Statistical considerations in indirect comparisons and network meta-analysis

Said Business School, Oxford, UK
March 18-19, 2013
Introduction

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Hay fever in adolescents and adults

Search date April 2008
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ABSTRACT
INTRODUCTION: Hay fever is found throughout the world. Epidemiological evidence suggests considerable geographical variation in its prevalence. Symptoms are caused by an IgE-mediated type 1 hypersensitivity reaction to airborne allergens such as pollen or fungal spores, and may also cause eye, sinus, respiratory, and systemic problems. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for hay fever in adolescents and adults? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2008 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 211 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: intranasal corticosteroids, oral antihistamines, intranasal antihistamines, oral leukotriene receptor antagonists, systemic corticosteroids, intranasal ipratropium bromide, oral decongestants, and combinations of these treatments.

QUESTIONS
What are the effects of treatments for hay fever in adolescents and adults?
### Option: Antihistamines (Oral)

**Symptom relief**

*Compared with placebo* Antihistamines (acrivastine, azatadine, brompheniramine, cetirizine, levocetirizine, ebastine, fexofenadine, loratadine, desloratadine, rupatadine, and mizolastine) are more effective at improving nasal and ocular symptoms (*moderate-quality evidence*).

*Compared with intranasal azelastine* Oral antihistamines seem equally effective at improving symptoms of rhinitis and nasal congestion (*moderate-quality evidence*).

*Compared with montelukast* We don't know how the effectiveness of loratadine and montelukast compare at reducing rhinitis symptoms (*low-quality evidence*).

*Compared with intranasal corticosteroids (beclometasone, budesonide, fluticasone, and triamcinolone)* Oral antihistamines (dexchlorpheniramine, terfenadine, astemizole, loratadine, and cetirizine) may be less effective at improving nasal symptoms, but may be equally effective at improving ocular symptoms (*low-quality evidence*).

*Compared with antihistamines plus leukotriene antagonists* Antihistamines alone may be equally effective at improving nasal symptoms (*low-quality evidence*).

*Compared with antihistamines plus pseudoephedrine* Antihistamines alone seem less effective at reducing nasal symptoms (*moderate-quality evidence*).
## TREATMENT OF HAY FEVER

### Beneficial
- Intranasal antihistamines (azelastine) .......................... 13
- Intranasal corticosteroids ........................................... 3
- Oral antihistamines (acrivastine, azatadine, brompheniramine, cetirizine, levocetirizine, ebastine, fexofenadine, loratadine, desloratadine, rupatadine, and mizolastine) ................................................................. 9
- Oral antihistamines plus pseudoephedrine (reduce nasal symptom severity compared with antihistamines alone) .................................................................................................................. 24

### Likely to be beneficial
- Intranasal antihistamines (levocabastine and olopatadine) ................................................................. 15
- Leukotriene receptor antagonists (oral) .............. 17
- Systemic corticosteroids ............................................. 22

### Unlikely to be beneficial
- Oral antihistamines plus leukotriene receptor antagonists (seem no more effective than either treatment alone) .... 9

### Likely to be ineffective or harmful
- Oral antihistamines (astemizole; associated with cardiac adverse effects) .................................................. 12
- Oral antihistamines (terfenadine; associated with cardiac adverse effects) .................................................. 12

### To be covered in future updates
- Effects of prophylactic treatments: allergen avoidance; sodium cromoglycate; immunotherapy (intranasal, subcutaneous, and sublingual); homeopathy; and anti-immunoglobulin E.

Hay fever in children
A new methodological framework

Other names:
Multiple-treatments meta-analysis, Mixed-treatment comparison

Many different intervention

Network meta-analysis

Meta-analysis of RCTs

Randomized Controlled trials (RCTs)

Cohort studies, Case-control studies

Two interventions
A network of trials: topical fluoride therapy
Conditions for valid inference about ‘best’ treatment

- High internal validity / low risk of bias
- Low risk of reporting bias
- Clinical diversity not relevant or low (high ‘combinability’)
- Good fit of statistical model

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Conditions for valid inference about ‘best’ treatment

Considerations extend across studies making different comparisons

- High internal validity / low risk of bias: Yes
- Low risk of reporting bias: Yes
- Clinical diversity not relevant or low (high ‘combinability’): Yes
- Good fit of statistical model: Yes

Considerations include possibility of inconsistency (conflict) between different types of evidence
Course objectives

• by the end of the course, participants should be able...
  – to understand the principles, steps and statistical methods involved in indirect comparisons and network meta-analyses;
  – to understand the biases that can distort indirect comparisons and network meta-analysis, including conflict among different sources of evidence, and ways to address these issues;
  – to be aware of current thinking in presenting findings from indirect comparisons and network meta-analyses, including issues related to risk of bias and quality (within Summary of Findings tables); and
  – to support Cochrane editorial bases in their support of review authors undertaking indirect comparisons and network meta-analysis.
Outline of the course: Monday

- Pair-wise meta-analysis
Outline of the course: Monday

- Pair-wise meta-analysis
- Indirect comparisons
Outline of the course: Monday

- Pair-wise meta-analysis
- Indirect comparisons
  - and mixed comparisons
  - ‘loops’ of evidence
Outline of the course: Monday

• Pair-wise meta-analysis
• Indirect comparisons
  – and mixed comparisons
  – ‘loops’ of evidence
• Meta-regression
  – for indirect comparisons
Outline of the course: Monday

• Pair-wise meta-analysis
• Indirect comparisons
  – and mixed comparisons
  – ‘loops’ of evidence
• Meta-regression
  – for indirect comparisons
  – for network meta-analysis
Outline of the course: Monday

- Pair-wise meta-analysis
- Indirect comparisons
  - and mixed comparisons
  - ‘loops’ of evidence
- Meta-regression
  - for indirect comparisons
  - for network meta-analysis
- Small group discussion
- Computer practicals
Outline of the course: Tuesday

• Problem of multi-arm studies
  – Full network meta-analysis
  – Multivariate meta-analysis
Outline of the course: Tuesday

• Problem of multi-arm studies
  – Full network meta-analysis
  – Multivariate meta-analysis

• Inconsistency (conflicting evidence)
Outline of the course: Tuesday

- Problem of multi-arm studies
  - Full network meta-analysis
  - Multivariate meta-analysis
- Inconsistency (conflicting evidence)
- Presentation of results
Outline of the course: Tuesday

- Problem of multi-arm studies
  - Full network meta-analysis
  - Multivariate meta-analysis
- Inconsistency (conflicting evidence)
- Presentation of results
- Presentations from small-group discussions
- Group discussion of implications for Cochrane Reviews
Cochrane Comparing Multiple Interventions Methods Group
Oxford Training event, March 2013

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