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Oral antihistamines for the symptom of nasal obstruction in persistent allergic rhinitis – a systematic review of randomized controlled trials

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Summary

Background Oral antihistamines are recommended by a World Health Organisation working group as a first-line pharmacological treatment in mild persistent allergic rhinitis. There is, however, uncertainty with respect to their effectiveness for a common symptom, that of nasal obstruction.

Objective To test the null hypothesis that oral antihistamines have no effect on the symptom of nasal obstruction in a clinical setting in patients with persistent allergic rhinitis.

Methods Protocol based review of double-blind randomized controlled trials of oral antihistamine (i.e. drugs considered to act as a histamine receptor type-1 antagonist) vs. placebo. A search was carried out for published and unpublished trials. Individuals had to be age 12 years or older (with a diagnosis confirmed by skin prick tests, IgE blood tests or nasal allergen challenge), experiencing their normal allergen exposure. A symptom score for nasal obstruction had to be recorded. Predetermined quality criteria were applied. Treating their data as 4-point scores, a meta-analysis was carried out for studies, which provided enough data to be pooled.

Results Meta-analysis found a weighted mean difference of -0.52 in favour of treatment for patient-assessed symptom scores (95% confidence interval (CI) -0.73, -0.31, $P<0.00001$), and of -0.33 in favour of treatment for healthcare worker assessed scores (95% CI -0.49, -0.16, $P=0.0001$).

Conclusion Oral antihistamines cause statistically significant improvement in the symptom of nasal obstruction in patients with persistent allergic rhinitis.

Keywords meta-analysis, nasal obstruction, oral antihistamines, persistent allergic rhinitis, randomized controlled trial, symptom score, systematic review

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Introduction

Allergic rhinitis is a global health problem [1], with an increasing prevalence [2]. A link between allergic rhinitis, particularly persistent allergic rhinitis, and asthma has recently been recognized. It has been suggested that optimal management of allergic rhinitis may help prevent the occurrence of asthma, or improve coexisting asthma [1].

The term 'persistent' rhinitis comes from a new classification. This is based on the duration of symptoms distinguishing allergic rhinitis as 'intermittent' or 'persistent' [3]. In 'persistent', symptoms occur for more than 4 days per week, and for more than 4 weeks**.** This is further classified into 'mild' or 'moderate-severe' depending on sleep disturbance, impairment of activities or how troublesome the symptoms are [3]. Patients for trial already carried out were chosen on the basis of the previous classification that identified patients as having perennial, seasonal or occupational allergic rhinitis. We therefore decided to search for trials in perennial rhinitis believing this category to be closest to persistent disease, in addition to searching for recent trials in 'persistent' rhinitis.

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Oral H1 receptor antagonists are referred to as oral antihistamines. They have been recommended by a recent working group, facilitated by the World Health Organisation, as one option for a first-line pharmacological treatment in mild persistent allergic rhinitis [3]. Although histamine, through its action on H1 receptors, appears to be a major mediator [4] in persistent allergic rhinitis, it may be more responsible for symptoms such as itching and sneezing rather than nasal obstruction. Nasal obstruction does not result solely from the effects of histamine on blood vessels, but involves other mediators such as leukotrienes and prostaglandins; therefore, it is unlikely that a single mediator antagonist will control this symptom completely [5].This review aims to assess the effectiveness of oral antihistamine for the symptom of nasal obstruction in persistent allergic rhinitis in a clinical setting.

Materials and methods

A protocol was written by all three authors.

Search

The Cochrane Controlled Trials Register was searched in June 2002. MEDLINE 1966 to June 2002 and EMBASE 1980

to June 2002 were searched with a strategy sensitive for randomized controlled trials, based on Greenhalgh 1997 [6]. Where the title, abstract or key words suggested a trial might be eligible for this review, an attempt was made to obtain the full text through the British Medical Association Library. A handsearch was made of one journal [7] and two conference abstracts [8, 9] that may have contained relevant studies.

Several attempts were also made to identify prospective trial registers (i.e. ones where a trial entry onto the register is made before the trial starts, and cannot therefore be influenced by the results) that could be searched for relevant studies. All oral antihistamine manufacturers identified from the British National Formulary Issue 41 2002 [10], the copyright holders/developers of outcome measures for health in general or specifically rhinitis and a sample of experts with an interest in rhinitis research were contacted, i.e. those who attended the Allergic Rhinitis and its Impact on Asthma Workshop 2001 [3]. An attempt to obtain information through the Contact Help and Information Network for Effective Healthcare in the UK was also made. Further leads to registers were also taken from texts on meta-analysis [11] and the Cochrane Handbook links [12].

Inclusion criteria

Participants had to be over 12 years old identified by that trial as having perennial, or for more recent trials 'persistent', allergic rhinitis, i.e. symptoms and either positive skin prick testing, raised IgE serum levels or nasal challenge tests, to allergens other than pollen [1]. Twelve years was used as the cut-off so the outcomes were more comparable. Some effort must have been made to exclude those likely to have seasonal allergic rhinitis symptoms at the time of the study. To ensure that the findings of the review to be as clinically relevant as possible, participants had to be as much as possible in their normal setting. More experimental studies, e.g. nasal allergen challenge trials, were therefore not included.

An oral antihistamine (i.e. any oral drug thought to act as a histamine receptor type-1 antagonists) must have been the intervention vs. placebo. As this review aimed to assess the effectiveness of oral antihistamines themselves, studies where another potentially active intervention was also used were not included.

A symptom score for nasal obstruction must have been collected. This is defined as a feeling of insufficient airflow through the nose [13].

Only placebo-controlled, double-blind randomized controlled trials were included.

Trials had to be graded adequate for each of four prospectively stated quality criteria to be taken forward to the data analysis part of the review. The minimum criteria needed were that a record of the trial states patients were 'randomized' to treatment or placebo, that its method was 'double-blind', loss to follow-up was less than 20% in either arm and that a subjective decision could be made that there were no other unanticipated methodological flaws.

Data analysis

A standardized data extraction form based on a template from the Ear Nose and Throat Cochrane Group was used. Where appropriate to pool different studies, symptom scores were converted to 4-point scores and then the mean and standard deviation at follow-up were calculated for antihistamine and placebo groups. The weighted mean difference was then calculated (based on a random effects model) with 95% confidence intervals (CI) using MetaView (in Revman 4.1) software.

It was intended to carry out one subgroup analysis comparing the effect size found in studies identified in prospective registers with those found from other sources, aiming to gain some insight into publication bias within this review.

Results

Of 89 potentially eligible studies identified, 60 were excluded as they did not obviously meet the inclusion or quality criteria (Table 1). For each study, once one reason had been found other reasons were not looked for. Twenty-two were not taken forward as results were not obtainable or it was not possible to assess whether they met stated inclusion and quality criteria (Table 2). Seven were taken forward to the results stage; their characteristics are summarized in Table 3. None of these included studies were found from prospective registers. The mean age of individuals, where given ranged from 25.2 to 35.4 years. The male to female ratio in studies was almost exactly 1 : 1. Eleven different antihistamine regimes were assessed between the seven studies. Eight regimes were given as a once daily dose. Three were given twice daily.

None gave any reference to the symptom score used having had its validity or reliability assessed. All studies treated their score as continuous data. Scores were recorded to assess effectiveness after between 2 and 12 weeks. Patient-assessed scores were recorded by four studies, and reported by two of these. Healthcare worker-assessed scores were recorded by all six studies and reported by five of these. Studies did not state how information about adverse events was obtained but all included made some attempt at the follow-up to record some information about adverse events that had occurred.

Three of the studies presented data in a way that could not be pooled [14–16]. Bousquet et al. [14] found no statistically significant reduction in 'stuffiness' in patients on antihista-

Table 1. Reasons 60 studies identified by broad search strategy as potentially eligible were excluded as failed to meet inclusion/quality criteria

Reason	Number of studies
Population = SAR	12
Population = (or may =) SAR+PAR	16
Population did not (or may not) fit ARIA 01 criteria for PAR for other reasons	8
Intervention – not oral antihistamine on its own	2
Outcome measure – symptom score not collected	4
Methodological – comparison group may have had active component	2
Methodological problem – no placebo group	12
Methodological problem – these are themselves reviews not trials	3
Did not reach quality criteria as single blind	1

mines compared with placebo. Bruttman et al. [15] found that nasal stuffiness improved in 50% patients on loratadine, 41% on terfenadine and 13% on placebo. Mansmann et al. [16] found a statistically significant reduction in 'stuffiness' in patients on Cetirizine 20 mg od ($P<0.01$ compared with placebo), but not on Cetirizine 10 mg od.

Four of the studies contained data that could be pooled [17–20].

The pooled results for patient-assessed scores are as follows:

Antihistamine group $n = 142$.
Placebo group $n = 126$.
Weighted mean difference $= -0.52$ in favour of treatment.
[95% CI] $= [-0.73, -0.31]$.
$z = 4.89$.
$P<0.00001$.
On the 0–3 scoring system the mean patient-assessed nasal obstruction symptom scores (pooled and weighted for sample size) are 1.65 before intervention. The weighted mean difference therefore represents a 31.5% change in symptoms on top of any placebo effect.

The pooled results for healthcare worker assessed scores are as follows:

Antihistamine group $n = 190$.
Placebo group $n = 181$.
Weighted mean difference $= -0.33$ in favour of treatment.
[95% CI] $= [-0.49, -0.16]$.
$z = 3.85$.
$P = 0.0001$.
On the 0–3 scoring system the mean healthcare worker assessed nasal obstruction symptom scores (pooled and weighted for sample size) are 1.48 before intervention. The

Table 2. Reasons a further 22 studies initially identifed by broad search strategy were not taken forward to results stage of this review

Reason not included	Number of studies
Not ongoing, but no details of results obtained	3
Only combined symptom score obtained (e.g. score for congestion+sneezing+discharge)	3
Translation needed	13
Full text not obtained	2

Table 3. Characteristics of seven studies meeting inclusion criteria

Study	Method+setting	Individuals randomized/loss to follow-up	Intervention	Outcome recorded at end of treatment
Bachert 98	Parallel multicentre countries = England+Germany	252 entered 20 in mizolastine and 17 in placebo 'left study prematurely'	Mizolastine 10 mg od or placebo od for 28 days	Investigator assessed 10 point symptom score of 'nasal blockade' (note: patient assessed diary score also recorded but not reported).
Bousquet 99	Parallel multicentre countries = France, Spain+Portugal	290 entered study 42 'withdrew'	Ebastine 10 mg od or Ebastine 20 mg od or placebo od for 12 weeks	Investigator assessed four point symptom score of 'nasal stuffiness'.
Bruttmann 89a	Crossover probable multi-centre countries probably = France+Belgium	33 entered two lost to follow up six protocol violations	Cetirizine 10 mg od (plus placebo od), placebo bd, Terfenadine 60 mg bd, in random sequence for 2 week each	Investigator assessed 4-point symptom score at end of each 2 week period, of 'nasal congestion'+patient recorded score (this actually done on daily basis, with data from day 5 onwards of each 2 week period being used).
Bruttmann 89b	Parallel multicentre countries = France, Austria+Germany	239 entered 11 'did not return' 13 not included in analysis of efficacy as 'violated study protocol'	Loratadine 10 mg od morning/ placebo od night or Terfenadine 60 mg bd or placebo bd for 28 days	Probable investigator assessment of 4-point score.
Ciprandi 01	Parallel probably single center Country = Italy	29 entered one in Fex. 120 mg Gp. Excluded from analysis as 'non- compliant with treatment'	Fexofendaine 120 mg od or Fexofenadine 180 mg od or placebo od for 28 days	Investigator assessed 5-point symptom score of 'nasal congestion' (it is possible to read off graphs number of people in each group with each score, but not individual scores).
Frolund 90	Parallel multi-centre country probably = Denmark+Norway+ Sweden	155 entered 25 excluded from analysis	Clemastine1 mg bd or Loratidine 10 mg od or placebo bd for 21 days	Patient diary assessed 4-point symptom score of 'nasal stuffiness' (note: investigator recorded results also obtained but not reported).
Mansmann 92	Parallel multicentre country = USA	220 entered 5 excluded from analysis	Cetirizine 10 mg od or Cetirizine 20 mg od or placebo od for 28 days	Physician assessed 4-point symptom score, at 4 weeks, of 'nasal congestion' (note: patient assessed diary scores were also collected but were not reported).

weighted mean difference therefore represents a 22% change in symptoms on top of any placebo effect.

Forrest plots are given in Figs 1 and 2.

No significant statistical heterogeneity was found between studies.

Funnel plots, to help assess publication bias within the review are given in Fig. 3.

Headache was the most common adverse event overall. There was, however, no statistically significant increase in this in the treatment group. Analysing the studies data especially for this review, one study was found to contain evidence of a statistically significant increase in fatigue in the antihistamine group [15] for Cetirizine 20 mg once daily, $P<0.03$. Another study however was found to contain evidence of a statistically significant increase in tiredness in the placebo group [19], compared with Loratidine 10 mg one daily, $P<0.02$.

Discussion

Where it was possible to pool data, this review found that oral antihistamines cause a statistically significant reduction in the symptom of nasal obstruction in a clinical setting. A recent trial of levocetirizine [21] published after the search for this review was carried out also found a statistically significant reduction.

The size of change in the symptom of nasal obstruction found in this review is of a reduction of between 22% and 31.5% on top of any placebo effect. Interviews with individuals, with mild persistent allergic rhinitis, would need to be carried out to try to establish whether such an improvement would be important enough for them to wish to take oral antihistamines, and would help establish the clinical significance of this finding.

Publication bias (i.e. researchers being more likely to submit positive results that show an association between an exposure and an outcome, than negative ones) is one of the greatest threats to the validity of this, or any systematic review [22–25]. One way we had hoped to explore this was by comparing the effect size of studies found in prospective trial registers with the effect size of studies found from the other sources. Unfortunately, none of the included trials came from prospective registers and so this was not possible. A further way we attempted to explore publication bias was with funnel plots of studies sample size and effect size. The funnel plot of the patient-assessed data does not suggest publication bias (Fig. 3). Initial inspection of the funnel plot of the healthcare worker-assessed data (Fig. 3) does suggest publication bias, as the study with the highest number of patients (Bachert 98) is to the right of the line representing the pooled effect size (i.e. it is closer to a point representing no effect). The smallest study is, however, also to the right of this line, suggesting that the pooled effect size is not purely because of small studies that were highly positive because of chance, and were then published. Publication bias is therefore not convincingly demonstrated by the funnel plots.

Reporting bias (i.e. only reporting results in favour of treatment within the published studies) is also a potential threat to the validity of reviews. Two studies recorded

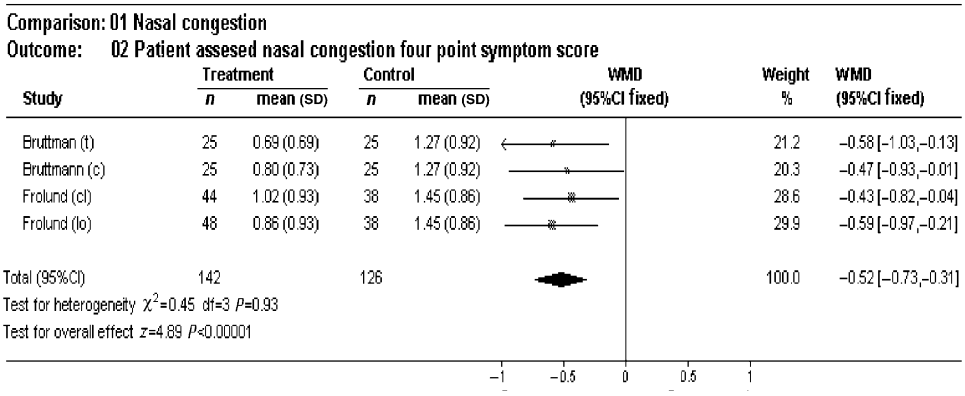

Fig. 1. Forrest plot of studies reporting patient-assessed symptom scores.

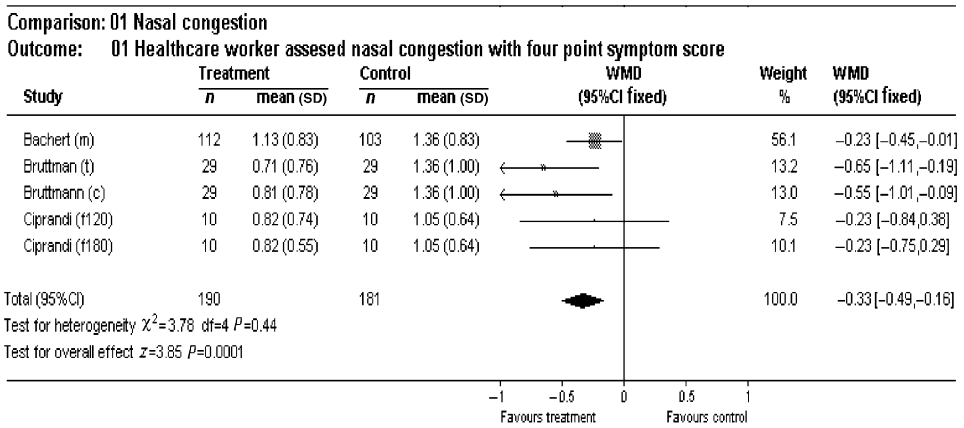

Fig. 2. Forrest plot of studies with clinician-assessed symptom scores.

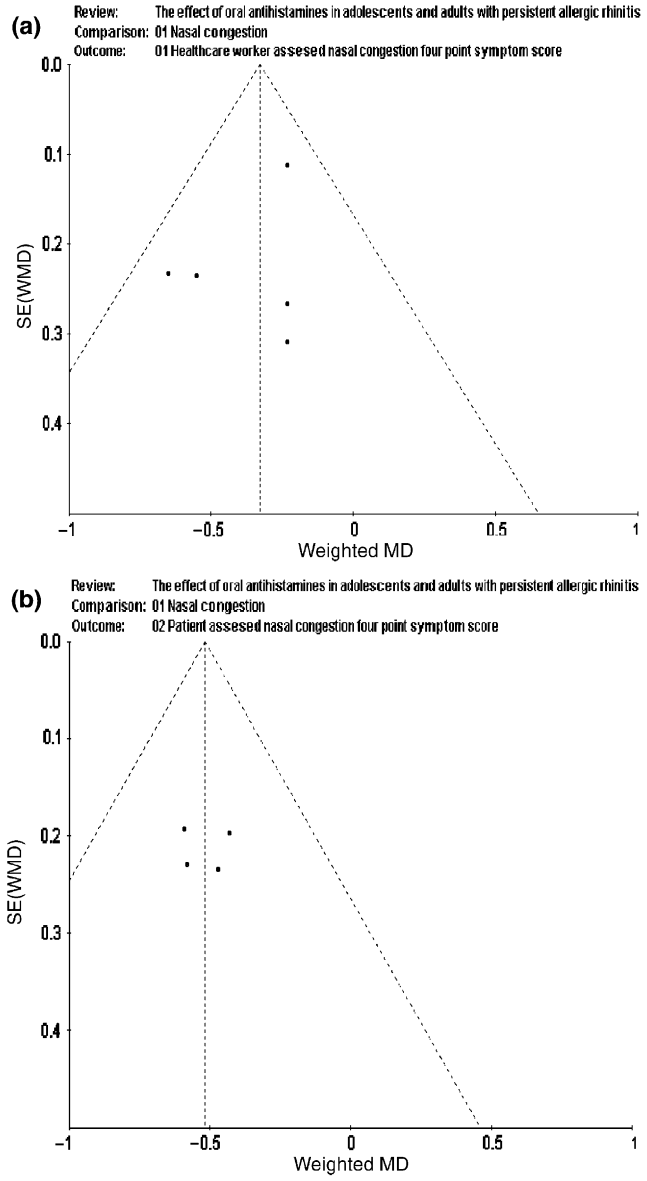

Fig. 3. Funnel plots.

patient-assessed outcomes without reporting them, while one study recorded healthcare worker-assessed outcomes without reporting them. As the outcomes most under-reported were the ones this review found to be most effective (i.e. patient-assessed outcomes), there is some reassurance of a lack of reporting bias.

With respect to potential publication and reporting bias, the number of potentially eligible studies excluded in Table 2 in this review does demonstrate the importance of making provision for translating facilities, and specifying the extent to which attempts would be made to contact trialists (where more information is needed) will be made before starting the review. These points were not addressed in the protocol of this review. Future reviews protocols would benefit from their inclusion.

A further point arising is the tendency of studies to treat symptom scores as continuous data. This has been repeated in the review. Symptom scores are, however, probably more correctly seen as ordinal data. In a future review of the allergic rhinitis literature, we hope to explore this issue.

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