Effects of antihistamines in adult asthma: a meta-analysis of clinical trials
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Authors' objectives
To investigate the positive and negative effects of antihistamines in asthma.

Searching
MEDLINE, Ringdoc, and Excerpta Medica: DRUGS, were searched for studies published between 1980 and 1990. MEDLINE and EMBASE were also searched for studies published since 1991. Additional publications were identified by reviewing the bibliographies of the retrieved articles, and by manually searching Index Medicus and major pneumology and allergy journals.

Study selection
Study designs of evaluations included in the review
Randomised, placebo-controlled trials were included. The duration of the studies ranged from 2 to 28 weeks.

Specific interventions included in the review
Oral antihistamines compared with placebo. The specific antihistamines examined were: ketotifen, oxatomide, terfenadine, loratadine, azelastine, picumast, pemirolast and cetirizine; the doses varied across studies. When different doses were examined within the same study, the data corresponding to the most effective dose (according to the authors' claim) were used. Where different treatment durations were examined, the data corresponding to the longest duration of exposure were used. Data comparing antihistamines to other asthma medication were not used.

Participants included in the review
Patients with mild, moderate or severe asthma were included in the review. All asthma definitions given by the authors were accepted; these usually defined asthma as a history of reversible airflow obstruction, with impaired lung function that improved considerably after the use of inhaled bronchodilators. The age of the participants in the included studies ranged from 7 to 74 years, and over 50% of the patients in each study had to be aged over 15 years. Patients had to have been treated with antihistamines for more than 2 weeks.

Outcomes assessed in the review
The primary outcome used was morning peak expiratory flow rate (PEFR). The secondary outcomes were evening PEFR, forced expiratory volume in one second (FEV1), and daily use of inhaled bronchodilators.

How were decisions on the relevance of primary studies made?
Blinded copies of the 'Materials and Methods' sections of each study that met the review's inclusion criteria were submitted to two pneumologists for review. Studies with an inadequate description of the patient selection process or treatment regimens were excluded.

Assessment of study quality
The studies were assessed on the basis of the quality criteria and scoring system developed by Chalmers et al. (see Other Publications of Related Interest). It was unclear who assessed the validity of the included studies. It is possible that this was conducted by the same two pneumologists who judged the relevance of the studies, but it is not explicitly stated in the paper.

Data extraction
The data were extracted from each study using a standard data extraction form. Only data comparing antihistamines with placebo were extracted. When the data were not tabulated, they were extracted from figures where possible.
Methods of synthesis
How were the studies combined?
Continuous variables and the effect size, along with the 95% confidence intervals (CIs), were computed for each study. The effect size was defined as the mean value measured in the antihistamine group under treatment, minus the mean value in the placebo group, divided by the standard deviation of the mean value measured in the placebo group. The overall mean effect size and 95% CI were computed for the individual studies.

How were differences between studies investigated?
For morning PEFR and daily use of inhaled bronchodilators, the homogeneity of the studies was investigated using a Cochran Q test. Sensitivity analyses were also conducted on the basis of the following: asthma severity; a quality score of greater than 70%; ketotifen versus 'new' antihistamines; and trials excluding co-therapy with inhaled or oral corticosteroids. A Mantel-Haenszel test was used to investigate differences between the groups in terms of sedation effects, and to test the homogeneity of the studies.

Results of the review
Nineteen randomised, placebo-controlled trials, with a total of 1,680 patients, were included.

The quality assessment delivered a total score ranging from 42 to 76%, with a mean score of 59%. Significant flaws were detected in all sections of the quality scoring.

The mean effect sizes for antihistamines versus placebos were.

for morning PEFR (15 studies), 0.13 (95% CI: 0.08, 0.18);
for evening PEFR (14 studies), 0.12 (95% CI: 0.08, 0.16);
for FEV1 (10 studies), 0.03 (95% CI: 0.01, 0.25); and
for inhaled beta-agonists (12 studies), 0.13 (95% CI: 0.01, 0.25), which corresponded to a reduction in daily use of 0.4 doses (95% CI: 0, 0.8).

The studies were homogeneous for the measurement of morning PEFR (Q=9.82, p=0.78) and for daily use of inhaled bronchodilators (Q=5.49, p=0.91). The incidence of sedation was significantly higher in antihistamine studies compared with placebo, although the studies were found to be heterogeneous for this variable (p<0.001). None of the sensitivity analyses had a significant impact on the overall result in terms of morning PEFR.

Authors' conclusions
Antihistamines and placebo differed little in their effects on asthma control, although the included studies were of an overall poor quality. Better-designed studies with standardised therapeutic outcomes are required to fully evaluate the use of antihistamines for asthma control.

CRD commentary
This was an excellent review which provided a clear and concise overview of the role of antihistamines for asthma control. The objective of the review was clear, the literature search was thorough, and the inclusion criteria were explicit. A comprehensive validity assessment was conducted, adequate details of the primary studies were provided, and the synthesis of the data was appropriate. The authors' conclusions appear to be fully justified.

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Record Status
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