidelines).

The clinical questions covered by this document were developed in consultation with the ARIA guideline panel. The key questions can be summarized briefly as:

- Should allergen avoidance methods be used by parents to avoid development of allergy in children?
- Should occupational allergen avoidance methods be used?
- Should patients with allergic rhinitis and/or conjunctivitis use H1-antihistamines, glucocorticosteroids, antileukotrienes, chromones, decongestants, or ipratropium bromide? What is the relative effect of these medications?
- Should allergen specific immunotherapy be used in patients with allergic rhinitis? What is the effect of subcutaneous, intranasal, and sublingual specific immunotherapy?
- Should complementary and alternative treatments be used for allergic rhinitis?
- Should medications for the treatment of allergic rhinitis be used in patients with concomitant asthma for the treatment of asthma?

The recommendations in this document do not apply to prevention or treatment of other types of rhinitis (i.e. non-allergic) or complications of allergic rhinitis (e.g. sinusitis). The recommendations in these guidelines about treatment of asthma apply only to patients with asthma and concomitant allergic rhinitis, and advise only on using interventions that can be used in treatment of both asthma and allergic rhinitis.

Therefore, these guidelines do not provide recommendations on treatment of asthma in patients without concomitant allergic rhinitis, and recommendations for treatment of asthma in general.

Methods

We described the methodology for development of this revision of ARIA guidelines in detail elsewhere (25). Here we provide a summary.

The clinical questions and scope of these guidelines were defined by ARIA guideline panel members. These questions originated from the previous edition of ARIA guidelines (1, 25) and the subsequent updates of the selected topics that the ARIA guideline panel published (26-30). This work was supplemented by efforts of an independent team of GRADE Working Group members (JLB and HJS supported by two biostatisticians and research personnel), who prepared summaries of evidence, based on systematic reviews and health technology assessments (see Summary of Findings Tables) according to the GRADE methodology described in the ―Guidelines for WHO guidelines" and elsewhere (31-34).

Group composition

The ARIA guideline panel included eight clinicians experienced in treating AR and asthma in adults and in children and two methodologists who were primarily responsible for collecting the evidence, developing evidence summaries, and drafting the guideline.

Formulation of questions and rating the importance of outcomes

The ARIA guideline panel identified clinical problems requiring guidance that led to formulation of thirty one specific clinical questions (35) about the treatment of AR, six questions about the prevention of allergy, and seven questions about the treatment of asthma in patients with coexisting AR and asthma.

The following outcomes were deemed by the guideline panel as important to patients: 1) development of allergy, allergic rhinitis, and/or asthma; 2) presence and severity of nasal, ocular, and bronchial symptoms; 3) exacerbations of asthma; 4) hospitalizations for asthma; 5) quality of life; 6) work/school performance; 7) adverse effects; and 8) resource utilization (cost). For this revision of ARIA guidelines we did not formally assess the relative importance of each outcome, but rather used an informal agreement of the guideline panel (36).

ARIA classifies AR as ―intermittent" or ―persistent" according to the duration of symptoms, and as ―mild" or ―moderate-severe" according to the severity (2). In this document we retained the terms ―seasonal" and ―perennial" to facilitate interpretation of published evidence. The panel also decided to use the terms ―old generation" as corresponding to the terms ―older", ―first generation" or ―sedating" and ―new generation" as corresponding to ―newer", ―second generation" or ―non-sedating" H_1-antihistamines. We chose not to use any functional designations, *e.g.* ―sedating" or ―non-sedating" because the degree of sedation is a continuum without a definite cut-off value and this terminology does not take into account other characteristics of H_1-antihistamines.

Preparation of evidence summaries

We prepared evidence profiles for each question following the GRADE approach (4, 37) using the GRADEpro© software version 3.1 (38). These concise evidence profiles allowed panel members to base their judgments on the same and concisely summarized evidence (39). The summaries of evidence were then peer reviewed and corrections and comments incorporated by the expert panel. The evidence profiles are shown in online supplement 2.

We based the evidence summaries on existing up-to-date well done systematic reviews. Systematic reviews were supplemented, if necessary, with additional recent randomized trials (until August 2007 and for selected clinical questions until January 2009). When there was no recent valid systematic review available, we did not perform rigorous systematic reviews, but we systematically searched MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) for relevant

studies (see appendix in this supplement for search strategies). When possible and justified we combined the results of identified studies using meta-analysis. The identified original studies were evaluated to inform judgements about the underlying evidence, if they addressed the relevant PICO question.
The GRADE system classifies the quality of evidence into four categories: high, moderate, low, and very low (40, 41). The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect is adequate to support a particular recommendation (42). When classifying evidence into one of the quality categories one considers the following factors: 1) study design and rigour of its execution or risk of bias (as described above for this revision we did not review all original studies, but rather relied on the judgement of the authors of a systematic review), 2) the extent to which available evidence can be directly applied to the target patients, interventions, and outcomes, 3) the consistency of results, 4) whether the results are precise, and 5) whether there is a likelihood of publication bias (in this publication we grouped the evaluation of selective outcome reporting and typical publication bias – please note that the GRADE working group has since categorized selective outcome reporting bias under limitations in study design and execution and separated it from publication bias based on methods of the Cochrane Collaboration). The following three factors lead to upgrading the quality of evidence: 1) a strong or very strong association, 2) a dose-effect relationship, and 3) all plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed (25). The overall quality of evidence is determined by the lowest quality of evidence for each of the critical outcomes. When outcomes point in the same direction (all critical outcomes suggesting benefit) then the overall quality of evidence reflects the quality of the better evidence (e.g., two critical outcomes showing convincing benefit are of low quality and a third of very low quality, the overall quality is not reduced from low to very low).

The following are the definitions of these categories:

- **High:** Further research is very unlikely to change confidence in the estimate of effect.
- **Moderate:** Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
- **Low:** Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
- **Very low:** Any estimate of effect is very uncertain.

Some outcomes in patients with allergic rhinitis are measured on a continuous scale (e.g. symptom scores and quality of life). When they are summarised across studies and combined in meta-analysis, they are often presented as standardised mean difference (SMD) that is expressed in standard deviation (SD) units. Results expressed as a SMD are challenging to interpret by clinicians. To facilitate understanding we used interpretation of the effect size suggested by Cohen (43). According to this interpretation, a 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 eother small, moderate or large.

Panel meetings

We held two meetings to discuss the clinical questions, the results of the evidence reviews, and to agree on recommendations. No recommendation required voting.

Balancing desirable and undesirable consequences of available treatment options and developing recommendations

Formulating the recommendations included consideration of the quality of evidence, desirable and undesirable consequences of following the recommended course of action, and values and

preferences of those for whom the recommendations are intended. For most recommendations resource utilization (cost) was also taken into account (44). Recommendations were classified as 'strong' or 'weak' as recommended by the GRADE working group (4). Statements about the underlying *values and preferences* as well as the *remarks* are *integral parts of the recommendations* and serve to facilitate accurate interpretation. *They should not be omitted when citing or translating recommendations in the ARIA guidelines.* In this document, the expression ―values and preferences" refers to the relative worth or importance of a health state or the consequences of a decision to follow a particular course of action (i.e. a relative weight one attributes to particular benefits, harms, burdens, and costs to determine their balance). Individuals usually assign less value to and have less preference for more impaired health states (e.g. death or impaired social functioning and work productivity due to severe rhinitis symptoms) compared to other health states (e.g. full health or having very mild symptoms that do not interfere with daily life). We used the decision framework described previously to determine the strength of recommendations (33, 45).
Little information about costs of prevention or treatment of allergic rhinitis was available to the panel and it is very likely that it varies considerably across geographical areas and jurisdictions. Cost, therefore, plays a limited role in these recommendations. However, whenever we considered cost and resource expenditure we used health system perspective (46). For individual patients cost may not be an issue if the medication is provided at reduced price or free of charge. Clinicians and patients should consider their local resource implications when interpreting these recommendations.

Following the GRADE approach, in these guidelines we classified **recommendations as either strong** or **conditional (weak)**. The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e. net clinical benefit), quality of available evidence, values and preferences, and cost (resource utilization) (45). In general, the higher the quality of the supporting evidence, the more likely it is for the recommendation to be strong. Conversely, if the quality is low or very low a conditional recommendation is more likely. Strong recommendations based on low or very low quality evidence are rare, but possible (25).
An alternative, acceptable term for conditional recommendation is weak. **For strong recommendations we used words "we recommend" and for conditional recommendations – "we suggest".** We offer the suggested interpretation of strong and conditional (weak) recommendations in the Table (33). Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision making.

Consultation

We asked 80 clinicians involved in the management of patients and/or research of AR from a variety of countries and 3 members of patient organizations to review the guidelines. As a result we performed additional searches for most recent studies and reassessed the evidence for several questions.

We think that the natural order of clinical reasoning starts from defining the patients (population) and the clinical problem and subsequently choosing one the available management options (interventions). Thus, when formulating the recommendations for ARIA guidelines, we followed PICO (population, intervention, comparison, outcomes) format (35).

Some outcomes in patients with allergic rhinitis are measured on a continuous scale (e.g. symptom scores and quality of life). When they are summarised across studies and combined in meta-analysis, they are often presented as standardised mean difference (SMD) that is expressed in standard deviation (SD) units. Results expressed as a SMD are challenging to interpret by clinicians. To facilitate understanding we used interpretation of the effect size suggested by Cohen (43). According to this interpretation, a 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 eother small, moderate or large.

Recommendations

In the following six sections we present specific recommendations for:

- prevention of allergy, allergic rhinitis, and/or asthma
- reducing allergen exposure for treatment of allergic rhinitis and/or asthma
- pharmacological treatment of allergic rhinitis
- immunotherapy in allergic rhinitis
- alternative and complementary treatment of allergic rhinitis
- treatment of asthma in patients with concomitant allergic rhinitis

Changing information about treatment of allergic rhinitis and paucity of up-to-date systematic reviews of available evidence will require a timely update of these guidelines. Future revisions of ARIA will include quality assessment of the individual studies cited in the systematic reviews we applied in making these recommendations.

Recommendations that address similar management options should be interpreted together. For instance, the recommendation to use oral H1-antihistamines (Question 11) should be interpreted in the context of other recommendations to use new-generation versus old-generation H1-antihistamines (Question 12), to use oral H1-anthistamines in children to prevent development of asthma (Question 13), and to use new-generation oral H1-antihistamines versus intranasal H1-antihistamines (Question 15), versus leukotriene receptor antagonists (Question 17) or versus intranasal glucocorticosteroids (Question 19).

I. Prevention of allergy

Question 1

Should exclusive breastfeeding be used in infants to prevent allergy?

Summary of findings

Seven systematic reviews addressed the question if exclusive breastfeeding prevents development of allergy. Three reviews focused on prevention of the development of atopic dermatitis (47), allergic rhinitis (48), and asthma (49) (see accompanying evidence profile). Their findings were summarised in overview of these reviews (50). The fifth systematic review explored if extending the period of exclusive breastfeeding beyond 3 months to up to 7 months influences child's health (including allergy), growth, and development (51) (see accompanying evidence profile). The sixth review summarised the available studies in a narrative form but did not provide any summary estimates (52). All reviews included prospective observational studies.
A recent systematic review (53) did not find any new studies investigating the risk of atopic dermatitis that would not be included in the analysis of Gdalevich and colleagues (47) and it found four more recent studies on the prevention of asthma (54-57).
We did not assess the quality of evidence supporting other benefits from breastfeeding except for development of allergy and asthma. For this revision of the ARIA guidelines we also have not assessed the relative benefit of exclusive breastfeeding compared to other alternative methods of infant nutrition, e.g. formulas containing hydrolysed protein for prevention of allergy and/or asthma in infants.

Benefits

There is evidence from observational studies that exclusive breastfeeding for at least 3 months may prevent atopic dermatitis, allergic rhinitis, and asthma. Some of the effect estimates are imprecise. Extending exclusive breastfeeding to at least 6 months may provide additional benefit, although the estimates are also imprecise and do not exclude no effect. All critical outcomes indicate beneficial effects in the same direction.

Harms

There were no important risks associated with exclusive breastfeeding reported in the systematic reviews. However, breastfeeding may not always be in the best interest of an infant when contraindications are present (e.g., classic galactosemia, active untreated tuberculosis or human immunodeficiency virus infection in mother, chemotherapeutic agents or radioactive isotopes being used in the mother for diagnostic or therapeutic purposes, some other medications until they clear from the milk, and bacterial or viral infection of a breast) (58).

Conclusions and research needs

Given the few specific possible undesirable effects of exclusive breastfeeding in situations that are relatively well described, exclusive breastfeeding for at least three months appears to be of net clinical benefit. However, the available evidence supporting its beneficial effect on development of allergy and asthma is limited and overall of low quality for the critical outcomes.

The relation between exclusive breastfeeding and the development of allergy or asthma needs further elucidation. However, it is unlikely to influence this recommendation.

What others are saying
Paediatric and obstetrical professional societies recommend breastfeeding for all infants unless there are contraindications (58-61), because of reduced risk of infections observed both in developing and in developed counties, lower risk of other diseases suggested in many studies, and because of maternal health benefits.

Recommendation

We suggest exclusive breastfeeding for at least the first three months for all infants irrespective of their family history of atopy (conditional recommendation | low quality evidence).

Values and preferences: This recommendation places a relatively high value on the prevention of allergy and asthma, and a relatively low value on challenges or burden of breastfeeding in certain situations.

Remarks: The evidence, that exclusive breastfeeding for at least the first three months reduces the risk of allergy or asthma, is not convincing and the recommendation to exclusively breastfeed is conditional. This recommendation applies to situations in which other reasons do not suggest harm from breastfeeding (e.g. classic galactosemia, active untreated tuberculosis or human immunodeficiency virus infection in the mother, antimetabolites, chemotherapeutic agents or radioactive isotopes used in the mother until they clear from the milk, and bacterial or viral infection of a breast).

Question 2

Should antigen avoidance diet be used in pregnant or breastfeeding women to prevent development of allergy in children?

Summary of findings

One systematic review reporting on 4 studies assessed maternal dietary antigen avoidance during pregnancy and/or lactation for preventing or treating atopic disease in the child (62) (see accompanying evidence profile).

Benefits

Results of available trials suggest that it is unlikely that antigen avoidance diet prevents development of allergy or asthma, although the results are inconsistent, very imprecise and the follow-up was limited to the first 18 months of life.

Harms

There is evidence of very low quality that antigen avoidance diet may increase the risk of preterm birth.

Conclusions and research needs

Any clinical benefit of antigen avoidance diet in pregnant or breastfeeding women to prevent development of allergy in children is very uncertain. Future research, if done, may have an important impact on this recommendation.

Recommendation

For pregnant or breastfeeding women, we suggest no antigen avoidance diet to prevent development of allergy in children (conditional recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on adequate nourishment of mothers and children, and a relatively low value on very uncertain effects on the prevention of allergy and asthma in this setting.

Question 3

Should children and pregnant women avoid environmental tobacco smoke (i.e. passive smoking) to reduce the risk of developing allergy, wheezing, or asthma in children?

Summary of findings

A series of systematic reviews of observational studies evaluated the relation between environmental tobacco smoke (ETS, secondhand smoke or passive smoking) exposure and respiratory health in children. These systematic reviews generally reported an increased risk of asthma, wheeze, and chronic cough in children in families where either parent smoked (63-68). A link between environmental tobacco smoke exposure and development of allergy was not found (69).
We identified two additional more recent reports of studies that showed increased risk of wheezing in children exposed to parental smoking (70, 71).

A World Health Organization Report on Tobacco Smoke and Child Health (72) found that ETS has adverse effects during gestation and has definite effects after birth including increased risks of lower respiratory tract infection during infancy and chronic respiratory symptoms in school-aged children. ETS increases the severity and frequency of symptoms in children with asthma, is causally associated with increased risk of acute and chronic middle ear disease and is a cause of small reductions in average birth weight (exposure of non-smoking women during pregnancy). Parental smoking is also associated with learning difficulties, behavioural problems, and language impairment. There is evidence that tobacco smoke exposure causes non-allergic wheezing in early life, but whether it does cause asthma is less clear. In addition, evidence does not support a role of parental smoking during the perinatal period for allergic sensitization. Nevertheless, ETS exposure causes exacerbations of symptoms in children with asthma. Although these increased risks are modest, these are common health problems around the world. Thus small increases in risk translate into a substantial absolute burden of disease for children arising from exposure to ETS.

The most recent report from Surgeon General on respiratory Effects in Children from Exposure to Secondhand Smoke (68) found sufficient evidence to infer a causal relationship between parental smoking and cough, phlegm production, wheeze, and breathlessness as well as ever having asthma among children of school age. The evidence was judged sufficient to infer a causal relationship between ETS exposure from parental smoking and the onset of wheeze in early childhood. It was

judged suggestive and not sufficient to infer a causal relationship between ETS exposure and the onset of childhood asthma. Authors of this report also found inadequate evidence to infer the presence or absence of a causal relationship between parental smoking and the risk of allergy in children. Irrespective of its effect on asthma and allergy, ETS has other detrimental respiratory and developmental effects in children.

The authors of that report (68) found only one small study of a population intervention on parental smoking and the symptoms of asthma in children. That study concluded by stating that exposure to smoking be eliminated for the 37 asthmatic children in whom this was a problem. At 6-month to 2-year follow-up, 20 of the 35 families had complied, and improvement was obtained in 18 of these children and in only 4 of the 15 who had failed to comply (73).

We did not find any other studies of interventions aimed on reduction of ETS exposure and development of asthma or wheeze or on the symptoms in children that already had asthma.

Benefits

Exposure to ETS increases the risk of many chronic diseases in infants and children. Although there is very limited evidence that stopping the exposure to ETS benefits infants and children, there is little doubt that avoiding exposure would be beneficial in these populations and in pregnant women.

Harms

There are no important harms from smoking cessation and no known harms from reducing the exposure to environmental tobacco smoke.

Conclusions and research needs

It appears that there is a net clinical benefit from not exposing pregnant women, infants and children to environmental tobacco smoke. Given no important harms of smoking cessation or reducing the exposure to second-hand smoke, clinical benefit from stopping the exposure is also very likely, if pregnant women or children are already exposed.
Further well designed and rigorously executed randomised trials of smoking cessation interventions that measure and properly report (74, 75) patient-important outcomes are needed. If done, they are likely to have an important impact on the quality of evidence supporting this recommendation.

Recommendation

In children and pregnant women, we recommend total avoidance of environmental tobacco smoke (i.e. passive smoking) (strong recommendation | very low quality evidence).

Remarks: Smoking and exposure to second-hand smoke are common health problems around the world causing a substantial burden of disease for children and adults. While it is very rare to make a strong recommendation based on low or very low quality evidence, the ARIA guideline panel felt that in the absence of important adverse effects associated with smoking cessation or reducing the exposure to second-hand smoke, the balance between the desirable and undesirable effects is clear.

Question 4

Should infants and preschool children avoid exposure to house dust mites to reduce the risk of developing dust mite allergy and asthma?

Summary of findings

No systematic review evaluated the association between early life exposure to house dust mite allergens and the risk of developing allergy and/or asthma in children.

A report from the Institute of Medicine (76) found that observational studies have shown an association between house dust mite sensitization and asthma (77-82). Some recent studies confirmed this effect (83, 84), but some did not (85). The results were consistent across different populations and showed odds ratios for asthma between 6 and 12 in individuals sensitized to house dust mite allergens. This report found that there was a dose-response relationship between exposure to house dust mite allergens and sensitization. However, the relationship between exposure and development of asthma was less clear.

No systematic review addressed the question if reducing the exposure to house dust mite allergens prevents the development of allergy or asthma.

Seven randomised trials of birth cohorts evaluated the effect of multifaceted interventions on the development of allergy and/or asthma – the Canadian Childhood Asthma Primary Prevention Study (86-88), the Prevention of Asthma in Children study (89), the Study on the Prevention of Allergy in Children in Europe (90, 91), the Isle of Wight study (92, 93), the Childhood Asthma Prevention Study (94, 95), the Prevention and Incidence of Asthma and Mite Allergy Study (96-99), and the Manchester Asthma and Allergy Study (100, 101).
In these seven trials, families of children considered to be at high risk of developing allergy and/or asthma (based on at least one first degree relative with asthma or other allergic disorder) were randomly assigned to multifaceted interventions (frequent ventilation of the child's room, encasings to parental and child's bed, washing bedding and soft toys at >55°C, use of acaricide, smooth flooring without carpets) or usual care provided by primary care physicians. In three of these studies, families were also advised to part with a pet or keep it outside (see Question 5), and in four studies they were advised to follow various allergen avoidance diets and not to smoke.

Benefits

After 2 years of observation there was no significant difference between the multifaceted intervention and control groups in the percentage of children who developed recurrent wheezing or atopic dermatitis (eczema). Multifaceted interventions seemed to reduce the risk of rhinitis (relative risk: 0.72, 95% CI: 0.49 to 1.06) and asthma (relative risk: 0.81, 95% CI: 0.61 to 1.06) after 2 years of follow-up, but the results were imprecise and did not exclude no effect.
Five studies reported results after 3 to 8 years of follow-up. There was no decreased risk of developing allergic rhinitis or atopic dermatitis (eczema). However, multifaceted interventions were associated with lower risk of wheezing (relative risk: 0.77, 95% CI: 0.62 to 0.98) and suggested protection against developing asthma (relative risk: 0.82, 95% CI: 0.66 to 1.01) in children 3 to 8 years of age.

Harms

There were no direct adverse effects of these prophylactic interventions but there is inconvenience, cost of using multiple preventive measures, and psychological burden on parents who cannot afford them.

Conclusions and research needs

Net clinical benefit from reducing exposure to house dust mite allergens in early childhood is uncertain. In children at high risk multifaceted interventions may reduce the risk of developing asthma, but it is unclear which aspects of the interventions would be most effective. The effect on development of allergic rhinitis is less certain and the effect on atopic dermatitis is unlikely. There is no evidence concerning children at average risk of developing allergy, but if present the effect would probably be even smaller in this population.

Recommendation

In infants and preschool children, we suggest multifaceted interventions to reduce early life exposure to house dust mite (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively low value on the burden and cost of using multiple preventive measures (*e.g.* encasings to parental and child's bed, washing bedding and soft toys at temperature exceeding 55°C [131°F], use of acaricide, smooth flooring without carpets, etc.), and relatively high value on an uncertain small reduction of the risk of developing wheeze or asthma. For some children at lower risk of developing asthma and in certain circumstances an alternative choice will be equally reasonable.

Remarks: Children at high risk of developing asthma are those with at least one parent or sibling with asthma or other allergic disease.

Question 5

Should infants and preschool children avoid exposure to pets at home to reduce the risk of developing allergy and asthma?

Summary of findings

Two systematic reviews of observational studies reported that early life exposure to pet allergens may increase the risk of asthma in children (102, 103), although the estimated effect was small and inconsistent including some studies that showed a reduced risk. Authors of the review suggested that this heterogeneity might have been caused by inappropriate time sequence of the exposure and outcome and a potential selection bias in individual studies. In studies ensuring the appropriate temporal sequence, previous exposure to pet allergens was not associated with increased risk of asthma (odds ratio: 0.99, 95% CI: 0.77 to 1.27) or wheezing (odds ratio: 0.80, 95% CI: 0.59 to 1.08) in children ≤6 years of age. In older children (>6 years) the risk might be higher both for asthma (odds ratio: 1.15, 95% CI: 0.86 to 1.56) or wheezing (odds ratio: 1.30, 95% CI: 1.11 to 1.52).

We did not identify any systematic review addressing the question if avoidance of pet allergens prevents the development of allergy or asthma. We also did not identify any randomised trial evaluating avoidance of pet allergens as a single intervention to prevent the development of allergy or asthma.

However, three randomised trials of birth cohorts evaluated the effect of multifaceted interventions on the development of allergy and/or asthma – the Canadian Childhood Asthma Primary Prevention Study (86-88), the Prevention of Asthma in Children study (89), and the Study on the Prevention of Allergy in Children in Europe (90, 91). We used data from these trials to estimate the overall effect in a meta-analysis and used them to prepare the evidence profile.
In these three trials families of children considered to be at high risk of developing allergy and/or asthma (at least one first degree relative with asthma or other allergic disorder) were randomly assigned to multifaceted interventions (frequent ventilation of the child's room, encasings to parental and child's bed, washing bedding and soft toys at >55ºC, use of acaricide, smooth flooring without carpets, various dietary interventions, and were advised to part with a pet or keep it outside). Compliance with the recommendation to part with a pet or keep it outside was variable; in one study 51% families complied with the recommendation (104), and in the other 17 families (34% of 50 families that had a cat at baseline) parted with the cat, but 6 families acquired a new cat over a period of 2 years (105).

Benefits

After 2 years of observation there was no significant difference between the multifaceted intervention and control groups in the percentage of children who developed rhinitis, recurrent wheezing, or atopic dermatitis (eczema), but results were not precise enough to exclude important benefit or important harm from the intervention. Multifaceted intervention seemed to reduce the risk of asthma after 2 years of follow-up, but the results were imprecise, including no effect.
Only one study (86) reported results after more than 2 years of follow-up. There was a similar risk of development of allergic rhinitis and atopic dermatitis (eczema) after 7 years, although the results were imprecise. However, multifaceted intervention was associated with lower risk of developing asthma after 7 years (relative risk: 0.44, 95% CI: 0.25 to 0.79).

Harms

There were no direct adverse effects of these prophylactic interventions except for inconvenience and cost of using multiple preventive measures.

Conclusions and research needs

All available evidence for the benefit from avoiding pet allergens in childhood comes from interventions in high-risk families, and is very indirect and imprecise. Any clinical benefit from avoiding exposure to pet allergens in childhood is therefore very uncertain, and there is even some uncertainty if there is a risk associated with the exposure. Further well designed and rigorously executed randomised trials of pet allergen avoidance that measure and properly report (74, 75) patient-important outcomes are needed.

Recommendation

In infants and preschool children, we suggest no special avoidance of exposure to pets at home (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on possible psychosocial downsides of not having a pet, and relatively low value on potential reduction in the uncertain risk of developing allergy and/or asthma.

Remarks: Clinicians and patients may reasonably choose an alternative action, considering circumstances that include other sensitized family members.

Question 6

Should specific measures reducing occupational agent exposure be used to decrease the risk of sensitization and subsequent development of occupational rhinitis and asthma?

Summary of findings

We found no systematic review of primary prevention of occupational rhinitis. There is paucity of evidence about epidemiology, diagnosis, prevention, and treatment of occupational allergic rhinitis.

One systematic review from the British Occupational Health Research Foundation assessed methods that reduce occupational agent exposure for the prevention and treatment of occupational asthma (106, 107).

Two systematic reviews assessed primary prevention of latex related sensitisation and occupational asthma (108, 109).

Benefits

Occupational rhinitis and occupational asthma frequently occur together and rhinitis usually precedes asthma (107). Nicolson and colleagues (106) found observational studies showing that reducing occupational exposure to airborne agents (acid anhydrides, enzymes, di-isotiocyanates, laboratory animal dander, and natural rubber latex) lowered the risk of sensitization and development of occupational asthma in workers. They also found that use of respiratory protection equipment reduced the risk of occupational asthma, but only when properly worn on every occasion, and it did not completely prevent asthma. The overall quality of evidence supporting the reduction of airborne allergens was low and for the use of respiratory protection equipment it was very low.

Bousquet and colleagues (108) and LaMontagne and colleagues (109) found nine observational studies of interventions aimed at reducing natural rubber latex in primary prevention of latex sensitivity, allergy, and asthma. These studies showed that substitution of powdered latex gloves with low-protein powder-free natural rubber latex gloves or latex-free gloves reduced latex aeroallergens, sensitisation, and asthma in healthcare workers.

Harms

There are no apparent downsides of interventions aimed at the reduction of exposure to occupational agents other than burden and cost of these interventions.

Conclusions and research needs

Specific measures reducing occupational agent exposure may be of net clinical benefit. The overall quality of evidence supporting the reduction of airborne allergens and substitution of natural rubber latex gloves with latex-free gloves was low, and for the use of respiratory protection equipment it was very low.

There is a need for rigorously designed and executed studies of primary prevention of occupational allergic rhinitis.

Recommendation

For individuals exposed to occupational agents, we recommend specific prevention measures eliminating or reducing occupational allergen exposure (strong recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on reducing the risk of sensitization to occupational allergens and developing occupational rhinitis and/or asthma with the subsequent adverse consequences, and a relatively low value on the feasibility and cost of specific strategies aimed at reducing occupational allergen exposure.

Remarks: Total allergen avoidance, if possible, seems to be the most effective primary prevention measure.

II. Treatment of allergic rhinitis

Reducing allergen exposure

Question 7

Should methods aimed at reducing exposure to house dust mites be used in patients allergic to dust mite allergens?

Summary of findings

Two systematic reviews assessed the efficacy of house dust mite avoidance measures in patients with perennial allergic rhinitis (110) (see evidence profiles 1 to 3 for question 7) or asthma (111, 112) (see evidence profiles 4 to 6 for question 7).

We found three randomised trials that examined multifaceted interventions to reduce environmental allergen exposure in children with atopic asthma leaving in inner city, i.e. in densely populated neighbourhoods in large metropolitan areas inhabited by low income families (113-116).

Benefits

No certain benefits were found from using single or combined physical or chemical methods aimed at reducing exposure to house dust mite allergens in patients with persistent allergic rhinitis. However, the available evidence is of very low quality. In contrast, there is moderate quality evidence showing that impermeable bedding has no effect on symptoms of rhinitis. Similarly, no benefits were observed in studies using physical and/or chemical methods to reduce exposure to house dust mite allergens in patients with asthma.

Of the three randomised trials that examined multifaceted interventions to reduce environmental allergen exposure in children with atopic asthma, the Inner-City Asthma Study (113, 114) found fewer days with symptoms, unscheduled clinic visits, and less use of beta-agonist inhalers in the intervention group, compared to the controls. However, the intervention aimed at reducing the exposure to many indoor allergens and environmental tobacco smoke, most of the children were sensitive to many indoor allergens, had moderate or severe asthma, and less than 50% of them were receiving appropriate maintenance treatment according to the guidelines. Another randomized controlled trial (115) of multiple methods to reduce environmental allergen exposure in the homes of asthmatic children living in the inner city found improved daytime symptom scores in the treatment group. On the contrary, a multifaceted environmental and educational intervention in children with asthma living in urban environments (116) did not find the difference in asthma severity scores, medication use, emergency department visits or hospitalization between the intervention and control groups. We considered overall quality of evidence supporting multifaceted environmental interventions as very low due to inconsistency and imprecision of the results, and the indirectness of the population, because of inappropriate baseline treatment in the majority of patients.

Harms

There are no apparent downsides of using methods of reducing exposure to hose dust mite allergens except for the burden and cost of these interventions. Multifaceted environmental interventions may consume substantial healthcare resources. Moreover, compliance with allergen avoidance was low in the inner city asthma studies (117).

Conclusions and research needs

There seems to be no net clinical benefit from house dust mite avoidance measures in patients with perennial allergic rhinitis and/or asthma. However, many studies do not report or do not achieve reduction in house dust mite levels. Thus, there is uncertainty whether the lack of effect on symptoms of allergic rhinitis in these trials is due to inadequate reduction in allergen exposure or to ineffectiveness of this approach in spite of reduction in house dust mite levels. There may be net benefit from multifaceted environmental interventions for children with asthma living in inner city homes. Further adequately designed and executed trials of new methods of avoiding house dust mite allergens exposure or multifaceted interventions that measure patient-important outcomes are needed. This research, if done, may have important impact on this recommendation. These conclusions reflect a recent ARIA guidelines update (26) that reviewed the effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma.

Recommendation

In patients with allergic rhinitis and/or asthma sensitive to house dust mite allergens, we recommend that clinicians do not administer and patients do not use currently available single chemical or physical preventive methods aimed at reducing exposure to house dust mites (strong recommendation | low quality evidence) or their combination (conditional recommendation | very low quality evidence), unless this is done in the context of formal clinical research.

We suggest multifaceted environmental control programmes be used in inner-city homes to improve symptoms of asthma in children (conditional recommendation | very low quality evidence).

Underlying values and preferences: The recommendation to use multifaceted environmental control programmes in inner-city homes places a relatively high value on possible reduction in the symptoms of asthma in children, and relatively low value on the cost of such programmes.

Question 8

Should patients allergic to indoor moulds avoid exposure to these allergens at home?

Summary of findings

We found no systematic review addressing this question. We found two randomised trials that evaluated remediation aimed at moisture sources (118) or ultraviolet irradiation of homes (119).

Benefits

In one randomized trial (118), 62 asthmatic children living in a home with indoor mould, received an intervention including an asthma action plan and education. The remediation group also received household repairs (reduction of water infiltration, removal of water-damaged building materials,

and heating/ventilation/air-conditioning alterations). The control group received only home cleaning information. After 1 year the remediation group had a significant decrease in symptom days after remodelling, whereas these parameters in the control group did not change. The remediation group had a lower rate of acute care visits compared with control group, but the difference was not significant (10.0% vs 28.1%).In a second randomised, cross-over trial (119) centrally installed ultraviolet (UV) irradiation units were investigated among 19 asthmatic children sensitized to moulds. The authors reported improvement in asthma symptom scores, the number of days with asthma symptoms, total asthma medication use in children provided with UV irradiation units versus placebo, but this trial had methodological limitations and it was not clear if the difference between the groups was clinically important.

Harms

There were no definite adverse effects of these interventions but there is burden and cost.

Conclusions and research needs

Any net clinical benefit from methods aimed at reducing exposure to household moulds is very uncertain. Trials had methodological limitations, results were inconsistent, and there is some uncertainty about the directness of multiple interventions used in the study by Kercsmar and colleagues (118).
Well designed and rigorously executed randomised trials of methods aimed at reducing exposure to household moulds that measure and properly report (74, 75) patient-important outcomes are needed. If done, they are likely to have an important impact on this recommendation.

Recommendation

In patients allergic to indoor moulds, we suggest avoiding exposure to these allergens at home (conditional recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on possible reduction in the symptoms of rhinitis and asthma, and a relatively low value on the burden and cost of interventions aimed at reducing exposure to household moulds.

Question 9

Should patients allergic to animal dander avoid exposure to these allergens at home?

Summary of findings

We did not identify any systematic review directly addressing the question of pet allergen control measures in patients with allergic rhinitis. However, one recent systematic review reported 2 studies that investigated the clinical efficacy of air filtration units and concomitant environmental interventions in the homes of people with pet-allergic asthma who had pets (120). Authors' last literature search in September 2006 did not reveal any new trials since the original review was published in 2001.

One randomised trial has evaluated the effect of reducing levels of cat allergen on clinical symptoms in patients with cat allergy (121).

Benefits

Eight months of environmental control intervention (removing carpeting and upholstered furniture from bedrooms, and washing all walls and floors at study entry, weekly vacuuming floors, carpets, and furniture as well as washing bedding at 60°C (130°F), bimonthly applying tannic acid (3%) to carpeting and upholstered furniture, using polyester-filled duvets and pillows and impermeable covers, washing a cat every 2 weeks and keeping it out of bedroom), compared to no change in environment, reduced symptoms of nasal congestion, itching, and rhinorrhea (121). However, the results were very imprecise and there is some uncertainty about the directness of the environmental control intervention that influenced the exposure to other allergens as well.
One of the two small trials in patients with asthma included seven patients with rhinitis and found no significant changes in symptom scores in either the placebo or active groups, after 3 months of environmental control intervention (keeping cats from entering the bedroom, washing bedding once a week, and using high-efficiency particulate air (HEPA) cleaner (122).
Two small trials included in the systematic review did not find any difference in asthma symptoms between intervention and control groups. In one study fewer patients reported difficulties in sleeping (4/9 vs. 12/14 in the intervention and control groups respectively) (122).

Harms

There are no direct harms associated with this intervention but there is burden and cost of using multiple environmental control measures.

Conclusions and research needs

Any benefit from avoiding exposure to animal dander at home of patients allergic to these allergens is very uncertain. Well designed and rigorously executed clinical studies of methods aimed at reducing exposure to animal dander at home that measure and properly report (74, 75) patient-important outcomes are needed to inform this recommendation. If done, they are likely to have an important impact on this recommendation.

Recommendation

In patients with allergic rhinitis due to animal dander, we recommend avoiding exposure to these allergens at home (strong recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on potential reduction of symptoms of AR, and a relatively low value on psychosocial downsides of not having a pet or the inconvenience and cost of environmental control measures.

Remarks: Based on biological rationale, there is little doubt that total avoidance of animal allergens at home, and probably also marked reduction in their concentration, can improve symptoms, despite paucity of published data to substantiate this statement.

Question 10

Should immediate and total cessation of exposure to an occupational agent or exposure control be used in patients with occupational rhinitis and asthma?

Summary of findings

One systematic review from the British Occupational Health Research Foundation (106) and one health technology assessment (123) assessed methods aimed at reducing occupational agent exposure for treatment of occupational asthma. The report by Beach and colleagues (123) was more extensive and provided more detailed information and we used it to inform this recommendation. Moreover, the findings of both reviews were consistent. Beach and colleagues found two small randomised trials (one employed respiratory devices in 26 farmers and the other compared reactions to various types of gloves in eight healthcare workers) and 52 cohort studies that investigated the effect of reducing exposure on asthma outcomes in workers with occupational asthma. Outcomes in workers with continued exposure was assessed in 14 studies, and reduced exposure in 18. Eight studies investigated the effectiveness of personal protection equipment. Most studies had methodological limitations and there was some uncertainty about the directness of the interventions due to confounding.

Benefits

Studies that assessed forced expiratory volume in one second (FEV_1) found that it improved over time in a minority of workers who were either removed from exposure or had reduced the exposure. In most studies symptoms either remained stable or deteriorated with continued exposure at work. On the other hand, the majority of studies that examined workers removed from exposure or whose exposure had been reduced reported improvement in asthma symptoms. Respiratory protective equipment reduced the severity, but did not eliminate symptoms. Only two studies measured quality of life and found that it did not differ among workers removed from exposure compared to those whose exposure had been reduced.

Harms

Seven studies examined socioeconomic outcomes among workers with occupational asthma and found that both workers removed from the workplace and those who continued the exposure suffered a loss in income. Two studies reported that a significant proportion of workers who were removed from exposure remained unemployed or took an early retirement (25% and 70% in each of the studies). The United Kingdom's Surveillance of Work-related and Occupational Respiratory Disease program found that 30% of people reported to have occupational asthma were unemployed when contacted later (124).

Conclusions and research needs

Specific measures reducing occupational agent exposure may be of net clinical benefit, but this likely depends on the type of causative agent. The overall quality of evidence supporting the reduction of exposure was very low.
Further research on cessation or reduction of occupational agent exposure is needed to inform this recommendation.

Recommendation

In patients with occupational asthma, we recommend immediate and total cessation of exposure to occupational allergen (strong recommendation | very low quality evidence). When total cessation of exposure is not possible, we suggest specific strategies aimed at minimizing occupational allergen exposure (conditional recommendation | very low quality evidence).

Underlying values and preferences: The recommendation to immediately and totally cease the exposure to occupational allergen places a relatively high value on reducing the symptoms of asthma and deterioration of lung function, and a relatively low value on the potential socioeconomic downsides (e.g. unemployment).

Pharmacological treatment of allergic rhinitis

Question 11

Should oral H1-antihistamines be used for the treatment of allergic rhinitis?

Questions 11 and 12 should be considered as complimentary and indivisible.
We begin this section with a note on classification of H1-antihistamines. Then we evaluate whether oral H1-antihistamines should be used at all (Question 11). We consider old and new generation oral H1-antihistamines separately. Following these recommendations we compare old to new generation oral H1-antihistamines (Question 12).

Note on classification and terminology

H_1-antihistamines are a class of agents that share some mechanisms of action – they are antagonists of histamine at H_1 receptor sites or they act as inverse agonists. However, in addition to antagonising the effect of histamine, they have other actions that may contribute to the difference in their effectiveness or safety. There are many classifications of H_1-antihistamines according to their chemical structure (e.g. alkylamines, piperazines, piperidines, etc.), time when they reached the market (e.g. first generation versus second generation), or their adverse effects (e.g. sedating versus non-sedating, interacting with cytochrome P450 versus non-interacting, cardiotoxic versus non-cardiotoxic, interacting with food versus non-interacting etc.). All the above properties, except for chemical structure, are not dichotomous but rather a continuum with any threshold being arbitrary. Furthermore, the magnitude of these effects should be estimated with a systematic review of literature which is not yet available. As a result there is no consensus which H_1-antihistamine belongs to which group and this causes confusion for clinicians and patients.
In this document we use terms ―old generation" or ―new generation" as corresponding to the terms ―older", ―first generation" or ―sedating" and ―newer", ―second generation" or ―non-sedating" H_1-antihistamines. We chose not to use any functional designation, e.g. ―sedating" or ―non-sedating", acknowledging that the degree of sedation is a continuum without a definite and reliable cut-off value and that this terminology does not take into account other potential adverse effects (e.g. cardiotoxicity or anticholinergic effect). We also did not rely on the commonly used definition of first and second generation based on the date threshold of 1980 when a particular medication reached the market (125).

Summary of findings

One systematic review addressed the question of the efficacy of oral H_1-antihistamines in reducing the symptom of nasal obstruction in adults with persistent allergic rhinitis (126).
Another systematic review of the effect of desloratadine in allergic rhinitis requires updating and could not be used to inform this recommendation (127).
One systematic review investigated the use of astemizole in allergic rhinitis and urticaria (128), but since astemizole and terfenadine have been withdrawn from the market and the review had considerable methodological limitations we did not consider it for this recommendation.
We did not identify any other systematic review of efficacy or safety of oral H_1-antihistamines compared to placebo in allergic rhinitis.

The ARIA guideline group has identified 78 trials of different oral H_1-antihistamines compared to placebo in patients with allergic rhinitis, that were published until the first quarter of 2007 (129-205).

Because no systematic review comparing oral H_1-antihistamines to placebo in patients with seasonal allergic rhinitis is available, we based the judgement about the quality of supporting evidence on an assumption that at least for two critical outcomes – quality of life and adverse effects – available evidence would be inconsistent and there would be a probability of publication and reporting bias. This assumption is based on the results of systematic reviews of trials that compared oral H1-antihistamines to active treatments (not to placebo) in allergic rhinitis.

Benefits

A systematic review found that oral H_1-antihistamines compared to placebo were more effective for nasal obstruction in patients with persistent allergic rhinitis (126). Since we could not identify any systematic review of the effectiveness of oral H_1-antihistamines compared to placebo in patients with seasonal allergic rhinitis overall effect and its magnitude are currently uncertain.

Harms

In the systematic review by Hore and colleagues (126) headache was the most common adverse event, but there was no statistically significant difference between the groups. The effect on fatigue was inconsistent across studies. In the absence of any other systematic review investigating the safety of oral H_1-antihistamines compared to placebo it is currently not feasible to estimate the magnitude of the risk of adverse effects. Based on unsystematic observations there is, however, concern about somnolence, headache, appetite stimulation, weight gain, QT interval prolongation, and altering of drug metabolism with some oral H_1-antihistamines, particularly those interacting with cytochrome P450 and P-glycoprotein (206-222).

Terfenadine and astemizole were withdrawn from the market in many countries because of serious cardiac adverse effects. Therefore, they were not considered for this recommendation.

Conclusions and research needs

Oral H_1-antihistamines may be of net clinical benefit in treatment of allergic rhinitis, but in absence of a systematic review the overall magnitude of the effect for both desirable and undesirable effects is not known. The only available systematic review of oral H1-antihistamines in patients with

allergic rhinitis focused exclusively on nasal obstruction ignoring other outcomes important to patients.
A complete rigorously performed and reported (223, 224) systematic review of all individual oral H1-antihistamines versus placebo in adults and children that provides information on all outcomes important to patients, including adverse effects, is required for the next update of the ARIA guidelines. We based our current judgements on a less systematic evaluation of the evidence by the ARIA guideline panel members.
The ARIA guideline panel strongly supports that new generation oral H1-antihistamines be available worldwide, in particular in low to middle income countries.

Recommendation

In patients with AR, we recommend new generation oral H_1-antihistamines that do not cause sedation and do not interact with cytochrome P450 (strong recommendation | low quality evidence).
In patients with AR, we suggest new generation oral H1-antihistamines that cause some sedation and/or interact with cytochrome P450 (conditional recommendation | low quality evidence).

Underlying values and preferences: The recommendation to use new generation oral H_1-antihistamines that cause some sedation and/or interact with cytochrome P450 places a relatively high value on a reduction of symptoms of AR, and a relatively low value on side effects of these medications.

Remarks: Astemizole and terfenadine were removed from the market due to cardiotoxic side effects.

Question 12

Should new generation oral H_1-antihistamines versus old generation oral H1-antihistamines be used for the treatment of allergic rhinitis?

See the note on classification and terminology for question 11 above.

Summary of findings

One health technology report addressed the relative efficacy and safety of new generation (“non-sedating”) compared to old generation (“sedating”) oral H_1-antihistamines (225). Ten out of twelve randomised trials included in this review investigated terfenadine or astemizole as “non-sedating” oral H_1-antihistamines. Because both medications were withdrawn from the market in many countries for safety reasons, it was not possible to rely on the report by Long and colleagues to inform this recommendation.

One systematic review examined sedation and performance impairment with new generation H_1-antihistamines compared to old generation oral H_1-antihistamine – diphenhydramine (226).

We identified 13 randomised trials that directly compared new generation (referred to as “non-sedating”) to old generation (referred to as “sedating”) oral H_1-antihistamines in patients with allergic rhinitis. Three trials compared desloratadine with diphenhydramine (193, 227, 228), two compared fexofenadine with diphenhydramine (229) or hydroxizine (230), two compared cetirizine with chlorphenamine (231) or ketotifen (232), and six compared loratadine with chlorphenamine (233), diphenhydramine (234), brompheniramine (235), azatadine (236), and clemastine (149, 173,

237). Five trials were done in a laboratory environment and reported only data on sedation (227, 229-231, 234).

Benefits

Results of the studies that reported comparative efficacy of new generation versus old generation oral H_1-antihistamines were inconsistent. Two studies reported similar relief in nasal symptoms (173, 228), two favoured old generation antihistamine (193, 235), and four favoured new generation antihistamine (232, 233, 236, 237), although one used a non-standard high dose of the new generation medication (237). These variable results were similar to the results of other studies with terfenedine and astemizole included in the health technology assessment by Long and colleagues (225).

Harms

In a systematic review of sedation and performance impairment of diphenhydramine and new generation oral H_1-antihistamines (226), diphenhydramine decreased performance scores in comparison with new generation H1-antihistamines to a small or moderate extent (SMD: 0.31; 95% CI: 0.17–0.45), but the results of individual studies were inconsistent. Statistically significant difference was observed for self-reported sedation, attention, and memory. A small negative effect on performance was also observed in studies comparing new generation H_1-antihistamines to placebo (SMD: 0.14; 95% CI: 0.01–0.26), but the result is imprecise and includes a negligible difference close to no effect. Significant difference was observed for self-reported sedation and approached significance for reaction time.
In addition, in the 13 studies in allergic rhinitis that we identified, all but three reported less sedation with new generation oral H_1-antihistamines. The three remaining trials were all done in children and concluded there was no difference between the two kinds of medications (231, 232, 234).

Conclusions and research needs

There appears to be a net clinical benefit from using new generation oral H_1-antihistamines compared to older ones. Although their comparative efficacy seems similar, there is likely benefit from avoiding sedation and impaired performance. Because we did not conduct our own systematic review, we based our judgements about the quality of available evidence on unsystematic examination of the available evidence.
An updated rigorously performed and reported (223, 224) systematic review of all individual new generation oral H1-antihistamines versus old generation oral H1-antihistamines that provides information on all outcomes important to patients, including adverse effects, is required for the next update of the ARIA guidelines.
The ARIA guideline panel strongly supports that new generation oral H1-antihistamines be available worldwide.

Recommendation

In patients with AR, we recommend new generation over old generation oral H_1-antihistamines (strong recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on the reduction of adverse effects, and a relatively low value on an uncertain comparative efficacy of new versus old generation oral H_1-antihistamines.

Question 13

Should oral H_1-antihistamines be used in preschool children with other allergic diseases for the prevention of wheezing or asthma?

Summary of findings

Four randomised trials addressed the question whether oral H_1-antihistamines used in children with other allergic diseases prevent development of wheezing or asthma.
Two trials evaluated the use of ketotifen in children aged <3 years that were considered at high risk of developing asthma because they had atopic dermatitis and/or at least one parent or grandparent with a history of asthma or allergy, and/or elevated serum total IgE (238, 239). Both trials were small and had limitations in the design or execution.
One trial evaluated the use of cetirizine in children <2 years of age with atopic dermatitis and at least one parent or sibling with a history of asthma or allergy (240, 241). Another trial evaluated the effect of levocetirizine on the development of asthma in a similar population of children (218, 242), but its full results have not yet been published.

Benefits

Two trials that used ketotifen found a large reduction in the risk of developing asthma after one to 3 years of treatment. The trial that used cetirizine found no effect among all children studied after 18 months treatment, and an uncertain moderate effect in a post-hoc analysis of a subgroup of children with an elevated IgE level, mainly to grass pollen or house dust mites, at baseline.

Harms

Of the trials that used ketotifen one reported three cases of sedation, one case of vomiting, and one case of alopecia in the ketotifen group, and no side effects in the placebo group; the second trial did not report adverse events. In the trial that used cetirizine there were no significant differences in adverse events between the groups except for urticaria which was less frequent in the cetirizine group(240, 241, 243).

Conclusions and research needs

Any net clinical benefit from using oral H_1-antihistamine in high risk infants in terms of preventing or delaying the development of asthma is very uncertain. Full efficacy results of the Early Prevention of Asthma in Atopic Children (EPAAC) Trial (218, 242), when published, are very likely to have important impact on this recommendation.

Recommendation

In infants with atopic dermatitis and/or family history of allergy or asthma (at high risk of developing asthma), we suggest clinicians do not administer and parents do not use oral H_1-antihistamines for the prevention of wheezing or asthma (conditional recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding side effects of oral H_1-antihistamines in infants, and a lower value on the very uncertain reduction in the risk of developing asthma or wheezing.

Remarks: The recommendation not to use oral H_1-antihistamines in these infants refers only to prevention of asthma or wheezing. The guideline panel did not consider other conditions in which these medications may be commonly used (e.g. urticaria).

Question 14

Should intranasal H_1-antihistamines be used for treatment of allergic rhinitis?

Summary of findings

One recent systematic review assessed the effect of intranasal azelastine for the treatment of allergic rhinitis (244). However, we could not use its results to inform this recommendation, since it did not include several smaller studies (245-250) and pooled results from studies in patients with non-allergic rhinitis (251) or with very different and on occasion inadequate (252-254) duration of follow-up.

We found 19 randomised trials of azelastine compared to placebo (245-250, 252-264). Four studies had inadequate duration of follow-up (2 days in seasonal allergic rhinitis and 1 week in persistent rhinitis) and we did not consider them for this recommendation (252-254, 256). Of the remaining studies all but one were done in adults with seasonal (245, 246, 250, 255, 257-262, 264) or perennial (247, 248, 263) allergic rhinitis. One study was done in children with perennial allergic rhinitis (249). No study measured quality of life.
In adults with seasonal allergic rhinitis point estimates nasal symptom scores showed from 3–30% difference favouring azelastine 0.56 mg daily and 8–30% difference favouring azelastine 1.12 mg daily. However, most studies did not report variability in results so no combined estimate could be calculated and it is impossible to assess the precision of these findings.
Three studies assessed use of azelastine in adults with perennial allergic rhinitis (247, 248, 263). One study that evaluated 19 patients used azelastine 1.12 mg daily and found a moderate effect favouring azelastine, but it did not exclude a large benefit or a small harm (effect size: -0.58, 95% CI: -1.51 to 0.35). Another study enrolled 130 patients and found no difference between the azelastine and placebo groups in nasal symptoms (data reported as graph with no variability) and the proportion of patients who rated their symptoms as improved (RB: 1.05, 95% CI: 0.80 to 1.36) (263). A third study reported that azelastine treatment was associated with the reduction in mean scores for sneezing, congestion, and rhinorrhea in selected time-points during the observation period, but it also reported the results as a graph only and did not provide any variability in results (247).
The only study performed in children with perennial allergic rhinitis enrolled 125 patients and found on average a 10–15% difference in symptoms favouring azelastine, but reported the results as a graph with no measure of variability (249). In this study children receiving azelastine were twice more likely to be rated by the investigator as improved (RB: 2.06, 95% CI: 1.38 to 3.17). (See evidence profiles 1–5 for question 14).

We did not identify any systematic review comparing other intranasal H1-antihistamines (olopatadine, levocabastine and antazoline) to placebo.

Our search for RCTs revealed two studies (published in four separate articles) done by the same group of investigators comparing olopatadine to placebo (265-268) and seven trials of levocabastine

versus placebo (269-275). We found no RCT of intranasal antazoline in patients with allergic rhinitis.

Two trials comparing olopatadine to placebo were done in adult patients with seasonal allergic rhinitis (265-268). Both studies measured quality of life with the Rhinoconjunctivitis Quality of Life Questionnaire and found that 0.6% solution of olopatadine improved quality of life by 0.45 points and 0.4% solution – by 0.35 points more than placebo compared to baseline values. However, the variability around these change estimates was not given in one trial hence it was not possible to combine their results (see evidence profile 7 and 8 for question 14). Both trials reported that symptoms of rhinitis improved more in the olopatadine treated patients compared to placebo. A mean difference in percentage change in symptom score from baseline was -11.7% (95% CI: -8.2 to -15.3) for 0.6% olopatadine compared to placebo and -8.9% (95% CI: -5.6 to -12.2) for 0.4% olopatadine compared to placebo. One additional study by the same group of investigators that was published only as an conference abstract confirmed these findings (276). Patients in the olopatadine groups were 16 to 27 times more likely to complain of bitter taste compared to placebo. Somnolence was 3 to 4 times more likely to occur in patients using olopatadine, but the estimates were very imprecise not excluding important harm or no effect.
We found only one study published as a conference abstract that investigated use of intranasal olopatadine in 924 adults with perennial allergic rhinitis (277). Authors concluded that olopatadine was superior to placebo in mean response to patient rated relief but did not provide a scale on which these were measured. Olopatadine also provided an increase in symptoms-free days compared to placebo (14.9% vs 9.5%). Epistaxis and bad/bitter taste were more common in patients receiving olopatadine.
We found one additional study published as a conference abstract that investigated use of intranasal olopatadine in 525 children aged 6–11 years with seasonal allergic rhinitis (278). Authors concluded that intranasal olopatadine 0.6% provided borderline statistically significant improvement in the overall Pediatric RQLQ and nose, practical problems and activity domains compared to placebo. However, authors reported neither estimated effects nor their precision.

All trials of intranasal levocabastine included adult patients with seasonal allergic rhinitis except for one that included also patients with non-allergic rhinitis (275). We did not consider this last trial for this recommendation, although it showed a mean difference in change from baseline of 0.9 point (0–12 point scale) indicating a small change of small clinical significance.
Of the six trials comparing intranasal levocabastine to placebo in adults with seasonal allergic rhinitis none reported quality of life. Nasal symptoms were reported inconsistently and most studies did not report measure of variation. Overall intranasal levocabastine seems to have a moderate effect on nasal symptoms (see evidence profile 6 for question 14) and probably some effect on ocular symptoms, but the reporting of results in individual studies does not allow to draw certain conclusions. Adverse events were reported inconsistently and there seemed to be no difference between the groups. Somnolence or fatigue was reported in 2.6% vs 0.6% patients receiving levocabastine compared to placebo.

Benefits

Compared to placebo, intranasal H1-antihistamines showed a small to moderate effect on nasal symptoms in adults with seasonal allergic rhinitis. However, many studies did not report variability in results and it was not possible to confidently estimate the magnitude of their effect and its precision. Quality of life was not measured in any study of intranasal azelastine and levocabastine, and it is not certain if the magnitude of effect observed in two studies of olopatadine would be important to patients.

Harms

The most frequently reported adverse effect of intranasal H1-antihistamines was unpleasant taste with azelastine and olopatadine (see evidence profiles for question 14). There is an increased risk of somnolence (see evidence profiles for question 14) with an pooled estimate of relative risk of 2.44 (95% CI: 1.22 to 4.87) over 7 studies of azelastine, 2 studies of levocabastine, and 2 studies of olopatadine. Assuming a baseline risk of somnolence of 0.5% (observed in these studies) this relative effect would translate into an absolute risk increase of 7 more patients experiencing somnolence per 1000 patients receiving intranasal H1-antihistamine (95% CI: 1–19 more per 1000).

Conclusions and research needs

A net clinical benefit of intranasal H_1-antihistamines is uncertain, because of imprecise estimates of the effects and poor reporting of many trials. Given the rare or mild adverse effects this class of agents may be beneficial in patients with seasonal allergic rhinitis.
Answering this question requires an updated rigorously performed and reported (223, 224) systematic review of all intranasal H1-antihistamines versus placebo that provides information on all outcomes important to patients, including adverse effects. Well designed and rigorously executed randomised trials of intranasal H1-antihistamines in patients with allergic rhinitis that measure and properly report (74, 75) patient-important outcomes, if done, are very likely to have important impact on this recommendation.

Recommendation

We suggest intranasal H_1-antihistamines in adults with seasonal allergic rhinitis (conditional recommendation | low quality evidence) and in children with seasonal allergic rhinitis (conditional recommendation | very low quality evidence). In adults and children with perennial/persistent AR, we suggest that clinicians do not administer and patients do not use intranasal H1-antihistamines until more data on their relative efficacy and safety is available (conditional recommendation | very low quality evidence).

Underlying values and preferences: The recommendation to use intranasal H_1-antihistamines in patients with seasonal allergic rhinitis places a relatively high value on reduction of symptoms, and a relatively low value on the risk of rare or mild side effects. The recommendation not to use intranasal H_1-antihistamines in patients with perennial/persistent allergic rhinitis places a relatively high value on their uncertain efficacy and possible side effects, and a relatively low value on possible small reduction in symptoms.

Question 15

Should new generation oral H_1-antihistamines versus intranasal H_1-antihistamines be used for treatment of allergic rhinitis?

Summary of findings

One recent systematic review assessed the relative effect of intranasal azelastine compared to new generation oral H_1-antihistamine for the treatment of allergic rhinitis (244). However, we could not use it to inform this recommendation, since it did not provide a meaningful estimate of the effect for the outcomes of interest for this guideline.

We found 9 randomised trials that compared intranasal H1-antihistamines to a new generation oral H1-antihistamines (255, 279-286). We did not consider studies that used old generation oral H1-antihistamines as well as studies that used astemizole or terfenadine as comparator, since they have been removed from the market because of adverse effects and no longer represent a therapeutic option in allergic rhinitis. An additional article (287) reported the results of the same study that we already included (282).
Seven studies compared intranasal versus oral H1-antihistamine in adults with seasonal allergic rhinitis (255, 280-284, 286), one study was done in adults with perennial allergic rhinitis (285), and one in children with perennial allergic rhinitis (279).

All studies done in adults with seasonal allergic rhinitis used azelastine as intranasal medication, except for one that used levocabastine (286). Of trials that used azelastine, four used a dose of 0.56 mg/d (255, 281, 282, 284) and two used 1.12 mg/d (280, 283). Many of these studies did not report a measure of variability in the results, thus obtaining a combined estimate of the effects was not possible. However, based on the studies that properly reported their results and on the point estimates from the other studies, it is likely that intranasal and oral H1-antihistamines have a similar effect on nasal and ocular symptoms in adults with seasonal allergic rhinitis (see evidence profile 1 for question 15). Incidence of somnolence was lower in patients receiving intranasal than in those receiving oral H1-antihistamines (RR: 0.39, 95% CI: 0.16 to 0.98). However, these results are very uncertain, because of the small number of events.

One study investigated the use of intranasal azelastine 0.56 mg/d compared to oral cetyrizine 10 mg in 40 adults with perennial allergic rhinitis (285). After 8 weeks of treatment mean total symprom score was lower in azelastine compared with cetirizine group, but authors reported neither the scale on which symptom score was measured nor the variability in these results. Rating of the efficacy of treatment by the investigators was also similar in azelastine and cetirizine treated patients (see evidence profile 2 for question 15).

One study with serious limitations compared intranasal levocabastine to oral cetirizine in children with perennial allergic rhinitis (279). This study found no difference between the two treatments but its results were very imprecise and indirect (see evidence profile 3 for question 15).

Benefits

Intranasal H1-antihistamines seem to equally effectively improve nasal and ocular symptoms as new generation oral H1-antihistamines. However, these estimates are imprecise.

Harms

Intranasal and oral H_1-antihistamines were well tolerated in these studies, but their adverse effects were reported inconsistently. The most common side effect with azelastine was bitter taste (up to 11% of patients). Somnolence was more frequent in the oral than in intranasal H1-antihistamine treated patients by the results were imprecise and it is likely that the oral H1-antihistamines differ in their potential of causing somnolence.

Conclusions and research needs

Intranasal H_1-antihistamines appear to be equally beneficial as new generation oral H_1-antihistamines in patients with allergic rhinitis. The net benefit with intranasal versus newer oral H_1-antihistamines may depend on patients' preference regarding the route of administration. There

is some evidence that patients prefer oral to intranasal medications, however this was shown in patients with migraine not in those with rhinitis (288). Intranasal H1-antihistamines may be beneficial in patients who experience somnolence while using oral medication.
Answering this question requires a rigorously performed and reported (223, 224) systematic review of all intranasal versus oral H1-antihistamines that provides information on all outcomes important to patients, including adverse effects. Well designed and rigorously executed randomised trials of intranasal versus oral H1-antihistamines in patients with allergic rhinitis that measure and properly report (74, 75) patient-important outcomes, if done, are likely to have important impact on this recommendation.

Recommendation

We suggest new generation oral H_1-antihistamines rather than intranasal H_1-antihistamines in adults with seasonal allergic rhinitis (conditional recommendation | moderate quality evidence) and in adults with perennial/persistent allergic rhinitis (conditional recommendation | very low quality evidence). In children with intermittent or persistent allergic rhinitis we also suggest new generation oral H_1-antihistamines rather than intranasal H_1-antihistamines (conditional recommendation | very low quality evidence).

Underlying values and preferences: These recommendations place a relatively high value on probable higher patient preference for oral versus intranasal route of administration as well as avoiding bitter taste of some intranasal H_1-antihistamines, and relatively low value on increased somnolence with some new generation oral H_1-antihistamines. In many patients with different values and preferences or those who experience adverse effects of new generation oral H_1-antihistamines an alternative choice may be equally reasonable.

Question 16

Should oral leukotriene receptor antagonists be used for treatment of allergic rhinitis?

Summary of findings

Three systematic reviews compared oral leukotriene receptor antagonists (LTRA) with placebo (289-291) in adults with seasonal allergic rhinitis. Two were published in 2006 (289, 291) and one in 2004 (290). Of two more recent reviews one was methodologically more sound, included trials of all LTRAs (289) and, therefore, we used this review to inform this recommendation and to create the evidence profiles. Findings of all three reviews were in agreement. Most studies were of high methodological quality. Montelukast was the LTRA used in all studies that reported outcomes considered for this recommendation.

No systematic review compared oral LTRA with placebo in patients with perennial or persistent allergic rhinitis.

Two randomised trials compared the use of oral LTRA with placebo in adults with perennial allergic rhinitis (292, 293) and one trial compared LTRA with placebo in children aged 2–6 years with perennial allergic rhinitis (294).

Benefits

In patients with seasonal allergic rhinitis oral montelukast compared to placebo reduced daytime (SMD: 0.24, 95% CI: 0.16 to 0.33) and night-time nasal symptoms (SMD: 0.23, 95% CI: 0.16 to 0.30), eye symptoms (SMD: 0.17, 95% CI: 0.08 to 0.27), and improved quality of life (SMD: 0.27, 95% CI: 0.19 to 0.34). However, the effect was small. One small trial with methodological limitations included 33 adults with seasonal allergic rhinitis and found no difference in total symptoms between zafirlukast and placebo (295).
In adults with perennial allergic rhinitis montelukast compared to placebo reduced daytime symptoms but the difference was very small and clinically negligible (292, 293). In preschool children with perennial allergic rhinitis montelukast compared to placebo moderately improved daytime symptoms, sleep at night, and quality of life, but the results were very imprecise (294).

Harms

Studies enrolling patients with seasonal or perennial allergic rhinitis showed a low incidence of adverse effects and there was no difference between treatment groups.

Conclusions and research needs

There is small net clinical benefit of oral leukotriene receptor antagonists in patients with seasonal allergic rhinitis. In patients with perennial allergic rhinitis there is a possible small benefit in preschool children but no clinically relevant benefit in adults.

Recommendation

We suggest oral leukotriene receptor antagonists in adults and children with seasonal allergic rhinitis (conditional recommendation | high quality evidence) and in preschool children with perennial allergic rhinitis (conditional recommendation | low quality evidence). In adults with perennial allergic rhinitis we suggest that clinicians do not administer and patients do not use oral leukotriene receptor antagonists (conditional recommendation | high quality evidence).

Underlying values and preferences: The recommendation to use oral leukotriene receptor antagonists in adults and children with seasonal allergic rhinitis and in preschool children with perennial allergic rhinitis places a relatively high value on their safety and tolerability, and relatively low value on their limited efficacy and high cost.

The recommendation not to use oral leukotriene receptor antagonists in adults with perennial allergic rhinitis places a relatively high value on their very limited efficacy and high cost, and relatively low value on potential small benefit in few patients.

Remarks: Evidence is available only for montelukast. This recommendation refers to the treatment of rhinitis, not to the treatment of asthma in patients with concomitant allergic rhinitis (see recommendation 45).

Question 17

Should oral leukotriene receptor antagonists versus oral H_1-antihistamines be used for treatment of allergic rhinitis?

Summary of findings

Three systematic reviews compared oral leukotriene receptor antagonists (LTRA) with oral H1-antihistamines in patients with seasonal allergic rhinitis (289-291). Of two more recent reviews one was methodologically more sound (289) and, therefore, used to create the evidence profile. Findings of all three reviews were in agreement. Most studies were of high methodological quality. Montelukast was the LTRA used in all studies.

No systematic review compared oral LTRA with oral H1-antihistamines in patients with perennial allergic rhinitis.

Three randomised trials compared the use of oral LTRA with oral H1-antihistamines in patients with perennial allergic rhinitis – two compared montelukast vs cetirizine in adults (292) and in children (294), and one compared zafirlukast vs loratadine or combined loratadine and pseudoephedrine (296).

Benefits

In patients with seasonal allergic rhinitis there was no difference between oral LTRA and oral H1-antihistamines in daytime and night-time nasal symptoms, eye symptoms, or quality of life.
In adults with perennial allergic rhinitis there was no difference between montelukast and cetirizine in standard doses in daytime and night-time symptom scores, eye symptom score, and quality of life.
In children with perennial allergic rhinitis differences in daytime and night-time symptom scores, eye symptom score, and quality of life between montelukast and cetirizine were small and inconsistent across outcomes.
Zafirlukast did not show a consistent benefit over loratadine or combined loratadine and pseudoephedrine in patients with perennial allergic rhinitis.

Harms

In studies in seasonal or perennial allergic rhinitis a low incidence of adverse effects was observed that was not different between groups. Zafirlukast has the potential for drug interactions (e.g. it increases the half-life of warfarin).

Conclusions and research needs

There is no apparent net clinical benefit of oral leukotriene receptor antagonists over oral H1-antihistamines, or vice versa, in patients with seasonal or perennial allergic rhinitis.

Recommendation

We suggest oral H_1-antihistamines over oral leukotriene receptor antagonists in patients with seasonal allergic rhinitis (conditional recommendation | moderate quality evidence) and in preschool children with perennial allergic rhinitis (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding resource expenditure.

Question 18

Should intranasal glucocorticosteroids be used for treatment of allergic rhinitis?

Summary of findings

One systematic review published in 2008 investigated the effects of mometasone fuorate nasal spray compared to placebo in patients with allergic rhinitis (297). We did not identify any systematic review of studies comparing intranasal glucocorticosteroids other than mometasone to placebo in adults.
One systematic review addressed the question of the efficacy of intranasal glucocorticosteroids in reducing the symptoms of nasal obstruction in children with intermittent and persistent allergic rhinitis, but found only three small trials in two of which the data analysis was flawed and in the third trial it was incomprehensible (298). However, this systematic review (298) excluded 17 other studies performed in children in which the use of a rescue medication was permitted. Should these studies be included in the analysis (provided that the medications were used similarly in experimental and control groups) the information on the effect of intranasal glucocorticosteroids in children could be estimated more accurately. Therefore, we did not use this review to inform this recommendation.

We found additional 117 randomised placebo-controlled trials of intranasal glucocorticosteroids other than mometasone fuorate in adults and children with allergic rhinitis (270, 299-328)(329-358)(250, 261, 272, 359-385)(263, 386-411). Despite the abundance of randomised trials, there is no systematic review comparing intranasal glucocorticosteroids other than mometasone fuorate to placebo in adults with allergic rhinitis. Therefore, we based our judgements on the systematic review of mometasone fuorate (297). We were not able to perform a complete systematic review of all individual intranasal glucocorticosteroids versus placebo for this revision of ARIA guidelines. Thus, we generalized the conclusions of the systematic review of mometasone to other intranasal glucocorticosteroids acknowledging that the evidence is indirect.

Intranasal glucocorticosteroids were also compared to other active treatments for allergic rhinitis. Two systematic reviews (412, 413) and one health technology assessment (225) compared intranasal glucocorticosteroids to oral H1-antihistamines (see Question 19), one systematic review compared them to intranasal H1-antihistamines (414) (see Question 20), and three systematic reviews compared them to oral leukotriene receptor antagonists (289-291) (see Question 21).

Benefits

Based on the systematic review of mometasone versus placebo (297), intranasal glucocorticosteroids moderately reduce nasal symptoms of congestion (SMD: 0.41 [95% CI: 0.27 to 0.56]), rhinorrhea (SMD: 0.44 [95% CI: 0.21 to 0.66]), sneezing (SMD: 0.40 [95% CI: 0.23 to 0.57]), and itching (SMD: 0.39 [95% CI: 0.25 to 0.53]) in adults with allergic rhinitis (see evidence profile 1 for question 18). The effect on nasal symptoms was similar in adults with seasonal (SMD: 0.52 [95% CI: 0.30 to 0.74) and perennial/persistent (SMD: 0.62 [95% CI: 0.41 to 0.83]) allergic rhinitis. None of the studies measured quality of life.
One study was performed in children with seasonal allergic rhinitis and found an effect of mometasone on nasal symptoms similar to that in adults (SMD: 0.41 [95% CI: 0.17 to 0.65]) (415).

Harms

In the systematic review of mometasone fuorate vs placebo the proportion of patients who experienced adverse events was similar in mometasone and placebo groups (RR: 0.99 [95% CI: 0.81 to 1.20]). Systematic reviews of other intranasal glucocorticosteroids compared to other active treatments reported low incidence of adverse effects. Epistaxis, headache, taste perversion, and pharyngitis were the most frequently reported side-effects of intranasal glucocorticosteroids in the reviews (225, 414). None of the short-term treatment studies analyzed in the reviews reported systemic side effects from intranasal glucocorticosteroids, although there has been concern that the prolonged use of intranasal glucocorticosteroids may be associated with systemic adverse effects including suppression of the hypothalamic-pituitary-adrenal axis and suppression of growth in children. Although these effects were observed in few studies we were not able to identify any systematic review to inform the assessment of the risk and its magnitude.

Conclusions and research needs

Intranasal glucocorticosteroids may be of net clinical benefit in patients with allergic rhinitis, but the overall magnitude of the effect for both desirable and undesirable effects compared to placebo is not known. However, intranasal glucocorticosteroids compared to other active treatments in allergic rhinitis show a consistent moderately better effect on nasal symptoms. Further research is needed to answer the question about the efficacy and safety of intranasal glucocorticosteroids in children. A complete rigorously performed and reported (223, 224) systematic review of all individual intranasal glucocorticosteroids versus placebo that provides information on all outcomes important to patients, including adverse effects, is required for the next update of the ARIA guidelines.

Recommendation

We recommend intranasal glucocorticosteroids for treatment of allergic rhinitis in adults (strong recommendation | high quality evidence) and suggest intranasal glucocorticosteroids in children with allergic rhinitis (conditional recommendation | moderate quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on the efficacy of intranasal glucocorticosteroids, and a relatively low value on avoiding their possible adverse effects.

Question 19

Should intranasal glucocorticosteroids versus oral H1-antihistamines be used in patients with allergic rhinitis?

Summary of findings

Two systematic reviews (412, 413) and one health technology assessment (225) addressed the relative effect of intranasal glucocorticosteroids compared to oral H1-antihistamines in patients with allergic rhinitis. We considered the two systematic reviews as outdated since they were published in 1998. The health technology assessment was published in 2002 and found 3 more randomised trials that were not included in the systematic review by Weiner et al. (412). Long et al. did not perform a formal meta-analysis, because many of the original studies did not report data on variability of the outcome estimates (225). The majority of the studies included in these reviews investigated astemizole or tefenadine – two oral H1-antihistamines that were withdrawn from the market due to their cardiotoxicity – leaving seven studies that used currently available medications.

Our search revealed four more randomised trials since the search performed by Long et al. (225) – two in children (416, 417) and two in adults with seasonal (418) and perennial allergic rhinitis (419).

Altogether 8 randomised trials were performed in adults with seasonal allergic rhinitis (one trial included also children) (418, 420-426), one in children with seasonal allergic rhinitis (417), one in adults with perennial allergic rhinitis (419), and one in children with perennial allergic rhinitis (416).

Two systematic reviews compared the use of intranasal glucocorticosteroids to oral H1-antihistamines plus oral leukotriene receptor antagonists (289, 291).

Benefits

In all studies conducted in adults with seasonal allergic rhinitis, except for one (424), intranasal glucocorticosteroids were superior to oral H1-antihistamines in relieving symptoms of rhinitis. On average the effect was moderate. Quality of life was assessed in 3 of these studies (418, 425, 426) and was found to be improved more with intranasal glucocorticosteroids, although the magnitude of effect is not possible to estimate without formal meta-analysis.
One relatively small randomised trial found that intranasal glucocorticosteroid compared to oral H1-antihistamine at least moderately reduced nasal symptoms in adults with perennial allergic rhinitis (419).
One small trial with serious methodological limitations and imprecise results showed that intranasal glucocorticosteroid may improve nasal symptoms and short-term memory compared to oral H1-antihistamine in children aged 8–17 years with seasonal allergic rhinitis (417). A very small trial showed improvement in nasal symptoms with intranasal glucocorticosteroid compared to oral H1-antihistamine in children 2–4 years of age with perennial rhinitis (416).
In randomised trials that compared intranasal glucocorticosteroid to combined oral H1-antihistamine plus oral leukotriene receptor antagonist there was no difference in nasal symptoms except for a possible effect of intranasal glucocorticosteroids on nasal congestion, but the results were very imprecise.

Harms

There were no major adverse effects reported in the included studies. Minor adverse effects were headache and pharyngitis that were inconsistent across the studies. In one study that used chlorphenamine sedation and dry mouth were most frequently reported adverse effects of an oral H1-antihistamine (420).

Conclusions and research needs

Intranasal glucocorticosteroids may be of net clinical benefit compared to oral H1-antihistamines in adults with seasonal and perennial allergic rhinitis. There is very little and low quality evidence, that there also may be a net benefit from intranasal glucocorticosteroids compared to oral H1-antihistamines in children.
A complete rigorously performed and reported (223, 224) systematic review of intranasal glucocorticosteroids versus oral H1-antihistamines that provides information on all outcomes important to patients, including adverse effects, is required for the next update of the ARIA guidelines.

There is a need for well designed and rigorously executed (74, 75) trials measuring patient-important outcomes in adults with persistent allergic rhinitis and in children.

Recommendation

In patients with seasonal AR, we suggest intranasal glucocorticosteroids over oral H_1-antihistamines in adults (conditional recommendation | low quality evidence) and in children (conditional recommendation | very low quality evidence). In patients with perennial/persistent AR, we suggest intranasal glucocorticosteroids over oral H_1-antihistamines in adults (conditional recommendation | moderate quality evidence) and in children (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on the likely higher efficacy of intranasal glucocorticosteroids. In many patients with strong preference for oral versus intranasal route of administration an alternative choice may be reasonable.

Question 20

Should intranasal glucocorticosteroids versus intranasal H_1-antihistamines be used in patients with allergic rhinitis?

Summary of findings

Two systematic reviews assessed the relative efficacy of intranasal glucocorticosteroids compared to intranasal H1-antihistamines in patients with allergic rhinitis (414, 427, 428). After evaluating the methodological quality of the reviews, we used the review by Yáñez and Rodrigo (414) to prepare the summary of evidence, but the results of both reviews were consistent providing similar results with the same clinical interpretation.
We identified one additional small randomised trial evaluating the relative effect of intranasal mometasone compared to intranasal levocabastine published since the search for these systematic reviews was done (429).

Benefits

In nine studies included in this review (414) that enrolled 648 subjects intranasal corticosteroids moderately more reduced total nasal symptoms (SMD: -0.36, 95% CI: -0.57 to -0.14), (SMD: 0.41, 95% CI: -0.57 to -0.24), rhinorrhea (SMD: 0.47, 95% CI: -0.64 to -0.29), itching (SMD: 0.38, 95% CI: -0.56 to -0.19), and nasal blockage (SMD: -0.86, 95% CI: -1.07 to -0.64) compared with intranasal H1-antihistamines. There was no difference between the treatments for ocular symptoms and nasal congestion. However, for ocular symptoms two studies that compared intranasal corticosteroid to azelastine showed greater benefit from intranasal corticosteroid (261, 307) and two studies using levocabastine as comparator showed small benefit from H1-antihistamine (272, 274). One additional study that we identified confirmed these findings (429).

Harms

A low incidence of adverse effects was observed and there was no difference between groups. Most adverse events were rated as mild or moderate. The most frequently reported adverse events were respiratory symptoms, headache, epistaxis, and taste perversion with intranasal H1-antihistamines.

Conclusions and research needs

Treatment with intranasal glucocorticosteroids compared to intranasal H1-antihistamines is of net clinical benefit.

Recommendation

In patients with AR, we recommend intranasal glucocorticosteroids rather than intranasal H_1-antihistamines (strong recommendation | high quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on efficacy of intranasal glucocorticosteroids, and a relatively low value on their rare adverse effects.

Question 21

Should intranasal glucocorticosteroids versus oral leukotriene receptor antagonists be used for treatment of allergic rhinitis?

Summary of findings

Three systematic reviews compared intranasal glucocorticosteroids with oral leukotriene receptor antagonists (LTRA) in patients with seasonal allergic rhinitis (289-291). Two were published in 2006 (289, 291) and one in 2004 (290). Of two more recent reviews one was methodologically more sound (289) and therefore was used to create evidence profile. Findings of all three reviews were in agreement. Most studies were of high methodological quality. Montelukast was the LTRA used in all studies.

No systematic review or randomised trial compared intranasal glucocorticosteroids with oral LTRA in patients with perennial allergic rhinitis.

Two systematic reviews reported information on adverse effects of intranasal glucocorticosteroids, but none reported quantitative data allowing estimating the magnitude of the risk (225, 414).

Benefits

Intranasal glucocorticosteroids compared to oral LTRA moderately reduced daytime and night-time nasal symptoms in patients with seasonal allergic rhinitis. No trial reported data on quality of life.

Harms

Low incidence of adverse effects was observed in patients taking oral LTRA, and there was no difference compared to placebo (289, 292, 293).
Systematic reviews of intranasal glucocorticosteroids reported low incidence of adverse effects – epistaxis, headache, taste perversion, and pharyngitis were the reported side-effects of intranasal glucocorticosteroids in the systematic reviews (225, 414). None of the short-term treatment studies included in the reviews reported systemic side effects from intranasal glucocorticosteroids.

Conclusions and research needs

There appears to be net clinical benefit of intranasal glucocorticosteroids over oral LTRA in patients with seasonal allergic rhinitis. Intranasal glucocorticosteroids are more efficacious, but they may have more adverse effects.

There is a need for rigorously designed and executed randomised trials of intranasal glucocorticosteroids versus oral LTRA in adults and children with seasonal allergic rhinitis that measure and properly report (74, 75) patient-important outcomes, including adverse effects.
A rigorously performed and reported (223, 224) systematic review of adverse effects of intranasal glucocorticosteroids, especially in children, is required.

Recommendation

In patients with seasonal allergic rhinitis we recommend intranasal glucocorticosteroids over oral leukotriene receptor antagonists (strong recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a high value on the efficacy of intranasal glucocorticosteroids.

Remarks: Evidence is available for montelukast only.

Question 22

Should oral glucocorticosteroids be used for treatment of allergic rhinitis in patients not responding to other therapy?

Summary of findings

We could not identify any systematic review, randomised trial, or controlled observational study that evaluated the use oral glucocorticosteroids in patient with allergic rhinitis not responding to other therapy.

Two randomised trials compared oral glucocorticosteroids in patients with allergic rhinitis, but one investigated the efficacy of different doses of methylprednisolone versus placebo in patients not treated with other medications (430), and the other compared prednisone 7.5 mg for 3 weeks with single intramuscular injection of betamethasone diproprionate also in patients not treated with other medications (431).

Benefits

In one of these studies oral methylprednisolone was significantly more effective than oral placebo (430) and in the other prednisone was equally effective in relieving symptoms as single intramuscular injection of betamethasone for three weeks (431). Systemic glucocorticosteroids, in contrast to intranasal treatment, reach all parts of the nose and the paranasal sinuses. Based on unsystematic observations, short courses of oral glucocorticosteroids in patients with severe perennial rhinitis or nasal polyps can be helpful.

Harms

Long-term treatment with oral glucocorticosteroids is associated with severe side effects. There is however little evidence that short-term is harmful. Two systematic reviews of treatment of acute asthma with systemic corticosteroids (432, 433) found that side effects were reported as being ~~"r~~are" in most studies and were similar in frequency in both groups receiving or not receiving systemic glucocorticosteroids (see recommendation 23).

Conclusions and research needs

Short courses of oral glucocorticosteroids may be of net clinical benefit in patients with allergic rhinitis not responding to other therapy, but the benefit is very uncertain and is based on unsystematic clinical observations. Well designed and rigorously executed randomised trial of short course of oral glucocorticosteroids in patients with allergic rhinitis not responding to other therapy that measure and properly report (74, 75) patient-important outcomes is needed. If done, it is very likely to have important impact on this recommendation.

Recommendation

In patients with allergic rhinitis and moderate to severe nasal and/or ocular symptoms that are not controlled with other treatments, we suggest short course of oral glucocorticosteroids (conditional recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on possible relief of severe symptoms, and a relatively low value on avoiding possible side effects of a short course of oral glucocorticosteroids.

Remarks: Systemic glucocorticosteroids should not be considered as a first line of treatment for AR. They can be used for few days as a last resort of treatment when combinations of other medications are ineffective. Oral glucocorticosteroids should be avoided in children, pregnant women, and patients with known contraindications.

Question 23

Should intramuscular glucocorticosteroids be used for treatment of allergic rhinitis?

Summary of findings

One recent systematic review reported 11 randomised trials and 7 case series of using intramuscular (i.m.) glucocorticosteroids in adults with seasonal allergic rhinitis (434). Included trials compared i.m. glucocorticosteroids to placebo in 5 trials, or other glucocorticosteroid – intranasal (2 trials), oral (1 trial), or other intramuscular (6 trials). Studies included altogether 1362 patients that were included in safety analysis. No study included children. All studies were conducted between the year 1960 and 1988. Majority of studies used single doses of i.m. glucocorticosteroid corresponding to 80 mg of methylprednisolone (equivalent to 100 mg oral prednisone).

Three other systematic reviews included trials of i.m. glucocorticosteroids in adults for early emergency department treatment of acute asthma (432), for preventing relapse following acute exacerbations of asthma (433), and investigating the risk of avascular joint necrosis associated with glucocorticosteroid use (435). These were also used to assess safety of single injection of i.m. glucocorticosteroid.

No systematic review or randomised trial assessed the use of i.m. glucocorticosteroids in children with allergic rhinitis. Three systematic reviews assessed studies of intramuscular glucocorticosteroids used in children hospitalised with acute asthma (3 trials, 103 children) (436), prevention and treatment of post-extubation stridor (2 trials, 89 children; adverse events were did

not measured) (437), and for improving recovery following tonsillectomy (9 studies, 695 children) (438). Data from these reviews were used to assess safety in children.

Benefits

Single injection of an intramuscular glucocorticosteroid at a dose corresponding to 80 mg of methylprednisolone (equivalent of 100 mg oral prednisone) significantly reduces nasal symptoms throughout the pollen season compared to placebo. In two trials that compared single injection of i.m. glucocorticosteroid (2 or 5 mg betamethasone disodium phosphate or 80 mg methylprednisolone) were superior to intranasal beclomethasone 100 µg twice daily in one study, and equally effective when compared to intranasal budesonide 400 µg once daily (with increased use of supplementary medicines in the nasal steroid group). Quality of life was not measured in any of the included studies. There is a benefit of convenience of one drug injection compared to regular daily use of other medications.

Harms

In five trials that compared i.m. glucocorticosteroid to placebo all reported clinical side effects were considered minor. There was no statistically significant difference in side effects between the groups, not even in one study in which three consecutive i.m. injections of 80 mg methylprednisolone were given at weekly intervals. Altogether in randomised trials and in case series of patients receiving i.m. glucocorticosteroid no side effects or miscellaneous minor side effects were reported in a few participants. Reported adverse effects were pain at the site of injections, menstrual irregularities, flushing, tiredness, nervousness, and blue skin marks. Subcutaneous irritations with slight atrophy in 1.5% out of 949 injections were reported in one study. One series of eight cases showed peptic ulcer symptoms, peripheral cramps, or uveitis in three of the participants (434).
In addition, a systematic review of avascular joint necrosis found that while risk is associated with increased daily glucocorticosteroid dosage, no increased risk was observed with single bolus dosing (435). Two systematic reviews of early emergency department treatment of acute asthma with systemic corticosteroids (432) and use of systemic glucocorticosteroids for preventing relapse following acute exacerbations of asthma (433) found that side effects were reported as being ~~"r~~are" in most studies and were similar in frequency in both groups.

None of three trials in children hospitalised with acute asthma formally addressed the issue of safety although all authors suggested that short courses of steroids were safe when used to treat acute exacerbations of asthma. Nine trials in children following tonsillectomy used dexamethasone in doses ranging from 0.15 to 1.0 mg/kg (maximum dose range = 8 to 25 mg). No adverse events attributable to dexamethasone were reported in these trials. Authors of the systematic review have additionally stated that ~~"i~~n their 10-year experience of routine use of intravenous dexamethasone during paediatric tonsillectomy (approximately 800 per year), there have been no attributable, adverse events". Authors have also not found any reports in the literature of complications from use of intravenous dexamethasone during paediatric tonsillectomy.

Conclusions and research needs

Net clinical benefit of intramuscular glucocorticosteroids compared to other treatment of allergic rhinitis in adults with seasonal allergic rhinitis is unlikely. Clinical importance of adverse effects and complications of intramuscular glucocorticosteroid injections, no matter how infrequent they are, seem to outweigh the importance of any burden of the symptoms of allergic rhinitis. Evidence for both benefit and harms in adults is of low quality. There is no evidence of use of intramuscular

glucocorticosteroids for allergic rhinitis in children. Further research is unlikely, because of ethical considerations.

Recommendation

In patients with AR, we recommend that clinicians do not administer intramuscular glucocorticosteroids (strong recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding possible side effects of a single or multiple injections of intramuscular glucocorticosteroids, and relatively low value on their efficacy and convenience of use.

Remarks: Possible side effects of intramuscular glucocorticosteroids may be far more serious than the condition they are supposed to treat (*i.e.* AR).

Question 24

Should intranasal chromones be used for treatment of allergic rhinitis?

Summary of findings

One systematic review reporting 25 studies (427, 428) and one health technology assessment reporting 32 studies (225) assessed the relative efficacy of intranasal chromones compared placebo in patients with seasonal or perennial allergic rhinitis. Authors of the health technology report did not perform a formal meta-analysis, because many studies did not report data on variability of the outcome estimates.

Benefits

In all trials reviewed by Long and colleagues (225), except for two, significant improvement in symptoms of rhinitis were observed in patients treated with chromones compared to placebo. In 16 of the studies, at least three of the five common symptoms associated with allergic rhinitis (nasal itch, sneezing, rhinorrhea, nasal congestion, or postnasal drip) were significantly improved by treatment with a chromone compared to placebo. Frequently one of the nonresponsive symptoms was congestion. In 17 of 18 studies (14 of seasonal and 4 of perennial allergic rhinitis) that reported patient preference for or patient willingness to use the medication in the future there was a clear-cut preference for the chromone. Overall, in the report by Long and colleagues (225) chromones were effective for reducing symptoms associated with allergic rhinitis, although the magnitude of the effect and its precision cannot be assessed without meta-analysis. Authors concluded, that chromones seemed to have higher efficacy in seasonal than in perennial allergic rhinitis. Higher doses (including higher frequency of dosing) seemed to be more effective.

In the systematic review by Lange and Bachert (427, 428) the risk of therapy failure as judged by the patients was lower when intranasal chromones were used instead of placebo (17 trials, 2299 patients; relative risk: 0.52, 95% CI: 0.38 to 0.70). Nasal symptoms were also improved with chromones compared to placebo (9 trials, 1036 patients; SMD: -0.26, 95% CI: -0.41 to -0.12).

Harms

In the trials included in the report by Long and colleagues (225) no major adverse events were reported. Minor side effects included a high frequency of nasal irritation (18/29 studies), headache, and nasal congestion.

Conclusions and research needs

Despite its limited efficacy, treatment with intranasal chromones may be of net clinical benefit for some patients because of mild side effects. We concluded that overall quality of evidence supporting the use of intranasal chromones in allergic rhinitis is moderate, since most included studies had important methodological limitations.

Recommendation

In patients with AR, we suggest intranasal chromones (conditional recommendation | moderate quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on excellent safety and tolerability of intranasal chromones, and relatively low value on their limited efficacy and on limiting resource expenditure.

Remarks: The need for administration 4 times daily is likely to reduce patient adherence and reduce efficacy.

Question 25

Should intranasal H_1-antihistamines versus intranasal chromones be used for treatment of allergic rhinitis?

Summary of findings

One systematic review reporting 4 studies and 332 patients assessed the relative efficacy of intranasal H_1-antihistamines compared to intranasal chromones (427, 428).

One additional randomised trial including 82 patients evaluated relative efficacy of levocabastine and disodium cromoglycate in patients with seasonal allergic rhinitis (429).

Benefits

The risk of therapy failure as judged by the patients was lower when using intranasal H_1-antihistamines compared to intranasal chromones (relative risk: 0.46, 95% CI: 0.31 to 0.68). Nasal symptoms and other efficacy data could not be summarised due to the lack of usable data, but studies showed that intranasal H_1-antihistamines were either more effective or similarly effective in relieving rhinitis symptoms compared to chromones; no study favoured chromones (428). One additional small trial showed no difference in symptom scores between levocabastine and cromoglycate, but it was designed to compare intranasal mometasone with levocabastine and placebo, and could be underpowered to show a small difference.

Harms

Adverse effects were inconsistently reported. There seemed to be no difference in adverse effects between the groups and they were usually confined to mild local reactions.

Conclusions and research needs

There may be a small net clinical benefit of intranasal H_1-antihistamines over intranasal chromones in patients with allergic rhinitis. We concluded that overall quality of evidence supporting the use of intranasal H_1-antihistamines over intranasal chromones in allergic rhinitis is low, since studies had important methodological limitations and the results were imprecise.

Recommendation

In patients with AR, we suggest intranasal H_1-antihistamines over intranasal chromones (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on possibly higher efficacy of intranasal H_1-antihistamines, and relatively low value on safety and tolerability of intranasal chromones.

Remarks: Chromones require administration 4 times daily that may limit patient adherence to treatment and reduce efficacy.

Question 26

Should intranasal ipratropium bromide be used for treatment of allergic rhinitis?

Summary of findings

We were not able to identify any systematic review assessing the use of intranasal ipratropium bromide in treatment of allergic rhinitis.

We found six randomised trials comparing intranasal ipratropium bromide to placebo that included adults with perennial allergic rhinitis (439-441) and mixed populations with allergic and non-allergic rhinitis – both adults (442, 443) and children (444).

One study compared intranasal ipratropium bromide to intranasal glucocorticosteroid in children (445).

Benefits

All trials found that ipratropium effectively controlled rhinorrhea. In one study combined use of ipratropium bromide nasal spray with beclomethasone dipropionate nasal spray was more effective in controlling rhinorrhea than either treatment alone (443). In another study in school children with allergic and non-allergic perennial rhinitis ipratropium bromide nasal spray was as effective as beclomethasone dipropionate nasal spray in controlling rhinorrhea and provided some relief from congestion (445).

Harms

There were no serious adverse events in these studies. Some patients complained of dry nose but there was no difference in from placebo.

Conclusions and research needs

Intranasal ipratropium bromide may be of net clinical benefit in patients with perennial allergic rhinitis in controlling rhinorrhea. In the absence of a systematic review, we judged the overall quality of the evidence supporting this recommendation as moderate, since most trials were old and had some limitations, and there is uncertainty about the magnitude of the effect and its precision.

Recommendation

In patients with perennial AR, we suggest intranasal ipratropium bromide for treatment of rhinorrhea (conditional recommendation | moderate quality evidence).

Remarks: Intranasal ipratropium bromide is effective for rhinorrhea. It is unlikely to be beneficial for other symptoms of AR.

Question 27

Should intranasal decongestant be used for treatment of allergic rhinitis?

Summary of findings

We were unable to identify any systematic reviews or randomised trials of intranasal decongestants in patients with allergic rhinitis.

We were also unable to identify any randomised trials comparing intranasal decongestants to placebo or to oral decongestants in allergic rhinitis. One clinical trial evaluated the effect xylometazoline nasal spray compared to cetirizine plus pseudoephedrine on nasal congestion in patients with persistent allergic rhinitis, but it used allergen challenge test and nasal cavity photographs to evaluate the results (446).

We did not search for observational studies evaluating intranasal decongestants for allergic rhinitis for this revision of the ARIA guidelines.

We found one systematic review of intranasal decongestants for the common cold (447), but we judged the evidence to be too indirect to inform this recommendation. We used it only to estimate the risk of harm.

Benefits

There are unsystematic observations that intranasal decongestants are modestly effective in the treatment of nasal obstruction in acute allergic and non-allergic rhinitis when used as rescue medications for up to three to five days. However, they seem not to improve other symptoms.

Harms

Systematic review of 7 trials in 740 adults (six studies assessed a single dose and three – multiple doses) found no serious side effects of intranasal decongestants (447). Insomnia occurred in 5% of participants receiving intranasal decongestant and was more likely to occur with pseudoephedrine (odds ratio: 6.18, 95% CI: 1.38 to 27.66). Headache and hypertension occurred in less than 4% of patients and did not differ from placebo.
However, there is a concern that a prolonged use of intranasal decongestants for more than three to five days may lead to rebound swelling of the nasal mucosa and to drug-induced rhinitis (*rhinitis medicamentosa*)(448-450).

Conclusions and research needs

Net clinical benefit of intranasal decongestants in treatment of allergic rhinitis is very uncertain. There may be a net clinical benefit from prompt relief of nasal obstruction with a short course of intranasal decongestant administered along with other medications. However, there is concern about safety of intranasal decongestant when inappropriately used for more than three to five days.
Well designed and rigorously executed randomised trial of an intranasal decongestant versus placebo in patients receiving other medications for allergic rhinitis that measure and properly report (74, 75) all patient-important outcomes is needed. If done, it is likely to have an important impact on this recommendation.

Recommendation

In adults with allergic rhinitis and severe nasal obstruction, we suggest very short course (not longer than five days and preferably shorter) of intranasal decongestant while co-administering other drugs (conditional recommendation | very low quality evidence). We suggest that clinicians do not administer and parents do not use intranasal decongestants in preschool children (conditional recommendation | very low quality evidence).

Underlying values and preferences: The recommendation for use of a very short course of an intranasal decongestant in adults with allergic rhinitis places a relatively high value on the prompt relief of nasal obstruction, and relatively low value on avoiding the risk of adverse effects with a prolonged use of intranasal decongestant.

The recommendation against the use of an intranasal decongestant in children and against long-term use in adults places a relatively high value on avoiding the risk of serious adverse effects, and relatively low value on a possible benefit from a reduced nasal blockage.

Question 28

Should oral decongestant be used for treatment of allergic rhinitis?

Summary of findings

One recent systematic review assessed the efficacy and safety of oral phenylephrine (451), but only two of the 15 studies were done in populations that may have included patients with allergic rhinitis, so no information on efficacy could inform this recommendation.

One systematic review assessed the effect of pseudoephedrine on blood pressure and heart rate (452).

No systematic review investigated use of oral decongestant in patients with allergic rhinitis.

We found four randomised trials that directly compared pseudoephedrine to placebo in patients with seasonal allergic rhinitis (453-456). None of these studies reported measures of variation in the symptom scores so it was not possible to combine their results. In all trials patients used pseudoephedrine regularly; no study investigated its use as a rescue medication.
No randomised trial assessed quality of life, the effect of oral decongestant in persistent or perennial allergic rhinitis, or use of oral decongestant in children.

Benefits

Results of all four studies point towards the small benefit from pseudoephedrine compared to placebo in relieving symptoms in patients with allergic rhinitis, although the exact magnitude of the effect and the precision of estimate are unknown. Response to treatment evaluated by physicians was fair on average both in patients receiving pseudoephedrine or placebo, with more patients taking pseudoephedrine judged to have excellent or good response, although the results were imprecise and included no difference.

Harms

In two of the four studies adverse events were reported by more patients taking pseudoephedrine with insomnia and dry mouth being the most pronounced side effects. In the other two studies it was not possible to estimate the difference in adverse events between pseudoephedrine and placebo.

Two systematic reviews found small increase in systolic blood pressure with phenylephrine 15 mg (2.7 mm Hg; 95% CI: 1.6 to 3.7), and with pseudoephedrine immediate-release formulations (1.53 mm Hg; 95% CI: 0.49–2.56), but not with sustained-release formulations (–0.98 mm Hg; 95% CI: –2.44 to 0.47).

Conclusions and research needs

Net clinical benefit from regular use of oral decongestants alone in seasonal allergic rhinitis is unlikely. Although there are no published reports supporting the use of oral decongestants alone as a rescue or ~~–as~~ needed" medication it may be of benefit for some patients.
Well designed and rigorously executed randomised trial of oral decongestant used as a rescue meditation versus placebo that measure and properly report (74, 75) all patient-important outcomes is needed. If done, it is likely to have an important impact on this recommendation.

Recommendation

In patients with AR, we suggest that clinicians do not administer and patients do not use oral decongestants regularly (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding adverse effects of oral decongestants, and a relatively low value on possible small reduction in symptoms of rhinitis.

Remarks: Oral decongestants may be of benefit for some patients as a rescue or ~~–as~~ needed" medication.

Question 29

Should combination of oral decongestant and H_1-antihistamine versus oral H1-antihistamine alone be used for treatment of allergic rhinitis?

Summary of findings

One health technology assessment reporting 13 studies compared the combination of an oral H1-antihistamine with pseudoephedrine to oral H1-antihistamine alone in patients with seasonal and/or perennial allergic rhinitis (457).

We identified three additional randomised trials that have been published since the literature search for the review by McCrory and colleagues was done. All compared a combination of desloratadine plus pseudoephedrine with desloratadine alone in patients with seasonal allergic rhinitis (458-460).

Benefits

Trials included in the systematic review and subsequently published studies found a consistent small added benefit of combination of an oral H_1-antihistamine with pseudoephedrine compared to oral H1-antihistamine alone in relieving nasal symptoms other than congestion as well as nasal congestion. Quality of life was not assessed in any of the studies.

Harms

Reporting of adverse events in the older studies was inconsistent. Overall headache seemed the most common adverse event reported in both groups. Commonly reported in H_1-antihistamine group was somnolence, and in combination group: also somnolence, dry mouth, and insomnia.
In three trials of desloratadine not included in the systematic review adverse events, in particular somnolence, insomnia, and dry mouth, were more frequent in the combination group compared to oral H1-antihistamine alone, but the results were imprecise.

Conclusions and research needs

Net clinical benefit from regular use of a combination of oral H_1-antihistamine and decongestant compared to oral H_1-antihistamine alone in allergic rhinitis is uncertain. Small improvement in nasal symptoms seems counterbalanced with increased risk of adverse effects.
We could not identify any published reports of using a combination of oral H_1-antihistamine and a decongestant as a rescue or ~~"a~~s needed" medication, which theoretically might have reduced the burden of adverse effects compared to regular use. Hence, the ARIA guideline panel felt ~~"u~~ncertain" about the effect of using a combination of these medications in patient with allergic rhinitis.
Well designed and rigorously executed randomised trials of a combination of oral H1-antihistamine and an oral decongestant used as a rescue meditation versus oral H1-antihistamine alone that measure and properly report (74, 75) patient-important outcomes are needed. If done, they are likely to have an important impact on this recommendation.

Recommendation

In patients with AR, we suggest clinicians do not administer and patients do not use regularly a combination of oral H_1-antihistamine and an oral decongestant, compared to oral H_1-antihistamine alone (conditional recommendation | moderate quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding adverse effects of oral decongestant, and a relatively low value on small additional reduction in symptoms of rhinitis.

Remarks: In adults with symptoms not controlled with oral H_1-antihistamine alone who are less averse to side effects of oral decongestants an alternative choice may be equally reasonable. Administration of a combined treatment as a rescue medication may also be beneficial to some patients.

Question 30

Should intraocular H_1-antihistamines be used for the treatment of ocular symptoms in patients with allergic rhinitis?

Summary of findings

One systematic review reporting 9 studies assessed the efficacy of intraocular H_1-antihistamines for treatment of allergic conjunctivitis (461). However, all except for two of included studies investigated topical H_1-antihistamines with allergen provocation tests. Moreover, many other trials were published since this review was done, so we could not use it to inform this recommendation.

We found seventeen placebo-controlled randomised trials that investigated intraocular H1-antihistamines in patients with allergic conjunctivitis. Six trials investigated two H1-antihistamines giving 23 comparisons. Seven trials investigated azelastine (462-468), one – epinastine (469), two – ketotifen (470, 471), nine – levocabastine (462, 463, 468, 469, 471-475), and four –olopatadine (470, 476-478). All studies enrolled adults and/or adolescents, and only one was done in children (468). Trials investigated patients with seasonal allergic conjunctivitis or rhinoconjuncivitis except for two that included patients with perennial allergic conjunctivitis (462, 467). No study was done explicitly in patients with allergic rhinitis.
Studies were of variable methodological quality. Most trials showed a consistent benefit from intraocular H1-antihistamines, but many did not report the measures of variation in the results, therefore a formal meta-analysis was not possible. No study reported quality of life.

Benefits

Based on patients' assessment, intraocular H1-antihistamines compared to placebo consistently improved ocular itching and redness, and had variable effect on other symptoms. None of the studies assessed quality of life. There is uncertainty about the effect of intraocular H1-antihistamines in patients with allergic rhinitis who already use other treatment for rhinitis, because in most studies concomitant treatment of rhinitis was not allowed.

Harms

Adverse events were reported variably. Application site reaction was the most frequent adverse effect reported. Based on the reported results it was three times more frequent with azelastine than with placebo, borderline statistically significantly more frequent with levocabastine than with placebo, and equally frequent with ketotifen, epinastine, olopatadine, and placebo. Azelastine caused taste perversion in 10–20% of patients.

Conclusions and research needs

Intraocular H1-antihistamines may be of net clinical benefit in patients with allergic rhinitis who have ocular symptoms, although in the absence of an up-to-date systematic review, poor reporting of results, and no information on quality of life the balance between desirable and undesirable effects is uncertain. We concluded overall quality of evidence supporting this recommendation to be low, because of important limitations in study execution and reporting, and uncertainty about how the results apply to patients with allergic rhinitis and concomitant ocular symptoms as opposed to patients with allergic conjunctivitis that were included in clinical trials. There is almost no information on the effect of intraocular H1-antihistamines in children.
A complete rigorously performed and reported (223, 224) systematic review of all intraocular H1-antihistamines versus placebo in patients with allergic rhinitis and ocular symptoms that provides information on all outcomes important to patients, including adverse effects, is required for the next update of the ARIA guidelines.

Recommendation

In patients with allergic rhinitis and symptoms of conjunctivitis, we suggest intraocular H_1-antihistamines (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on consistent effectiveness of intraocular H_1-antihistamines, and relatively low value on their side effects and uncertain effectiveness in patients already using other medications for AR.

Remarks: Only one study was done in children.

Question 31

Should intraocular chromones be used for treatment of ocular symptoms in patients with allergic rhinitis?

Summary of findings

One systematic review(461) reporting 13 randomised trials examined the difference between the use of intraocular sodium cromoglycate or nedocromil sodium compared to placebo.
Since the literature search for this systematic review had been done one additional trial was published that compared sodium cromoglycate to placebo in allergic conjunctivitis(465).
No trials were identified directly comparing one chromone with another.

Benefits

Sodium cromoglycate and nedocromil sodium when compared to placebo improved a variety of subjective symptoms (ocular itching, burning, soreness, and lacrimation), but the results of trials were inconsistent and poorly reported not allowing for a formal meta-analysis. Patients using intraocular sodium cromoglycate were 1.6 to 7 times more likely to perceive benefit than those using placebo, but the authors of a systematic review suggested a likelihood of publication bias in these studies. Adults using intraocular nedocromil sodium were 1.2 to 1.8 times more likely to perceive a benefit than those using placebo and there was no evidence of clinical benefit in one small trial that included only children.

Harms

No important side effects were reported with the sodium cromoglycate treatment. There was an unpleasant taste reported immediately after instillation of the nedocromil sodium.

Conclusions and research needs

Despite its limited effectiveness treatment with intraocular chromones may be of net clinical benefit because of no adverse effects and very mild side effects.

Recommendation

In patients with allergic rhinitis and symptoms of conjunctivitis, we suggest intraocular chromones (conditional recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on excellent safety and tolerability of intraocular chromones and relatively low value on their limited effectiveness.

Remarks: In adults and children with limited ocular symptoms, chromones may be tried first because of their excellent safety and tolerability. Chromones require administration 4 times daily that may limit patient compliance with treatment and reduce efficacy.

Specific allergen immunotherapy for allergic rhinitis

Question 32

Should subcutaneous specific immunotherapy be used for treatment of allergic rhinitis in adults without concomitant asthma?

Summary of findings

One systematic review (479) assessed the efficacy of allergen specific subcutaneous immunotherapy (SCIT) for seasonal allergic rhinitis and one health technology assessment (457) assessed its efficacy in both seasonal and perennial allergic rhinitis.

Additional review of the literature done by the ARIA group members (28) identified 2 more randomised trials of SCIT in adults with perennial allergic rhinitis and/or asthma that were published since the literature search for the systematic review by McCrory and colleagues (457) was done.

We used information from the systematic review by Calderon and colleagues (479) to prepare summaries of evidence for SCIT in seasonal allergic rhinitis and we described the findings of the remaining studies in perennial allergic rhinitis.

McCrory and colleagues found 12 randomised trials of SCIT in perennial allergic rhinitis of which 5 had very serious limitations in design and execution, and there was very serious uncertainty about directness of the intervention, so they were excluded by the authors of the review. Of the remaining trials SCIT with house dust mite allergen was assessed in four (251 patients enrolled, 205 evaluated,

11 children under 12 years of age), and cat (n = 28), latex (n =17), and *Alternaria* (n = 24) were assessed in one trial each. Range of treatment duration was 10 to 18 months.

Benefits

Systematic review of the studies in seasonal allergic rhinitis showed a consistent small to large effect of SCIT compared to placebo on the symptoms of allergic rhinitis, ocular symptoms, and quality of life. It also showed a reduction of medication use for control of allergic rhinitis.

All trials that used house dust mite allergens reported significant improvement in nasal symptoms, although the actual magnitude of the effect is not known without a meta-analysis. Trial that used cat, and mould allergens also reported improvement in nasal symptoms, but one small trial of SCIT with natural rubber latex had inconsistent results.

Harms

In a systematic review of the studies in seasonal allergic rhinitis no fatal events were reported in any of the studies.
There were 834 local reactions not requiring treatment in 907 patients in the SCIT group and 227 events in 697 patients in the placebo group. There were 21 local reactions requiring treatment in 208 patients in the SCIT group and eight events in 186 patients in the placebo group.
Early (occurring in less than 30 minutes) mild systemic reaction – mild rhinitis and/or asthma (PEFR over 60% of predicted or of the personal best values) – responding adequately to antihistamine or inhaled β_2-agonist): there were 154 events among 706 patients in the SCIT group and 44 events among 566 patients in the placebo group.
Early non-life-threatening systemic reaction – urticaria, angioedema, or severe asthma (PEFR under 60% of predicted or of personal best values) responding well to treatment: there were 43 events among 615 patients in the SCIT group and three events among 463 patients in the placebo group.
There were 458 late (>30 minutes) systemic reactions among 514 patients in the SCIT group and 148 events among 412 patients in the placebo group.
There were three anaphylactic shocks among 417 patients in the SCIT group and one among 303 patients in the placebo group.
Adrenaline had been used in 19 times per 14,085 injections in the SCIT group and once per 8278 injections in the placebo group.

In studies of SCIT in allergic rhinitis due to house dust mites local injection site reactions occurred in 30% to 90% of patients receiving active immunotherapy and 0% to 33% of those receiving placebo, although only two studies reported them. Systemic reactions were reported in 3 studies: one stated there were three systemic reactions of which one required use of adrenaline not specifying in which group (33 patients in the study), another reported no anaphylaxis and 3% vs 1% systemic reactions in treated and placebo groups respectively, and in the third one (n = 72) there were 3 vs 0 cases of anaphylaxis and 18 vs 6 asthma exacerbations in the SCIT and placebo groups. Need for hospitalization or death were not reported.
In the trial of SCIT with cat allergen there were 7 local and 3 systemic reactions, but authors did not specify in which group (28 patients in the study). In the trial with *Alternaria* there were 2 asthma exacerbations in active treatment group (15%) and no systemic reactions in placebo group.

Conclusions and research needs

Subcutaneous allergen specific immunotherapy may be of net clinical benefit in adults with seasonal allergic rhinitis due to pollens. Net clinical benefit of allergen specific immunotherapy in

adults with allergic rhinitis due to house dust mites is uncertain. We judged overall quality of evidence supporting the SCIT for the treatment of perennial allergic rhinitis due to house dust mites as low, since the trials had important limitations and the results were imprecise. Any net clinical benefit of SCIT for other perennial allergens is very uncertain.
Additional well designed (480) and executed clinical trials that measure and carefully report (74, 75) all patient-important outcomes are needed to assess the effectiveness of SCIT for the treatment of perennial allergic rhinitis.

Recommendation

We suggest subcutaneous allergen specific immunotherapy in adults with seasonal (conditional recommendation | moderate quality evidence) and perennial allergic rhinitis due to house dust mites (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on relieving the symptoms of AR, and a relatively low value on avoiding adverse effects and on resource expenditure.

Question 33

Should subcutaneous specific immunotherapy be used for treatment of allergic rhinitis in children without concomitant asthma?

Summary of findings

One recently published systematic review included 6 trials that examined the use of subcutaneous allergen specific immunotherapy (SCIT) in children with allergic rhinitis and/or asthma (481). Four studies were conducted in children with seasonal (482-485) and 2 in children with perennial allergic rhinitis (486, 487).
Authors of a systematic review of SCIT in children with allergic rhinitis did not provide any combined estimates of effects, because in many trials point estimates and measures of variability were reported in a way that precluded meta-analysis (481) (see evidence profile for question 33).

Benefits

Four studies found no difference between the SCIT and untreated groups in symptom scores or medication use (482, 485-487). One small study reported beneficial effect on symptoms (484) and the other stated that the nasal symptoms were significantly lower in SCIT group, but failed to report the magnitude of this effect (483). In this latter study – the Preventive Allergy Treatment (PAT) study, SCIT reduced the risk of development of asthma (relative risk: 0.46, 95% CI: 0.27 to 0.77) in a subgroup of children that had no asthma at baseline.

Harms

Data on adverse events were reported in five of six studies. Adverse effects were poorly reported and the definitions of an adverse event were often unclear. Local side-effects were more frequently reported in the intervention groups. Systemic side-effects (e.g. asthma) were rare and mild. Systemic anaphylactic reactions did not occur. Thus, an estimate of the risk of adverse events in children with allergic rhinitis may only be extrapolated from the systematic review of randomised trials of SCIT in seasonal allergic rhinitis including adult and mixed – paediatric and adult –

populations (479). In this review only 9 of 51 included trials extended the age range to participants younger than 18 years of age. The risk of non-life threatening systemic adverse events was estimated to be 7% in SCIT and 0.65% in placebo groups, and the risk of anaphylactic shock was estimated to be 0.72% and 0.33% respectively. There were no fatal events reported in any of the studies. Adrenalin was used in 19 per 14,085 injections given in the SCIT groups and in 1 per 8278 injections in the placebo groups.

Conclusions and research needs

Net clinical benefit of subcutaneous allergen specific immunotherapy in children with allergic rhinitis is very uncertain. However, based on the results of studies in adults it may be of some benefit in children with seasonal allergic rhinitis. There is a need for rigorously designed and executed randomised trials of SCIT in children with allergic rhinitis that measure and properly report (74, 75) patient-important outcomes and adverse events. Further research, if done, will have important impact on this recommendation.

Recommendation

In children with AR, we suggest subcutaneous specific immunotherapy (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on probable reduction in symptoms of allergic rhinitis and the potential prevention of the development of asthma, and relatively low value on avoiding adverse effects in children and resource expenditure.

Question 34

Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in adults without concomitant asthma?

Summary of findings

One systematic review including 22 trials (16 in adults) addressed the question of the efficacy and safety of sublingual specific immunotherapy (SLIT) in adults with allergic rhinitis (488, 489).
We identified 27 additional studies of SLIT in patients with seasonal allergic rhinitis that were not included in this review or published after this review as done (490-515). We also identified additional four additional studies in patients with perennial allergic rhinitis (516-519). Therefore, we could not use the review by Wilson and colleagues to inform this recommendation.
We excluded four studies reporting safety outcomes only with no parallel information on efficacy (520-523) and six publications that were reporting the results of other studies already included in our analysis (524-529).
We extracted data from all original publications of 36 studies in adults with seasonal allergic rhinitis (490-515, 530-540) and 8 studies in adults with perennial rhinitis (516-519, 541-544). We combined the results in meta-analysis when possible. Many studies did not report variability in the outcome measures, so it was not possible to combine their results. Some studies did not report variability, but were included in the meta-analysis by Wilson and colleagues (488). We assumed that authors used unpublished data and we used these in our analysis. For this recommendation we examined results of both analyses: including and excluding studies that did not report variability in results in the original publication (see evidence profile 1 and 2 for question 34).

Eight studies measured quality of life. Seven included patients with seasonal allergic rhinitis – three reported statistically significant improvement in quality of life, however, they reported their results in a way that precluded combining their results (496, 497, 510). Two studies found an improvement that was statistically not significant, but did not report variability (495, 507). Two studies found no difference: one did not report what were the results (501) and the other found almost no change in score from baseline in both SLIT and placebo groups (509). One study in adults with perennial allergic rhinitis used a generic instrument (SF-36) and found no difference between the treated and placebo groups (517).
Two studies used sublingual spit technique, three did not report the details of administration, and all remaining studies used sublingual swallow immunotherapy.

Benefits

In adults with seasonal allergic rhinitis SLIT compared to placebo had a small to moderate beneficial effect on nasal and ocular symptoms, and may have improved quality of life, but the magnitude and precision of this effect was impossible to assess due to shortcomings in reporting. In adults with perennial allergic rhinitis the effect of SLIT on nasal symptoms may be large, but the estimates were imprecise.

Harms

There were no serious adverse effects reported in any of 44 studies of SLIT in adults with allergic rhinitis (altogether 2424 patients receiving SLIT). However, local adverse effects – most commonly oral pruritus, oral and labial oedema – and gastrointestinal intolerance were frequent in the SLIT groups and significantly more often led to discontinuation of treatment (see evidence profile 1 and 2 for question 34).

Cox and colleagues (545) have recently reviewed 66 studies, including observational studies with and without a control group that provided any information on safety of SLIT. Most of the studies did not report the actual number of doses given and the authors of the review estimated number of doses from the immunotherapy schedule, treatment duration, the number of included patients and completeness of follow-up. In the 66 studies (excluding studies of SLIT in latex allergy, ultrarush, or using allergoid) nearly 1,200,000 doses of SLIT were administered to 4378 patients. There were no life-threatening reactions reported. In studies that reported only total number adverse events there were 1047 adverse events per 386,149 doses given (27 reactions per 10,000 doses; 41 studies). In studies that reported number of patients with an adverse event 529 patients of 4378 (12%) reported an adverse event (49 studies). In studies that specified severity of reaction, systemic reactions occurred in 169 of 314,959 (54 per 100,000 doses administered). There were 16 serious adverse events reported – 14 were probably SLIT-related of which 7 were asthma exacerbations (one required hospitalization) – in 3984 patients treated for 5377 treatment years with 1,019,826 doses of SLIT (1 serious adverse event per 64,000 doses; 58 studies). There were 244 moderate adverse events requiring dose adjustment or causing withdrawal from the study in 2939 patients treated for 4586 treatment years with 810,693 doses of SLIT (50 studies). Majority of these reactions were gastrointestinal symptoms, exacerbation of rhinitis or conjunctivitis, and/or urticaria. There were 823 local reactions (oral mucosal itch and burning, lip swelling) in 66 included studies (68 per 100,000 doses). This however is likely an underestimated number since many studies reported information on adverse events as a general statement with no numeric data.

Other considerations

Swallow SLIT is considered more appropriate than sublingual spit immunotherapy (546). Dosing regimens in clinical trials varied from daily to weekly. Daily dosing seems to be preferred, but the optimal dosing frequency of SLIT has not been established yet. There is a general tendency toward initiating of once-daily SLIT in constant dose without updosing that was proven to be safe in clinical trials (547). Optimal duration of SLIT also has not been established. Preliminary results suggest that the optimal duration of a SLIT might be 4 years (548, 549). Other aspects of SLIT requiring investigation include the optimal maintenance dose, criteria for the selection of patients who are likely to obtain most benefit, and cost-effectiveness.
There is also some concern about the directness of patient population included in the available trials of SLIT, that on average have milder symptoms and better quality of life than patients enrolled in other trials assessing medications.

Conclusions and research needs

Sublingual allergen specific immunotherapy may be of net clinical benefit in adults with allergic rhinitis. In patients with seasonal allergic rhinitis the effect on nasal symptoms is probably small to moderate and in patients with perennial symptoms the current estimate of the effect is very imprecise. There is inconsistent information on quality of life. Small reduction in symptoms seems counterbalanced by frequent local adverse effects. Sublingual specific immunotherapy seems to be safe and induce rare systemic reactions. However, once they develop they may pose a serious problem, since they occur at home.
A complete, rigorously performed and reported (223, 224) systematic review of sublingual specific immunotherapy versus placebo in adults with allergic rhinitis that provides information on all outcomes important to patients, including adverse effects, is required for the next update of the ARIA guidelines.

Recommendation

We suggest sublingual allergen specific immunotherapy in adults with rhinitis due to pollen (conditional recommendation | moderate quality evidence) or house dust mites (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on alleviating the symptoms of rhinitis, and relatively low value on avoiding adverse effects and resource expenditure.

Remarks: Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable, if patients' values or preferences differ from those described here.

Question 35

Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in children without concomitant asthma?

Summary of findings

Four systematic reviews (481, 488, 489, 550, 551) evaluated sublingual allergen specific immunotherapy (SLIT) in children with allergic rhinitis. However, these reviews had different inclusion criteria and thus described different trials. The most recent review did not combine the data from individual studies (481). Our additional search performed for this revision of ARIA guidelines found eight more randomised trials, not included in these systematic reviews, that

evaluated SLIT in children with allergic rhinitis and/or asthma and reported nasal symptoms (552-559).
We excluded one study since it reported only safety outcomes with no parallel information on efficacy (560) and another study, because it was published in Chinese language (561). This last study, however, found a significant improvement in symptoms compared to placebo and a trend towards less rescue medication use.
We extracted data from all original publications of 22 studies in children with seasonal or perennial allergic rhinitis (552-559, 562-575). We combined the results in meta-analysis when possible. Many studies did not report variability in the outcome measures, so it was not possible to combine their results. Some studies did not report variability, but were included in meta-analyses in previous systematic reviews by Penagos or Wilson (488, 551). We assumed that authors used unpublished data and we used these in our analysis. For this recommendation we examined results of both analyses: including and excluding studies that did not report variability in results in the original publication (see evidence profile 1 and 2 for question 35).
One study (n = 66) reported its results on a graph as several measurements over time (573). Authors of each of the three systematic reviews that combined results in meta-analysis extracted different values from the same graph showing different effects on nasal symptoms ranging from large benefit from SLIT (effect size: -1.18, 95% CI: -0.65 to -1.70) (551), through small and statistically insignificant benefit from SLIT (effect size: -0.23, 95% CI: - 0.71 to +0.26)(550), to small detrimental effect of SLIT (effect size: +0.17, 95% CI: -0.32 to +0.65)(488). Using end-of-study values for meta-analysis was not possible, because they did not reflect the actual symptoms during the study, and we did not attempt calculating an average effect over duration of the study, therefore we did not use this study results.
Another study (572) including 58 children reported results on a graph with likely mislabelled measures of variability. For this recommendation we examined results of both analyses: assuming the measure of variability as labelled by the authors (i.e. standard deviation) and as it likely should be labelled (i.e. standard error; see evidence profile 2 for question 35).

Benefits

In children with seasonal allergic rhinitis SLIT compared to placebo has small effect on nasal symptoms and probably also on ocular symptoms and rescue medication use, although the results of clinical studies did not exclude no effect. Only one study (559) measured quality of life, but the results were inconsistent and imprecise precluding any reliable conclusions (see evidence profile 1 for question 35). One trial performed in children with grass pollen allergy found that fewer children receiving SLIT plus standard symptomatic treatment, compared to standard symptomatic treatment alone, developed asthma after 3 years (relative risk: 0.43; 95% CI: 0.21 to 0.87) (568). However, this trial had serious methodological limitations and the results are imprecise.

Studies that used SLIT in children allergic to house dust mite did not find evidence of its efficacy – there was no effect on nasal symptoms and medication use, however, these studies had serious methodological limitations and results do not exclude a small benefit or small harm (see evidence profile 1 for question 35). No study measured quality of life.

Harms

There were no serious adverse effects in any of included studies of SLIT in children with allergic rhinitis that reported measuring this outcome (altogether 580 children receiving SLIT). Other adverse effects were poorly reported in the included studies. Similar to SLIT in adults, local adverse effects (oral and labial pruritus and oedema) were frequent in the SLIT groups and more often led to

discontinuation of treatment, but these estimates are very imprecise (see evidence profile 1 and 2 for question 34).

Cox et al. also reviewed observational studies that provided any information on safety or tolerance of SLIT in children (545). Two observational studies (98 children) and one post-marketing survey (126 children) assessed safety of SLIT in 2–7 years old children with allergic rhinitis or asthma. In one study children received SLIT with a monomeric allergoid (22,200 doses altogether) and were followed for 22 months. Two children had abdominal pain (1 episode each; 5% of patients; 7.1 per 100,000 doses). In a second study children received SLIT to various pollens or house dust mites for 8 months. There were 13 adverse events in 11 children (6 episodes of urticaria, 4 gastrointestinal symptoms, and 3 oral itch; all were reported to be mild or moderate, and none required discontinuation of treatment). A post-marketing survey of children treated with SLIT to various allergens for 2 years (39,000 doses) found 9 adverse events recorded by parents on diary cards in 7 children (5.6% of children; 2.3 per 10,000 doses). Of these 7 were systemic reactions (1 mild abdominal pain, 6 moderate abdominal pain with diarrhoea), and 2 were oral itching. All events occurred during the induction phase.

Other considerations

See question 34 above.

Conclusions and research needs

Net clinical benefit of sublingual immunotherapy in children with allergic rhinitis is very uncertain. Small reduction in symptoms seems counterbalanced by frequent local adverse effects. Sublingual specific immunotherapy seems to be safe and induce rare systemic reactions. However, once the develop they may pose a serious problem, since they occur at home.
A complete, rigorously performed and reported (223, 224) systematic review of sublingual specific immunotherapy versus placebo in adults with allergic rhinitis that provides information on all outcomes important to patients, including adverse effects, is required for the next update of the ARIA guidelines. There is also a need for rigorously designed and executed randomised trials of SLIT in children, especially with perennial/persistent allergic rhinitis, that measure and properly report (74, 75) patient-important outcomes and adverse events. Further research, if done, will have important impact on this recommendation.

Recommendation

In children with allergic rhinitis due to pollens, we suggest sublingual allergen-specific immunotherapy (conditional recommendation | moderate quality evidence). In children with allergic rhinitis due to house dust mites, we suggest that clinicians do not administer sublingual immunotherapy outside rigorously designed clinical trials (conditional recommendation | very low quality evidence).

Underlying values and preferences: The recommendation to use sublingual immunotherapy in children with seasonal allergic rhinitis places a relatively high value on small reduction in nasal symptoms, and relatively low value on avoiding adverse effects in children and resource expenditure. The recommendation to use sublingual immunotherapy in children with perennial allergic rhinitis only in the context of clinical research places a relatively high value on avoiding adverse effects and resource expenditure, and relatively low value on possible small reduction in nasal symptoms.

Remark: Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable, if patients' values or preferences differ from those described here.

Question 36

Should local nasal specific immunotherapy be used for treatment of allergic rhinitis?

Summary of findings

We found one systematic review of local nasal immunotherapy (LNIT) in children (481) that included four studies (576-579). We found no systematic review addressing this question in adults, however, there is a protocol of a systematic review recently registered in the Cochrane Library (580).

We found 19 randomised trials that compared intranasal specific immunotherapy to placebo in adults with allergic rhinitis (581-599). We did not consider studies in which histamine was given intranasally in the control group (600-605). We could not use two studies of LNIT with grass allergens (67 patients total) (595, 597) to inform this recommendation, because we were not able to obtain their full reports in time given to revise this ARIA guidelines. However, based on the available information, both studies found statistically significant improvement in symptoms in the LNIT groups and reported only mild local adverse effects.
Two studies in adults (583, 590) and one in children (578) were performed in patients allergic to house dust mite; two additional studies in adults included a subgroup of patients allergic to these allergens (586, 593). All other studies included patients allergic to seasonal allergens.
Seven studies reported the effect of LNIT on nasal symptoms, but did not provide variability in results (581, 582, 584, 585, 589, 593, 594), so we could not combine their results with other studies. However, these studies also reported number of patients who rated their symptoms as improved or absent and we used these estimates of effect to infer about symptoms (see evidence profile 1 for question 36).

Benefits

Almost all studies showed moderate to large improvement in nasal symptoms and need for rescue medications during the pollen season. Patients receiving LNIT were twice as likely to rate their symptoms as improved (see evidence profile 1 for question 36). No study measured quality of life.

Harms

Serious adverse events did not occur in any of included studies. Local adverse effects were reported inconsistently (only 35% of studies provided actual numbers), but they were more frequent in the LNIT groups during treatment, despite in most studies intranasal chromones were used prior to application of LNIT (see evidence profile 1 and 2 for question 36).
Bronchoconstriction has been described after dry powder extract application that was attributed to incorrect technique of administration.

Other considerations

Optimal form of administration has not been established – intranasal allergen immunotherapy may be administered as aqueous extracts of unmodified or chemically modified allergens (allergoids) or as dry powder. Optimal duration of LNIT has not yet been determined, but no sustained effect

following discontinuation of treatment has been demonstrated yet. There is also no data on possible preventive effect against development of asthma.

Conclusions and research needs

Net clinical benefit from intranasal specific immunotherapy is uncertain. Benefits seem to be closely balanced by local adverse effects during treatment.
A complete rigorously performed and reported (223, 224) systematic review of intranasal specific immunotherapy versus placebo that provides information on all outcomes important to patients, including adverse effects, is required for the next update of the ARIA guidelines.

Recommendation

We suggest intranasal allergen specific immunotherapy in adults (conditional recommendation | low quality evidence) and in children with allergic rhinitis due to pollens (conditional recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on the reduction of symptoms of allergic rhinitis during pollen season, and a relatively low value on avoiding local side effects and cost. An alternative choice may be equally reasonable.

Alternative and complementary treatment for allergic rhinitis

Question 37

Should homeopathy be used for treatment of allergic rhinitis?

Summary of findings

We found no systematic review of homeopathy in allergic rhinitis.

A review of literature published by the ARIA group members (27) found six randomised trials that compared homeopathy to placebo and one that compared it to intranasal chromones in patients with allergic rhinitis. We identified one additional study published after the search for this review was done (606).

We found only one overview with meta-analysis of trials of *Galphimia glauca* in treatment of allergic rhinitis, but it was researchers' review of their own trials on the topic (607).

Benefits

Reviewed studies reported conflicting results of homeopathy on nasal symptoms and quality of life, and many studies had important limitations. The evidence is promising for *Galphimia glauca* for allergic rhinitis, but requires confirmation.
There are a variety of homeopathic dilutions available and in the absence of a systematic review it is probably not feasible to assess their individual effects. Many systematic reviews of homeopathy in various conditions suggested that homeopathy may be more effective than placebo, but the findings were inconsistent, and the evidence for a specific effect of homeopathy is weak compared to the evidence for conventional (allopathic) treatments (608-614).

Harms

Homeopathic remedies are much diluted and contain very small doses of active compounds. Because of this they are assumed to be safe and not interacting with conventional medicines. However, we could not identify any systematic review of adverse or side effects of homeopathy, and most trials were very small possibly underpowered to reveal infrequent but important adverse effects.

Conclusions and research needs

Any clinical benefit from homeopathy in patients with allergic rhinitis is very uncertain. We concluded that the overall quality of the evidence supporting the use of homeopathy in allergic rhinitis would be very low, because of the limitations in the design of the studies, and inconsistent and imprecise results.
Well designed and rigorously executed randomised trials of homeopathy that measure and properly report (74, 75) all patient-important outcomes are needed. If done, they are likely to have an important impact on this recommendation.

Recommendation

In patients with AR, we suggest that clinicians do not administer and patients do not use homeopathy (conditional recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding possible adverse effects and resource expenditure, and a relatively low value on any possible, but unproven, benefit of these treatments in AR.

Question 38

Should acupuncture be used for treatment of allergic rhinitis?

Summary of findings

A review of literature published by the ARIA group members found three randomised trials that compared acupuncture to sham acupuncture in patients with allergic rhinitis (27).

Additional search for randomised trials published after the review by Passalacqua and colleagues was done, found two more trials (615, 616).

Three systematic reviews (617-619) and three large observational studies (620-622) assessed the safety of acupuncture. We used information from these reviews to determine the safety of acupuncture.

A systematic review of the efficacy and safety of acupuncture in allergic rhinitis has been published in April 2008 (623). This review included only trials described above and its results were consistent with those of our previous assessment.

Benefits

Two randomised trials showed an improvement in symptoms with acupuncture compared to sham procedure. One involved 30 patients with seasonal rhinitis and showed that acupuncture significantly reduced symptoms without changing the need for rescue medications (624). The other included 52 adults who had typical symptoms of seasonal allergic rhinitis and were assigned to acupuncture and Chinese herbs, or a control group which received sham acupuncture and a nonspecific Chinese herbal formula. After 3 weeks of treatment patients in the active treatment group showed improvement in rhinitis symptoms and quality of life (616).
One trial in children with perennial allergic rhinitis (3-month treatment plus 3-month follow-up) reported a significant improvement in daily symptoms (limited to the follow-up period) and an increase of symptom-free days in the active group with no change in the use of symptomatic medications (625).
Two additional trials did not find a difference between the acupuncture and sham acupuncture groups. One compared the effect of active versus sham acupuncture in 40 patients with a history of allergic rhinitis and a positive skin test after 12 months. No differences in clinical symptoms were seen between active versus sham acupuncture (615). The other also failed to demonstrate a difference in symptoms and use of rescue medication between real and sham acupuncture (626).

Harms

A systematic review of life-threatening adverse events associated with acupuncture reported two cases of fatal staphylococcal septicaemia, 65 cases of pneumothorax, four cases of cardiac tamponade (one fatal), and one case of fatal asthma exacerbation being described in the medical literature (617). In another systematic review of safety of acupuncture that included 9 prospective observational studies with almost 250,000 treatments the most serious adverse effects were pneumothorax (2 patients) and broken needle (2 patients) (618).
Two large prospective observational studies of acupuncture practices in the United Kingdom found no serious adverse events in over 66 000 acupuncture treatments provided by experienced practitioners (620, 621). The most serious adverse events reported were exacerbation of symptoms (12 patients), fainting (10 patients), pain at needle insertion site (6 patients), needle being left in place (5 patients), seizure (1 patient with epilepsy), and slurred speech (1 patient). However, acupuncturists interfered with the prescribed medications of 3% of patients that might be considered an indirect risk of acupuncture (620). Another large observational study from Sweden found no serious adverse events in almost 9300 acupuncture treatments, except for minor bleeding being reported in 15% of treatments (622).
Despite the evidence of the relative safety of acupuncture procedure, there is a substantial concern about the risk of infection with hepatitis virus, human immunodeficiency virus, or bacteria when non-disposable needles are used (617, 619).

Conclusions and research needs

Net benefit from acupuncture in treatment of allergic rhinitis is uncertain. The risks seem to outweigh the very imprecise data on the efficacy of acupuncture in allergic rhinitis.
Well designed and rigorously executed randomised trials of acupuncture that describe the procedure in sufficient detail so it can be reproduced and that measure and properly report (74, 75) all patient-important outcomes are needed. If done, they are likely to have an important impact on this recommendation.

Recommendation

In patients with AR, we suggest clinicians do not administer and patients do not use acupuncture (conditional recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding the potential complications of acupuncture, and a relatively low value on uncertain reduction in symptoms of rhinitis.

Remarks: In patients who choose to be treated with acupuncture ONLY disposable needles should be used.

Question 39

Should butterbur be used for treatment of allergic rhinitis?

Summary of findings

One systematic review assessed the efficacy and safety of butterbur (*Petasites hybridus*) in patients with allergic rhinitis (627), although it did not include several recently published trials, therefore we did not use it to inform this recommendation.

We found five randomised trials that evaluated butterbur compared to placebo or oral H1-antihistamine in patients with allergic rhinitis (628-634), but one reported only changes in physiological parameters (628). Two papers were reports of the same study (632, 633).
All studies had important methodological limitations. Studies supported by the manufacturer of butterbur extract concluded that it was effective, while studies not supported by industry found small or no effect.

A systematic review of the efficacy and safety of herbal medicines, including butterbur, in allergic rhinitis has been published in December 2007(635), therefore we did not use it when reviewing the evidence for this recommendation. However, this review included the same studies of butterbur we described above and its results were consistent with those of our previous assessment.

Benefits

Overall all studies, except for one (631), suggested that butterbur was superior to placebo or equal to oral H1-antihistamine in reducing symptoms of rhinitis and improving quality of life. However, reporting of the results was either flawed or did not allow drawing any clinical conclusions. Follow-up in one very small trial in patients with perennial allergic rhinitis (630) was most likely too short to assess the efficacy of butterbur – current requirement for the optimal duration of clinical trials to assess drug efficacy in perennial allergic rhinitis is 4 weeks (636-638).

Harms

Long-term effects and interaction of butterbur with other drugs have not been studied. There is however concern about safety, since native unpurified butterbur contains pyrrolizidine alkaloidsthat have been shown to be both hepatotoxic and carcinogenic (639).

Treatment considerations

If used, only commercial preparations of butterbur should be considered in which extracts are required to contain lower-than-detectable amounts of pyrrolizidine alkaloids.

Conclusions and research needs

Net clinical benefit of butterbur in treatment of allergic rhinitis is very uncertain. We judged overall quality of evidence supporting the use of butterbur in allergic rhinitis as very low since all studies had important methodological limitations, their results were inconsistent, there is a high probability of reporting bias, and there is little evidence about long-term safety. Further well designed and rigorously executed randomised trials that measure and properly report (74, 75) all patient-important outcomes are needed. If done, they are likely to have an important impact on this recommendation.

Recommendation

In patients with AR, we suggest clinicians do not administer and patients do not use butterbur (conditional recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding the uncertain adverse effects of butterbur, and a relatively low value on equally uncertain reduction in symptoms of rhinitis.

Remarks: In patients who are less risk averse an alternative may be equally reasonable. However, if one chooses to use butterbur one should consider only commercial preparations in which butterbur extract does not contain toxic pyrrolizidine alkaloids.

Question 40

Should herbal medicines other than butterbur be used for treatment of allergic rhinitis?

Summary of findings

A review of literature published by the ARIA group members (27) found four randomised trials that compared herbal medicines other than butterbur to placebo in patients with allergic rhinitis. Search for trials published after this review was done did not find additional studies.

Three recent systematic reviews assessed the safety of herbal medicines (640-642).

A systematic review of the efficacy and safety of herbal medicines in allergic rhinitis has been published in December 2007 (635), therefore we did not use it when reviewing the evidence for this recommendation. This review included several older studies that the ARIA guideline panel did not identify previously. However, the assessment of the quality of available evidence and the results were consistent with our assessment of a smaller sample of studies. Using this review would not change the recommendation.

Benefits

One study in patients with seasonal rhinitis found that a mixture of 18 Chinese herbs was significantly better than placebo relieved symptoms and increased quality of life (643). Another study in perennial rhinitis found significant effects of the Chinese herb formulation biminne (644). The third trial included 52 adults who had typical symptoms of seasonal allergic rhinitis and were assigned to acupuncture and Chinese herbs, or a control group which received sham acupuncture and a nonspecific Chinese herbal formula. After 3 weeks of treatment patients in the active

treatment group showed improvement in rhinitis symptoms and quality of life (616).An additional randomised trial found that grape seed extract (100 mg twice daily) was no more effective than placebo for ragweed-induced rhinitis (645).

Harms

Herbal remedies contain several active pharmacologic ingredients that may be responsible for their clinical effect. However, laws and regulations of the manufacturing of traditional herbal products are much less strict than for pharmaceuticals (646). Despite the common belief that phytotherapy is safe, systematic reviews of safety of herbal medicines reported several serious adverse events associated with herbal products (640-642). The reported causes of adverse reactions associated with herbal medicines include toxic ingredients either inherent to the plant or due to growing conditions, misidentification of toxic herbs, contamination or adulteration during manufacturing process, interactions with other medicines, overdose, and allergic reactions (646-649). Many herbal remedies have been reported to cause allergic sensitization or photosentization and various skin reactions (650). One review of Chinese literature found that only during 1993 and 1994 there were 1133 reports of adverse events associated with herbal medicines, including 59 fatal events related to raw herbs and 6 deaths attributed to final herbal products (646).

Conclusions and research needs

Net clinical benefit from herbal remedies in allergic rhinitis is very uncertain. Although mixture of Chinese herbs seems to be efficacious there is a concern about reproducibility of the intervention and serious concern about safety. We concluded that the overall quality of evidence supporting use of herbal medicines for allergic rhinitis is very low, because at least for one critical outcome – adverse effects – available data come from unsystematic observations of cases of serious adverse effects including fatal events. Future adequately designed and conducted research, standardisation of herbal mixtures, and adequate laws and regulations of manufacturing herbal medicines to ensure their safety may have an important impact on this recommendation.

Recommendation

In patients with AR, we suggest clinicians do not administer and patients do not use herbal medicines (conditional recommendation | very low quality evidence).

Underlying values and preferences: The recommendation places a relatively high value on avoiding possible serious adverse events and drug interactions, and a relatively low value on possible reduction in symptoms of rhinitis.

Question 41

Should physical techniques and other alternative therapies be used for treatment of allergic rhinitis?

Summary of findings

No systematic review addressed this question.

A recent literature review by the ARIA group members found two trials of phototherapy in patients with allergic rhinitis (27). Authors did not find trials performed in rhinitis with other forms of

alternative or complementary procedures: aromatherapy, chromotherapy, Bach's flowers, anthroposophy, Hopi candles, hydro-colon, urine therapy, clinical ecology, and iridology.
For this revision of the ARIA guidelines we did not search for observational studies evaluating these treatments.

Benefits

One study used a low-energy narrow-band red light intranasal therapy in perennial rhinitis. Active treatment produced a significant improvement of symptoms, but the methodological quality of this study was poor (651). The other trial in seasonal allergic rhinitis reported that a combination of ultraviolet light (UV-B and UV-A) compared with visible light improved sneezing, rhinorrhea, nasal itching, and total nasal symptoms in the UV group but none of the scores improved significantly in the control group (652).

Harms

Side effects are not known.

Conclusions and research needs

Any clinical benefit from phototherapy, other physical techniques, or alternative therapies is very uncertain. We judged the overall quality of evidence supporting this recommendation as very low, since the available studies had methodological limitations, the results were imprecise, and there is a high probability of reporting bias.
Further research, if done, may have an important impact on this recommendation.

Recommendation
In patients with AR, we suggest that clinicians do not administer and patients do not use phototherapy or other physical techniques (conditional recommendation | very low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding potential adverse effects of these therapies, and a relatively low value on their very uncertain effect on symptoms of rhinitis.

III. Treatment of asthma in patients with allergic rhinitis and asthma

Allergic rhinitis and asthma often co-exist and appear to produce a continuum of airway disease (see section 9 of ARIA 2008 Update (2)). Despite increasing interest in the epidemiological, molecular, and environmental links between allergic rhinitis and asthma, there is a relative paucity of data in the literature describing the characteristics of asthma in patients with coexisting rhinitis. In allergic patients, seasonal exposure to pollens and/or moulds induces intermittent or persistent rhinitis. Some patients present concomitant symptoms suggestive of asthma (e.g. shortness of breath, wheeze, or cough) (653) and a nonspecific bronchial hyper-reactivity, that may be present during the allergen and for few weeks thereafter (654, 655). Bronchial inflammation may also increase during the pollen season in patients with rhinitis (656). These symptoms have been termed "seasonal asthma". However, what is exactly meant by this is still unclear – many patients with allergic rhinitis and chest symptoms (cough, wheeze, and/or shortness of breath) neither exhibit

relevant airflow obstruction nor demonstrate reversibility of forced expiratory volume in 1 s (FEV_1) following bronchodilator administration and increased peak flow variability (657-660). Therefore, there is some uncertainty if the magnitude of effect of treatments shown to be effective in patients with persistent asthma is similar in patients with allergic rhinitis and concomitant symptoms of ~~–s~~easonal asthma".

Question 42

Should oral H_1-antihistamines be used for treatment of asthma in patients with allergic rhinitis and asthma?

Summary of findings

One systematic review published in 1997 assessed the use of oral H_1-antihistamines for treatment of asthma, but it reported only the results of pulmonary function tests, rescue medication use, and adverse events (661). H_1-antihistamines used in these studies were: ketotifen (6 studies), azelastine (4 studies), terfenadine (3 studies), cetirizine (2 studies), and oxatomide, picumast, pemirolast, and loratadine (1 study each).

One systematic review investigated the use of ketotifen alone or as additional medication for long-term control of asthma and wheeze in children (662). Authors' last search for additional literature in May 2006 did not reveal any new articles.

We identified eight trials that compared oral H_1-antihistamines to placebo in patients with allergic rhinitis and concomitant asthma (168, 179, 196, 203, 657, 663-665). Two of these trials (663, 664) had a cross-over design without a washout period and one was published in Chinese language (665), therefore we did not use them to inform this recommendation. Of the remaining trials four included adults (168, 179, 196, 657) and one included children (203). Most of these studies had various limitations in execution and reporting. Of the five included trials three investigated cetirizine (168, 203, 657), one desloratadine (179), and one levocetirizine (196).

Benefits

Randomised trials in adults showed a larger reduction in asthma symptoms among patients receiving oral H_1-antihistamine compared to placebo, although the results did not exclude the possibility of no effect and there were serious problems with reporting of this outcome. One small study measured quality of life and showed a small improvement, the precision of which was not possible to assess due to reporting issues.
The systematic review of ketotifen for the control of asthma and wheeze in children found that ketotifen alone or in combination with other co-interventions improved asthma and wheezing symptoms, reduced the risk of exacerbations, and reduced the need for oral glucocorticosteroids and bronchodilators in children with mild and moderate asthma (662). However, in most studies inhaled glucocorticosteroids (currently considered an initial maintenance treatment)were not used so the additional benefit from ketotifen in children already using inhaled corticosteroids is not known.
The only trial in children that we identified evaluated cetirizine and presented the results the way that did not allow for drawing valid conclusions.

Harms

Adverse events were inconsistently reported in randomised trials performed in adults and it was not possible to calculate any overall effect without making several assumptions. Overall number of all adverse events in patient receiving oral H1-antihistamine or placebo seemed to have been similar. One study reported 17 versus 4 events of fatigue or somnolence among patients receiving cetirizine 10 mg and placebo respectively.
The systematic review of different oral H1-antihistamines in adults with asthma (661) found an incidence of sedation was mentioned in 11 of 19 studies and ranged from 0 to 39% in the placebo and 0 to 70% in the H1-antihistamine groups. An overall effect for all studies showed that the difference in incidence of sedation between oral H1-antihistamines and placebo was statistically significant, but the authors did not report the magnitude of the effect and the results were inconsistent. Besides sedation, several other side-effects (weight gain, altered taste, headache, and dry mouth) were mentioned in the studies, but again the actual values were not reported. Since many included studies used sedating H1-antihistamines there is some uncertainty about the directness of these findings.
Systematic review of ketotifen in children found more side effects – sedation and weight gain – among children receiving ketotifen, but the estimates were very imprecise.

Conclusions and research needs

Any clinical benefit from oral H1-antihistamines in adults and children with asthma and allergic rhinitis is very uncertain. Further research on long-term use of oral H1-antihistamines in patients with asthma and allergic rhinitis reporting control of asthma symptoms, quality of life, and adverse effects – if done – is very likely to have an important impact on this recommendation. There may be a net clinical benefit from ketotifen when used alone for treatment of symptoms of asthma and wheeze in children with concomitant allergic rhinitis, however, an additional benefit from ketotifen in children already using inhaled corticosteroid is not known. More research seems justified to determine the effect of ketotifen as an add-on therapy to inhaled glucocorticosteroids in children with asthma or wheeze and concomitant allergic rhinitis.

What others are saying

Guidelines for the treatment of asthma prepared by other organizations do not recommend oral H1-antihistamines, stating that they are ineffective or have limited role in patients with established asthma when administered in the usual doses (666, 667). One guideline stated that current evidence does not suggest a primary role for oral H1-antihistamines in the treatment of asthma, but they may have a small beneficial effect on asthma in subjects with concurrent rhinitis (668).

Recommendation

In patients (both children and adults) with allergic rhinitis and asthma, we suggest clinicians do not administer and patients do not use oral H_1-antihistamines for the treatment of asthma (conditional recommendation | very low quality evidence).

Underlying values and preferences: The recommendation not to use oral H_1-antihistamines in adults with allergic rhinitis and asthma for the treatment of asthma places a relatively high value on avoiding their adverse effects, and a relatively low value on their very uncertain effect on symptoms of asthma. The recommendation not to use oral H_1-antihistamines in children with allergic rhinitis for the treatment of asthma or wheeze, despite the evidence of efficacy of ketotifen when used alone in children with mild to moderate asthma, places a relatively high value on avoiding its side effects, and a relatively low value on its unknown efficacy in children already using inhaled corticosteroids, since inhaled corticosteroids are currently considered medications of first choice in treatment of chronic asthma.

Remarks: This recommendation suggests that oral H_1-antihistamines should not be used to treat symptoms of asthma, but they may still be used in patients with asthma and rhinitis for treatment of rhinitis (recommendations 11 and 12).

Question 43

Should combination of oral H_1-antihistamine and oral decongestant be used for treatment of asthma in patients with allergic rhinitis and asthma?

Summary of findings

We did not identify any systematic reviews that addressed this question.

We found two randomised trials that investigated efficacy and safety of a combination of oral H_1-antihistamine and pseudoephedrine compared to placebo in patients with seasonal allergic rhinitis and concomitant mild to moderate asthma (669, 670).
We did not find any clinical trial comparing these management options in patients with persistent allergic rhinitis and concomitant asthma.

Benefits

There was imprecise and poorly reported improvement in asthma symptoms and quality of life with combined treatment compared to placebo, but there is uncertainty if the magnitude of the observed effect is clinically important.

Harms

In one study more patients in the combined treatment group experienced asthma exacerbation, but results were very imprecise, not excluding benefit or serious harm. Risk of insomnia was higher with combined treatment compared to placebo, but again the results were very imprecise.

Conclusions and research needs

Any net clinical benefit of a combination of oral H_1-antihistamine and oral decongestant for the treatment of asthma in patients with concomitant allergic rhinitis is very uncertain. Possible small benefits are closely balanced with adverse effects. Further research, if done, is likely to have an important impact on this recommendation.

What others are saying

Guidelines for the treatment of asthma prepared by other organizations do not mention a combination of oral H1-antihistamine and oral decongestant for the treatment of asthma (666-668, 671).

Recommendation

In patients with allergic rhinitis and asthma, we suggest clinicians do not administer and patients do not use a combination of oral H1-antihistamine and oral decongestant for treatment of asthma (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding adverse effects of combination of oral H1-antihistamine and oral decongestant, and a relatively low value on possible small reduction in asthma symptoms of uncertain clinical significance.

Question 44

Should intranasal glucocorticosteroids be used for treatment of asthma in patients with allergic rhinitis and asthma?

Summary of findings

One systematic review investigated the use of intranasal glucocorticosteroids for control of asthma in patients with coexisting asthma and rhinitis (672). However, this review had many limitations, e.g. it included also trials that explicitly excluded patients with asthma but measured asthma symptoms, or that were cross-over trials without washout period. Therefore we could not use its results to inform this recommendation.

Our search found three more randomised trials (319, 362, 673) published after the search for literature by Taramarcaz and colleagues (672) was done. We re-examined the trials included in this systematic review and the additional three trails that we identified. Of the ten trials included in the systematic review, that reported various asthma symptom scores, we excluded six: two because they enrolled patients without asthma or with unclear diagnosis of asthma (250, 674), one because patients with asthma were a subgroup (50%) of all patients in this study (675), one because it investigated airway responses to cat exposure challenges (676), and two because they had cross-over design without a washout period (677) or a washout period was too short (372).
Of the remaining randomised trials four included patients with seasonal allergic rhinitis (319, 362, 678, 679) and two with perennial allergic rhinitis (673, 680). Two of these trials did not allow inhaled glucocorticosteroids during the study period (678, 679) and the use of inhaled corticosteroids was unclear in one study that was also the only one performed in children (680). None of the studies reported quality of life.

Benefits

Of the three randomised trials that compared combined treatment with inhaled and intranasal glucocorticosteroid to inhaled glucocorticosteroid alone (376 patients in treatment and 369 in control groups), one found no difference in asthma-free days, drug-free days, and night-time awakenings, the other stated only that symptoms improved in both groups, and the third one measured but did not report asthma symptoms. We judged overall quality of evidence from these trials as low due to very serious limitations in design and reporting.
Of the three trials that did not allow inhaled glucocorticosteroids or did not state if they were used (87 patients in treatment and 61 in control groups), one found ~~–si~~gnificantly" less asthma symptoms with intranasal glucocorticosteroid, second found no statistically significant difference, but the symptoms improved in treated patients and worsened in those receiving placebo, and the third reported a similar mean symptom score of about 0.3 point (on a 4-point scale, where 0 – no symptoms to 3 – severe symptoms) in all groups suggesting almost no symptoms in all groups

during the study. We judged overall quality of evidence from these studies as very low, because all studies had limitations in design or execution, number of patients was very small, and there is uncertainty about the directness of the results (in the largest study providing 63% of patients symptom scores suggested no symptoms during the trial in all groups and all trials did not allow inhaled glucocorticosteroids).

Harms

Studies either reported that the incidence of adverse events was similar in all groups or did not report adverse events. For more information on adverse effects of intranasal glucocorticosteroids see recommendation 18.

Conclusions and research needs

Net clinical benefit of intranasal glucocorticosteroids in the treatment of asthma in patients with concomitant allergic rhinitis is uncertain, but seems unlikely.
An updated rigorously performed and reported (223, 224) systematic review of all individual intranasal glucocorticosteroids versus placebo that provides information on asthma symptoms, quality of life, and adverse effects is required for the next update of the ARIA guidelines. Well designed and executed randomised trials among patients with allergic rhinitis and asthma that measure and properly report (74, 75) asthma symptoms, quality of life, and adverse effects, if done, may have an important impact on this recommendation.

What others are saying

Guidelines for the treatment of asthma prepared by other organizations do not make explicit recommendations for use of intranasal glucocorticosteroids in patients with asthma and concomitant rhinitis. They state that there is limited benefit of intranasal glucocorticosteroids or that they have not been shown to improve asthma symptoms or reduce asthma morbidity (667, 668).A recent guideline from National Asthma Education and Prevention Program (671)only reported three retrospective observational studies (681-683) with methodological limitations that found the use intranasal steroids decreased emergency department visits for asthma.

Recommendation

In patients with allergic rhinitis and asthma, we suggest that clinicians do not administer and patients do not use intranasal glucocorticosteroids for treatment of asthma (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding adverse effects, albeit minor burden, and cost of intranasal glucocorticosteroids, and a relatively low value on a small clinical benefit.

Remarks: This recommendation suggests that intranasal glucocorticosteroids are not used to treat symptoms of asthma, but they may still be used in patients with asthma and rhinitis for treatment of rhinitis (recommendations 18–21).

Question 45

Should leukotriene receptor antagonists be used for treatment of asthma in patients with allergic rhinitis and asthma?

Summary of findings

Two systematic reviews assessed leukotriene receptor inhibitors (LTRA) for the treatment of chronic asthma – compared to inhaled glucocorticosteroids (684) or as an add-on therapy in patients already receiving inhaled glucocorticosteroids (685). Authors of both systematic reviews pointed out that it was not possible to examine the effect of allergic rhinitis on the effectiveness of compared treatments due to inadequate reporting. However, five included trials comparing LRTA in licensed dose + inhaled corticosteroids (ICS) versus same dose of ICS reported including more than 50% patients with allergic triggers of asthma (yet it was still not clear how many had concomitant allergic rhinitis) (686-690). Two trials (~75% patients with allergic rhinitis) found no statistically significant difference between the groups (686, 688), two trials (patients with atopy – 100% (687) and 66% (689)) did not report any patient-important outcomes, and one trials reported the results in a way that precluded meaningful clinical interpretation of the effect (690).
We were not able to identify any systematic review that assessed the use of LTRA compared to placebo in patients with asthma.

We found seven trials that compared LTRA to inhaled glucocorticosteroid published after the search for the systematic reviews by Ducharme and colleagues was done. Five trials included children (691-695) and two included adults (696, 697). Four of these trials reported 62–80% of patients being either atopic or having allergic rhinitis and three did not mention atopic/allergic status of the patients (692, 694, 695). Results of these additional trials consistently confirmed the findings of an earlier systematic review (684).

We used the available systematic review of LTRA as an add-on therapy in patients receiving inhaled glucocorticosteroids (685) to prepare an evidence profile, since we did not find any more recent trials.
We also used the available systematic review of LTRA versus inhaled glucocorticosteroids (684) acknowledging that there were more trials subsequently published, but their results consistently confirmed the findings of the review.

Our search for trials comparing LTRA to placebo in patients with asthma that assessed patient-important outcomes revealed 28 trials of which 21 included adults (179, 698-716), two explicitly included school children and adolescents (717, 718), and five included preschool and school children (309, 719-722).

An additional systematic review of montelukast as an add-on therapy in patients receiving inhaled glucocorticosteroids was published in 2008 after our final search date in September 2007 (723). Joos and colleagues (723) included only studies that followed patients for more than 12 weeks and included the same studies that were included in the analysis done by Ducharme et al. (685). Joos and colleagues do not provide a pooled estimate of the effect, whereas the review by Ducharme and colleagues does. Moreover, inclusion of the results of the review by Joos and colleagues would not change this recommendation as they are similar.

Benefits

In patients with mild to moderate persistent asthma oral LTRA used as an add-on therapy to inhaled glucocorticosteroids improved lung function and there was a trend towards improvement in clinical outcomes, but the results were very imprecise (685). There was no evidence of the effect of oral LTRA on patient-important outcomes in the trials that reported including patients with allergy or atopy.
Oral LTRA in monotherapy were less effective than inhaled glucocorticosteroids in relieving symptoms and reducing exacerbations of asthma both in adults and in children.
Oral LTRA compared to placebo were little more effective in reducing symptoms and inhaled β-agonist use or improving quality of life, both in adults and children. However, the results of the trials were inconsistent. In the absence of a systematic review and meta-analysis is not possible to estimate the effect, but based on examination of identified studies it is small at most. The results of six trials that reported including 64–100% patients with concomitant allergic rhinitis and/or asthma aggravated by exposure to seasonal allergens seemed not to differ for the results of all other studies.

Harms

In both systematic reviews, there were no significant differences between the experimental and control groups in overall adverse events or in withdrawals due to adverse events, but results were again imprecise. Zafirlukast can increase the half-life of warfarin.

Conclusions and research needs

There is no net clinical benefit from oral leukotriene receptor antagonists compared to inhaled glucocorticosteroids used in monotherapy in patients with asthma – inhaled glucocorticosteroids are more beneficial. Net clinical benefit of oral leukotriene receptor antagonists in patients with asthma who already use inhaled glucocorticosteroids is uncertain. Considerable proportion of patients included in these trials had concomitant allergic rhinitis, although the exact number is impossible to estimate due to inadequate reporting. In trials that reported including more than 50% of patients with allergy or atopy there was no apparent clinical benefit from adding an oral leukotriene receptor antagonist to inhaled glucocorticosteroid. There is uncertainty if the results obtained in studied populations apply equally to patients who have both asthma and allergic rhinitis. The ARIA guideline panel did not make a recommendation about the relative benefit of using a combination of leukotriene receptor antagonists and inhaled glucocorticosteroids compared to inhaled glucocorticosteroids alone, because the available evidence was inconsistent and imprecise. Panel members felt it was not feasible to tell which option would be better for patients. that there may be subgroups of patients that would benefit from combined treatment, and therefore more research in patients with allergic rhinitis and asthma is needed to inform clinical recommendation. In the absence of a systematic review of trials that compared oral LTRA with placebo, net clinical benefit from using oral LTRA alone in patients who cannot use inhaled glucocorticosteroids or in children whose parents are concerned about use of inhaled glucocorticosteroids is uncertain. However, it is likely to be small at most. In the absence of a systematic review we concluded that the quality of available evidence supporting the use of oral LTRA compared to placebo would be moderate at best, because of the inconsistency in the results.
Well designed and rigorously executed randomised trials among patients with allergic rhinitis and allergic asthma that compare LTRA to placebo both in monotherapy or as add-on medication to inhaled glucocorticosteroids are needed. These trials should measure and properly report (74, 75) all asthma-related outcomes that are important to patients. If done, they are likely to have an important impact on this recommendation.

What others are saying

Guidelines for the treatment of asthma prepared by other organizations recommend LTRA as an add-on treatment to an initial therapy with inhaled glucocorticosteroid, but they acknowledge that this is less efficacious than adding long-acting β_2-agonist (666-668, 671). Guidelines also recommend LTRA as an optional single controlling medication for mild persistent asthma, but state that inhaled glucocorticosteroids are a preferred choice (666, 668, 671).

Recommendation

In patients with allergic rhinitis and asthma, we recommend inhaled glucocorticosteroids over oral leukotriene receptor antagonists as a single controlling medication for asthma (strong recommendation | moderate quality evidence).

In patients with allergic rhinitis and asthma who prefer not to use or cannot use inhaled glucocorticosteroids or in children whose parents do not agree to use inhaled glucocorticosteroids, we suggest oral leukotriene receptor antagonists for treatment of asthma (conditional recommendation | moderate quality evidence).

Underlying values and preferences: These recommendations place a relatively high value on a limited efficacy of LTRA and additional cost of treatment. The suggestion to use oral LTRA in patients who do not use inhaled glucocorticosteroids places relatively high value on small reduction in symptoms of asthma and improvement in quality of life, and a relatively low value on limiting the cost of treatment.

Remarks: These recommendations do not apply to the treatment of rhinitis (recommendations 16, 17, 21).

Question 46

Should subcutaneous allergen-specific immunotherapy be used in patients with allergic rhinitis and asthma?

Summary of findings

One systematic review of 75 randomised trials assessed the efficacy of subcutaneous allergen immunotherapy for asthma (724). We estimated that the limitations in the design and execution of the majority of included trials were not serious enough to downgrade the quality of evidence for this criterion.

Eight additional randomised trials published after the search for literature for this review was done were identified by the ARIA group members and summarised in ARIA update on allergen immunotherapy (28). Results of these trials confirmed the findings of the systematic review by Abramson and colleagues (724).

Benefits

Asthma symptoms were reported in 28 studies included in the systematic review by Abramson and colleagues (724). There was a significant moderate to large reduction in asthma symptoms, compared to placebo, following the subcutaneous immunotherapy with pollens (14 trials, 547 patients; SMD: -0.66; 95% CI: -0.99 to -0.33), house dust mite (9 trials, 304 patients; SMD: -0.78; 95% CI: -1.27 to -0.29), and cat allergens (2 trials, 54 patients; SMD: -1.74; 95% CI: -2.70 to -0.78). There was no improvement following immunotherapy noted after immunotherapy with dog or multiple allergen extracts (one very small study each). Twenty two studies reported symptoms as

worse, the same or improved. Symptoms were less likely to be rated as worsened following subcutaneous immunotherapy with pollen (RR: 0.25, 95% CI: 0.07 to 0.90), animal dander (RR: 0.46, 95% CI: 0.22 to 0.94), house dust mite (RR: 0.62, 95% CI: 0.44 to 0.87), and other allergens (RR: 0.46, 95% CI: 0.33 to 0.64).
Three trials compared subcutaneous immunotherapy to no treatment and noted similar effect on asthma symptoms (SMD: -1.84; 95% CI: -3.21 to -0.47). Only one trial of those included in the review measured quality of life in 44 patients with seasonal allergic rhinitis and asthma (655). Impairment of overall quality of life during the pollen season was less in the immunotherapy group than in the placebo group (median difference 0.8 point, 95% CI: 0.18 to 1.5 on a 7-point scale).

Harms

Abramson and colleagues did not report adverse effects of subcutaneous immunotherapy in these trials. An estimate of the risk of adverse events may be extrapolated from the systematic review of 51 randomised trials of SCIT in seasonal allergic rhinitis (479). In this review the risk of non-life threatening systemic adverse events was estimated to be 7% in SCIT and 0.65% in placebo groups, and the risk of anaphylactic shock was estimated to be 0.72% and 0.33% respectively. Adrenalin was used in 19 per 14,085 injections given in the SCIT groups and in 1 per 8278 injections in the placebo groups. There were no fatal events reported in any of the studies included in the review by Calderon and colleagues (479). However, there are observational data suggesting that there is a risk of death with subcutaneous immunotherapy, particularly in patients with asthma (725-727). In the report of the Committee of the Safety of Medicine sixteen of 26 patients that died from anaphylaxis induced by desensitising agent had asthma, one had allergic rhinitis, and nine had undocumented reason for immunotherapy (727). Estimated incidence of death was one per 97,285 courses of treatment sold (the number of injections in a course of treatment varied from three to 18, depending on the product). The Immunotherapy Committee of the American Academy of Allergy, Asthma and Immunology reports there were 17 (11 with asthma) fatal cases in 1985–1989 (725) and 41 fatal cases in 1990–2001 (726). Detailed data was available for 17 of 41 cases described by Bernstein and colleagues. Fifteen of these patients had asthma, and the majority had either labile asthma or had experienced prior hospital admission, emergency room visit, and/or respiratory arrest for asthma. It was estimated that fatal reactions occurred in 1 per 2,500,000 injections, with an average of 3.4 deaths per year (726).

Conclusions and research needs

Net clinical benefit from subcutaneous specific immunotherapy in patients with allergic rhinitis and concomitant asthma is uncertain. There is a moderate to large reduction in asthma symptoms, compared to placebo, following the subcutaneous immunotherapy, but the risk of serious adverse events is substantial. There is also small, but serious risk of death. In the absence of an updated systematic review, we concluded that an overall quality of evidence for subcutaneous immunotherapy with pollen, house dust mite, and cat allergens to be moderate, since the evidence is imprecise due to small number of patients in the trials.
An updated rigorously performed and reported (223, 224) systematic review of subcutaneous specific immunotherapy in patients with allergic rhinitis and concomitant asthma that provides information on all outcomes important to patients, including adverse effects, is required for the next update of the ARIA guidelines.

What others are saying

Guidelines for the treatment of asthma prepared by other organizations either recommend that subcutaneous specific immunotherapy is considered for patients who have persistent asthma and for

whom there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive (666, 671) or do not make explicit recommendations for use of subcutaneous specific immunotherapy (668, 728). Those that do not make explicit recommendations state that immunotherapy may reduce asthma symptoms and use of asthma medications, but further comparative studies are needed (667) or that the role of specific immunotherapy in adult asthma is limited and it should be considered only after strict environmental avoidance and pharmacologic intervention have failed to control a patient's asthma(668).

Recommendation

In patients with allergic rhinitis and asthma, we suggest subcutaneous specific immunotherapy for treatment of asthma (conditional recommendation | moderate quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on reducing the symptoms of asthma, and a relatively low value on avoiding adverse effects and limiting the cost of subcutaneous specific immunotherapy. In patients who are more averse to the side effects of subcutaneous specific immunotherapy an alternative choice may be equally reasonable.

Remarks: Subcutaneous specific immunotherapy may also be used in patients with asthma and concomitant allergic rhinitis for treatment of rhinitis. Resource limitations will have stronger implications for the implementation of this recommendation.

Question 47

Should sublingual specific immunotherapy be used in patients with allergic rhinitis and asthma?

Summary of findings

Four systematic reviews assessed the efficacy of sublingual immunotherapy in asthma. One included randomised trials performed in adults and children (729), and the other three focused on children (550, 730, 731). We could not use any of these reviews to inform this recommendation, because they were done before newer important studies were published and there was high likelihood of errors during data extraction from primary studies.

Most studies in adults and children with allergic rhinitis (see questions 34 and 35) included also some patients with asthma. We identified five trials of SLIT in adults that explicitly enrolled patients with asthma (493, 494, 503, 516, 542) and another four trials in which at least 50% of patients had asthma (502, 505, 537, 540). Of these studies we used only two (493, 516) to inform this recommendation (see evidence profile 1 for question 47). We excluded other studies, because they either measured overall symptoms, did not report variability in results or did not specify what measure of variability was used. Thus, the results were highly inconsistent and there was very serious concern about directness of composite symptom scores that at least in some studies were explicitly designed to emphasize nasal symptoms.
We identified ten studies of SLIT that explicitly enrolled children with asthma (555, 562, 564, 566, 569, 571, 732-735) and another three trials in which at least 50% of children had asthma (553, 565, 573). We could not use data from two studies. One reported variability in a way that could not be reliably used in meta-analysis (of note, the authors of three systematic reviews of SLIT used different values of effect on asthma symptoms from this study, none of which was actually reported

in the original publication) (562) and the other reported its results on a graph as several measurements over time (573) in a way that it was not possible to use any values for meta-analysis that would reflect the actual symptoms during the study (see description of studies for question 35). All other studies of SLIT in adults and children with allergic rhinitis either included less than 50% patients with concomitant asthma or did not report the proportion of patients with asthma, despite some of them measured asthma symptoms (557, 570, 575). We considered results of these studies too indirect to inform this recommendation (pooled estimate from these three studies showed no effect and was very imprecise SMD: -0.13, 95% CI: -0.67 to 0.41).
We included only studies that explicitly enrolled children with asthma in our primary analysis (see evidence profile 2 for question 47). Including all studies that enrolled at least 50% children with asthma would not substantially change the estimate of effect (SMD: -0.80, 95% CI: -0.20 to -1.41). Including all above studies plus those that enrolled less than 50% of children with asthma but reported asthma symptoms and were included in previous systematic reviews (557, 570, 572, 575) would also not change the estimate of effect on asthma symptoms (SMD: -0.62, 95% CI: -0.18 to -1.06).
One additional study (568) reported its results as number of children whose asthma improved and fond a benefit from SLIT (relative risk: 1.23, 95% CI: 1.00 to 1.53; risk difference: 157 more per 1000, 95% CI: from 1 more to 307 more), however, the results did not exclude no effect.

Benefits

Sublingual specific immunotherapy may have a small to moderately beneficial effect on asthma symptoms in adults and children (see evidence profile 1 and 2 for question 47), but the results do not exclude no effect. Asthma exacerbations and quality of life were not measured or reported in any of the studies.

Harms

There were no serious adverse effects in the included studies, however, there was a consistent increased risk of local adverse reactions (oral pruritus and oedema) with sublingual specific immunotherapy (see discussion of harms for questions 34 and 35).

Other considerations
See discussion of other considerations for questions 34 and 35.

Conclusions and research needs

Net clinical benefit of sublingual specific immunotherapy in treatment of asthma is uncertain. There is uncertainty if beneficial effects are large enough to counterbalance frequent local adverse effects. An updated rigorously performed and reported (223, 224) systematic review of sublingual specific immunotherapy versus placebo among adults and children with allergic rhinitis and asthma that provides information on all outcomes important to patients, including adverse effects, is required for the next update of the ARIA guidelines. There is also a need for rigorously designed and executed randomised trials of SLIT in adults and children that measure and properly report (74, 75) patient-important outcomes and adverse effects. Further research, if done, is very likely to have important impact on this recommendation.

What others are saying

Guidelines for the treatment of asthma prepared by other organizations do not make recommendations about sublingual specific immunotherapy and either do not mention it at all (667,

668) or state that it has been reported to be effective in asthma (671) and more clinical trials are needed (666).

Recommendation

In patients with allergic rhinitis and asthma, we suggest sublingual specific immunotherapy for treatment of asthma (conditional recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on possible reduction of asthma symptoms, and a relatively low value on avoiding adverse effects and limiting the cost of sublingual specific immunotherapy.

Remarks: Sublingual specific immunotherapy may also be used in patients with asthma and concomitant allergic rhinitis for treatment of rhinitis. Resource limitations will have stronger implications for the implementation of this recommendation.

Question 48

Should a monoclonal antibody against IgE be used for treatment of asthma in patients with allergic rhinitis and asthma?

Summary of findings

One systematic review reporting 14 studies assessed the efficacy and safety of monoclonal antibody against IgE (anti-IgE) compared with placebo in patients with allergic asthma (736). Another systematic review reporting 5 trials focused exclusively on the quality of life (737).
We used systematic review by Walker and colleagues to prepare summary of evidence and to inform this recommendation, because it was methodologically more sound, reported all outcomes, and included more studies. Trials assessing the efficacy of monoclonal anti-IgE compared to placebo in patients with asthma not receiving inhaled glucocorticosteroids did not report any patient-important outcomes (736).
All studies included adult or adolescent patients, except for one that enrolled children aged 6–12 years (738). Positive result of skin test to common aero-allergens was an entry criterion in all studies.In the trials that examined subcutaneous monoclonal anti-IgE patients had moderate to severe asthma.
One non-systematic review examined omalizumab manufacturer's clinical trials and postmarketing surveillance data on anaphylaxis (739).

Benefits

In patients with moderate/severe allergic asthma monoclonal anti-IgE used as an add-on to inhaled glucocorticosteroids moderately reduced asthma symptoms and exacerbations, and improved quality of life compared to placebo. Considerable placebo effect on quality of life and global evaluation of treatment was observed. Subcutaneous administration of monoclonal anti-IgE allowed reducing the usage of inhaled glucocorticosteroids by a mean of 118 μg (95% CI: 83 to 154) budesonide equivalents with almost twice as many patients being able to reduce their inhaled corticosteroid dose by more than 50% compared to placebo (relative benefit: 1.79, 95% CI: 1.59 to 1.99). However, clinical significance of this effect is uncertain, since there was a large mean improvement in the placebo group of 320 μg daily in patients with moderate/severe asthma. This reduction in inhaled corticosteroid dose was accompanied with reduced risk of exacerbation.
Among patients with severe asthma who used oral glucocorticosteroids, monoclonal anti-IgE did

not influence the probability of oral corticosteroid withdrawal (relative risk: 0.99, 95% CI: 0.50 to 1.74) or daily dose reduction (median 69% vs. 75%, p=0.68) compared to placebo, but these results were very imprecise.
One trial focused specifically on patients with asthma and concomitant allergic rhinitis (740). Its results were consistent with the results of other trials in patients with allergic asthma regardless of allergic rhinitis status.

Harms

Subcutaneous monoclonal anti-IgE was generally well tolerated, although it requires subcutaneous injections. Injection site reactions were present in 10% of patients and were twice as frequent with monoclonal anti-IgE as with placebo (relative risk 1.91, 95% CI: 1.35 to 2.67). In a review of randomised trials and observational studies that examined the risk of anaphylaxis there were 41 anaphylactic reactions (35 patients) in 39 510 patients that received omalizumab, that represents a risk of 9 per 10 000 patients (739). None of the patients died or required intubation and mechanical ventilation. There is also uncertainty about the risk of malignancy, that although statistically not significant does not exclude a serious harm (relative risk: 2.17, 95% CI: 0.84 to 5.57; risk difference: 3 more per 1000, 95% CI: from 1 less per 1000 to 6 more per 1000)(741).

Conclusions and research needs

Net clinical benefit from a monoclonal antibody against IgE in patients with asthma is uncertain, because clinical benefits seem to be very closely balanced with risks, burden, and cost of treatment. Monoclonal anti-IgE reduces symptom severity and the risk of exacerbation, and improves quality of life when added to inhaled corticosteroids in patients with moderate/severe allergic asthma. It also allows reducing the dose of inhaled corticosteroids, although clinical significance of this effect is uncertain. In patients with severe asthma receiving oral glucocorticosteroids monoclonal anti-IgE did not allow reducing their dose, although the estimated effect is very imprecise.
Because of these downsides, any net clinical benefit from monoclonal antibody against IgE seems to be confined to patients with severe asthma not responding to other treatment.

What others are saying

Guidelines for the treatment of asthma prepared by other organizations recommend that monoclonal anti-IgE may be considered as adjunctive therapy for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose inhaled corticosteroids and long-acting β_2-agonists (671). Others do not make explicit recommendations, but either state its registered indications(667) or that a monoclonal anti-IgE is a treatment option limited to patients with elevated serum levels of IgE and has been shown to improve control of allergic asthma when it has not been achieved with a combination of other controller medications including high-doses of inhaled or oral glucocorticosteroids(668). Guidelines for the treatment of asthma in children state that no data are yet available for a paediatric population and further research is needed (666).

Recommendation

In patients with allergic rhinitis and asthma with a clear IgE-dependent allergic component, uncontrolled despite optimal pharmacologic treatment and appropriate allergen avoidance, we suggest monoclonal antibody against IgE for treatment of asthma (conditional recommendation | moderate quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on reduction of symptoms of asthma and exacerbations in patients with severe asthma, and a relatively low value on avoiding the burden of subcutaneous injections, cost of treatment, small risk of anaphylaxis and some uncertainty about the risk of malignancy.

Priorities for revision of the guidelines

Plans for updating the guidelines

Guidelines are living documents. To remain useful, they need to be updated regularly as new information becomes available. A revision of this document will be needed because for many clinical questions it asked there were no systematic reviews of current evidence. This document will be updated when these reviews are performed, major new research is published or new treatments become available. This update is planned in 2012.

Updating or adapting recommendations locally

The methods used to develop the guidelines are transparent. The recommendations have been developed to be as specific and detailed as possible without losing sight of the user-friendliness of this document and the individual recommendations. Since recommendations in ARIA guidelines are developed as international guidelines, the ARIA guideline panel encourages feedback on all aspects of these guidelines including their applicability in individual countries. This feedback will be considered when revising the document.

Inclusion of additional information

These guidelines cover a limited number of clinical questions. Many other questions relevant to the management of allergic rhinitis and its impact on asthma have been identified as potentially important. ARIA will develop a process to register and prioritize additional questions to be included in subsequent revisions. Topics that were identified during the consultation as potential priorities for update and additional evidence reviews include:

- recommendations on using special formulas containing hydrolysed protein for prevention of allergy in infants
- relative effectiveness and safety of different homeopathic methods and herbal medicines
- recommendations on using intranasal saline in perennial allergic rhinitis
- recommendations on prevention and treatment of complications of allergic rhinitis
- refinement of recommendations on the use of particular medications considering the intermittent/seasonal or persistent/perennial allergic rhinitis

Priorities for research

General comments

During the guideline development process we often identified a need for more data on specific topics. This results in the following recommendations for research. We summarize these gaps in the evidence as research recommendations, to assist those in a position to provide such information by the design and execution of specific research projects and programmes to answer these questions. Any Recommendation in these guidelines that was supported by low or very low evidence clearly indicates an area in which there is need for more evidence through systematic research. Examining the available evidence for this revision of ARIA guidelines we found serious limitations in investigating and reporting some critical outcomes, particularly quality of life and adverse effects. We encourage investigators to measure and properly report all outcomes that are important to patients.

Most prominent specific research questions to be addressed

Prevention of allergy
1. Should formulas containing hydrolysed protein instead of cow's milk be used in infants not being able to be breastfed for the prevention of allergy and/or asthma?

Allergen avoidance measures for allergic rhinitis and/or asthma
2. Should patients allergic to indoor moulds avoid exposure to these allergens at home? (a well designed and executed randomised trials of different methods of removing moulds are needed)

Pharmacotherapy for allergic rhinitis
3. What is the relative efficacy and safety of individual oral H1-antihistamines in treatment of allergic rhinitis? (a systematic review addressing patient-important outcomes is needed)
4. Should oral H1-antihistamine be used as a rescue medication (as-needed) versus regularly for treatment of allergic rhinitis? (a systematic review addressing patient-important outcomes is needed)
5. What is the efficacy and safety of intranasal glucocorticosteroids in treatment of allergic rhinitis? (a systematic review addressing patient-important outcomes is needed)
6. Should oral glucocorticosteroids be used for treatment of allergic rhinitis in patients not responding to other therapy? (a well designed and executed randomised trial investigating the effect of a short course of oral glucocorticosteroids as an add-on therapy on patient-important outcomes is needed)
7. Should short courses of intranasal decongestant be used for treatment of nasal obstruction in allergic rhinitis? (a well designed and executed randomised trial investigating the effect of a short course of intranasal decongestant as an add-on therapy on patient-important outcomes is needed)
8. Should oral decongestant be used as a rescue medication (as-needed) for treatment of allergic rhinitis? (a well designed and executed randomised trial measuring patient-important outcomes is needed)
9. Should combination of oral decongestant and H1-antihistamine versus oral H1-antihistamine alone be used as a rescue medication (as-needed) for treatment of allergic rhinitis? (a well designed and executed randomised trial measuring patient-important outcomes is needed)

Allergen specific immunotherapy for allergic rhinitis

10. Should subcutaneous specific immunotherapy be used for treatment of allergic rhinitis in adults and children without concomitant asthma? (a well designed and executed randomised trial that measure and carefully report patient-important outcomes is needed)
11. Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in adults and children without concomitant asthma? (a complete rigorously performed systematic review that reports all patient-important outcomes is needed; a well designed and executed randomised trial that measure and carefully report patient-important outcomes is needed; optimal dose, dosing schedule, and duration of sublingual specific immunotherapy have to be established)
12. Should local nasal specific immunotherapy be used for treatment of allergic rhinitis in adults and children? (a complete rigorously performed systematic review that reports all patient-important outcomes is needed)

Complementary and alternative treatments for allergic rhinitis
13. Should butterbur extract be used for treatment of allergic rhinitis? (an independent well designed and executed randomised trial that measures and carefully reports patient-important outcomes is needed)

Treatment of asthma in patients with concomitant allergic rhinitis
14. Should leukotriene receptor antagonists be used for treatment of asthma in patients with concomitant allergic rhinitis? (a well designed and executed randomised trial that measure and carefully report patient-important outcomes in this particular population of patients with seasonal or perennial/persistent allergic rhinitis is needed)
15. Should sublingual specific immunotherapy be used in patients with allergic rhinitis and concomitant asthma? (a well designed and executed randomised trial that measure and carefully report patient-important outcomes is needed)

Adaptation and/or localisation of guidelines

As described above, adaptation of these guidelines will be necessary in many circumstances Depending on when such a process takes place, advice to the WHO describes that the following steps should be taken(742):

- Appointing a guideline committee comprising clinicians and methodologists
- Determining the scope of the guidelines
- Defining the clinical questions to be addressed
- Updating the evidence tables if necessary
- Reviewing the recommendations in the guidelines (the recommendations may need to be modified at a national level, depending on the local values, availability of medications, and costs)
- Disseminating the guidelines, with a ~~"u~~se by" date
- Developing a method to obtain feedback and plans for review and update.

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Potential conflicts of interest

The following statements follow the template of declaring potential conflict of interests for the World Health Organization.

J.L.B. is an editor of a clinical journal where various drugs are advertised, including those that are the subject of this guideline; he received honoraria for speaking at conferences from GlaxoSmithKline and is a member of the GRADE working group.
J.B. received fees and honoraria for lectures, expert panel participation and consultations from Allmiral, AstraZeneca, Centocor, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Novartis, Nycomed-Altana, Pfizer, Roche, Sanofi-Aventis, Stallergènes, Schering Plough, UCB and Uriach.
C.B.C. received fees for consultancy, speaker bureau participation, lectures and research grants from Sanofi-Aventis, Novartis, GSK, Schering Plough, ALK and Abello.

S.B. has no conflict of interest, but declares membership in the Agenzia Italiana del Farmaco (AIFA) Research & Development panel.
G.W.C. received fees and honoraria for lectures, expert panel participation and consultations and research support from A. Menarini, Alcon, Alk-Abellò, Almirall, Altana, Anallergo, AstraZeneca, Aventis Pharma, Bayer, Biofutura Pharma, Boehringer Ingelheim, Chiesi Farmaceutici, Chiron, Essex, Fujisawa, Genentech, Gentili, GlaxoSmithKline, Lofarma, Merck Sharp & Dome, Novartis, Pfizer, Pharmacia & Upjohn, Schering Plough, SigmaTau, Stallergenes, Yamanuchi, UCB Pharma and Valeas.
R.GvW. received fees for lectures and expert panel participation from Allmiral, Alcon, Merck Sharp & Dome, Novartis, Stallargènes and UCB.
H.J.S. is co-chair of the GRADE working group and he supports the implementation of the GRADE approach worldwide. From non-profit organizations he has accepted honoraria and consulting fees for activities in which his work with GRADE is relevant. In the past five years, HJS received no personal payments for service from pharmaceutical for profit organizations. No financial support was received for the preparation of the evidence profiles or provided to the evidence synthesis team that HJS led as part of this work.
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Appendix – search strategies

I. General search terms for identifying systematic reviews and randomized trials

For systematic reviews we searched:

1. the Cochrane Library of Systematic Reviews
2. PubMed MEDLINE using the following search terms: systematic[sb] OR medline[Title/Abstract] OR meta-analysis[Title] OR meta-analysis[Publication Type] OR "systematic review"[Title]

If no systematic review was found we searched Google Scholar using the terms: meta-analysis OR "systematic review"

For randomized trials we searched:

1. the Cochrane Central Register of Controlled Trials (CENTRAL)
2. PubMed MEDLINE using the following search terms: (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))

If no RCT was found we searched PubMed MEDLINE using the following search terms: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

If no RCT was found we searched Google Scholar using the terms: randomized OR randomised

I. Specific search terms for identifying evidence about each clinical question

Question 1

(breastfeeding OR breast feeding) AND (atopy OR sensitization OR allergy OR allergic OR asthma)

Question 2

(diet OR dietary) AND (atopy OR sensitization OR allergy OR allergic OR asthma)

Question 3

(tobacco OR smoke OR smoking) AND (atopy OR sensitization OR allergy OR allergic OR asthma)

Questions 4 & 7

(mite OR mites OR dermatophagoides OR euroglyphus) AND (atopy OR atopic OR allergy OR allergic OR asthma* OR wheez*)

Question 5 & 9

(atopy OR atopic OR allergy OR allergic OR asthma* OR wheez*) AND (prevent* OR develop* OR avoid*) AND (pet[tiab] OR pets[tiab] OR dog[tiab] OR dogs[tiab] OR canine[tiab] OR cat[tiab] OR cats[tiab] OR feline[tiab] OR bird[tiab] OR birds[tiab] OR animal[tiab] OR animals[tiab]) NOT (animal[mh] NOT human[mh]))

Question 6 & 10

(occupational OR workplace OR "work related" OR worker OR workers) AND (atopy OR atopic OR allergy OR allergic OR asthma* OR wheez*)

Question 8

(mold[tiab] OR molds[tiab] OR dampness[tiab]) AND (atopy OR atopic OR allergy OR allergic OR asthma* OR wheez*)

Question 11–13

(antihistamine* OR "Histamine H1 Antagonists"[mh] OR mepyramine OR pyrilamine OR antazoline OR diphenhydramine OR carbinoxamine OR doxylamine OR clemastine OR dimenhydrinate OR pheniramine OR chlorphenamine OR chlorpheniramine OR brompheniramine OR triprolidine OR hydroxyzine OR promethazine OR cyproheptadine OR azatadine OR ketotifen OR acrivastine OR cetirizine OR loratadine OR mizolastine OR fexofenadine OR levocetirizine OR desloratadine) AND ("allergic rhinitis" OR "hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR "nasal congestion" OR "nasal itching" OR rhinorrhea)

Question 14

(((antihistamine* OR —Histamine H1 Antagonists”[mh]) AND (nasal OR intranasal OR topical)) OR azelastine OR levocabastine OR olopatadine) AND (allergic rhinitis OR —hay fever” OR hayfever OR nasal allergy OR nasal allergies OR nasal congestion OR nasal itching OR rhinorrhea)

Question 15 & 25

(azelastine OR levocabastine OR olopatadine) AND (cetirizine OR loratadine OR mizolastine OR fexofenadine OR levocetirizine OR desloratadine) AND (allergic rhinitis OR —hay fever” OR hayfever OR nasal allergy OR nasal allergies OR nasal congestion OR nasal itching OR rhinorrhea)

Question 16–17 & 21

(leukotriene antagonists[mh] OR antileukotriene* OR leukotriene* OR montelukast OR zafirlukast OR pranlukast OR zileuton) AND (allergic rhinitis OR —hay fever” OR hayfever OR nasal allergy OR nasal allergies OR nasal congestion OR nasal itching OR rhinorrhea)

Question 18

(steroid* OR steroids OR corticosteroid* OR glucocorticoid* OR beclomethasone OR fluticasone OR triamcinolone OR budesonide OR mometasone OR flunisolide OR ciclesonide OR (–Anti-Inflammatory Agents”[pa] NOT –Anti-Inflammatory Agents, Non-Steroidal”[pa])) AND ("allergic rhinitis" OR "hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR "nasal congestion" OR "nasal itching" OR rhinorrhea)

Question 19

(antihistamine* OR (–Histamine H1 Antagonists”[mh]) OR mepyramine OR pyrilamine OR antazoline OR diphenhydramine OR carbinoxamine OR doxylamine OR clemastine OR dimenhydrinate OR pheniramine OR chlorphenamine OR chlorpheniramine OR brompheniramine OR triprolidine OR hydroxyzine OR promethazine OR cyproheptadine OR azatadine OR ketotifen OR acrivastine OR cetirizine OR loratadine OR mizolastine OR fexofenadine OR levocetirizine OR desloratadine) AND (steroid* OR steroids OR corticosteroid* OR glucocorticoid* OR beclomethasone OR fluticasone OR triamcinolone OR budesonide OR mometasone OR flunisolide OR ciclesonide) AND ("allergic rhinitis" OR "hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR "nasal congestion" OR "nasal itching" OR rhinorrhea)

Question 20

(steroid* OR steroids OR corticosteroid* OR glucocorticoid* OR beclomethasone OR fluticasone OR triamcinolone OR budesonide OR mometasone OR dexamethasone OR flunisolide OR ciclesonide OR (–Anti-Inflammatory Agents”[pa] NOT –Anti-Inflammatory Agents, Non-Steroidal”[pa])) AND (((antihistamine* OR —Histamine H1 Antagonists”[mh]) AND (nasal OR intranasal OR topical)) OR azelastine OR levocabastine OR olopatadine)

Question 22

(steroid* OR steroids OR corticosteroid* OR glucocorticoid* OR dexamethasone OR prednisone OR prednisolone OR methylprednisolone OR (–Anti-Inflammatory Agents”[pa] NOT –Anti-Inflammatory Agents, Non-Steroidal”[pa])) AND (oral[tiab] OR orally[tiab] OR –per os”[tiab] OR systemic[tiab]) AND ("allergic rhinitis" OR –hay fever” OR hayfever OR "nasal allergy" OR "nasal allergies" OR "nasal congestion" OR "nasal itching" OR rhinorrhea)

Question 23

(steroid* OR steroids OR corticosteroid* OR glucocorticoid* OR dexamethasone OR methylprednisolone OR diprophos OR betamethasone OR hydrocortisone OR (–Anti-Inflammatory Agents”[pa] NOT –Anti-Inflammatory Agents, Non-Steroidal”[pa])) AND (depot OR intramuscular OR prolong*) AND (allergic rhinitis OR –hay fever” OR hayfever OR nasal allergy OR nasal allergies OR nasal congestion OR nasal itching OR rhinorrhea)

Question 24

(chromones OR nedocromil OR cromolyn OR cromoglycate OR lodoxamide) AND (allergic rhinitis OR –hay fever” OR hayfever OR nasal allergy OR nasal allergies OR nasal congestion OR nasal itching OR rhinorrhea)

Question 26

ipratropium AND ("allergic rhinitis" OR –hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR "nasal congestion" OR "nasal itching" OR rhinorrhea)

Question 27

(((nasal OR intranasal) AND decongestant) OR phenylephrine OR naphazoline OR xylometazoline OR oxymetazoline) AND ("allergic rhinitis" OR –hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR "nasal congestion" OR "nasal itching" OR rhinorrhea)

Question 28 & 29

((oral* AND decongestant*) OR ephedrine OR pseudoephedrine) AND ("allergic rhinitis" OR –hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR "nasal congestion" OR "nasal itching" OR rhinorrhea)

Question 30

(antihistamine* OR —Histamine H1 Antagonists"[mh] OR azelastine OR emedastine OR levocabastine OR olopatadine OR ketotifen)

Question 31

("chromones"[MeSH Terms] OR chromones[Text Word]) OR ("nedocromil"[MeSH Terms] OR nedocromil[Text Word]) OR (("cromolyn sodium"[TIAB] NOT Medline[SB]) OR "cromolyn sodium"[MeSH Terms] OR cromoglycate[Text Word]) OR ("lodoxamide ethyl"[Substance Name] OR lodoxamide[Text Word]) AND (intraocular OR ocular OR eye OR eyes OR conjunctiv* OR drops)

Question 32–36 & 46 & 47

(immunotherapy OR desensiti* OR hyposensiti*) AND ("allergic rhinitis" OR –hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR "nasal congestion" OR "nasal itching" OR rhinorrhea)

Question 37

homeopat* AND ("allergic rhinitis" OR –hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR –nasal congestion" OR –nasal itching" OR rhinorrhea)

Question 38

accupuncture AND ("allergic rhinitis" OR –hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR –nasal congestion" OR –nasal itching" OR rhinorrhea)

Question 39

(butterbur OR petasites) AND ("allergic rhinitis" OR –hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR –nasal congestion" OR –nasal itching" OR rhinorrhea)

Question 40

(herbal OR herb) AND ("allergic rhinitis" OR –hay fever" OR hayfever OR "nasal allergy" OR "nasal allergies" OR –nasal congestion" OR –nasal itching" OR rhinorrhea)

Question 41

We relied on the search done by Passalacqua and colleagues (J Allergy Clin Immunol 2006;117:1054–1062)

Question 42

(asthma OR wheez*) AND (antihistamine* OR –Histamine H1 Antagonists"[mh] OR mepyramine OR pyrilamine OR antazoline OR diphenhydramine OR carbinoxamine OR doxylamine OR clemastine OR dimenhydrinate OR pheniramine OR chlorphenamine OR chlorpheniramine OR brompheniramine OR triprolidine OR hydroxyzine OR promethazine OR cyproheptadine OR azatadine OR ketotifen OR acrivastine OR cetirizine OR loratadine OR mizolastine OR fexofenadine OR levocetirizine OR desloratadine)

Question 43

(asthma OR wheez*) AND (decongestant OR ephedrine OR pseudoephedrine)

Question 44

(steroid* OR steroids OR corticosteroid* OR glucocorticoid* OR beclomethasone OR fluticasone OR triamcinolone OR budesonide OR mometasone OR dexamethasone OR flunisolide OR

ciclesonide OR (―Anti-Inflammatory Agents"[pa] NOT ―Anti-Inflammatory Agents, Non-Steroidal"[pa])) AND (asthma OR wheez*) AND (nasal OR intranasal OR nose OR topical)

Question 45

(leukotriene antagonists[mh] OR antileukotriene* OR leukotriene* OR montelukast OR zafirlukast OR pranlukast OR zileuton) AND (asthma OR wheez*)

Question 48

omalizumab OR xolair

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Table 1. Interpretation of strong and conditional (weak) recommendations		
	Strong recommendation	**Conditional (weak) recommendation**
Implications		
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 in most situations	Policy making will require substantial debate and involvement of various stakeholders

Table. Interpretation of "strong" and "weak" recommendations		
	Strong recommendation	**Conditional (weak) recommendation**
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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 in most situations	Policy making will require substantial debates and involvement of various stakeholders