ALLERGIC RHINITIS: Evidence Based Medicine

Cancun, December 5, 2011

Prof. Giorgio Walter Canonica
Allergy and Respiratory Diseases Department
University of Genoa

Past President

1° vice President
Prof. Giorgio Walter CANONICA, in the last five years, has been:
- scientific consultant as a single scientist or in national/international boards,
- researcher in scientific trials in his university or in collaboration with other research institutions,
- speaker in scientific meetings, seminars and educational activities devoted to specialists, general practitioners and other healthcare professionals,
totally or partially supported by the following commercial companies:

- A.Menarini
- Alk-Abello’
- Almirall
- Allergy Therapeutics
- Anallergo
- AstraZeneca
- Boeringher Ingelheim

- Chiesi Farmaceutici
- Danone
- Faes
- Glaxo Smith Kline
- Hal
- Lallemand
- Lofarma
- Merck Sharp & Dome
- Nycomed Takeda
- Novartis

- Pfizer
- Sanofi
- SigmaTau
- Stallergenes
- Thermo Fisher
- URIACH
- Valeas
Table 2. Opinion-based medicine

Physicians always try to base their decisions on the best available evidence, all too often this evidence represents:

- extrapolations from physiopathology
- conditioning from pre- and postgraduate training,
- clinical experience
- logic, rather than established facts

*Bousquet J. et al., Allergy 2004*
Opinion Based Medicine

POSITION PAPER
ITALIAN SOCIETY of ALLERGY
& CLINICAL IMMUNOLOGY

IMMUNOTERAPIA SPECIFICA delle ALLERGIE

G.W.CANONICA

SLIT:

.......................... Risk of severe reactions
DUE TO THE RAPID ABSORPTION
of the allergen............
Absorption and distribution kinetics of the major *Parietaria Judaica* (Par J 1) allergen administered by non-injectable to healthy humans beings.

M. Bagnasco, G. Mariani, G. Passalacqua, C. Motta, M. Bartolomei, P. Falagiani, G. Mistrello, G. W. Canonica

*JACI* 1997; 100:199
% dose/liter

$^{123}$I-Prj alternative routes

- Subl 1
- Subl 2
- Subl 3
- Oral
- Nasal

Bagnasco et al. J.A.C.I. 1997
Pharmacokinetics of an allergen and a Monomeric Allergoid for oromucosal immunotherapy in allergic volunteers

Bagnasco M., et al

Clin Exp. Allergy 2001
Der p1 monomeric allergoid. Allergic volunteer
E.B.M.
Evidence Based Medicine
Evidence-Based Medicine

A New Approach to Teaching the Practice of Medicine

Evidence-Based Medicine Working Group

JAMA, November 4, 1992—Vol 268, No. 17
ARIA Guidelines: Recommendations for Management of Allergic Rhinitis

Mild intermittent
- Intranasal corticosteroid
- Local chromone
- Leukotriene receptor antagonists
- Second-generation nonsedating H1-antihistamine
- Intranasal decongestant (<10 days) or oral decongestant
- Allergen and irritant avoidance

Check for asthma

Moderate/severe intermittent
- Intranasal corticosteroid
- Local chromone
- Leukotriene receptor antagonists
- Second-generation nonsedating H1-antihistamine
- Intranasal decongestant (<10 days) or oral decongestant
- Allergen and irritant avoidance
- Consider immunotherapy

Mild persistent

Moderate/severe persistent

## Strength of Evidence for Treatment of Rhinitis: ARIA 2008

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Adult</th>
<th>Children</th>
<th>Adult</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IAR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral anti-H₁</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Intranasal anti-H₁</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Intranasal CS</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Intranasal chromone</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Antileukotriene</td>
<td>A</td>
<td>A</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Subcutaneous SIT</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Sublingual/nasal SIT B</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Allergen avoidance</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>B</td>
</tr>
</tbody>
</table>

From OBM to EBM

(GINA 1995)

opinion-based medicine

guidelines

1998–
(GINA 2002,
ARIA)

"evidence-based medicine"

implementations of guidelines by adequate trials and interventions

Bousquet J. et al., Allergy 2004
From EBM to recommendation

Evidence-based medicine

Clinical recommendations on efficacy for an intervention
Clinical guidelines

Developing guidelines

Paul G Shekelle, Steven H Woolf, Martin Eccles, Jeremy Grimshaw

Classification schemes

Category of evidence:
Ia—evidence for meta-analysis of randomised controlled trials
Ib—evidence from at least one randomised controlled trial
IIa—evidence from at least one controlled study without randomisation
IIb—evidence from at least one other type of quasi-experimental study
III—evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV—evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Strength of recommendation:
A—directly based on category I evidence
B—directly based on category II evidence or extrapolated recommendation from category I evidence
C—directly based on category III evidence or extrapolated recommendation from category I or II evidence
D—directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Opinion Based

metanalysis
EAACI/GA²LEN/EDF Guidelines for Management of Urticaria

Position paper

EAACI/GA²LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria

This guideline, together with its sister guideline on the management of urticaria [Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Giménez-Arnau AM et al. EAACI/GA²LEN/EDF/WAO Guideline: Management of urticaria. Allergy, 2009; 64:1427–1443] is the result of a consensus reached during a panel discussion at the 3rd International Consensus Meeting on Urticaria, Urticaria 2008, a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO). Urticaria is a common disease. The lifetime...
ARIA/EAACI Requirements for Antihistamines in the Treatment of AR

**Efficacy**
- Effective in the treatment of intermittent and persistent rhinitis as defined in the ARIA document
- Effective for all nasal symptoms including nasal obstruction
- Improvement of eye symptoms
- If a claim for asthma is made:
  - Improvement of asthma symptoms (short term studies)
  - Reduction of asthma exacerbations (long term studies)
- An improvement of the pulmonary function tests, although in pollen-induced bronchial symptoms, FEV₁ and peak flow rates are usually not altered.
- If a claim for a preventive effect is proposed, appropriate trials should be conducted
- Studies should be carried out in young children and elderly patients to assess efficacy

**Side effects**
- No sedation or cognitive or psychomotor impairment
- No anti-cholinergic effects
- No weight gain
- No cardiac side effects
- Possible use in pregnancy and breast feeding
- Studies should be carried out in young children and elderly age patients to assess safety
- Prospective postmarketing safety analyses should be conducted

EBM Hierarchy

EBM Guidelines

Evidence-Based Medicine

Case Report, Ideas
Editorials, Expert Opinion

Case series

Meta-analysis and Systematic Reviews

Case
series

Cohort Studies

Dr. Cochrane

GUIDELINES
Review article

**Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis***

**Intranasal corticosteroids versus topical H₁ receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis**

Anshi Yañez, MD* and Gustavo J. Rodrigo, MD†

**Inhaled magnesium sulfate in the treatment of acute asthma**

Blitz M, Blitz S, Beasely R, Diner BM, Hughes R, Knopp JA, and Allen D

**Allergen immunotherapy for asthma**

Abramson MJ, Puy RM, Weiner JM

**Anti-IgE for chronic asthma in adults and children**

Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH

**Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials**

Martin Penagos, MD, MSc*; Enrico Compalati, MD*; Francesco Tarantini, MD*; Rodrigo Baena-Cagnani, MD*; Jose Huerta, MD*; Giovanni Passalacqua, MD*; and Giorgio Walter Canonica, MD*
Number of Published Metanalysis Studies
METANALYSIS - Forrest Plot

VMD (fixed) 95% CI

VMD (fixed) 95% CI

VMD (random) 95% CI

OUT

GOAL!!!!

NO
Systematic review on the efficacy of fexofenadine in seasonal allergic rhinitis: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials.

COMPALATI E 1, BAENA-CAGNANI R 2-3, PENAGOS M 1, BADELLINO H 2-3, BRAIDO F 1, GÓMEZ RM 3, CANONICA GW 1, BAENA-CAGNANI CE 1-2-3.
Methods

• All double-blind, placebo-controlled randomized trials assessing the efficacy of fexofenadine in AR were searched in OVID, MEDLINE, EMBASE databases up to December 2007
• Outcomes were extracted from original articles; when this information was not available, authors of each trial were contacted
• Some graphics were digitalized. RevMan 5 program was used to perform the analysis.
• GradePro 3.2.2 was used to assess the quality of the evidence for paediatric population.
Methods

- Initial search: 2,152 records identified through database searching
- 2,024 excluded during screening as duplicates or not related to the topic
  - 108 excluded
    - Reasons for exclusion:
      - Review = 58
      - Other purposes = 16
      - Not clinical outcomes = 10
      - Not placebo controlled = 8
      - Safety = 6
      - Open studies = 4
      - Pharmacodynamics = 2
      - QoL = 2
      - Pooled analysis = 2
- 128 records assessed in full text
- 20 potentially relevant DBRPC trials on fexofenadine in AR
- 8 DBRPC trials on fexofenadine in AR satisfied the inclusion criteria
- 12 excluded
  - Reasons for exclusion:
    - Challenge exposition = 7
    - Incorrect allocation arms = 1
    - Atypical scale for symptoms = 1
    - Different outcomes = 2
    - Cross-over design = 1
## Methods

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Gender</th>
<th>Age Group</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcome</th>
<th>Site</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rizzo et al. (26)</td>
<td>DEEP</td>
<td>N</td>
<td>B</td>
<td>3.5 y</td>
<td>45</td>
<td>PXE 63</td>
<td>RL</td>
<td>150 mg/dl</td>
<td>14</td>
</tr>
<tr>
<td>Vacher et al. (27)</td>
<td>DEEP</td>
<td>D</td>
<td>B</td>
<td>6</td>
<td>Medium</td>
<td>PXE 52</td>
<td>RL</td>
<td>150 mg/dl</td>
<td>14</td>
</tr>
<tr>
<td>Crocker et al. (28)</td>
<td>DEEP</td>
<td>D</td>
<td>N</td>
<td>4.2</td>
<td>Medium</td>
<td>PXE 51</td>
<td>RL</td>
<td>150 mg/dl</td>
<td>14</td>
</tr>
<tr>
<td>The Washington et al. (29)</td>
<td>DEEP</td>
<td>D</td>
<td>N</td>
<td>4.2</td>
<td>Medium</td>
<td>PXE 60</td>
<td>RL</td>
<td>150 mg/dl</td>
<td>14</td>
</tr>
<tr>
<td>Barnsley et al. (30)</td>
<td>DEEP</td>
<td>D</td>
<td>N</td>
<td>4.2</td>
<td>Medium</td>
<td>PXE 120</td>
<td>RL</td>
<td>150 mg/dl</td>
<td>14</td>
</tr>
<tr>
<td>Romeo et al. (31)</td>
<td>DEEP</td>
<td>D</td>
<td>N</td>
<td>4.2</td>
<td>Medium</td>
<td>PXE 51</td>
<td>RL</td>
<td>150 mg/dl</td>
<td>14</td>
</tr>
<tr>
<td>Moraldo et al. (32)</td>
<td>DEEP</td>
<td>D</td>
<td>N</td>
<td>4.2</td>
<td>Medium</td>
<td>PXE 120</td>
<td>RL</td>
<td>150 mg/dl</td>
<td>14</td>
</tr>
<tr>
<td>Repi et al. (33)</td>
<td>DEEP</td>
<td>D</td>
<td>A</td>
<td>6.0</td>
<td>6.0%</td>
<td>PXE 180</td>
<td>RL</td>
<td>150 mg/dl</td>
<td>14</td>
</tr>
</tbody>
</table>

*Notes: CHD = Coronary Artery Disease; SAR = Stable Angina Ressl.
• Of 2152 identified articles, **20 were potentially relevant trials.** Eight studies satisfied inclusion criteria and were included in the meta-analysis. The main reasons for exclusion were: not natural exposition, strong study limitations, atypical outcome measurement, design for other outcomes, not placebo-controlled, single blind studies. **Seven trials investigated a mixed population of adults and children, one only children and one only adults.**

• In **1,833 patients** receiving fexofenadine

• **1,699 placebo**
### 12-24h Reflective TSS

**1.1.1 12-hour reflective TSS**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Fexofenadine mean</th>
<th>SD</th>
<th>total</th>
<th>Placebo mean</th>
<th>SD</th>
<th>total</th>
<th>weight, %</th>
<th>Std. mean difference IV, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berger</td>
<td>6.26</td>
<td>2.37</td>
<td>260</td>
<td>7.03</td>
<td>2.37</td>
<td>126</td>
<td>9.8</td>
<td>-0.32 (-0.54, -0.11)</td>
</tr>
<tr>
<td>Bernstein</td>
<td>6.55</td>
<td>2.4</td>
<td>144</td>
<td>7.32</td>
<td>2.37</td>
<td>141</td>
<td>8.3</td>
<td>-0.32 (-0.56, -0.09)</td>
</tr>
<tr>
<td>Bronsky</td>
<td>6.5</td>
<td>2.11</td>
<td>137</td>
<td>7.45</td>
<td>2.11</td>
<td>138</td>
<td>7.9</td>
<td>-0.45 (-0.69, -0.21)</td>
</tr>
<tr>
<td>Schapowal</td>
<td>6.63</td>
<td>4.81</td>
<td>113</td>
<td>9.16</td>
<td>4.81</td>
<td>107</td>
<td>6.2</td>
<td>-0.52 (-0.79, -0.26)</td>
</tr>
<tr>
<td>Wahn</td>
<td>4.86</td>
<td>2.15</td>
<td>463</td>
<td>5.86</td>
<td>2.16</td>
<td>469</td>
<td>26.6</td>
<td>-0.46 (-0.59, -0.33)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1,117</td>
<td></td>
<td></td>
<td>981</td>
<td>58.8</td>
<td></td>
<td></td>
<td>-0.42 (-0.51, -0.34)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 2.50$, d.f. = 4 ($p = 0.65$); $I^2 = 0$

Test for overall effect: $Z = 9.51$ ($p < 0.00001$)

**1.1.2 24-hour reflective TSS**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Fexofenadine mean</th>
<th>SD</th>
<th>total</th>
<th>Placebo mean</th>
<th>SD</th>
<th>total</th>
<th>weight, %</th>
<th>Std. mean difference IV, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casale</td>
<td>6.07</td>
<td>1.85</td>
<td>282</td>
<td>6.78</td>
<td>1.88</td>
<td>292</td>
<td>16.5</td>
<td>-0.38 (-0.55, -0.22)</td>
</tr>
<tr>
<td>Howarth</td>
<td>4.1</td>
<td>2.34</td>
<td>202</td>
<td>5.4</td>
<td>2.34</td>
<td>201</td>
<td>11.4</td>
<td>-0.55 (-0.75, -0.36)</td>
</tr>
<tr>
<td>Van Cauwenberge</td>
<td>4.56</td>
<td>2.56</td>
<td>232</td>
<td>5.42</td>
<td>2.81</td>
<td>225</td>
<td>13.2</td>
<td>-0.32 (-0.50, -0.14)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>716</td>
<td></td>
<td></td>
<td>718</td>
<td>41.2</td>
<td></td>
<td></td>
<td>-0.41 (-0.51, -0.30)</td>
</tr>
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</table>

Heterogeneity: $\chi^2 = 3.07$, d.f. = 2 ($p = 0.22$); $I^2 = 35$

Test for overall effect: $Z = 7.66$ ($p < 0.00001$)

Total (95% CI) 1,833 1,699 100.0  -0.42 (-0.49, -0.35)

Heterogeneity: $\chi^2 = 5.62$, d.f. = 7 ($p = 0.58$); $I^2 = 0$

Test for overall effect: $Z = 12.21$ ($p < 0.00001$)

Test for subgroup differences: $\chi^2 = 0.05$, d.f. = 1 ($p = 0.82$); $I^2 = 0$
### Morning instantaneous TSS

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Fexofenadine</th>
<th>Placebo</th>
<th>Std. mean difference IV, fixed, 95% CI</th>
<th>Std. mean difference IV, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean SD total</td>
<td>mean SD total weight, %</td>
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<td></td>
</tr>
<tr>
<td>Berger</td>
<td>6.04 2.07 260</td>
<td>6.91 2.07 126 13.2</td>
<td>-0.42 (-0.63, -0.20)</td>
<td></td>
</tr>
<tr>
<td>Bernstein</td>
<td>6.81 2.28 144</td>
<td>7.36 2.37 141 11.2</td>
<td>-0.24 (-0.47, -0.00)</td>
<td></td>
</tr>
<tr>
<td>Bronsky</td>
<td>6.58 2.11 137</td>
<td>7.38 2 138 10.7</td>
<td>-0.39 (-0.63, -0.15)</td>
<td></td>
</tr>
<tr>
<td>Casale</td>
<td>6.33 1.85 282</td>
<td>6.74 1.88 292 22.6</td>
<td>-0.22 (-0.38, -0.06)</td>
<td></td>
</tr>
<tr>
<td>Howarth</td>
<td>4.2 2.34 202</td>
<td>4.6 2.34 201 15.9</td>
<td>-0.17 (-0.37, 0.03)</td>
<td></td>
</tr>
<tr>
<td>Schapowal</td>
<td>20.2 12.34 113</td>
<td>26.8 12.34 107 8.4</td>
<td>-0.53 (-0.80, -0.26)</td>
<td></td>
</tr>
<tr>
<td>Van Cauwenberge</td>
<td>4.46 2.71 232</td>
<td>5.06 2.73 225 18.0</td>
<td>-0.22 (-0.40, -0.04)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1,370</td>
<td>1,230 100.0</td>
<td>-0.28 (-0.36, -0.21)</td>
<td></td>
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</tbody>
</table>

Heterogeneity: $\chi^2 = 8.06$, d.f. = 6 ($p = 0.23$); $I^2 = 26$

Test for overall effect: $Z = 7.15$ ($p < 0.000001$)

Favours treatment Favours control
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Fexofenadine</th>
<th>Placebo</th>
<th>Std. mean difference</th>
<th>Std. mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>SD</td>
<td>total</td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>1.3.1 Sneezing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronsky</td>
<td>1.49</td>
<td>0.58</td>
<td>137</td>
<td>1.76</td>
</tr>
<tr>
<td>Casale</td>
<td>1.34</td>
<td>0.5</td>
<td>282</td>
<td>1.57</td>
</tr>
<tr>
<td>Wahn</td>
<td>1.2</td>
<td>0.67</td>
<td>463</td>
<td>1.48</td>
</tr>
<tr>
<td>Van Cauwenberge</td>
<td>1.14</td>
<td>0.75</td>
<td>232</td>
<td>1.45</td>
</tr>
<tr>
<td>Bernstein</td>
<td>1.5</td>
<td>0.72</td>
<td>141</td>
<td>1.66</td>
</tr>
<tr>
<td>Howarth</td>
<td>1</td>
<td>1.42</td>
<td>202</td>
<td>1.3</td>
</tr>
<tr>
<td>Berger</td>
<td>-0.49</td>
<td>0.58</td>
<td>200</td>
<td>-0.33</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1,720</td>
<td>1,587</td>
<td>24.8</td>
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</tr>
<tr>
<td><strong>1.3.2 Rhinorrhea</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bernstein</td>
<td>1.94</td>
<td>0.72</td>
<td>144</td>
<td>1.97</td>
</tr>
<tr>
<td>Bronsky</td>
<td>1.98</td>
<td>0.58</td>
<td>137</td>
<td>2.06</td>
</tr>
<tr>
<td>Casale</td>
<td>1.73</td>
<td>0.5</td>
<td>282</td>
<td>1.88</td>
</tr>
<tr>
<td>Howarth</td>
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<td>0.14</td>
<td>202</td>
<td>1.4</td>
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<tr>
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<td>463</td>
<td>1.6</td>
</tr>
<tr>
<td>Berger</td>
<td>-0.61</td>
<td>0.38</td>
<td>260</td>
<td>-0.56</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1,720</td>
<td>1,587</td>
<td>25.1</td>
<td></td>
</tr>
<tr>
<td><strong>1.3.3 Nasal congestion</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bernstein</td>
<td>2.09</td>
<td>0.6</td>
<td>144</td>
<td>2.16</td>
</tr>
<tr>
<td>Bronsky</td>
<td>2.08</td>
<td>0.58</td>
<td>137</td>
<td>2.17</td>
</tr>
<tr>
<td>Casale</td>
<td>1.96</td>
<td>0.5</td>
<td>282</td>
<td>2.04</td>
</tr>
<tr>
<td>Howarth</td>
<td>1.4</td>
<td>1.42</td>
<td>202</td>
<td>1.5</td>
</tr>
<tr>
<td>Van Cauwenberge</td>
<td>1.44</td>
<td>0.74</td>
<td>232</td>
<td>1.66</td>
</tr>
<tr>
<td>Wahn</td>
<td>1.6</td>
<td>0.64</td>
<td>463</td>
<td>1.71</td>
</tr>
<tr>
<td>Berger</td>
<td>-0.48</td>
<td>0.44</td>
<td>260</td>
<td>-0.4</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1,720</td>
<td>1,587</td>
<td>25.2</td>
<td></td>
</tr>
<tr>
<td><strong>1.3.4 Nasal itching</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernstein</td>
<td>1.59</td>
<td>0.72</td>
<td>144</td>
<td>1.76</td>
</tr>
<tr>
<td>Bronsky</td>
<td>1.69</td>
<td>0.7</td>
<td>137</td>
<td>1.82</td>
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<tr>
<td>Casale</td>
<td>1.51</td>
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<td>282</td>
<td>1.69</td>
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<tr>
<td>Howarth</td>
<td>1</td>
<td>1.42</td>
<td>202</td>
<td>1.4</td>
</tr>
<tr>
<td>Van Cauwenberge</td>
<td>1.18</td>
<td>0.61</td>
<td>232</td>
<td>1.3</td>
</tr>
<tr>
<td>Wahn</td>
<td>1.17</td>
<td>0.67</td>
<td>463</td>
<td>1.43</td>
</tr>
<tr>
<td>Berger</td>
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<td>0.63</td>
<td>260</td>
<td>-0.52</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1,720</td>
<td>1,587</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>6,880</td>
<td>6,348</td>
<td>100.0</td>
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</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 41.98$, df. = 27 (p = 0.03); $I^2 = 36%$</td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 15.39$ (p &lt; 0.00001)</td>
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<td></td>
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<tr>
<td>Test for subgroup differences: $\chi^2 = 17.51$, df. = 3 (p = 0.0006), $I^2 = 82.9%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Sneezing**: Bronsky, Casale, Wahn, Van Cauwenberge, Bernstein, Howarth, Berger, Subtotal (95% CI)
- **Rhinorrhea**: Bernstein, Bronsky, Casale, Howarth, Van Cauwenberge, Wahn, Berger, Subtotal (95% CI)
- **Nasal congestion**: Bernstein, Bronsky, Casale, Howarth, Van Cauwenberge, Wahn, Berger, Subtotal (95% CI)
- **Nasal itching**: Bernstein, Bronsky, Casale, Howarth, Van Cauwenberge, Wahn, Berger, Subtotal (95% CI)
## doses

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Fexofenadine</th>
<th>Placebo</th>
<th>Std. mean difference (IV, fixed, 95% CI)</th>
<th>Std. mean difference (IV, fixed, 95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>mean  SD</td>
<td>total</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.5.1 &gt;120 mg daily</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger</td>
<td>6.26 2.37</td>
<td>260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernstein</td>
<td>6.55 2.4</td>
<td>144</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casale</td>
<td>6.07 1.85</td>
<td>282</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Howarth</td>
<td>4.1 2.34</td>
<td>202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schapowal</td>
<td>6.63 4.81</td>
<td>113</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1,001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.5.2 120 mg or less daily</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronsky</td>
<td>6.5 2.11</td>
<td>137</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Cauwenberge</td>
<td>4.56 2.56</td>
<td>232</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wahn</td>
<td>4.86 2.15</td>
<td>463</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>832</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1,833</td>
<td>1,699</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 3.99$, d.f. = 4 ($p = 0.41$); $\eta^2 = 0$

Test for overall effect: $Z = 8.77$ ($p < 0.00001$)

Heterogeneity: $\chi^2 = 1.62$, d.f. = 2 ($p = 0.44$); $\eta^2 = 0$

Test for overall effect: $Z = 8.50$ ($p < 0.00001$)

Test for subgroup differences: $\chi^2 = 5.62$, d.f. = 7 ($p = 0.58$); $\eta^2 = 0$

Test for overall effect: $Z = 12.21$ ($p < 0.00001$)

Test for subgroup differences: $\chi^2 = 0.01$, d.f. = 1 ($p = 0.93$); $\eta^2 = 0$
<table>
<thead>
<tr>
<th>Reference</th>
<th>Total Patients</th>
<th>No. of patients reporting adverse event (active/placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wain et al.</td>
<td>80/88</td>
<td>Headache (23/13), Erythema (7/5), Upper respiratory infection (7/5), Pharyngitis (6/1), Sore throat (6/1), Nasal congestion (5/1), Rash (3/1), Accidental injury (4/9), Asthma (3/9), Infection (1/7), Gastro-intestinal pain (1/1)</td>
</tr>
<tr>
<td>Bossy et al.</td>
<td>18/18</td>
<td>Headache (14/9)</td>
</tr>
<tr>
<td>Caruso et al.</td>
<td>80/88</td>
<td>Headache (39/22), Upper respiratory infection (9/8), Pharyngitis (6/8), Back pain (8/4), Pains (5/10)</td>
</tr>
<tr>
<td>Van Cunnemberg et al.</td>
<td>39/33</td>
<td>Headache (7/3), Drowsiness (4/3), Asthma (1/1), Pharyngitis (1/1), Diarrhoea (4/9), Nausea (1/3)</td>
</tr>
<tr>
<td>Brestain et al.</td>
<td>10/13</td>
<td>Headache (1/4), Throat irritation (1/2), Dry mouth (1/2), Cough (1/2), Leukopenia (1/1)</td>
</tr>
<tr>
<td>Howarth et al.</td>
<td>50/53</td>
<td>Headache (8/15), Fatigue (3/2), Drowsiness (14/7)</td>
</tr>
<tr>
<td>Schapoval et al.</td>
<td>8/7</td>
<td>Headache(6/1), Sore throat (6/1), Common cold (1/2), Sins pain (1/0), Nausea (1/0)</td>
</tr>
<tr>
<td>Berger et al</td>
<td>52/10</td>
<td>Headache (11/2), Somnia (3/0), Nausea (3/0), Upper respiratory infection (3/1)</td>
</tr>
</tbody>
</table>
## Adverse effects

Is it GOAL????????????
You should use the funnel plot to investigate the presence of publication bias in your review.
The vertical axis is some measure of the precision of the estimate of the treatment effect. So the smaller the confidence interval, the more precise the study, and the further up the study is placed.

The horizontal axis measures the treatment effect.
The point estimate from each study is then plotted...

...a vertical line added, where the pooled estimate from the meta-analysis lies

more precise studies

less precise studies
Funnel plot **ASYMMETRY** may be due to:
- *publication bias*
- clinical heterogeneity between studies
- methodological heterogeneity between studies.

There are some statistical tests for detecting funnel plot asymmetry:

- Egger's linear regression test
- Begg's rank correlation test
12-24 h reflective TSS
N. Congestion

Subgroups

- Nasal congestion
N. Itching

The graph shows a scatter plot with the x-axis labeled as SMD and the y-axis labeled as SE(SMD). The plot includes subgroups indicated by blue squares labeled "Nasal itching."
Sneezing
This study has five major aspects: it represents the first attempt to evaluate the
efficacy and safety of fexofenadine in the treatment of AR by means of meta-
analysis of RCTs;

• Consistency between positive results in terms of efficacy in
  TSS and in individual symptoms;
• Large population studied;
• Not relevant inter-study heterogeneity;
• Adverse events frequency was similar in both groups (placebo).

All these values encourage the recommendation of fexofenadine for AR.
Treatment of allergic rhinitis (ARIA)
Allergic Rhinitis and its Impact on Asthma

- **Mild intermittent**
  - Intra-nasal steroid
  - Local cromone
  - Oral or local non-sedative H1-blocker
  - Intra-nasal decongestant (<10 days) or oral decongestant
  - Allergen and irritant avoidance

- **Moderate persistent**
- **Mild severe intermittent**
- **Moderate severe persistent**

**Immunotherapy**
A general process in guidelines evolution
Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision

Jan L. Brożek, MD, PhD, Jean Bousquet, MD, PhD, Carlos E. Baena-Cagnani, MD, Sergio Bonini, MD, G. Walter Canonica, MD, Thomas B. Casale, MD, Roy Gerth van Wijk, MD, PhD, Ken Ohta, MD, PhD, Torsten Zuberbier, MD, and Holger J. Schünemann, MD, PhD, MSc

Hamilton, Ontario, Canada, Montpellier, France, Córdoba, Argentina, Rome, Naples, and Genoa, Italy, Omaha, Neb, Rotterdam, The Netherlands, Tokyo, Japan, and Berlin, Germany
Interpretation of Recommendations

<table>
<thead>
<tr>
<th>Implications</th>
<th>Strong recommendation</th>
<th>Conditional (weak) recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients</td>
<td>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.</td>
<td>The majority of individuals in this situation would want the suggested course of action, but many would not.</td>
</tr>
<tr>
<td>For clinicians</td>
<td>Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.</td>
<td>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.</td>
</tr>
<tr>
<td>For policy makers</td>
<td>The recommendation can be adapted as policy in most situations.</td>
<td>Policy-making will require substantial debate and involvement of various stakeholders.</td>
</tr>
</tbody>
</table>

*Guideline panels applying GRADE use the term “conditional” and “weak” synonymously.*
Antihistamines

III. Pharmacologic treatment of AR

11. Should oral H<sub>1</sub>-antihistamines be used for the treatment of AR? Recommendation. In patients with AR, we recommend new-generation oral H<sub>1</sub>-antihistamines that do not cause sedation and do not interact with cytochrome P450 (strong recommendation | low-quality evidence). In patients with seasonal AR, we recommend new-generation oral H<sub>1</sub>-antihistamines that cause some sedation and/or interact with cytochrome P450 (conditional recommendation | low-quality evidence).

12. Should new-generation oral H<sub>1</sub>-antihistamines versus old-generation oral H<sub>1</sub>-antihistamines be used for the treatment of AR? Recommendation. In patients with AR, we recommend new-generation oral H<sub>1</sub>-antihistamines (strong recommendation | low-quality evidence).

13. Should oral H<sub>1</sub>-antihistamines be used in preschool children with other allergic diseases for the prevention of wheezing or asthma? 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<sub>1</sub>-antihistamines for the prevention of wheezing or asthma (conditional recommendation | very low-quality evidence).

14. Should intranasal H<sub>1</sub>-antihistamines be used for treatment of AR? Recommendation. We suggest intranasal H<sub>1</sub>-antihistamines in adults with seasonal AR (conditional recommendation | low-quality evidence) and in children with seasonal AR (conditional recommendation | very low-quality evidence). In adults and children with persistent AR, we suggest that clinicians do not administer and patients do not use intranasal H<sub>1</sub>-antihistamines until more data on their relative efficacy and safety are available (conditional recommendation | very low-quality evidence).

15. Should newer oral H<sub>1</sub>-antihistamines versus intranasal H<sub>1</sub>-antihistamines be used for treatment of AR? Recommendation. We suggest new-generation oral H<sub>1</sub>-antihistamines rather than intranasal H<sub>1</sub>-antihistamines in adults with seasonal AR (conditional recommendation | moderate-quality evidence) and in adults with persistent AR (conditional recommendation | very low-quality evidence). In children with intermittent or persistent AR, we also suggest new-generation oral H<sub>1</sub>-antihistamines rather than intranasal H<sub>1</sub>-antihistamines (conditional recommendation | very low-quality evidence).
Weak: 84%

Very low

Strength of recommendation

2010
Grade of evidence
Clinical Implications

Clinical implications: Patients, clinicians, and policy makers can use these systematically developed and transparent recommendations to inform their judgments about the choice of the most appropriate treatment for patients with AR.
Take Home Message
FEXOFENADINE

Is fulfilling the ARIA criteria for Anti-H1

Is fulfilling the ARIA-GRADE recommendations
FEXOFENADINE

Ranks at the Top in E.B.M.
Evidence-Based Medicine in the EMR Era

Jennifer Frankovich, M.D., Christopher A. Longhurst, M.D., and Scott M. Sutherland, M.D.
EMR

ELECTRONIC MEDICAL RECORD

STRIKE

STANFORD INTEGRATED DATABASE ENVIRONMENT
<table>
<thead>
<tr>
<th>Outcome or Risk Factor</th>
<th>Keywords Used to Conduct Expedited Electronic Search</th>
<th>Prevalence of Thrombosis no./total no. (%)</th>
<th>Relative R (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Outcome — thrombosis</strong></td>
<td>“Thrombus,” “Thrombosis,” “Blood clot”</td>
<td>10/98 (10)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Thrombosis risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy proteinuria (&gt;2.5 g per deciliter)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present at any time</td>
<td>“Nephrosis,” “Nephrotic,” “Proteinuria”</td>
<td>8/36 (22)</td>
<td>7.8 (1.7–</td>
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<tr>
<td>Present &gt;60 days</td>
<td>“Urine protein”</td>
<td>7/23 (30)</td>
<td>14.7 (3.3–</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>“Pancreatitis,” “Lipase”</td>
<td>5/8 (63)</td>
<td>11.8 (3.8–</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>“Aspirin”</td>
<td>6/51 (12)</td>
<td>1.0 (0.3–</td>
</tr>
</tbody>
</table>
CONCLUSION

know. We will, however, know that we made the decision on the basis of the best data available — acting, as the fictional detective Nero Wolfe would say, “in the light of experience as guided by intelligence.”5 In the practice of medicine, one can’t do better than that.
SO...WE CAN TREAT PROPERLY ALSO THE BIG NOSES
Thank You

canonica@unige.it