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# Antihistamines for the common cold (Review)

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De Sutter AIM, Saraswat A, van Driel ML.
Antihistamines for the common cold.
*Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD009345.
DOI: 10.1002/14651858.CD009345.pub2.

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[Intervention Review]

# Antihistamines for the common cold

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**Editorial group:** Cochrane Acute Respiratory Infections Group.
**Publication status and date:** New, published in Issue 11, 2015.
**Review content assessed as up-to-date:** 19 August 2015.

**Citation:** De Sutter AIM, Saraswat A, van Driel ML. Antihistamines for the common cold. *Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD009345. DOI: 10.1002/14651858.CD009345.pub2.



## ABSTRACT

### Background

The common cold is an upper respiratory tract infection, most commonly caused by a rhinovirus. It affects people of all age groups and although in most cases it is self limiting, the common cold still causes significant morbidity. Antihistamines are commonly offered over the counter to relieve symptoms for patients affected by the common cold, however there is not much evidence of their efficacy.

### Objectives

To assess the effects of antihistamines on the common cold.

### Search methods

We searched CENTRAL (2015, Issue 6), MEDLINE (1948 to July week 4, 2015), EMBASE (2010 to August 2015), CINAHL (1981 to August 2015), LILACS (1982 to August 2015) and Biosis Previews (1985 to August 2015).

### Selection criteria

We selected randomised controlled trials (RCTs) using antihistamines as monotherapy for the common cold. We excluded any studies with combination therapy or using antihistamines in patients with an allergic component in their illness.

### Data collection and analysis

Two authors independently assessed trial quality and extracted data. We collected adverse effects information from the included trials.

### Main results

We included 18 RCTs, which were reported in 17 publications (one publication reports on two trials) with 4342 participants (of which 212 were children) suffering from the common cold, both naturally occurring and experimentally induced. The interventions consisted of an antihistamine as monotherapy compared with placebo. In adults there was a short-term beneficial effect of antihistamines on severity of overall symptoms: on day one or two of treatment 45% had a beneficial effect with antihistamines versus 38% with placebo (odds ratio (OR) 0.74, 95% confidence interval (CI) 0.60 to 0.92). However, there was no difference between antihistamines and placebo in the mid term (three to four days) to long term (six to 10 days). When evaluating individual symptoms such as nasal congestion, rhinorrhoea and sneezing, there was some beneficial effect of the sedating antihistamines compared to placebo (e.g. rhinorrhoea on

day three: mean difference (MD) -0.23, 95% CI -0.39 to -0.06 on a four- or five-point severity scale; sneezing on day three: MD -0.35, 95% CI -0.49 to -0.20 on a four-point severity scale), but this effect is clinically non-significant. Adverse events such as sedation were more commonly reported with sedating antihistamines although the differences were not statistically significant. Only two trials included children and the results were conflicting. The majority of the trials had a low risk of bias although some lacked sufficient trial quality information.

**Authors' conclusions**

Antihistamines have a limited short-term (days one and two of treatment) beneficial effect on severity of overall symptoms but not in the mid to long term. There is no clinically significant effect on nasal obstruction, rhinorrhoea or sneezing. Although side effects are more common with sedating antihistamines, the difference is not statistically significant. There is no evidence of effectiveness of antihistamines in children.

## PLAIN LANGUAGE SUMMARY

**Antihistamines for the common cold**

**Review question**

We reviewed evidence for the effectiveness of antihistamines on signs and symptoms of the common cold. We identified 18 trials with 4342 participants.

**Background**

On average, young children have six to eight colds per year and adults have two to four. Common cold symptoms include sore throat, nasal stuffiness and discharge, sneezing and cough. It is caused by viruses and usually resolves by itself within one to two weeks. However, the common cold has a large impact on time off work or school.

As there is no cure for the common cold, only symptomatic treatment is available. Antihistamines are effective for allergic symptoms such as hay fever. Nasal symptoms of hay fever are similar to common cold symptoms and so trials have been conducted to see whether antihistamines improve common cold symptoms.

**Study characteristics**

The evidence is current to August 2015.

The participants were adults or children with a common cold. We excluded studies with participants suffering from hay fever, asthma or eczema. The effect of different antihistamines was compared to placebo. A beneficial effect meant a decrease in the severity or duration of the general feeling of illness and/or of specific symptoms such as stuffy nose, runny nose or sneezing. We also investigated whether side effects were more common with antihistamines than placebo.

As the common cold usually resolves in seven to 10 days, most studies were of short duration. Where possible we studied the immediate effect and the effect after six to 10 days. Most studies were of good quality although in some studies information to allow us to assess quality was lacking. We considered five out of 16 adults studies and one out of two paediatric studies to be of excellent quality.

All trials outlined the financial support received from pharmaceutical companies in the form of grants, supplying the respective intervention drug or having an author currently employed by a pharmaceutical company.

**Key results**

In adults, there is a short-term beneficial effect on severity of overall symptoms on the first or second day of treatment (45% felt better versus 38% with placebo), but there was no difference between antihistamines and placebo in the mid to long term. The effect of sedating antihistamines on rhinorrhoea and sneezing is too small to be relevant to the patient and involves a risk of side effects such as sedation (9% versus 5.2% with placebo). Trials in children were smaller and of lower quality and lacked evidence of effectiveness.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

**Antihistamines compared to placebo for the common cold**

**Patient or population:** patients with the common cold
**Settings:** ambulatory care
**Intervention:** antihistamines
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Antihistamines | | | | |
| **Change in severity of overall symptoms: short-term**<br>Subjective severity score<br>Follow-up: 1 to 2 days | **Study population** | | **OR 0.74**<br>(0.60 to 0.92) | 1490<br>(3 studies) | ⊕⊕⊕◯<br>**moderate**[1] | - |
| | **623 per 1000** | **550 per 1000**<br>(498 to 603) | | | | |
| | **Moderate** | | | | | |
| | **600 per 1000** | **526 per 1000**<br>(474 to 580) | | | | |
| **Change in severity of overall symptoms: intermediate-term (3 to 4 days)**<br>Subjective severity score<br>Follow-up: 3 to 4 days | **Study population** | | **OR 1.19**<br>(0.67 to 2.11) | 234<br>(1 study) | ⊕⊕⊕⊕<br>**high** | - |
| | **704 per 1000** | **739 per 1000**<br>(615 to 834) | | | | |
| | **Moderate** | | | | | |
| | **704 per 1000** | **739 per 1000**<br>(614 to 834) | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Change in severity of overall symptoms: long-term (6 to 10 days)**<br>Subjective severity score<br>Follow-up: 6 to 10 days | **Study population** | | **OR 0.71**<br>(0.41 to 1.22) | 1551<br>(3 studies) | ⊕⊕⊕⊕<br>**high** | - |
| | **297 per 1000** | **231 per 1000**<br>(148 to 340) | | | | |
| | **Moderate** | | | | | |
| | **362 per 1000** | **287 per 1000**<br>(189 to 409) | | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] One small study with serious risk of bias (Henauer 1988); other studies with unclear risks of bias.

# BACKGROUND

## Description of the condition

The common cold is described as "an acute, self-limiting inflammation of the upper respiratory tract mucosa that may involve any or all of the nose, throat, sinuses and larynx". Symptoms include sore throat, sneezing, blocked and/or runny nose, headache, cough, malaise and low-grade fever. Most of the population experience at least one episode per year; these are usually self limited and resolve within a few days (http://bestpractice.bmj.com/best-practice/monograph/252/basics.html).

The incidence of acute upper respiratory tract infections (URTI), such as the common cold, is difficult to define because of seasonal and locational variability. Children younger than one year commonly experience an average of six to eight episodes per year of URTI but this figure decreases to three to four episodes per year by adulthood (Heikkinen 2003). The list of agents that cause the common cold is large but 66% to 75% of cases are due to 200 antigenically distinct viruses from eight different genera. The most common of these are the rhinoviruses (25% to 80% of cases), followed by coronaviruses (10% to 20%), influenza viruses (10% to 15%) and adenoviruses (5%) (Heikkinen 2003). The pathogenic mechanisms of the various respiratory viruses can be very different.

Rhinoviruses, the most common cause of the common cold, are transmitted to susceptible individuals by direct contact or by aerosol particles, beginning with deposition of the virus in the anterior nasal mucosa or in the eye (via the lacrimal duct). The viruses are then transported to the posterior nasopharynx by mucociliary action. In the posterior nasopharynx, the viruses gain entry to the epithelial cells by binding to the specific receptors located on the cells. Once inside the cell, the virus replicates rapidly (Heikkinen 2003). Detectable histopathology that causes the associated 'cold and flu' symptoms is lacking but it is hypothesised that the host immune response plays a major role in rhinovirus pathogenesis. Infected cells release interleukin-8 (IL-8), which is a potent polymorphonuclear chemo-attractant. Concentrations of IL-8 in secretions correlate proportionally with the severity of common cold symptoms. Inflammatory mediators, such as kinins and prostaglandins, may cause vasodilatation, increased vascular permeability and exocrine gland secretion. These, together with local parasympathetic nerve-ending stimulation, lead to common cold symptoms (Heikkinen 2003; Papadopoulos 2000).

Symptoms develop one to two days after the infection with viruses, peaking two to four days after inoculation and lasting on average for seven to 10 days. Illness begins with a sore throat, which is frequently the most bothersome of the early symptoms. This is followed by nasal discharge, nasal congestion and sneezing, which intensify over the next two to three days. Thirty per cent of infected individuals develop a cough and 20% develop hoarseness, both of which may persist for up to a week. Systemic signs and symptoms (for example, fever, malaise) are unusual and if they are present an alternative diagnosis should be considered (Heikkinen 2003). Physical signs presented by patients include red nose, glistening glassy appearance of nasal mucous membrane and dripping nasal discharge (which can be green/yellow in colour after 24 to 48 hours) (Innes 2006).

Although not associated with fatal disease, the common cold is associated with significant morbidity. URTIs are estimated to cause 30% to 50% of time lost from work by adults and 60% to 80% of time lost from school by children. Complications of common cold include otitis media, sinusitis, lower respirator tract infections (for example, bronchitis, pneumonia) and exacerbations of other respiratory conditions (for example, asthma) (Innes 2006).

A myriad of treatments have been investigated for the common cold including zinc (Singh 2013), corticosteroids (Hayward 2012), vitamin C (Hemila 2013), non-steroidal anti-inflammatory drugs (Kim 2013), paracetamol (Li 2013) and ipratropium bromide ( AlBalawi 2013). In this review we focus on antihistamines.

## Description of the intervention

Antihistamines or $H_1$-receptor antagonists are a diverse group of drugs that possess the ability to inhibit various histaminic actions. Principally they act to prevent histamine-receptor interaction through competition with histamine for histamine receptors, rather than inhibiting histamine release. Consequently, they are helpful therapeutically in preventing histaminic actions such as allergic rhinitis and allergic skin conditions (Mann 1989; Pearlman 1976; Rossi 2010).

This class of drugs is divided into two groups: sedating and non-sedating.

- Sedating antihistamines were the first generation of antihistamines. They are associated with various adverse events largely because of their propensity to cross the blood brain barrier and their cholinergic activity causing symptoms of drowsiness and reduced concentration, as well as dry mouth, blurry vision and urinary retention (Gonzalez 1998; Rossi 2010).
- Non-sedating antihistamines or second-generation antihistamines are lipo-phobic and pass the blood brain barrier to a much lesser extent. They have the advantage of a lack of central nervous system (CNS) and cholinergic effects (Gonzalez 1998).

## How the intervention might work

There is no vaccination or cure for the common cold and treatment therefore focuses on alleviating symptoms. Infection caused by a virus leads to the dispersion of cytokines resulting in further immune cell recruitment. Cytokines and other mediators induce skin redness and temperature, nasal congestion, rhinorrhoea, watery eyes and sneezing (Heikkinen 2003; Papadopoulos 2000). In comparison, histamine is involved in type 1 hypersensitivity reac-

tions (a type of allergic reaction, mediated by IgE) along with other chemicals and acts on the $H_1$-receptor to contribute to symptoms like itchy skin, sneezing, red/watery eyes and rhinorrhoea, as described above. As such, symptoms of infectious rhinitis (the common cold) and allergic rhinitis (hypersensitivity type I) are similar, although the mechanisms of pathogenesis are quite different. Antihistamines may play a minor role in alleviating symptoms through potentially overlapping immune system mediators.

### Why it is important to do this review

The original publication of this review was published in 2003 (De Sutter 2003) and subsequently withdrawn in 2009. This is a new review, following on from the Cochrane protocol published in 2011 (Saraswat 2011). It summarises the evidence on the efficacy of antihistamines (sedating and non-sedating) as monotherapy in relieving symptoms of the common cold. As antihistamines are available over the counter in many countries, this review provides important information for consumers who self treat. In addition, it assists clinicians in making choices when prescribing symptomatic treatment, in particular prescribing antihistamines for the common cold. A rational use of antihistamines for the common cold will aid in the reduction of unnecessary consumption and unwanted adverse effects or complications from their use.

## OBJECTIVES

To assess the effects of antihistamines on the common cold.

More specifically we want to investigate:

1. the clinical efficacy of antihistamines in alleviating overall symptoms of illness and nasal symptoms (nasal congestion, rhinorrhoea and sneezing) in adults and children suffering from a common cold;

2. the clinical efficacy of antihistamines in shortening the duration of the illness; and

3. the evidence on side effects of antihistamines and hence the risk to benefit considerations of this type of medication for the common cold.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs) on the treatment of the common cold with antihistamines, used as monotherapy.

#### Types of participants

Otherwise healthy adults (19 years or older) and children (newborns up to 18 year of age) with common cold symptoms that meet the following criteria:

1. recent onset of symptoms of runny and/or stuffy nose; and
2. sneezing with or without symptoms of headache and cough.

Participants will be excluded if they:

1. have allergic rhinitis;
2. have concurrent acute or chronic lower respiratory tract infections, such as pneumonia, bronchitis, bronchiolitis;
3. have another chronic disease, atopic eczema, asthma, fever (> 38 °C), sinusitis or exudative pharyngitis; or
4. take any other medication.

#### Types of interventions

Treatment with antihistamines (either sedating or non-sedating) as monotherapy, which is administered either orally or intranasally and is compared with a control group. The control group can be either placebo or no treatment. We also report dosage, frequency of administration, duration of therapy and frequency of assessment.

#### Types of outcome measures

In adults and children separately:

##### Primary outcomes

1. The change in severity of overall symptoms of the common cold (for example, absent, mild, moderate, severe).
2. The change in duration of overall symptoms of the common cold (for example, days to resolution).

##### Secondary outcomes

1. The change in severity of individual symptoms, for example, nasal congestion, rhinorrhoea, sneezing (for example, absent, mild, moderate, severe).
2. The change in duration of individual symptoms, for example, nasal congestion, rhinorrhoea, sneezing (for example, days to resolution).
3. Side effects from using antihistamines.

### Search methods for identification of studies

#### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 6) (accessed 1 August 2015), which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (1948 to July week 3, 2015), EMBASE (2010 to August 2015), CINAHL (1981 to August 2015), LILACS (1982 to August 2015) and Biosis Previews (1985 to August 2015).

We used the search strategy described in Appendix 1 to search CENTRAL and MEDLINE. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search EMBASE (Appendix 2), CINAHL (Appendix 3), LILACS (Appendix 4) and Biosis Previews (Appendix 5).

### Searching other resources

We searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov trials registers for completed and ongoing trials (latest search 1 August 2015). We also searched reference lists of the retrieved articles and contacted experts and pharmaceutical companies to find any other potentially relevant published or unpublished data. There were no language, date or publication restrictions.

## Data collection and analysis

### Selection of studies

Two review authors (AS, MVD) independently screened the titles and abstracts of citations. We excluded trials failing to meet the inclusion criteria. We retrieved full texts of identified trials when an abstract was not available or provided insufficient information, and assessed them for inclusion. A third review author (ADS) was consulted if disagreements were not resolved by discussion.

### Data extraction and management

Two review authors (AS, MVD) independently extracted data into RevMan 2014 by using a pre-designed data extraction form. We contacted trial authors for additional data where necessary. A third review author (ADS) was available for consultation if disagreements could not be resolved by discussion.

### Assessment of risk of bias in included studies

We assessed the risk of bias of the included studies using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors (AS, MVD) independently assessed the risk of bias by assessing randomisation sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias. A third review author (ADS) was available if disagreements could not be not resolved by discussion. We report the results in the 'Risk of bias' tables. See Characteristics of included studies table.

For assessments of the overall quality of evidence for each outcome that included pooled data from RCTs only, downgrading the evidence from 'high quality' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias was unnecessary as the trials were of high quality.

### Measures of treatment effect

We identified studies of effectiveness reporting change in severity of overall symptoms (for example, complete relief, marked relief, moderate relief, slight relief or no relief) or a decrease in the severity of individual common cold symptoms assessed by severity scales. We did not extract data where individual severity scores were added up and effectiveness was evaluated by comparing these sum scores, as the clinical meaning of sum scores is unclear.

We express dichotomous data as odds ratio (OR) or risk ratio (RR) with 95% confidence intervals (CI). We expressed continuous data as mean differences (MD) with a standard deviation (SD). We used a P value of less than 0.05 (P value < 0.05) as our cut-off for statistical significance. We calculated the number needed to treat to benefit (NNTB) for an additional beneficial outcome using the OR and the average control event rate described in the relevant studies, where applicable (Higgins 2011).

### Unit of analysis issues

We did not identify any cluster-RCTs for inclusion and therefore adjusting for clustering if the unit of analysis is not the same as the unit of randomisation, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), was not necessary.

### Dealing with missing data

We contacted trial authors for missing data where possible. We performed on treatment analysis for all outcomes, which generates a 'best case scenario'. We also employed intention-to-treat (ITT) analysis for the outcome 'change in severity of overall symptoms', which assigns all participants to their randomised groups regardless of whether they completed the treatment. We considered all missing data as treatment failures when pooling the data, which generates a 'worst case scenario' for the estimate of effect.

### Assessment of heterogeneity

We assessed heterogeneity among studies in two ways. First, we assessed heterogeneity at face value by comparing between studies

the included population, the interventions and the reported outcomes. Second, we used the $I^2$ statistic to assess the presence of statistical heterogeneity (with > 50% as the cut-off value for considerable heterogeneity). We did not pool data if considerable heterogeneity existed at face value. We used a random-effects model for pooling data, which will default to the same result as a fixed-effect method when there is no heterogeneity (Brockwell 2001).

### Assessment of reporting biases

We assessed any potential conflict of interest of funding and/or authors and report this in the Characteristics of included studies table. We were not able to perform funnel plot analysis to assess potential publication bias as the number of studies available for inclusion was insufficient (i.e. fewer than 10). We did not contact pharmaceutical companies for unpublished data, because contacting pharmaceutical companies for the previous version of this review only yielded one additional unpublished trial that did not provide any useful data for the review (De Sutter 2003).

### Data synthesis

We included in the meta-analysis the results from studies that met the inclusion criteria and reported any of the selected outcomes. We summarised data statistically if available, sufficiently similar and of sufficient quality as described in Measures of treatment effect. We performed statistical analyses using RevMan 2014 according to the statistical guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

### GRADE and 'Summary of findings' table

We employed the GRADE approach to interpret findings ( Langendam 2013). We created two 'Summary of findings' tables using GRADEpro Guideline Development Tool (GRADEpro GDT 2015) using the following primary outcome: change in severity of overall symptoms. We used the five GRADE (Atkins 2004) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcome. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEproGDT software (GRADEpro GDT 2015). We justified all decisions to down- or up-grade the quality of studies using footnotes.

### Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis for children and adults and for sedating and non-sedating antihistamines where feasible.

### Sensitivity analysis

Due to the limited number of studies eligible to enter into a meta-analysis and the low risk of bias of many trials, we did not perform the planned sensitivity analysis.

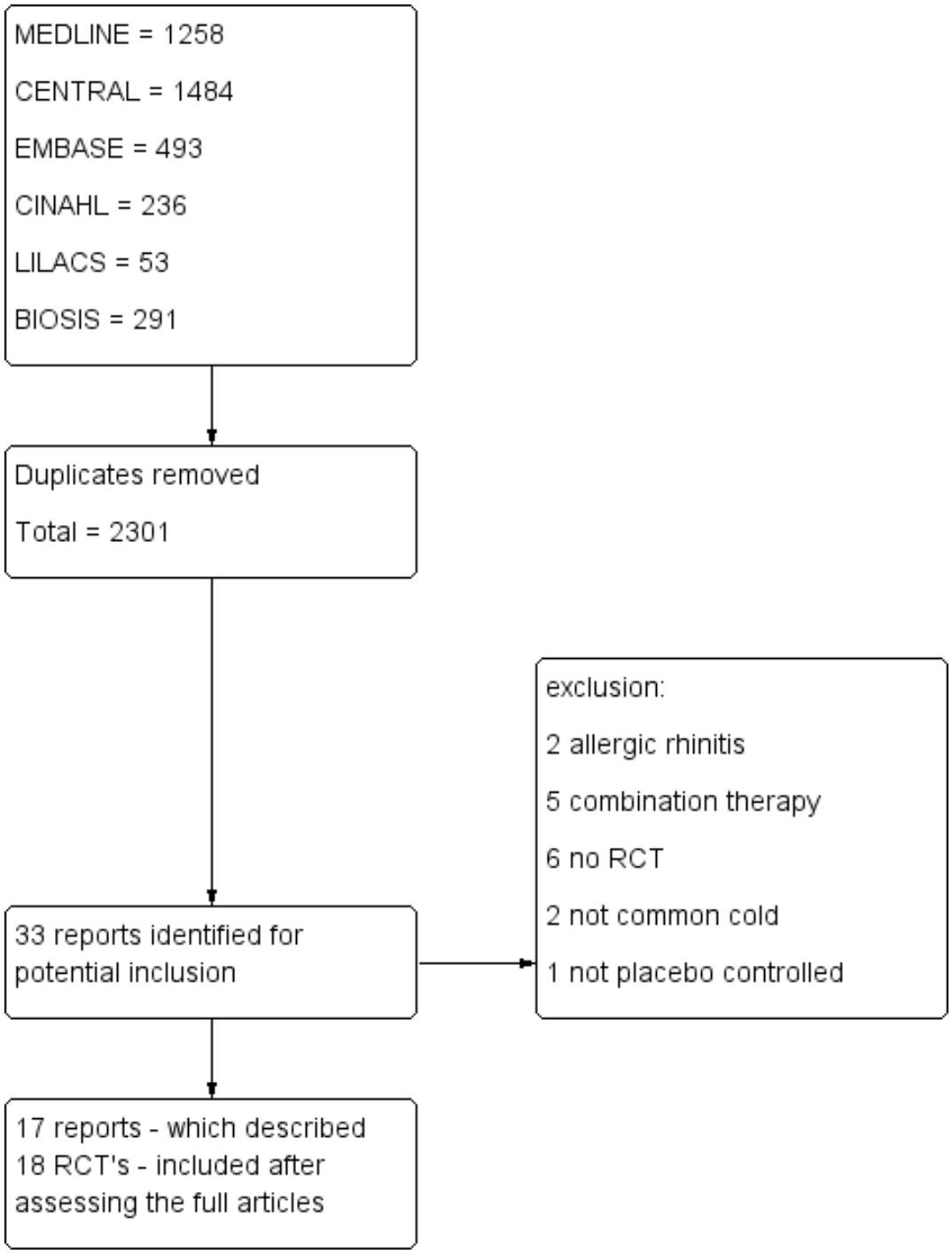
## RESULTS

### Description of studies

#### Results of the search

The electronic searches identified 2124 records in total. Searching MEDLINE identified 1186 records, searching CENTRAL identified 1451 records, 395 records were retrieved from EMBASE, 229 records were retrieved from CINAHL, the LILACS search identified 52 records and the BIOSIS search identified 291 records (see Figure 1).

**Figure 1. Flow chart of study selection and inclusion process.**



## Included studies

Out of 2124 studies identified from the search 18 trials reported in17 publications met our inclusion criteria. There was complete agreement between the review authors assessing the trials.
In the Characteristics of included studies table, details of quality, included population, setting, inclusion and exclusion criteria, interventions and dosage, outcome measures and main methodological shortcomings are summarised per study.
In total, 18 randomised controlled trials (RCTs) were described in 17 publications. One publication was reported in two trials.The interventions consisted of an antihistamine as monotherapy compared with placebo. Thirteen trials used a sedating antihistamine as the intervention, the most common of which was chlorpheniramine maleate in five trials (Crutcher 1981; Doyle 1988; Gaffey 1987b; Howard 1979; Sakchainanont 1990), followed by clemastine fumarate in three trials (Gwaltney 1996; Sakchainanont 1990; Turner 1997). The remaining sedating antihistamines were brompheniramine maleate, doxylamine succinate, diphenhydramine hydrochloride, triprolidine, thonzylamine and diphenylpyraline. Six trials used a non-sedating antihistamine as the intervention, with three trials utilising terfenadine (Berkowitz 1991; Gaffey 1988; Henauer 1988), and the remaining trials using loratadine, astemizole and cetirizine. The 17 papers included a total of 4342 patients suffering from the common cold, both naturally occurring and experimentally induced. The majority of trials included adult participants, with some trials specifying an age range of 18 to 65 years old. Two trials recruited paediatric patients; one trial included patients between two and 15 years old (Hugenin 1988), and the other trial only included patients who were five years and under (Sakchainanont 1990).

### Inclusion criteria

For the seven trials involving experimentally induced colds, the inclusion criteria were typically a healthy adult volunteer who was free of cold symptoms and an elevated temperature for two weeks prior to inclusion in the trial (Doyle 1988; Ectors 1994; Gaffey 1987a; Gaffey 1987b; Gwaltney 1996; Gwaltney 1997; Muether 2001). For the 11 trials involving naturally occurring colds, the inclusion criteria revolved around those symptoms described by Jackson (Jackson 1958): sneezing, nasal discharge, nasal obstruction, headache, sore throat, chilliness, cough and malaise (Berkowitz 1991; Bye 1980; Crutcher 1981; Eccles 1995; Gaffey 1988; Henauer 1988; Howard 1979; Hugenin 1988; MRC (Part 2) 1950; Sakchainanont 1990; Turner 1997). Most required rhinorrhoea that was classified as moderate to severe and at least one other symptom as described above. In one trial, a participant's own judgement of "having a cold" was sufficient to be included (Turner 1997).

### Setting

Some trials did not specify the setting. When mentioned, settings included universities, community clinics and hospital outpatient departments. Eight trials were multicentre (Bye 1980; Eccles 1995; Gwaltney 1996; Henauer 1988; Howard 1979; MRC (Part 2) 1950; Sakchainanont 1990; Turner 1997). Eleven trials were performed in the USA (Berkowitz 1991; Crutcher 1981; Doyle 1988; Gaffey 1987a; Gaffey 1987b; Gaffey 1988; Gwaltney 1996; Gwaltney 1997; Howard 1979; Muether 2001; Turner 1997). Two trials were conducted in England (Bye 1980; MRC (Part 2) 1950), one in Thailand (Sakchainanont 1990), two in Switzerland (Henauer 1988; Hugenin 1988), and one in Belgium (Ectors 1994). One trial was conducted in multiple countries across Europe such as England, Belgium, Denmark and Germany (Eccles 1995).

### Financial support

All trials outlined their financial support received from pharmaceutical companies in the form of grants (Doyle 1988; Gaffey 1988; Muether 2001), supplying the respective intervention drug (Berkowitz 1991; Crutcher 1981; Gaffey 1987a; Gaffey 1987b; Gaffey 1988; Hugenin 1988; MRC (Part 2) 1950; Sakchainanont 1990), or having an author currently employed by a pharmaceutical company (Bye 1980; Gwaltney 1996; Gwaltney 1997; Henauer 1988; Howard 1979; Turner 1997), except for Ectors 1994 where this is not mentioned.

## Excluded studies

Out of the 1946 papers, we considered 35 for inclusion and judged them by assessing the entire article. We excluded 16 for reasons such as being related to allergic rhinitis (Aaronson 1968; Simons 1991), being combination therapy and not monotherapy (Andre 1974; Ashe 1968; Debelic 1973; Elia 1967), not being a RCT (D'Agostino 1998; Henahan 1983; Knowelden 1959; Shaughnessy 1999; Smith 1993; Tarchalska 2000; West 1975), only assessing cough (Yoder 2006), having a control group receiving active treatment (McGuinness 1976), or analysing the effect of topical eye drops (Dumitrescou 1965). See Characteristics of excluded studies table.

## Risk of bias in included studies

Details of included studies can be found in Characteristics of included studies. The majority of the studies were of good quality, although in one trial the data were insufficient to judge the risk of

bias (Ectors 1994). Follow-up varied between 69.2% and 100%. We were unable to contact the trial authors for any missing data or the manufacturers for any unpublished data. See Figure 2 and Figure 3.

**Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**

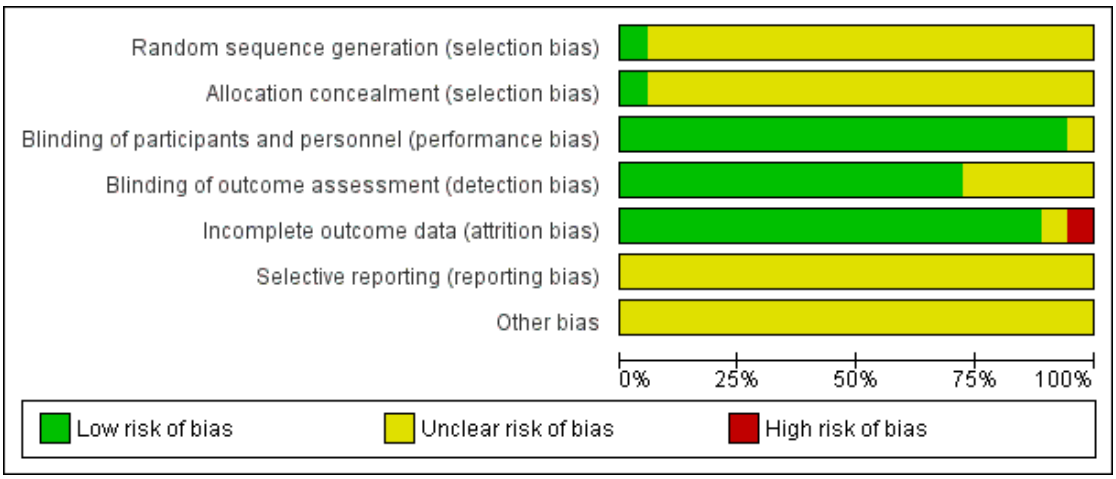
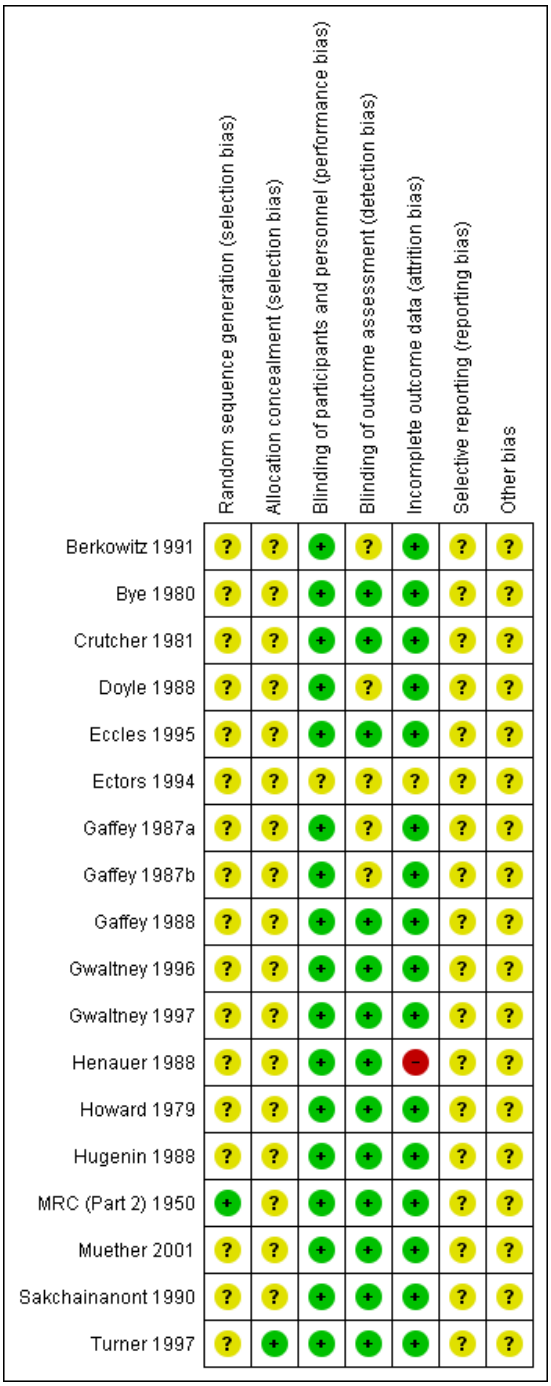


**Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.**



### Allocation

Most included studies had low risk of bias related to random sequence generation, except Ectors 1994 and Hugenin 1988, where this was unclear and not specified. All studies were reported to be double-blinded. Most studies did not specify the allocation concealment process and thus had an unclear risk of bias, except Gwaltney 1996, Howard 1979, MRC (Part 2) 1950, Muether 2001, Sakchainanont 1990 and Turner 1997.

### Blinding

All included studies had a low risk of performance bias. There was similarly a low risk of detection bias in most studies, except Berkowitz 1991, Doyle 1988, Ectors 1994 and Gaffey (Gaffey 1987a; Gaffey 1987b), where the risk was unclear as blinding of outcome data was not specified.

### Incomplete outcome data

All studies had a low risk of attrition bias, except Ectors 1994, where the risk was unclear due to lack of specific details. In Henauer 1988 the study protocol was not followed causing many participants to be excluded, which could have contributed to attrition bias due to incomplete outcome data. We contacted several authors and received detailed unpublished data on relevant outcomes from Muether 2001, Gwaltney 1996, Gwaltney 1997 and Gaffey 1988.

### Selective reporting

All studies had an unclear risk of reporting bias as this was not clearly specified in the trial process. We were unable to contact the manufacturers for any unpublished data.

### Other potential sources of bias

All studies were financially supported by the pharmaceutical industry, which obviously has an interest in a beneficial effect.

## Effects of interventions

See: **Summary of findings for the main comparison** Antihistamines compared to placebo for the common cold; **Summary of findings 2** Sedating antihistamines compared to placebo for the common cold

### Primary outcomes

#### Antihistamines in adults

**1. The change in severity of overall symptoms of the common cold**

Nine trials, evaluating 2906 participants, assessed the change in severity of overall symptoms of antihistamines on the course of the common cold in adults (Berkowitz 1991; Bye 1980; Crutcher 1981; Gaffey 1988; Gwaltney 1996; Gwaltney 1997; Henauer 1988; Howard 1979; MRC (Part 2) 1950). Four trials using sedating antihistamines showed some effect.

- A Medical Research Council trial included 1550 participants to study the effectiveness of thonzylamine (MRC (Part 2) 1950). More participants were improved or cured after one day with thonzylamine than compared to placebo (P value = 0.04). However, this was not the case after two or seven days and 25% of participants were lost to follow-up.
- In the trial Bye 1980, the effect of triprolidine was studied in 180 cold episodes in 124 participants. Some participants were entered several times while having several cold episodes during the course of the study. In significantly more cold episodes, participants at final evaluation (eight to 10 days after the start of therapy) improved with triprolidine compared to placebo (P value = 0.009).
- The trial Crutcher 1981, examining the effect of chlorpheniramine in 106 adults, found that volunteers considered themselves significantly better in comparison to the start of the cold after two to seven days with active treatment compared to placebo (P value = 0.05).
- In the trial Gwaltney 1997, studying the effect of brompheniramine in 264 experimentally infected symptomatic adult volunteers, participants were asked at final evaluation to rate their change in severity of overall symptoms on a 10-point visual analogue scale (VAS). Participants in the active treatment group scored significantly higher than in the placebo group (P value < 0.01).

Five other trials (three studying non-sedating antihistamines) failed to show any significant beneficial effect.

- In the study Howard 1979, 271 participants reported daily the change in severity of overall symptoms of the treatment received during seven days of therapy (chlorpheniramine or placebo); this was rated on a five-point scale (markedly improved, moderately improved, slightly improved, no improvement, worse). There was no significant difference between the active and placebo group in the number of participants feeling

markedly to moderately improved after one day or six days of treatment (day 1: P value = 0.11; day 6: P value = 0.55).

- In the trial by Henauer 1988, the effectiveness of terfenadine was studied in 91 participants. In this trial, recruitment was difficult because at first a number of participants not meeting the eligibility criteria were entered but then subsequently removed. The results of the eligible group showed that the therapy was evaluated as moderately to excellently efficacious by more patients in the terfenadine group than in the placebo group, but this difference was not statistically significant (P value = 0.10).
- Gaffey 1988 also studied the effect of terfenadine and included 250 participants. The proportion of participants with complete or marked symptom relief at study conclusion (3.5 days) was not significantly different between the treatment groups (P value = 0.55).
- In the study Berkowitz 1991, which again studied the effect of terfenadine, the assessment of change in severity of overall symptoms by physicians on a five-point scale (complete relief, marked relief, moderate relief, slight relief, no relief or worse) after four to five days of treatment was similar in both treatment and placebo groups.
- Gwaltney 1996 found no difference in overall treatment effect between clemastine and placebo in 150 experimentally infected participants, although more detailed data on this outcome were not reported.

We entered data from five of the trials into a meta-analysis (Bye 1980; Gaffey 1988; Henauer 1988; Howard 1979; MRC (Part 2) 1950).

- All these trials reported the proportion of participants with a beneficial effect in both treatment groups at a certain time point after the start of the treatment. However, different populations and different interventions are studied and the results must be considered with caution.
- All trials reported ratings by the study participants. Some have methodological shortcomings as mentioned in Risk of bias in included studies.
- We pooled the following data (see Data and analyses 1 and 2):
    - Comparison of proportion of patients without beneficial effect - all trials: short-term effect (one to two days - Analysis 1.1), intermediate-term effect (three to four days - Analysis 1.2) and long-term effect (six to 10 days - Analysis 1.3). See Summary of findings for the main comparison.
    - Comparison of proportion of patients without beneficial effect - trials with sedating antihistamines: short-term effect (one to two days - Analysis 2.1) and long-term effect (six to 10 days - Analysis 2.2). See Summary of findings 2.
- In both comparisons there is a short-term beneficial effect of antihistamines on severity of overall symptoms (odds ratio (OR) 0.74, 95% confidence interval (CI) 0.60 to 0.92 (Analysis 1.1) and OR 0.76, 95% CI 0.61 to 0.95 (Analysis 2.1)). However, the difference is small, with a number needed to treat to benefit (NNTB) of approximately 14. None of the other comparisons showed any significant effect.

We performed intention-to-treat (ITT) analysis for the outcome 'change in severity of overall symptoms' in order to test the robustness of the effect estimate. Given the low attrition in most included studies this worst case scenario analysis did not change the overall effect estimate (Analysis 1.4; Analysis 1.5; Analysis 1.6). Some data could not be entered into the meta-analysis because different outcome measures were used, or adequate data were not available in the published papers. This concerns data from four trials (Berkowitz 1991; Crutcher 1981; Gwaltney 1996; Gwaltney 1997). Two of these trials show some effect as stated previously.

- In the trial Crutcher 1981, insufficient data were available to assess the size of this effect. In the trial Gwaltney 1997, participants in the active treatment group rated their change in severity of overall symptoms after four days of treatment on a 10-point visual analogue scale (VAS) 1.1 point better than in the placebo group, which is also a small effect. Therefore it is unlikely that the results of these trials would change the conclusions of the meta-analysis. Data are summarised in Table 1

**2. The change in duration of overall symptoms of the common cold**

None of our included studies evaluated the change in duration of the overall symptoms of the common cold.

## Secondary outcomes

### Antihistamines in adults

**1. The change in severity of individual symptoms, for example, sneezing, nasal congestion, rhinorrhoea**

***a) Nasal congestion***

Six trials showed no favourable treatment effect.

- In the study Bye 1980, severity ratings of nasal obstruction using a four-point scale were noted in the patient diary. These scores did not decrease significantly more in the 59 participants receiving triprolidine compared with the 60 participants taking placebo.
- In the study Gaffey 1988, 250 participants registered their mean severity score twice a day, three hours after each dose of terfenadine (in total seven doses). A four-point scale was used. After the sixth dose on day three, nasal stuffiness was worse with terfenadine (P value < 0.05).

- In the trial Berkowitz 1991, including 100 participants, physicians used a four-point scale to evaluate the severity of nasal obstruction after four or five days of treatment, approximately three hours after the last dosage of trial medication (terfenadine or placebo). They found similar severity in both treatment groups (P value = 0.084).
- Gwaltney 1996, in 150 experimentally inoculated and symptomatic patients, recorded the participants' assessments of severity on a five-point scale and found no significant difference in favour of clemastine (P value > 0.10).
- Muether 2001 studied the effect of loratadine in 66 participants. This study design was different (treatment was started seven days before virus inoculation and continued five days afterwards). Severity scores (using a five-point scale) for nasal obstruction were recorded during five days after inoculation for participants with proven infection but not necessarily symptoms (N = 53). Only 37 of these participants got a clinical cold. There was no significant difference in severity scores between placebo and loratadine (P value > 0.10).
- In the study Doyle 1988, 27 participants who developed a cold after experimental virus inoculation were interviewed on days three to six after inoculation. The severity scores (mild, moderate, severe) obtained on these four days by interview were summed and averages were compared between chlorpheniramine (N = 12) and placebo (N = 15) treated treatment groups. There was no significant difference (P value = 0.11). In the same study the average number of days with nasal obstruction was counted in both treatment groups. There was also no significant difference (P value = 0.14).

In contrast with these results, three trials show some effect.

- Gwaltney 1997, using a similar experimental design (N = 225) as in the 1996 study, found a significant effect of brompheniramine on subjective nasal obstruction on the third day of therapy (P value = 0.04) but not on the other days.
- Ectors 1994, studying the effect of cetirizine in 40 experimentally infected participants, found a significantly larger decrease in nasal obstruction severity score after two days of treatment in the active treatment group (P value = 0.035). It is not clear from the available report how these scores were obtained.
- In one trial rhinoscopy was performed. In the trial Henauer 1988, the same participants who underwent rhinometry were also examined by rhinoscopy. At two and 24 hours after the first tablet of terfenadine or placebo, redness, swelling, obstruction and secretion were less severe in participants on terfenadine when compared with placebo (no P values mentioned). However, in this trial there were several methodological problems.

We entered data from five trials into a meta-analysis (Berkowitz 1991; Gaffey 1988; Gwaltney 1996; Gwaltney 1997; Muether 2001). However, these trials are quite different from one another. Two trials recruited participants with natural colds and three trials recruited experimentally infected participants. Three trials studied non-sedating antihistamines and the other two studied sedating antihistamines. Three trials used a five-point severity score and the other two, a four-point severity score.

- The trial Muether 2001 had a special design and only 70% of participants had a clinical cold.
- In the Gaffey 1988 trial only data at a single time point were available, where a significant difference was found.
- We made the following comparisons (see Data and analyses 3 to 5).
    - Subjective severity assessment of nasal obstruction - all trials: mean severity assessment of nasal obstruction after one day of treatment and mean severity assessment of nasal obstruction after three to five days of treatment (Gaffey 1988; Gwaltney 1996; Gwaltney 1997; Muether 2001 day three; Berkowitz 1991 days four to five).
    - Subjective severity assessment of nasal obstruction - sedating antihistamines: mean severity assessment of nasal obstruction after one day of treatment and mean severity assessment of nasal obstruction after three to five days of treatment (Gaffey 1988; Gwaltney 1996; Gwaltney 1997; Muether 2001: day three, Berkowitz 1991: days four to five).
    - Subjective severity assessment of nasal obstruction - non-sedating antihistamines: mean severity assessment of nasal obstruction after one day of treatment and mean severity assessment of nasal obstruction after three to five days of treatment (Gaffey 1988; Gwaltney 1996; Gwaltney 1997; Muether 2001: day three, Berkowitz 1991: day four to five).
- None of these comparisons showed any significant effect in favour of antihistamines. However, when looking at the pooled results after three to five days of therapy with non-sedating antihistamines we observed a higher severity score in the participants receiving antihistamines (P value = 0.05) (mean difference (MD) 0.21, 95% CI 0.00 to 0.41) (Analysis 4.2).

Results from the trial Ectors 1994 in 40 experimentally infected symptomatic participants, the trial Henauer 1988 in 91 participants and the trial Bye 1980 in 119 naturally acquired colds could not be entered into the meta-analysis due to inadequate data in the reports. Results from the trial Doyle 1988, in 27 participants who developed a cold after experimental virus inoculation, also could not be entered into the meta-analysis because different outcome measures were used. All data from these trials are in Table 2.

### *b) Rhinorrhoea*

Six trials failed to show any effect of antihistamines (Berkowitz 1991; Bye 1980; Doyle 1988; Ectors 1994; Gaffey 1988; Muether 2001). In these trials severity of rhinorrhoea was assessed in the same way as severity of nasal obstruction.

- In the study Bye 1980, severity ratings for rhinorrhoea using a four-point scale were noted in the patient diary. These

scores did not decrease significantly more in the 59 participants receiving triprolidine compared with the 60 participants taking placebo.

- In the study Gaffey 1988, 250 participants registered their mean severity score twice a day, three hours after each dose of terfenadine (in total seven doses). A four-point scale was used. The severity score for rhinorrhoea did not differ between groups.
- In the trial Berkowitz 1991, including 100 participants, physicians used a four-point scale to evaluate the severity of rhinorrhoea after four or five days of treatment, approximately three hours after the last dosage of trial medication (terfenadine or placebo). They found similar severity in both treatment groups (P value = 0.91).
- Ectors 1994, studying the effect of cetirizine in 40 experimentally infected participants, did not find any difference in the rhinorrhoea severity score in either group. It is not clear from the available report how these scores were obtained.
- Muether 2001 studied the effect of loratadine in 66 participants. This study design was different (treatment was started seven days before virus inoculation and continued for five days afterwards). Severity scores (using a five-point scale) for rhinorrhoea were recorded during five days after inoculation for participants with proven infection but not necessarily symptoms (N = 53). In only 37 of these participants this resulted in a clinical cold. There was no significant difference in severity scores between placebo and loratadine.
- In the study Doyle 1988, in 27 participants who developed a cold after experimental virus inoculation, the severity scores for rhinorrhoea (mild, moderate, severe) obtained by interview on four treatment days were summed and the averages are compared between the chlorpheniramine (N = 12) and placebo (N = 15) treated participants. There was no significant difference (P value = 0.16). Doyle 1988 also counted the average number of days with rhinorrhoea in both treatment and placebo groups. There was also no significant difference for this outcome (P value = 0.6).

In six trials some effect was found (Eccles 1995; Gwaltney 1996; Gwaltney 1997; Henauer 1988; Howard 1979; Turner 1997).

- In the study Howard 1979, participants were observed during the first two days of treatment. Severity scores were measured on a four-point scale every two hours (daytime) during the 48 hours and afterwards three times a day. The total study observation period was seven days. At 18 of the 24 time points, the rhinorrhoea severity score was significantly lower with chlorpheniramine (P values not mentioned).
- In the study Turner 1997, 1000 participants were observed during a whole winter and were entered into the trial when developing a cold. Four hundred and three participants developed a cold and the effect of clemastine was compared with placebo. Rhinorrhoea severity was scored from day two until day four of treatment on a five-point scale and was significantly less severe on day three and four with active treatment (P value < 0.001).
- Eccles 1995 studied the effect of doxylamine in 688 cold patients. Severity scores were recorded twice daily during three days, on a five-point scale. Rhinorrhoea severity scores were significantly lower in the doxylamine group on the second treatment day (P value < 0.01).
- Rhinoscopy was performed with assessment of nasal secretion in the trial by Henauer 1988. At two hours and 24 hours after the first tablet of terfenadine or placebo, secretion was less severe in participants with terfenadine when compared with placebo. Methodological problems with this trial are mentioned previously.
- The studies by Gwaltney respectively studied clemastine in 150 experimentally infected symptomatic volunteers and brompheniramine in 225 experimentally infected symptomatic volunteers, also scoring rhinorrhoea severity on a five-point scale (Gwaltney 1996; Gwaltney 1997). Significantly lower scores were found with active treatment on treatment days two and three in the 1996 trial (P value < 0.05) and on treatment days two to four in the 1997 trial (day two P value < 0.05; day three and four P value < 0.02).

We pooled data from seven trials (Berkowitz 1991; Eccles 1995; Gaffey 1988; Gwaltney 1996; Gwaltney 1997; Muether 2001; Turner 1997). We point out again that, in spite of the fact that data were obtained in similar ways, these trials are still quite different from one another in the way the participants were recruited or infected, in the way they were treated or in the way severity was assessed.

- We made the following comparisons (see Data and analyses 6 to 8).
    - Subjective severity assessment of rhinorrhoea - all trials: mean severity assessment of rhinorrhoea - first day of treatment (Analysis 6.1), mean severity assessment of rhinorrhoea - second day of treatment (Analysis 6.2), mean severity assessment of rhinorrhoea - third day of treatment (Analysis 6.3), mean severity assessment of rhinorrhoea - fourth day of treatment (Analysis 6.4).
    - Subjective severity assessment of rhinorrhoea - non-sedating antihistamines: mean severity assessment of rhinorrhoea - fourth day of treatment (Analysis 7.1). We chose this day because the most complete data were available.
    - Subjective severity assessment of nasal rhinorrhoea - sedating antihistamines: mean severity assessment of rhinorrhoea - first day of treatment (Analysis 8.1), mean severity assessment of rhinorrhoea - second day of treatment (Analysis 8.2), mean severity assessment of rhinorrhoea - third day of treatment (Analysis 8.3), mean severity assessment of rhinorrhoea - fourth day of treatment (Analysis 8.4).
- These comparisons showed that there is some effect of antihistamines on days two, three and four (MD -0.15, 95% CI -0.27 to -0.04); MD -0.09, 95% CI -0.25 to 0.07; MD -0.14, 95% CI -0.24 to -0.03). The effect of all antihistamines can be attributed to the sedating antihistamines. Trials with non-

sedating antihistamines showed no effect on rhinorrhoea, while pooling results from studies with only sedating antihistamines showed a more significant effect (MD -0.18, 95% CI -0.27 to -0.08) (Analysis 8.2); MD -0.23, 95% CI -0.39 to -0.06 (Analysis 8.3); (MD -0.24, 95% CI -0.35 to -0.12) (Analysis 8.4). This effect seemed to increase with duration of treatment.

- However, the differences are still very small. A difference of one would mean that participants rate, on average, one severity category lower with active treatment than with placebo (e.g. from moderate to mild). However, the observed MD is at most 0.24, which is not clinically significant.

Data from five trials could not be meta-analysed (Bye 1980; Doyle 1988; Ectors 1994; Henauer 1988; Howard 1979). Data are summarised in Table 3.

- In the study Howard 1979 chlorpheniramine (sedating) showed some significant effect and in the study Ectors 1994 cetirizine (non-sedating) did not. This is in line with the results of the meta-analysis.
- The study Bye 1980 is the only trial in which a sedating antihistamine (triprolidine) had no effect on rhinorrhoea on any of the observation days. However, it is unlikely that adding data from this study would alter the conclusion of the meta-analysis.

### *c) Sneezing*

Four trials failed to show any effect (Berkowitz 1991; Ectors 1994; Gaffey 1988; Muether 2001). Severity of sneezing was assessed in the same way as severity of nasal obstruction. All of these trials studied non-sedating antihistamines: terfenadine, loratadine and cetirizine.

Seven trials - all studying sedating antihistamines - showed some effect. Severity of sneezing was assessed in the same way as severity of other nasal symptoms. For the description: see "effect on subjective severity of rhinorrhoea on different treatment days" (Eccles 1995; Gwaltney 1996; Gwaltney 1997; Howard 1979; Turner 1997) or "effect on subjective severity of nasal obstruction on different treatment days" (Bye 1980).

- In the study Howard 1979, at all time points sneezing severity scores were significantly lower with chlorpheniramine (P values not mentioned).
- In the study Bye 1980, on day two, there was a significantly larger reduction in the mean severity score of patients treated with triprolidine (P values not mentioned).
- In the study Turner 1997, sneezing severity was significantly less severe on days two, three and four with active treatment (P value < 0.001).
- In the study Eccles 1995, sneezing severity scores were significantly lower in the doxylamine group on days two and three (P value < 0.01).
- Doyle 1988 interviewed 27 participants who developed a cold after experimental virus inoculation on days three to six after inoculation. The severity scores (mild, moderate, severe) obtained on these four days by interview were summed and averages are compared between chlorpheniramine (N = 12) and placebo (N = 15) treated patients; a significant difference in favour of active treatment was found (P value < 0.01). In the same study, the average number of days with sneezing was counted. With chlorpheniramine there was virtually no sneezing (0.1 day on average); without chlorpheniramine sneezing took on average more than a day. This difference was significant (P value < 0.01).
- The studies by Gwaltney respectively studied clemastine in 150 experimentally infected symptomatic volunteers (Gwaltney 1996; Gwaltney 1997). Significantly lower scores were found with active treatment on treatment days two and three in the 1996 trial (day two: P value < 0.02, day three: P value < 0.01) and on treatment days two and four in the 1997 trial (P value < 0.001).

Data from six trials could be pooled (Berkowitz 1991; Eccles 1995; Gwaltney 1996; Gwaltney 1997; Muether 2001; Turner 1997). As mentioned before, these trials are quite different from one another.

- We made the following comparisons (see Data and analyses 9 and 10).
    - Subjective severity assessment of sneezing - all trials: mean severity assessment of sneezing - first day of treatment (Analysis 9.1), mean severity assessment of sneezing - second day of treatment (Analysis 9.2), mean severity assessment of sneezing - third day of treatment (Analysis 9.3), mean severity assessment of sneezing - fourth day of treatment (Analysis 9.4).
    - Subjective severity assessment of sneezing - sedating antihistamines: mean severity assessment of sneezing - first day of treatment (Analysis 10.1), mean severity assessment of sneezing - second day of treatment (Analysis 10.2), mean severity assessment of sneezing - third day of treatment (Analysis 10.3), mean severity assessment of sneezing - fourth day of treatment (Analysis 10.4).
    - Subjective severity assessment of sneezing, non-sedating antihistamines: data from one trial only were available for each observation day, hence comparison was not possible. These trials did not show a significant effect.
- Both comparisons show a significant decrease in sneezing severity on all four treatment days (all trials: MD -0.07, 95% CI -0.15 to 0.00; MD -0.26, 95% CI -0.37 to -0.15; MD -0.31, 95% CI -0.46 to -0.15; MD -0.28, 95% CI -0.36 to -0.20. Sedating: MD -0.07, 95% CI -0.14 to -0.00; MD -0.29, 95% CI -0.37 to -0.21; MD -0.35, 95% CI -0.49 to -0.20; MD -0.29, 95% CI -0.38 to -0.21). This effect is due to the sedating antihistamines. None of the trials with non-sedating antihistamines showed a significant effect. However, the difference between the treatment groups is small: at most 0.35, while a difference of one would mean a difference of one severity category (e.g. moderate to mild).

Data from five trials could not be meta-analysed (Bye 1980; Doyle 1988; Ectors 1994; Gaffey 1988; Howard 1979).

- Two trials studying non-sedating antihistamines showed no effect (Ectors 1994; Gaffey 1988), and two trials studying sedating antihistamines showed some effect (Bye 1980; Howard 1979). These results are in line with the results of the meta-analysis. All data are in Table 4.

**2. The change in duration of individual symptoms for example, sneezing, nasal congestion, rhinorrhoea**

***a) Nasal congestion***

- In the study Doyle 1988, 27 participants who developed a cold after experimental virus inoculation were interviewed on days three to six after inoculation. In this study the average number of days with nasal obstruction was counted in both treatment groups. There was no significant difference (P value = 0.14).

***b) Rhinorrhoea***

- In the study Doyle 1988, 27 participants who developed a cold after experimental virus inoculation were interviewed on days three to six after inoculation. In this study the average number of days with rhinorrhoea was counted in both treatment groups. There was no significant difference (P value = 0.6).

***c) Sneezing***

- In the study Doyle 1988, 27 participants who developed a cold after experimental virus inoculation were interviewed on days three to six after inoculation. In this study the average number of days with rhinorrhoea was counted in both treatment groups. With chlorpheniramine there was virtually no sneezing (0.1 day on average); without chlorpheniramine sneezing took on average more than a day. This difference was significant (P value < 0.01).

**3. Side effects from using antihistamines**

In 14 trials side effects were evaluated (Berkowitz 1991; Bye 1980; Crutcher 1981; Eccles 1995; Gaffey 1987a; Gaffey 1987b; Gaffey 1988; Gwaltney 1996; Gwaltney 1997; Henauer 1988; Howard 1979; MRC (Part 2) 1950; Muether 2001; Turner 1997).
Many different side effects are described: sedation, fatigue, sleepiness, somnolence, drowsiness, lassitude, listlessness, tiredness, dopey feeling, sleeplessness, insomnia, vertigo, dizziness, giddiness, urinary complaints, dry mouth, dry nose, dry throat, dry eyes, headache, depression, nausea, gastric upset, muscular pain, temperature rise. For intranasal therapy, nasal burning and bleeding sites in the nose were observed.
We first compared the total number of participants reporting any side effect between intervention and control groups. Subsequently we compared the number of participants reporting sedation as this is the most common side effect of antihistamines, and finally we assessed other reported side effects.
We pooled data from the different trials where possible in Data and analyses 11.

***a) Total number of participant-reported side effects***

- Nine trials reported the total number of patients with one or more side effects (Berkowitz 1991; Bye 1980; Crutcher 1981; Gwaltney 1997; Henauer 1988; Howard 1979; MRC (Part 2) 1950; Muether 2001; Turner 1997). In total, 2590 participants were included, 1284 with active treatment, of which 20.2% reported side effects and 1306 participants treated with placebo, of which 17.6% reported side effects. This difference is not statistically significant (Analysis 11.1) (OR 1.18, 95% CI 0.97 to 1.44).
- When we looked at trials using sedating and non-sedating antihistamines separately, we found that side effects were more frequent in participants with sedating antihistamines (22%) but there was no significant difference from the placebo group (OR 1.13, 95% CI 0.80 to 1.59) (Analysis 11.7). In trials using non-sedating antihistamines side effects were less frequent (12%), but again there was no significant difference between treatment groups (OR 1.21, 95% CI 0.52 to 2.81) (Analysis 11.2).

***b) Participant-reported sedation (drowsiness, sleepiness, fatigue, somnolence, sedative, dopey feeling)***

- In six trials the number of participants with "sedative" side effects were reported (Berkowitz 1991; Eccles 1995; Gaffey 1987b; Gaffey 1988; MRC (Part 2) 1950; Turner 1997). In total, 2624 participants were included: 1314 with active treatment, of which 8.9% reported sedation, and 1310 with placebo, of which 5.6% felt sedated. This difference was not statistically significant (OR 1.64, 95% CI 0.69 to 3.85) (Analysis 11.4).
- Assessing trials using sedating and non-sedating antihistamines separately, we observed that sedation was more frequent in participants treated with sedating antihistamines, although the difference was not statistically significant: 8.9% versus 5.2% (OR 2.04, 95% CI 0.64 to 6.56) (Analysis 11.6). In trials using non-sedating antihistamines there was virtually no difference: 8.6% versus 8.0% (OR 1.08, 95% CI 0.50 to 2.31) (Analysis 11.5).

*c) Participant-reported other side effects that are possibly more frequent with antihistamines*

- Gastrointestinal side effects were reported in five trials with 1586 participants (Berkowitz 1991; Gaffey 1987b; Gaffey 1988; MRC (Part 2) 1950; Muether 2001). Four per cent of participants reported gastrointestinal side effects with the active treatment, compared to 2.7% of participants with placebo (OR 1.46, 95% CI 0.84 to 2.56) (Analysis 11.3).
- Sleeplessness was mentioned in two trials with 1406 participants (Gaffey 1988; MRC (Part 2) 1950). This is an infrequent side effect: 0.9% with active treatment, 0.3% with placebo (OR 3.00, 95% CI 0.60 to 14.95).
- In two trials, dry nose was mentioned (Gaffey 1987a; Gwaltney 1996). In Gwaltney 1996, 150 experimentally infected patients reported a dry feeling in the nose very frequently (36% with clemastine versus 18% with placebo). In Gaffey 1987a, which used an intranasal therapy in 23 participants, a dry nose was less frequent with active treatment. Overall, the difference is not significant (OR 0.82, 95% CI 0.05 to 12.87).

*d) Participant-reported side effects that are not more frequent with antihistamines*

- Frequency of headache (5.4% with active and 4.5% with placebo), vertigo and dizziness (3.4% with active and 2.3% with placebo) and dry mouth (11.8% with active and 11% with placebo) was not significantly different between treatment groups.
- Muscular pain, temperature rise, urinary complaints, dry eyes, nasal burning and bleeding sites in nose were all very infrequent and there was no significant difference between treatment groups.

## Primary outcomes

### Antihistamines in children

Only two trials included children and their results were conflicting (Hugenin 1988; Sakchainanont 1990). Hugenin 1988 studied the effect of astemizole on cold symptoms in 62 children from the age of two to 15 years. Inclusion criteria were: watery or mucous rhinorrhoea, cough and malaise. A major problem with this trial was the long duration of symptoms before inclusion (mean six days, ranging from one to 365). Some children obviously did not have a common cold. In the trial Sakchainanont 1990, the effect of clemastine (N = 48) and chlorpheniramine (N = 48) was compared with placebo (N = 47) in children younger than five years of age with rhinorrhoea for three days. All results are summarised in Table 1, Table 2 and Table 3.

**1. The change in severity of overall symptoms of the common cold (for example, absent, mild, moderate, severe)**

This outcome measure was not studied.

**2. The change in duration of overall symptoms of the common cold (for example, days to resolution)**

In the study Hugenin 1988, astemizole seemed to have some effect on the number of days until normalisation to general condition in comparison with placebo (P value = 0.06).

## Secondary outcomes

### Antihistamines in children

**1. The change in severity of individual symptoms, for example, sneezing, nasal congestion, rhinorrhoea (for example, absent, mild, moderate, severe)**

In the Sakchainanont 1990 trial, after three days of treatment the amount of nasal discharge and the amount of oedema at the nasal turbinates were compared in children receiving active treatment or placebo. There was no significant difference (P value = 0.53 and P value = 0.95, respectively).

**2. The change in duration of individual symptoms, for example, sneezing, nasal congestion, rhinorrhoea (for example, days to resolution)**

In the Sakchainanont 1990 trial, the proportion of children free from rhinorrhoea after seven days of treatment was higher (P value = 0.015).

**3. Side effects from using antihistamines**

In Hugenin 1988, no side effects occurred. In Sakchainanont 1990, there was also no significant difference in the frequency of side effects (all side effects: P value= 0.80; sleepiness/drowsiness: P value = 0.64).

## ADDITIONAL SUMMARY OF FINDINGS [Explanation]

**Sedating antihistamines compared to placebo for the common cold**

**Patient or population:** patients with the common cold
**Settings:** ambulatory care
**Intervention:** sedating antihistamines
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Sedating antihistamines | | | | |
| **Change in severity of overall symptoms: short-term (1 to 2 days)**<br>Subjective severity score<br>Follow-up: 1 to 2 days | **Study population** | | **OR 0.76**<br>(0.61 to 0.95) | 1427<br>(2 studies) | ⊕⊕⊕⊕<br>**high** | - |
| | **624 per 1000** | **558 per 1000**<br>(503 to 612) | | | | |
| | **Moderate** | | | | | |
| | **695 per 1000** | **634 per 1000**<br>(582 to 684) | | | | |
| **Change in severity of overall symptoms: long-term (6 to 10 days)**<br>Subjective severity score<br>Follow-up: 6 to 10 days | **Study population** | | **OR 0.71**<br>(0.41 to 1.22) | 1551<br>(3 studies) | ⊕⊕⊕⊕<br>**high** | - |
| | **297 per 1000** | **231 per 1000**<br>(148 to 340) | | | | |
| | **Moderate** | | | | | |
| | **362 per 1000** | **287 per 1000**<br>(189 to 409) | | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

# DISCUSSION

## Summary of main results

### 1. Antihistamine monotherapy for adults

In summary, antihistamines as monotherapy do not have a clinically significant effect on overall subjective improvement of the common cold or on individual symptoms such as nasal congestion, rhinorrhoea and sneezing. Additionally, we found sedating antihistamines to result in more side effects, especially sedation, compared to placebo although this difference was not statistically significant.

One trial showed a statistically significant difference between treatment groups when asking "After taking the trial tablets did your cold symptoms improve, worsen or remain unchanged" only once at the final evaluation (Bye 1980). All other trials reported clinically non-significant outcomes. The trial by Bye 1980 had a different approach to the rest of the trials, where the participants were periodically assessed on their improvement during the treatment course rather than at a single time point at the end of the trial. This different approach could explain the difference in outcome.

Considering individual symptoms, meta-analysis of data for nasal obstruction showed no beneficial effect in patients taking antihistamines.

Although meta-analysis of data for rhinorrhoea showed a clinically significant effect, this only relates to the sedating antihistamines. The subjective severity scores from the second day onwards are lower in the antihistamine group compared to placebo. This could be explained by the inhibition of cholinergic stimulation, predominantly present in the sedating antihistamines compared to the more selective non-sedating antihistamines. However, the effect sizes are very small, with the largest mean difference (MD) between groups being 0.24, while a change of one point would mean a change of one severity category (e.g. severe to moderate).

A meta-analysis of data for sneezing showed similar findings to the meta-analysis for rhinorrhoea. Sedating antihistamines reduced the subjective severity of sneezing compared to placebo but, again, the effect sizes were small and probably not clinically significant.

Finally, in regards to adverse effects, trials using sedating antihistamines showed more frequent adverse effects in both active treatment and placebo groups. It is likely that some of these adverse effects may actually be attributed to cold symptoms rather than the medication. Adverse effects were less prevalent with non-sedating antihistamines than with sedating antihistamines according to our analysis. Overall, the most frequent adverse effect was sedation, where 9% of participants treated with sedating antihistamines reported sedation compared to 5% in the placebo group. This large number of participants complaining of sedation in the placebo group again is likely attributable to the cold itself, as people get a sensation of fatigue and lethargy when inflicted with the common cold. Trials using non-sedating antihistamines, which are more selective in their effect, also report sedation as an adverse effect but to a lesser degree. This suggests that some sedative adverse effects are actually a symptom of the common cold itself.

### 2. Antihistamine monotherapy for children

Very little is known about the effect of antihistamines in children. We only identified two trials, which included a total of 205 children (Hugenin 1988; Sakchainanont 1990). Hugenin 1988 included older and younger children. The diagnosis of common cold in Hugenin 1988 was unclear and some participants had a very long duration of symptoms before being included.

In these trials we looked for two primary outcomes of interest (duration and severity of general cold symptoms) . However, neither trial measured severity. The smaller trial suggested a change in the duration of general cold symptoms, but it was not statistically significant (Hugenin 1988). The secondary results from the larger trial found a significantly larger proportion of children free of stuffy nose after seven days of treatment, but the severity of cold symptoms was no different from children receiving placebo (Sakchainanont 1990). Neither trial found significant side effects associated with antihistamines. The lack of evidence of the effectiveness of antihistamine use in children combined with the results from adult trials, which indicated no significant improvement, leads us to the conclusion that there is insufficient evidence to support the use of antihistamines for colds in children.

## Overall completeness and applicability of evidence

Our search strategy identified any trials of the treatment of the common cold from 1950 to the present day. From our search, we selected all trials using antihistamines as monotherapy. Although antihistamines have been studied since the late 1940s, we considered the chances of finding trials of sufficient methodological quality in the period between 1940 and 1950 to be very low. We searched all the major existing databases. We contacted pharmaceutical companies for the first version of the review (De Sutter 2003), but not for this 2015 new version. It is possible that other unpublished data from pharmaceutical companies since 2003 on the effects of antihistamines on the common cold exist but it is likely these were unpublished because the findings were negative. Therefore, we are fairly confident that our overall conclusion will remain unchanged, regardless of including or excluding such unpublished trials or data.

We selected as our primary outcome "overall improvement of symptoms of the common cold" from the large variety of reported outcomes in the included trials, as that is what matters most to the patient - to feel better. For the "improvement of individual

symptoms" we chose nasal obstruction, rhinorrhoea and sneezing, as they are the most frequent cold symptoms (Jackson 1960). Our review focused on subjective improvement rather than objective measures. Even though objective measures are useful for research purposes, they are not practical in real life scenarios. Moreover, improvements in objective measurements are only relevant when subjectively experienced by the patient.

Many of the included trials were conducted in the 1980s and 1990s, with the most recent trial from 2001. Different antihistamines were compared - not only sedating versus non-sedating antihistamines but also different products within the groups. The sedating antihistamines studied were triprolidine, chlorpheniramine, doxylamine, diphenhydramine, brompheniramine, thonzylamine and clemastine; many of these products are not used any more. The non-sedating antihistamines studied were cetirizine, loratadine, terfenadine and astemizole. The latter two are no longer available due to the risk of serious cardiac side effects. The design of the studies varied between experimental infection of participants versus naturally acquired colds. Comparison of such studies in a meta-analysis is expected to show heterogeneity, which is also evident in our review. However, even with the many differences in methods and interventions amongst studies, their results are generally similar. This suggests that favourable results are not particularly linked to one product or to one infection method and that there are other more subtle differences between the trials' methodology, recruitment and inclusion and exclusion criteria that may explain the heterogeneity of results.

### Quality of the evidence

In a number of trials, data were insufficiently reported, or were not in the appropriate format to enter into a meta-analysis. Some authors provided additional data but for many trials we did not succeed in retrieving extra data because the authors did not respond when contacted, could not be located, data were no longer on file or data were passed on to the sponsors of the trial. Therefore, because trials showed important differences in study participants, interventions, outcomes or designs, we mainly performed a systematic review with only a limited number of pooled analyses. The meta-analyses mostly include only some of the available trials and provide an incomplete assessment of the quality of evidence. Although four of the five meta-analyses are graded a high and one as moderate, this fragmentary evidence does not provide a robust basis on which conclusions can be made.

### Potential biases in the review process

A potential bias in our review process is that for the updated version of this review we did not contact pharmaceutical companies for any unpublished data. In the previous version of this review, De Sutter 2003, contacting pharmaceutical companies only yielded one additional unpublished trial that did not provide any useful data for the review. We also did not contact any trial authors to obtain any missing or incomplete data as there were no new trials since the previous version. Finally, the subgroup analysis of sedating and non-sedating antihistamines was a post hoc analysis, which had not been planned in the protocol.

### Agreements and disagreements with other studies or reviews

As no new data were available, this review reached the same conclusion concerning antihistamines as monotherapy as the previous version of this review (De Sutter 2003). Another review, De Sutter 2012, investigates the effects of antihistamines in combination with analgesics and decongestants for the common cold. This review reports some positive effects of antihistamine-analgesic-decongestant combinations for symptomatic relief of the common cold. However, several adverse effects were also reported. The findings of this review on antihistamines as monotherapy alongside the findings of the review on combination products strongly suggest that antihistamines are not the main agent causing symptom relief in patients with the common cold. Analgesics and decongestants seem to convey the desired symptomatic relief, although caution needs to be applied in light of the potential adverse effects of these agents (De Sutter 2012).

## AUTHORS' CONCLUSIONS

### Implications for practice

Antihistamines have a limited short-term (days one and two of treatment) beneficial effect on severity of overall symptoms but not in the mid to long term. There is no clinically significant effect on nasal obstruction, rhinorrhoea or sneezing. Although side effects were more common with antihistamines, the difference was not statistically significant. There is no evidence of effectiveness of antihistamines in children. On the basis of this review, there is insufficient evidence to support the prescribing or purchasing over-the-counter antihistamines for common colds to alleviate symptoms of the common cold.

### Implications for research

Antihistamines as monotherapy for the common cold have been studied widely. Over the last 50 or more years many trials have been conducted in different settings, with different products and on different populations. Many of the studied products are no longer available. Although some studies have reported benefits of antihistamines, no trial has provided convincing evidence that antihistamines really alleviate the symptoms of the common cold.

This updated review confirms the conclusions of the previous version (De Sutter 2003), and it seems highly unlikely that more research on antihistamines as monotherapy will change the conclusions.

## ACKNOWLEDGEMENTS

We would like to thank the previous authors of this review (Lemiengre M, Campbell H, Mackinnon HF) and to acknowledge their now withdrawn review (De Sutter 2003). We would also like to thank Selvakumar DI, Dahiya N, Tambimuttu EG and Gnanasingham AD for their contribution towards the protocol and we thank the following people for commenting on the draft protocol: Hanan Khalil, Linda Hornbeek, David Rabago, Emin Unuvar, Max Bulsara and Meenu Singh. We would like to thank the following people for commenting on the draft of this review: Dilip Raghavan, Jodi Duke, Rashmi Das, Felix Ram, Mark Jones and Meenu Singh.

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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Berkowitz 1991**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Naturally occurring colds<br>100 participants included<br>97% follow-up<br>Single-centre (USA) |
| Participants | 12 to 65 years of age<br>Included if they had acute symptoms of common cold with runny/stuffy nose rated moderate or severe and at least 1 other symptom (sniffles, sneezing, post-nasal drip, cough and/or sore, scratchy or itchy throat)<br>Excluded if they were smokers, had fever > 100° F, exudative pharyngitis, perennial rhinitis, were pregnant, lactating or taking antihistamines/decongestants/decongestant nasal sprays/cold preparations/corticosteroids/antibiotics/depot corticosteroids already<br>Duration of symptoms before inclusion = 6 to 48 hours |
| Interventions | Terfenadine 60 mg twice daily<br>Non-sedating antihistamine<br>Compared to placebo<br>Duration = 4 days |
| Outcomes | Severity score for runny nose/stuffy nose/sneezing after 4 days of treatment<br>Physician's evaluation of change in severity of overall symptoms |
| Notes | - |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified<br>Similar participant demographics in both groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Matching placebo tablets used |

**Berkowitz 1991** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not specified but assumed adequate as double-blind study |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 97%<br>3 participants excluded as they did not comply with the study protocol |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

**Bye 1980**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Naturally occurring colds<br>124 participants included<br>96% follow-up<br>Multicentre (UK) |
| Participants | 20 to 41 years of age<br>Included when healthy then enrolled when they developed symptoms of cold after being assessed by a nurse<br>Excluded if they were using other medications that may possibly interfere with the study or if have allergic disorders<br>Duration of symptoms before inclusion = 20.7 ± 17.7 hours |
| Interventions | Triprolidine 2.5 mg up to 3 times a day<br>Sedating antihistamine<br>Compared to placebo<br>Duration = as long as the participant deems it necessary (max 20 tablets or 7 days) |
| Outcomes | Daily score on a 4-point severity scale of 12 common cold symptoms<br>Daily score on a 4-point severity scale of 7 side effects<br>Overall impression of improvement of symptoms after 8 to 10 days |
| Notes | This study also evaluated pseudoephedrine and triprolidine/pseudoephedrine combination |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

**Bye 1980** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment using lists, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Similar demographics ensured by interview questionnaire used to check for homogeneity within the treatment groups for age, sex, usual number of colds each winter, absence of allergic disorders, smoking habits, duration of symptoms and signs of fever |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | All tablets were identical in appearance<br>All tablets were specially made and differed in appearance from marketed preparations |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants self assessed their symptom severity in a daily diary |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 96%<br>2 participants from the active treatment group stopped taking medication and keeping diary due to side effects<br>3 participants from the placebo group stopped taking medication and keeping diary without any explanation |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

**Crutcher 1981**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Naturally occurring colds<br>106 participants included<br>91.5% follow-up<br>Single-centre (USA) |
| Participants | Exact age range not specified, mean age = 24 to 26 years of age<br>Included if they had symptoms of a cold included runny/stuffy nose, sneezing, postnasal drip, cough and sore throat. The signs of a cold were nasal swelling, redness, secretions and obstruction of either flares. Each symptom or sign was given a numerical value: 0 points, |

**Crutcher 1981** (*Continued*)

| | |
|---|---|
| | symptom or sign absent; 1 point, mild symptom or sign; 2 points, moderate symptom or sign; 3 points, severe symptom or sign. A minimal score of at least 6 subjective and 5 objective points was necessary<br>Excluded if they had fever, exudative tonsillitis, allergies, asthma, eczema, sinusitis or used concomitant steroids, antibiotics and/or other cold preparations<br>Duration of symptoms before inclusion = less than 48 hours |
| Interventions | Chlorpheniramine 4 times a day (dose not specified)<br>Sedating antihistamine<br>Compared to placebo<br>Duration = 7 days |
| Outcomes | During the first 48 hours of the study, the volunteers completed a symptom checklist every 2 hours using the same symptoms and scoring system as for eligibility. For the rest of the week a patient diary checklist was filled out twice daily<br>Participants were also evaluated by an examiner, twice on day 1, 3 times on day 2, once on day 3 and once on day 7 of the study period using the same objective signs and scoring system as for eligibility<br>Open-ended questions regarding side effects |
| Notes | - |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Similar participant demographics in both groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Both groups were given tablets, identical in appearance, 4 times daily under medical supervision for the first 48 hours and then as self administration for the rest of the week |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants self assessed their symptom severity in a diary<br>Participants were assigned randomly to 1 of 2 examiners for evaluation |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 91.5%<br>Direct questioning and a pill count at the end of the week served as a measure of compliance during the self medication period<br>Total of 9 dropouts, 6 from the treated and |

**Crutcher 1981** (*Continued*)

| | | |
|---|---|---|
| | | 3 from the control group. 2 dropouts (1 from each group) left because of increasing severity of illness. The remainder failed to complete the required symptom checklists |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

**Doyle 1988**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Experimental cold virus<br>40 participants included<br>100% follow-up<br>Single-centre (USA) |
| Participants | 18 to 44 years of age<br>Included when healthy then given inoculated rhinovirus type 39 to cause symptoms of a cold<br>Excluded if they had previous or current ear disease, allergy or systemic illness or if serologic testing revealed elevated serum neutralising antibodies to rhinovirus type 39<br>Duration of symptoms before inclusion = therapy to commence 48 hours after inoculation |
| Interventions | Chlorpheniramine 4 mg 6 times a day<br>Sedating antihistamine<br>Compared to placebo<br>Duration = 7 days |
| Outcomes | Nasal airway patency, Eustachian tube function, mucociliary nasal transport time and mucus weight was objectively assessed<br>Symptom scores were subjectively assessed for severity (mild, moderate or severe) and recorded in a diary by the participant |
| Notes | - |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Recruited healthy participants randomly and allocated randomly to either placebo or treatment, although details of the ran- |

**Doyle 1988** (*Continued*)

| | | |
|---|---|---|
| | | domisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Baseline participant demographics not mentioned |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Active drug and placebo were prepared as gelatin capsules identical in appearance and were administered by study personnel<br>Participants remained in a controlled environment at the study centre for the 7-day duration of drug administration |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not specified but assumed adequate as double-blind study |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 100% follow-up was achieved |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail and some outcomes are reported in a different manner to other similar studies. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

**Eccles 1995**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Naturally occurring colds<br>688 participants included<br>99.6% follow-up<br>Multicentre (UK, Germany, Denmark and Belgium) |
| Participants | Exact age range not specified, mean age = 25 years of age<br>Included if they had a history of common cold with runny nose (had to score 2 or greater on a 5-point scale where 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe and at least 1 or greater on the same scale for one other symptom such as blocked nose, sore throat, cough, headache and sneezing) and 0.2 g or more nasal secretion after 15 minutes without nose blowing<br>Excluded if they had a history of perennial allergic rhinitis, exacerbation of seasonal allergic rhinitis or if any systemic disease which may have compromised respiratory function<br>Duration of symptoms before inclusion = less than 72 hours |

**Eccles 1995** (*Continued*)

| | |
|---|---|
| Interventions | Doxylamine 7.5 mg 4 times a day<br>Sedating antihistamine<br>Compared to placebo<br>Duration = 3 days |
| Outcomes | Self scoring of symptoms (runny nose and sneezing) severity on a 5-point scale where 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe, 90 minutes after second and fourth dose daily<br>Side effects |
| Notes | - |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Similar participant demographics in both groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Both groups were given the intervention as syrup, which was identical in appearance |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants self assessed their symptom severity in a diary |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 99.6%<br>3 participants withdrew from the study due to severe adverse effects |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

**Ectors 1994**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Experimental cold virus<br>40 participants included<br>100% follow-up<br>Single-centre |
| Participants | Exact age range not specified; abstract states "adults"<br>Included healthy volunteers, who developed a cold after virus inoculation (considered to have a cold if sum of symptom scores of sneezing, rhinorrhoea and nasal congestion is 4 or more)<br>Excluded if they had a history of known allergy<br>Duration of symptoms before inclusion = treatment commenced immediately after onset of cold |
| Interventions | Cetirizine 5 mg twice daily<br>Non-sedating antihistamine<br>Compared to placebo<br>Duration = not specified in abstract but assumed to be 2 days |
| Outcomes | Decrease in severity score for rhinorrhoea, nasal congestion and/or sneezing between the start of treatment and day 2<br>Decrease in weight of nasal secretions between the start treatment and day 2 |
| Notes | Full study not available, abstract only |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Only abstract available<br>Reported as randomised study |
| Allocation concealment (selection bias) | Unclear risk | Only abstract available<br>No details provided |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Only abstract available<br>Reported as double-blind study |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Only abstract available<br>Reported as double-blind study |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Only abstract available<br>No follow-up data reported |
| Selective reporting (reporting bias) | Unclear risk | Only abstract available |

**Ectors 1994** (*Continued*)

| | | |
|---|---|---|
| Other bias | Unclear risk | - |

**Gaffey 1987a**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Experimental cold virus<br>23 participants included<br>100% follow-up<br>Single-centre (USA) |
| Participants | Exact age range not specified, study states "adult male volunteers"<br>Included when healthy then given inoculated rhinovirus type 39 to cause symptoms of a cold<br>Excluded if they had upper respiratory tract infection or fever within a week of study, concurrent use of other oral/intranasal medications, history of atopy/sinusitis/asthma/chronic rhinitis/chronic medical illness or if serum-neutralising antibody to rhinovirus type 39 greater than 1:2<br>Duration of symptoms before inclusion = treatment commenced 24 hours after inoculation |
| Interventions | Intranasal diphenhydramine (0.5%, weight/volume) 0.5 mg per spray, 2 sprays in each nostril 4 times daily<br>Sedating antihistamine<br>Compared to placebo<br>Duration = 5 days |
| Outcomes | Clinical symptoms score, recorded 3 times a day and averaged to obtain a score for rhinorrhoea and nasal congestion (day 1 to 8)<br>Expelled nasal mucus weight (days 1 to 5)<br>Nasal tissue count (days 1 to 5)<br>Side effects |
| Notes | Treatment started in all inoculated participants before start of symptoms<br>Only 17 of the 23 participants developed a cold but all participants were evaluated |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Participant demographics in both groups not specified |

**Gaffey 1987a** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Both treatment and placebo were supplied in identical metered-spray devices, calibrated to deliver 100 microlitres per spray<br>Participants self administered the sprays under supervision |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not specified but reported as double-blind study |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 100% follow-up was achieved |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail |
| Other bias | Unclear risk | - |

**Gaffey 1987b**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Experimental cold virus<br>21 participants included<br>100% follow-up<br>Single-centre (USA) |
| Participants | Exact age range not specified, study states "adult male volunteers"<br>Included when healthy then given inoculated rhinovirus type 29 to cause the symptoms of a cold<br>Excluded if they had upper respiratory tract infection or fever within a week of study, concurrent use of other oral/intranasal medications, history of atopy/sinusitis/asthma/chronic rhinitis/chronic medical illness or if serum-neutralising antibody to rhinovirus type 39 greater than 1:2<br>Duration of symptoms before inclusion = treatment commenced 48 hours after inoculation |
| Interventions | Chlorpheniramine 4 mg 4 times a day<br>Sedating antihistamine<br>Compared to placebo<br>Duration = 4 days |
| Outcomes | Clinical symptoms score, recorded 3 times a day and averaged to obtain a score for rhinorrhoea and nasal congestion (day 1 to 5)<br>Expelled nasal mucus weight (days 3 to 6)<br>Nasal tissue count (days 3 to 6)<br>Side effects |

**Gaffey 1987b** (*Continued*)

| | |
|---|---|
| Notes | Treatment started in all inoculated participants before the start of symptoms<br>Only 14 of the 21 participants developed a cold but all participants were evaluated |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Demographics of the participants in both groups not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Treatment and identically matching placebo tablets were supplied by the manufacturer<br>Every dose administered under supervision |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not specified but reported as a double-blind study |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 100% follow-up was achieved |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail |
| Other bias | Unclear risk | - |

**Gaffey 1988**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Naturally occurring colds<br>250 participants included<br>93.6% follow-up<br>Single-centre (USA) |
| Participants | 18 to 65 years of age<br>Included if they had a primary complaint of runny/stuffy nose (has to be rated moderate or severe on a scale where 0 = absent, 1 = mild, 2 = moderate and 3 = severe) and at least 1 other respiratory symptom (sniffles, sneezing, post-nasal drip, cough or sore throat)<br>Excluded if they had a history of exudative pharyngitis, fever within week of enrolment, concurrent use of antihistamine or other cold preparations, history of atopy/sinusitis<br>Duration of symptoms before inclusion = 6 to 48 hours |

**Gaffey 1988** (*Continued*)

| | |
|---|---|
| Interventions | Terfenadine 60 mg twice daily<br>Non-sedating antihistamine<br>Compared to placebo<br>Duration = 4 days |
| Outcomes | Severity of symptoms self recorded by participant 3 hours after each dose (on a scale where 0 = absent, 1 = mild, 2 = moderate and 3 = severe)<br>Asessment of change in severity of overall symptoms at final visit (on a scale where 0 = complete symptom relief, 1 = marked symptom relief, 2 = moderate symptom relief, 3 = slight symptom relief and 4 = no symptom relief)<br>Side effects |
| Notes | - |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Similar participant demographics in both groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Both groups were given the intervention, which was identical in appearance<br>Participants self administered the interventions (only supervised at initial visit) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants self assessed their symptom severity in a diary |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 93.6%<br>16 participants were not included in the efficacy result as they did not comply with the study protocol |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail |
| Other bias | Unclear risk | - |

**Gwaltney 1996**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Experimental cold virus<br>150 participants included<br>99.3% follow-up<br>Multicentre (USA) |
| Participants | 18 to 56 years of age<br>Included healthy participants required to have been free of cold symptoms or a fever (temperature > 100°F) for 2 weeks then given inoculated Hank's strain rhinovirus to cause symptoms of a cold<br>Excluded if history of hypersensitivity to antihistamines, history of allergic rhinitis, bronchial asthma or other lower respiratory tract diseases such as chronic obstructive pulmonary disease or emphysema, used antihistamines, any cough and/or cold medication, any medications thought to interfere with the study drug or monoamine oxidase inhibitors 7 days before entry, pregnancy or lactation, poorly controlled hypertension or heart disease, hyperthyroidism, nasal abnormalities and other medical conditions that might alter the absorption, distribution, metabolism and excretion of study drug<br>Duration of symptoms before inclusion = treatment commenced 24 to 60 hours after virus challenge |
| Interventions | Clemastine 1.34 mg twice daily<br>Sedating antihistamine<br>Compared to placebo<br>Duration = 4 days |
| Outcomes | Severity of symptoms (sneezing, rhinorrhoea, nasal obstruction, sore throat, cough, headache, malaise and chilliness) on a 5-point scale where 0 = absent, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe<br>Nasal secretion weight<br>Sneeze and cough count<br>Side effects |
| Notes | - |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Similar participant demographics in both groups |

**Gwaltney 1996** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Observers as well as participants were blinded to treatment status<br>Both groups were given the intervention, which was identical in appearance<br>Participants remained in isolation until day 5 post viral challenge |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants self assessed their symptom severity |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 99.3%<br>1 patient did not receive a complete course of the intervention due to adverse effects |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail and some outcomes are reported in a different manner to other similar studies |
| Other bias | Unclear risk | - |

**Gwaltney 1997**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Experimental cold virus<br>264 participants included<br>85.2% follow-up<br>Single-centre (USA) |
| Participants | 18 to 43 years of age<br>Included healthy participants required to have been free of cold symptoms or a fever (temperature > 38°C) for 2 weeks then given inoculated rhinovirus type 16 to cause the symptoms of a cold<br>Excluded if pregnant or lactating, history of allergic rhinitis, bronchial asthma, excessive use of alcohol or drugs, use of an antihistamine or any cough or cold medication within 48 hours of virus challenge, use of Hismanal within the prior 30 days, use of monoamine oxidase inhibitors within the prior 7 days, difficulty in urination or glaucoma or if they were currently taking any other medications (except for birth control), were hypersensitive to brompheniramine or had taken an investigational drug within the prior 30 days<br>Duration of symptoms before inclusion = treatment commenced 24 to 48 hours after virus challenge |
| Interventions | Brompheniramine 12 mg twice daily<br>First-generation antihistamine<br>Compared to placebo<br>Duration = 4 days |

**Gwaltney 1997** (*Continued*)

| | |
|---|---|
| Outcomes | Severity of symptoms (sneezing, rhinorrhoea, nasal obstruction, sore throat, cough, headache, malaise and chilliness) on a 5-point scale where 0 = absent, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe<br>Nasal secretion weight<br>Sneeze and cough count<br>Side effects |
| Notes | - |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Similar participant demographics in both groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Both groups were given the intervention, which was identical in appearance<br>Participants remained in isolation until day 5 post viral challenge |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants self assessed their symptom severity |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 85.2%<br>8 participants were excluded because they were infected with a wild strain of rhinovirus instead of type 16<br>23 participants were excluded as they were not infected after the viral challenge<br>6 participants were excluded as they had a serum neutralising antibody titre of > 4<br>2 participants were excluded as they did not develop symptoms 60 hours after the viral challenge |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail and some outcomes are reported in a different manner to other similar studies. We did not contact the study authors for additional information |

**Gwaltney 1997** (*Continued*)

| | | |
|---|---|---|
| Other bias | Unclear risk | - |

**Henauer 1988**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Naturally occurring colds<br>91 participants included<br>69.2% follow-up<br>Multicentre (Switzerland) |
| Participants | 18 to 43 years of age<br>Included if runny nose rated moderate or severe (primary complaint) and at least 1 additional symptom (stuffy nose, sneezing/itchy nose, headache/fullness in head, watery eyes/itchy eyes)<br>Excluded if history of exudative pharyngitis, fever > 38°C, participants feeling seriously ill, known history of allergic rhinitis, asthma, or atopic eczema, use of common cold medication (combination of antihistamines, decongestants and/or analgesics), corticosteroids, antibiotics during past week, known hypersensitivity to terfenadine, other serious disease or underlying conditions, pregnancy or possibility of becoming pregnant during the study<br>Duration of symptoms before inclusion = 6 to 48 hours |
| Interventions | Terfenadine 60 mg twice daily<br>Non-sedating antihistamine<br>Compared to placebo<br>Duration = 24 hours (3 doses) |
| Outcomes | Severity of symptoms (runny nose, stuffy nose, sneezing/itchy nose, headache/fullness in head and tears/itchy eyes) on a 4-point rating scale (absent, mild, moderate or severe)<br>Overall efficacy<br>Rhinoscopy and rhinomanometry |
| Notes | - |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Patients were randomly allocated but no details on sequence generation provided |
| Allocation concealment (selection bias) | Unclear risk | Not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Both groups were given the intervention, which was identical in appearance |

**Henauer 1988** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants self assessed their symptom severity |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Follow-up rate 69.2%<br>16 participants were excluded as they had a history of chronic rhinitis<br>11 participants were excluded as they took cold preparations prior or during the study<br>1 participant was excluded due to not having the symptoms of cold<br>Participants were not included according to protocol of the study |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail and some outcomes are reported in a different manner to other similar studies |
| Other bias | Unclear risk | Study protocol was not followed for participant recruitment |

**Howard 1979**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Naturally occurring colds<br>271 participants included<br>100% follow-up<br>Multicentre (USA) |
| Participants | Exact age range not specified, mean age = 23.5 years of age<br>Included if total subjective symptom score was 6 or above and the symptoms considered were nasal discharge/congestion, sneezing, post-nasal drip, cough (0 = none, 1 = mild, 2 = moderate and 3 = severe) and/or sore throat (separate scoring scale from other symptoms, where 0 = absent, 1 = throat irritation, 2 = mild pain, 3 = moderate pain and 4 = severe pain) and a total objective symptom score evaluated by the physician was 5 or above (0 = absent, 1 = mild, 2 = moderate and 3 = severe)<br>Excluded if history of exudative pharyngitis, fever > 37.8°C, known history of allergic rhinitis, asthma or atopic eczema, use of aspirin, antihistamines, decongestants, steroids, antibiotics and analgesics, concomitant pulmonary or pharyngeal infection, in an occupation where giving antihistamines could be hazardous, other serious disease or underlying conditions affecting the lungs<br>Duration of symptoms before inclusion = 24 to 48 hours |
| Interventions | Chlorpheniramine 4 times a day (dose not specified)<br>Sedating antihistamine<br>Compared to placebo |

**Howard 1979** (*Continued*)

| | |
|---|---|
| | Duration = 6 days |
| Outcomes | Total subjective symptom score where symptoms considered were nasal discharge/congestion, sneezing, post-nasal drip, cough (0 = none, 1 = mild, 2 = moderate and 3 = severe) and/or sore throat (separate scoring scale from other symptoms, where 0 = absent, 1 = throat irritation, 2 = mild pain, 3 = moderate pain and 4 = severe pain)<br>Total objective symptom score evaluated by the physician (0 = absent, 1 = mild, 2 = moderate and 3 = severe)<br>Individual symptom severity score for nasal discharge, sneezing, nose blowing<br>Side effects |
| Notes | - |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Similar participant demographics in both groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Both groups were given the intervention, which was identical in appearance<br>Participants remained in isolation until day 2 |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Investigators as well as participants were blinded to treatment status<br>Participants self assessed their symptom severity and were also assessed by a physician who was blinded to the treatment status |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 100% follow-up was achieved |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail and some outcomes are reported in a different manner to other similar studies. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

**Hugenin 1988**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Naturally occurring colds<br>62 participants included<br>80.6% follow-up<br>Single-centre (Switzerland) |
| Participants | 2 to 15 years of age<br>Included if had rhinorrhoea, cough and malaise<br>Excluded if history of allergy, signs of bronchitis, signs of bacterial infection, positive *Streptococcus* A on throat swab, > 10,000 leucocytes/$mm^3$, fever<br>Duration of symptoms before inclusion = 6 to 7 days |
| Interventions | Astemizole 0.2 mg/kg daily<br>Non-sedating antihistamine<br>Compared to placebo<br>Duration = 7 days |
| Outcomes | Mean daily score (0 = absent, 1 = mild, 2 = mild, 3 = severe) and percentage decrease in severity score of rhinorrhoea compared from baseline<br>Time until severity of rhinorrhoea, cough and general condition has decreased by 50%<br>Proportion of participants "cured" after 3 days and 7 days |
| Notes | No mention of the randomisation process |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Both groups were given the intervention, which was identical in appearance |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Parents recorded the symptom severity score in a daily diary |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 80.6%<br>10 participants were excluded as they developed signs of bacterial infection<br>2 participants were excluded as they did not follow the protocol |

**Hugenin 1988** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail and some outcomes are reported in a different manner to other similar studies. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

**MRC (Part 2) 1950**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, non-placebo-controlled<br>Naturally occurring colds<br>1550 participants included<br>74.6% follow-up<br>Multicentre (UK) |
| Participants | Exact age range not specified, trial states > 15 years of age<br>Included if catarrhal inflammation upper respiratory passages, usually without pyrexia but with watery or mucous discharge from the nose and associated with sneezing, fullness in the head and nose and sometimes with cough, headache, sore throat, hoarseness and running eyes<br>Excluded if chronic catarrh or sinusitis, acute tonsillitis, suspected influenza, fever > 37. 8°C, antihistamine in previous week, present attack of hay fever of allergic rhinitis (previous history of allergic states were included but registered)<br>Duration of symptoms before inclusion = under 48 hours |
| Interventions | Thonzylamine 50 mg 3 times a day<br>Sedating antihistamine<br>Compared to placebo (see Notes)<br>Duration = 3 days |
| Outcomes | Subjective evaluation of overall symptom severity (cured, improved, unchanged, worse or recurred)<br>Side effects |
| Notes | The placebo consisted of lactose with 5 mg quinine sulphate. Quinine in this dose cannot be considered as an active control |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Those who were to be treated and those who were to be "controls" were prearranged in random order by the use of random sampling numbers, with the one restriction that |

**MRC (Part 2) 1950** (*Continued*)

| | | |
|---|---|---|
| | | each batch of 50 volunteers should include 25 treated (T) and 25 controls (C) (a restriction not known at the centres) |
| Allocation concealment (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, no details provided<br>Similar participant demographics in both groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Investigators as well as participants were blinded to treatment status<br>Both groups were given the intervention, which was identical in appearance |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants self assessed their symptom severity in to a diary |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 74.6%<br>394 participants (196 from treatment group and 194 from placebo group) were excluded due to failure to complete the treatment as per protocol or to report back on the days specified by the protocol |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail and some outcomes are reported in a different manner to other similar studies. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

**Muether 2001**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Experimental cold virus<br>66 participants included<br>80.3% follow-up<br>Single-centre (USA) |
| Participants | 18 to 40 years of age<br>Included healthy participants with neutralising antibody titres of less than 2 to rhinovirus type 16 and required to have been free of cold symptoms and fever > 37.8°C for 1 week prior to entering the trial then given inoculated rhinovirus type 16 to cause symptoms of a cold<br>Excluded if they had a history of allergic rhinitis, bronchial asthma or other lower |

| | |
|---|---|
| | respiratory tract diseases such as chronic obstructive lung disease or emphysema, a history of alcohol and drug abuse, volunteers who had used investigational drugs within 30 days, antihistamines and/or cold preparations within 14 days, monoamine oxidase inhibitors within 7 days, astemizole within 90 days, or any other medication thought to interfere with the study drug, pregnancy or lactation, glaucoma and renal, hepatic, endocrine, digestive, genitourinary, neurologic or psychologic disease<br>Duration of symptoms before inclusion = treatment commenced before virus challenge |
| Interventions | Loratadine 10 mg daily<br>Non-sedating antihistamine<br>Compared to placebo<br>Duration = commenced 7 days before virus challenge and continued for 5 days after |
| Outcomes | Severity of symptoms (sneezing, runny nose, nasal obstruction, sore throat, cough, headache, malaise and chilliness) on a 5-point scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe<br>Nasal secretion weight<br>Sneeze and cough count<br>Side effects |
| Notes | Does not state whether the participants who did not meet the criteria for illness had symptoms or not - they have been included in the results |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Similar participant demographics in both groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Investigators as well as participants were blinded to treatment status<br>Both groups were given the intervention, which was identical in appearance |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants self assessed their symptom severity<br>Participants remained in isolation after viral challenge on day 8 until day 13 (5 days duration) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 80.3%<br>5 participants were excluded because they were infected with a wild strain of rhi- |

**Muether 2001** (*Continued*)

| | | |
|---|---|---|
| | | novirus instead of type 16<br>7 participants were excluded as they were not infected after the viral challenge<br>1 participant withdrew from the study due to side effects<br>16 participants were included but they did not develop symptoms according to the illness criteria set by the investigators (does not specify if they developed any symptoms at all or not) |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes are reported in a different manner to other similar studies. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

**Sakchainanont 1990**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Naturally occurring colds<br>150 participants included<br>95.3% follow-up<br>Multicentre (Thailand) |
| Participants | 1.5 to 60 months of age<br>Participants were included if they had rhinorrhoea with or without occasional non-productive cough of 3 days duration<br>Participants were excluded if they had a history of allergies, received any other medication, fever > 38.3°C, nasal eosinophil count above 10% or bacterial infections<br>Duration of symptoms before inclusion = 3 days |
| Interventions | Clemastine 0.05 mg/kg twice daily (n = 48)<br>Chlorpheniramine 0.11 mg/kg 3 times a day (n = 48)<br>Both sedating antihistamines<br>Compared to placebo<br>Duration = 3 days |
| Outcomes | Severity, character and amount of nasal discharge<br>Frequency of cough (if any)<br>Nasal turbinates for oedema<br>Sleepiness/drowsiness |
| Notes | - |
| ***Risk of bias*** | |

**Sakchainanont 1990** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Allocated randomly to either placebo or treatment, although details of the randomisation process were not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified<br>Similar participant demographics in all groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Investigators as well as the parents of the participants were blinded to treatment status<br>Both groups were given the intervention, which was identical in appearance |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Parents of the participants self assessed their symptom severity daily<br>The participants were assessed by the physician, who also was blinded, after 3 days of intervention |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 95.3%<br>6 participants were excluded because they did not follow up according to follow-up guidelines set by the investigators<br>1 participant was excluded due to developing measles |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes reported lack detail and some outcomes are reported in a different manner to other similar studies. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

**Turner 1997**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Double-blind, placebo-controlled<br>Naturally occurring colds<br>403 participants included<br>88.6% follow-up<br>Multicentre (USA) |
| Participants | Exact age range not specified, mean age = 34.4 years of age<br>Participants were included if they had runny nose and/or sneezing, had at least 2 different symptoms, had recorded symptoms in their diary for no more than 1 day and responded "Yes" to the question "Have you had the onset of a cold within the last 24 hours?"<br>Participants were excluded if they had a history of medication use that can interfere with antihistamines or that may make evaluation of common cold symptoms difficult, underlying illnesses that might be exacerbated by antihistamines or that might affect the assessment of common cold symptoms, present allergies (history of seasonal or perennial allergic rhinitis is not an exclusion criterion but present symptomatic allergy complaints is) or pregnancy<br>Duration of symptoms before inclusion = 24 hours |
| Interventions | Clemastine 1.34 mg twice daily<br>Sedating antihistamines<br>Compared to placebo<br>Duration = 5 days |
| Outcomes | Severity of symptoms (sneezing, runny nose, nasal obstruction, sore throat, cough, headache, malaise, chilliness and post-nasal drip) on a 5-point scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe<br>Side effects |
| Notes | - |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not specified |
| Allocation concealment (selection bias) | Low risk | Allocated randomly to either placebo or treatment, distributed in sequentially numbered blister packs provided to each study participant in the order they were admitted to the treatment phase of the study<br>Similar participant demographics in both groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Investigators as well as the participants were blinded to treatment status<br>Both groups were given the intervention, |

**Turner 1997** (*Continued*)

| | | |
|---|---|---|
| | | which was identical in appearance |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants self assessed their symptom severity daily |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Follow-up rate 88.6%<br>23 participants withdrew from the study as they did not follow-up<br>6 participant withdrew from the study due to side effects<br>2 participants withdrew from the study and did not complete the intervention as their symptoms resolved<br>1 participant withdrew from the study due to treatment failure<br>14 participants withdrew from the study due to unrelated reasons from their illness or study medications |
| Selective reporting (reporting bias) | Unclear risk | Reports all outcomes intended, although some outcomes are reported in a different manner to other similar studies. We did not contact the study authors for additional information |
| Other bias | Unclear risk | - |

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Aaronson 1968 | Evaluated participants with allergic rhinitis |
| Andre 1974 | Effect of combination products analysed |
| Ashe 1968 | Effect of combination products analysed |
| D'Agostino 1998 | Not a randomised controlled trial (RCT) |
| Debelic 1973 | Effect of combination products analysed |
| Dumitrescou 1965 | Effect of topical antihistamine eye-drops analysed |
| Elia 1967 | Effect of combination products analysed |

(*Continued*)

| | |
|---|---|
| Henahan 1983 | Not a randomised controlled trial (RCT) |
| Knowelden 1959 | Not a randomised controlled trial (RCT) |
| McGuinness 1976 | Not placebo-controlled |
| Shaughnessy 1999 | Not a randomised controlled trial (RCT) |
| Simons 1991 | Evaluated participants with allergic rhinitis |
| Smith 1993 | Effect of combination products analysed |
| Tarchalska 2000 | Not a randomised controlled trial (RCT) |
| West 1975 | Not a randomised controlled trial (RCT) |
| Yoder 2006 | Only cough assessed |

## DATA AND ANALYSES

### Comparison 1. Change in severity of overall symptoms - all trials

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Short-term (1 to 2 days) | 3 | 1490 | Odds Ratio (M-H, Random, 95% CI) | 0.74 [0.60, 0.92] |
| 2 Intermediate-term (3 to 4 days) | 1 | 234 | Odds Ratio (M-H, Random, 95% CI) | 1.19 [0.67, 2.11] |
| 3 Long-term (6 to 10 days) | 3 | 1551 | Odds Ratio (M-H, Random, 95% CI) | 0.71 [0.41, 1.22] |
| 4 Short-term ITT analysis | 3 | 1912 | Odds Ratio (M-H, Random, 95% CI) | 0.78 [0.65, 0.95] |
| 5 Intermediate-term ITT analysis | 1 | 250 | Odds Ratio (M-H, Random, 95% CI) | 1.16 [0.66, 2.04] |
| 6 Long-term ITT analysis | 3 | 1945 | Odds Ratio (M-H, Random, 95% CI) | 0.71 [0.42, 1.20] |

### Comparison 2. Change in severity of overall symptoms - trials with sedating antihistamines

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Short-term (1 to 2 days) | 2 | 1427 | Odds Ratio (M-H, Random, 95% CI) | 0.76 [0.61, 0.95] |
| 2 Long-term (6 to 10 days) | 3 | 1551 | Odds Ratio (M-H, Random, 95% CI) | 0.71 [0.41, 1.22] |

### Comparison 3. Subjective severity assessment of nasal obstruction - all trials

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mean severity score after 1 day of treatment | 3 | 428 | Mean Difference (IV, Random, 95% CI) | -0.09 [-0.23, 0.06] |
| 2 Mean severity score after 3 to 5 days of treatment | 5 | 758 | Mean Difference (IV, Random, 95% CI) | 0.04 [-0.20, 0.27] |

### Comparison 4. Subjective severity assessment of nasal obstruction - non-sedating antihistamines

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mean severity score after 1 day of treatment | 1 | 53 | Mean Difference (IV, Random, 95% CI) | -0.10 [-0.48, 0.28] |
| 2 Mean severity score after 3 to 5 days of treatment | 3 | 383 | Mean Difference (IV, Random, 95% CI) | 0.21 [0.00, 0.41] |

### Comparison 5. Subjective severity assessment of nasal obstruction - antihistamines

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mean severity score after 1 day of treatment | 2 | 375 | Mean Difference (IV, Random, 95% CI) | -0.07 [-0.29, 0.15] |
| 2 Mean severity score after 3 to 5 days of treatment | 2 | 375 | Mean Difference (IV, Random, 95% CI) | -0.10 [-0.41, 0.22] |

### Comparison 6. Subjective severity assessment of rhinorrhoea - all trials

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 First treatment day | 5 | 1350 | Mean Difference (IV, Random, 95% CI) | -0.07 [-0.14, 0.00] |
| 2 Second treatment day | 5 | 1350 | Mean Difference (IV, Random, 95% CI) | -0.15 [-0.27, -0.04] |
| 3 Third treatment day | 5 | 1350 | Mean Difference (IV, Random, 95% CI) | -0.09 [-0.25, 0.07] |
| 4 Fourth treatment day | 5 | 758 | Mean Difference (IV, Random, 95% CI) | -0.14 [-0.24, -0.03] |

### Comparison 7. Subjective severity assessment of rhinorrhoea - non-sedating antihistamines

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Fourth treatment day | 3 | 383 | Mean Difference (IV, Random, 95% CI) | -0.08 [-0.26, 0.09] |

### Comparison 8. Subjective severity assessment of rhinorrhoea - sedating antihistamines

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 First treatment day | 4 | 1466 | Mean Difference (IV, Random, 95% CI) | -0.04 [-0.13, 0.06] |
| 2 Second treatment day | 4 | 1465 | Mean Difference (IV, Random, 95% CI) | -0.18 [-0.27, -0.08] |
| 3 Third treatment day | 4 | 1466 | Mean Difference (IV, Random, 95% CI) | -0.23 [-0.39, -0.06] |
| 4 Fourth treatment day | 3 | 762 | Mean Difference (IV, Random, 95% CI) | -0.24 [-0.35, -0.12] |

### Comparison 9. Subjective severity assessment of sneezing - all trials

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 First treatment day | 4 | 1466 | Mean Difference (IV, Random, 95% CI) | -0.07 [-0.15, 0.00] |
| 2 Second treatment day | 5 | 1518 | Mean Difference (IV, Random, 95% CI) | -0.26 [-0.37, -0.15] |
| 3 Third treatment day | 5 | 1510 | Mean Difference (IV, Random, 95% CI) | -0.31 [-0.46, -0.15] |
| 4 Fourth treatment day | 5 | 911 | Mean Difference (IV, Random, 95% CI) | -0.28 [-0.36, -0.20] |

### Comparison 10. Subjective severity assessment of sneezing - sedating antihistamines

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 First treatment day | 4 | 1466 | Mean Difference (IV, Random, 95% CI) | -0.07 [-0.15, 0.00] |
| 2 Second treatment day | 4 | 1465 | Mean Difference (IV, Random, 95% CI) | -0.29 [-0.38, -0.21] |
| 3 Third treatment day | 4 | 1457 | Mean Difference (IV, Random, 95% CI) | -0.35 [-0.49, -0.20] |
| 4 Fourth treatment day | 3 | 762 | Mean Difference (IV, Random, 95% CI) | -0.29 [-0.39, -0.19] |

### Comparison 11. Side effects

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 All side effects - all trials | 9 | 2590 | Odds Ratio (M-H, Fixed, 95% CI) | 1.18 [0.97, 1.44] |
| 2 All side effects - non-sedating antihistamines | 3 | 215 | Odds Ratio (M-H, Random, 95% CI) | 1.21 [0.52, 2.81] |
| 3 Gastrointestinal side effects | 5 | 1586 | Odds Ratio (M-H, Random, 95% CI) | 1.46 [0.84, 2.56] |
| 4 Sedation - all trials | 6 | 2624 | Odds Ratio (M-H, Random, 95% CI) | 1.64 [0.69, 3.85] |
| 5 Sedation - non-sedating antihistamines | 2 | 349 | Odds Ratio (M-H, Random, 95% CI) | 1.08 [0.50, 2.31] |
| 6 Sedation - sedating antihistamine | 4 | 2275 | Odds Ratio (M-H, Random, 95% CI) | 2.04 [0.64, 6.56] |
| 7 All side effects - sedating antihistamines | 6 | 2265 | Odds Ratio (M-H, Random, 95% CI) | 1.13 [0.80, 1.59] |
| 8 Sleeplessness | 2 | 1406 | Odds Ratio (M-H, Random, 95% CI) | 3.0 [0.60, 14.95] |
| 9 Dry nose | 2 | 173 | Odds Ratio (M-H, Random, 95% CI) | 0.82 [0.05, 12.87] |
| 10 Headache | 4 | 1558 | Odds Ratio (M-H, Random, 95% CI) | 1.21 [0.76, 1.92] |
| 11 Vertigo/dizziness | 3 | 1283 | Odds Ratio (M-H, Random, 95% CI) | 1.49 [0.77, 2.91] |
| 12 Dry mouth | 3 | 421 | Odds Ratio (M-H, Random, 95% CI) | 1.17 [0.60, 2.26] |

## Analysis 1.1. Comparison 1 Change in severity of overall symptoms - all trials, Outcome 1 Short-term (1 to 2 days).

Review: Antihistamines for the common cold

Comparison: 1 Change in severity of overall symptoms - all trials

Outcome: 1 Short-term (1 to 2 days)

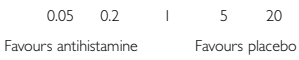
| Study or subgroup | Antihistamines n/N | Placebo n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Henauer 1988 | 11/28 | 21/35 | | 4.3 % | 0.43 [ 0.16, 1.19 ] |
| Howard 1979 | 97/133 | 112/138 | | 13.5 % | 0.63 [ 0.35, 1.11 ] |
| MRC (Part 2) 1950 | 301/579 | 334/577 | | 82.2 % | 0.79 [ 0.62, 0.99 ] |
| **Total (95% CI)** | **740** | **750** | | **100.0 %** | **0.74 [ 0.60, 0.92 ]** |

Total events: 409 (Antihistamines), 467 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.69$, df = 2 (P = 0.43); $I^2 = 0.0\%$

Test for overall effect: Z = 2.75 (P = 0.0059)

Test for subgroup differences: Not applicable



### Analysis 1.2. Comparison 1 Change in severity of overall symptoms - all trials, Outcome 2 Intermediate-term (3 to 4 days).

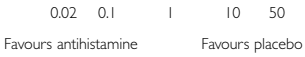
Review: Antihistamines for the common cold

Comparison: 1 Change in severity of overall symptoms - all trials

Outcome: 2 Intermediate-term (3 to 4 days)

| Study or subgroup | Antihistamine n/N | Placebo n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Gaffey 1988 | 88/119 | 81/115 | | 100.0 % | 1.19 [ 0.67, 2.11 ] |
| **Total (95% CI)** | **119** | **115** | | **100.0 %** | **1.19 [ 0.67, 2.11 ]** |

Total events: 88 (Antihistamine), 81 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable




### Analysis 1.3. Comparison 1 Change in severity of overall symptoms - all trials, Outcome 3 Long-term (6 to 10 days).

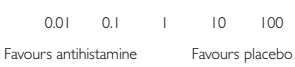
Review: Antihistamines for the common cold

Comparison: 1 Change in severity of overall symptoms - all trials

Outcome: 3 Long-term (6 to 10 days)

| Study or subgroup | Antihistamine n/N | Placebo n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Bye 1980 | 34/61 | 49/63 | | 24.1 % | 0.36 [ 0.16, 0.78 ] |
| Howard 1979 | 38/133 | 50/138 | | 33.5 % | 0.70 [ 0.42, 1.17 ] |
| MRC (Part 2) 1950 | 137/579 | 132/577 | | 42.4 % | 1.04 [ 0.80, 1.37 ] |
| **Total (95% CI)** | **773** | **778** | | **100.0 %** | **0.71 [ 0.41, 1.22 ]** |

Total events: 209 (Antihistamine), 231 (Placebo)
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 7.31$, df = 2 (P = 0.03); $I^2 = 73\%$
Test for overall effect: Z = 1.24 (P = 0.22)
Test for subgroup differences: Not applicable



## Analysis 1.4. Comparison 1 Change in severity of overall symptoms - all trials, Outcome 4 Short-term ITT analysis.

Review: Antihistamines for the common cold

Comparison: 1 Change in severity of overall symptoms - all trials

Outcome: 4 Short-term ITT analysis

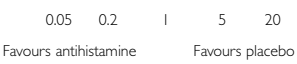
| Study or subgroup | Antihistamine n/N | Placebo n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Henauer 1988 | 27/44 | 33/47 | | 4.9 % | 0.67 [ 0.28, 1.61 ] |
| Howard 1979 | 97/133 | 112/138 | | 11.4 % | 0.63 [ 0.35, 1.11 ] |
| MRC (Part 2) 1950 | 497/775 | 532/775 | | 83.7 % | 0.82 [ 0.66, 1.01 ] |
| **Total (95% CI)** | **952** | **960** | | **100.0 %** | **0.78 [ 0.65, 0.95 ]** |

Total events: 621 (Antihistamine), 677 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.86$, df = 2 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 2.46 (P = 0.014)

Test for subgroup differences: Not applicable



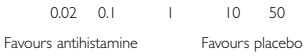
### Analysis 1.5. Comparison 1 Change in severity of overall symptoms - all trials, Outcome 5 Intermediate-term ITT analysis.

Review: Antihistamines for the common cold

Comparison: 1 Change in severity of overall symptoms - all trials

Outcome: 5 Intermediate-term ITT analysis

| Study or subgroup | Antihistamine n/N | Placebo n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Gaffey 1988 | 95/126 | 90/124 | | 100.0 % | 1.16 [ 0.66, 2.04 ] |
| **Total (95% CI)** | **126** | **124** | | **100.0 %** | **1.16 [ 0.66, 2.04 ]** |
| Total events: 95 (Antihistamine), 90 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.51 (P = 0.61) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |



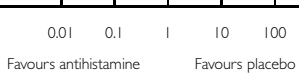

### Analysis 1.6. Comparison 1 Change in severity of overall symptoms - all trials, Outcome 6 Long-term ITT analysis.

Review: Antihistamines for the common cold

Comparison: 1 Change in severity of overall symptoms - all trials

Outcome: 6 Long-term ITT analysis

| Study or subgroup | Antihistamine n/N | Placebo n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Bye 1980 | 34/61 | 49/63 | | 23.3 % | 0.36 [ 0.16, 0.78 ] |
| Howard 1979 | 38/133 | 50/138 | | 32.7 % | 0.70 [ 0.42, 1.17 ] |
| MRC (Part 2) 1950 | 333/775 | 330/775 | | 44.1 % | 1.02 [ 0.83, 1.24 ] |
| **Total (95% CI)** | **969** | **976** | | **100.0 %** | **0.71 [ 0.42, 1.20 ]** |
| Total events: 405 (Antihistamine), 429 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$ = 0.15; $Chi^2$ = 7.55, df = 2 (P = 0.02); $I^2$ =74% | | | | | |
| Test for overall effect: Z = 1.28 (P = 0.20) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |



**Analysis 2.1. Comparison 2 Change in severity of overall symptoms - trials with sedating antihistamines, Outcome 1 Short-term (1 to 2 days).**

Review: Antihistamines for the common cold

Comparison: 2 Change in severity of overall symptoms - trials with sedating antihistamines

Outcome: 1 Short-term (1 to 2 days)

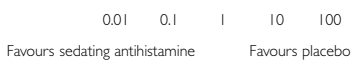
| Study or subgroup | Antihistamine sedating n/N | Placebo n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Howard 1979 | 97/133 | 112/138 | | 14.1 % | 0.63 [ 0.35, 1.11 ] |
| MRC (Part 2) 1950 | 301/579 | 334/577 | | 85.9 % | 0.79 [ 0.62, 0.99 ] |
| **Total (95% CI)** | **712** | **715** | | **100.0 %** | **0.76 [ 0.61, 0.95 ]** |

Total events: 398 (Antihistamine sedating), 446 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.53$, df = 1 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 2.47 (P = 0.014)

Test for subgroup differences: Not applicable

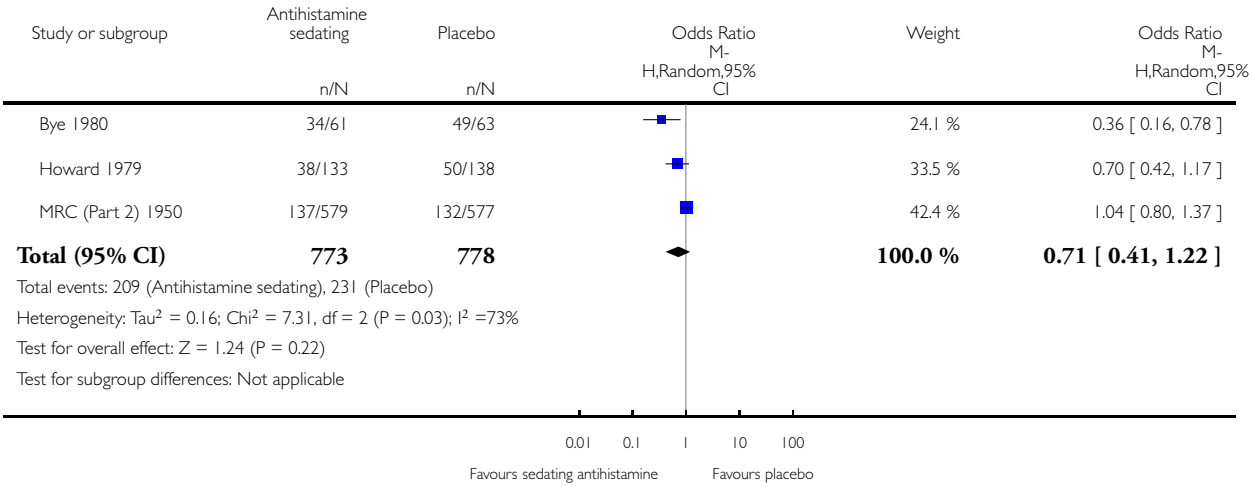


## Analysis 2.2. Comparison 2 Change in severity of overall symptoms - trials with sedating antihistamines, Outcome 2 Long-term (6 to 10 days).

Review: Antihistamines for the common cold

Comparison: 2 Change in severity of overall symptoms - trials with sedating antihistamines

Outcome: 2 Long-term (6 to 10 days)



## Analysis 3.1. Comparison 3 Subjective severity assessment of nasal obstruction - all trials, Outcome 1 Mean severity score after 1 day of treatment.

Review: Antihistamines for the common cold

Comparison: 3 Subjective severity assessment of nasal obstruction - all trials

Outcome: 1 Mean severity score after 1 day of treatment

| Study or subgroup | Antihistamine N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Gwaltney 1996 | 75 | 0.83 (0.76) | 75 | 0.77 (0.76) | | 32.2 % | 0.06 [ -0.18, 0.30 ] |
| Gwaltney 1997 | 113 | 0.42 (0.64) | 112 | 0.59 (0.74) | | 53.8 % | -0.17 [ -0.35, 0.01 ] |
| Muether 2001 | 29 | 0.28 (0.6) | 24 | 0.38 (0.78) | | 14.0 % | -0.10 [ -0.48, 0.28 ] |
| **Total (95% CI)** | **217** | | **211** | | | **100.0 %** | **-0.09 [ -0.23, 0.06 ]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.22$, df = 2 (P = 0.33); $I^2 = 10\%$

Test for overall effect: Z = 1.16 (P = 0.25)

Test for subgroup differences: Not applicable

## Analysis 3.2. Comparison 3 Subjective severity assessment of nasal obstruction - all trials, Outcome 2 Mean severity score after 3 to 5 days of treatment.

Review: Antihistamines for the common cold

Comparison: 3 Subjective severity assessment of nasal obstruction - all trials

Outcome: 2 Mean severity score after 3 to 5 days of treatment

| Study or subgroup | Antihistamine N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Berkowitz 1991 | 48 | 1.21 (1.04) | 48 | 1.25 (0.97) | | 16.7 % | -0.04 [ -0.44, 0.36 ] |
| Gaffey 1988 | 119 | 1.3 (0.8) | 115 | 1 (0.9) | | 25.7 % | 0.30 [ 0.08, 0.52 ] |
| Gwaltney 1996 | 75 | 1.2 (0.76) | 75 | 1.13 (0.87) | | 23.4 % | 0.07 [ -0.19, 0.33 ] |
| Gwaltney 1997 | 113 | 1.04 (0.85) | 112 | 1.29 (0.95) | | 24.7 % | -0.25 [ -0.49, -0.01 ] |
| Muether 2001 | 29 | 1.52 (1.02) | 24 | 1.38 (1.3) | | 9.5 % | 0.14 [ -0.50, 0.78 ] |
| **Total (95% CI)** | **384** | | **374** | | | **100.0 %** | **0.04 [ -0.20, 0.27 ]** |

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 11.55$, df = 4 (P = 0.02); $I^2 = 65\%$

Test for overall effect: Z = 0.32 (P = 0.75)

Test for subgroup differences: Not applicable

### Analysis 4.1. Comparison 4 Subjective severity assessment of nasal obstruction - non-sedating antihistamines, Outcome 1 Mean severity score after 1 day of treatment.

Review: Antihistamines for the common cold

Comparison: 4 Subjective severity assessment of nasal obstruction - non-sedating antihistamines

Outcome: 1 Mean severity score after 1 day of treatment

| Study or subgroup | Antihistamine non-sedating N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Muether 2001 | 29 | 0.28 (0.6) | 24 | 0.38 (0.78) | | 100.0 % | -0.10 [ -0.48, 0.28 ] |
| **Total (95% CI)** | **29** | | **24** | | | **100.0 %** | **-0.10 [ -0.48, 0.28 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable


### Analysis 4.2. Comparison 4 Subjective severity assessment of nasal obstruction - non-sedating antihistamines, Outcome 2 Mean severity score after 3 to 5 days of treatment.

Review: Antihistamines for the common cold

Comparison: 4 Subjective severity assessment of nasal obstruction - non-sedating antihistamines

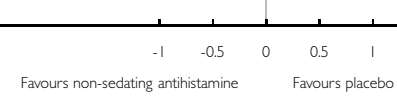
Outcome: 2 Mean severity score after 3 to 5 days of treatment

| Study or subgroup | Antihistamine non-sedating N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Berkowitz 1991 | 48 | 1.21 (1.04) | 48 | 1.25 (0.97) | | 23.3 % | -0.04 [ -0.44, 0.36 ] |
| Gaffey 1988 | 119 | 1.3 (0.8) | 115 | 1 (0.9) | | 66.9 % | 0.30 [ 0.08, 0.52 ] |
| Muether 2001 | 29 | 1.52 (1.02) | 24 | 1.38 (1.3) | | 9.7 % | 0.14 [ -0.50, 0.78 ] |
| **Total (95% CI)** | **196** | | **187** | | | **100.0 %** | **0.21 [ 0.00, 0.41 ]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.18$, df = 2 (P = 0.34); $I^2 = 8\%$

Test for overall effect: Z = 1.99 (P = 0.047)

Test for subgroup differences: Not applicable



**Analysis 5.1. Comparison 5 Subjective severity assessment of nasal obstruction - antihistamines, Outcome 1 Mean severity score after 1 day of treatment.**

Review: Antihistamines for the common cold

Comparison: 5 Subjective severity assessment of nasal obstruction - antihistamines

Outcome: 1 Mean severity score after 1 day of treatment

| Study or subgroup | Antihistamine sedating N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Gwaltney 1996 | 75 | 0.83 (0.76) | 75 | 0.77 (0.76) | | 43.5 % | 0.06 [ -0.18, 0.30 ] |
| Gwaltney 1997 | 113 | 0.42 (0.64) | 112 | 0.59 (0.74) | | 56.5 % | -0.17 [ -0.35, 0.01 ] |
| **Total (95% CI)** | **188** | | **187** | | | **100.0 %** | **-0.07 [ -0.29, 0.15 ]** |

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.21$, df = 1 (P = 0.14); $I^2 = 55\%$

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable

### Analysis 5.2. Comparison 5 Subjective severity assessment of nasal obstruction - antihistamines, Outcome 2 Mean severity score after 3 to 5 days of treatment.

Review: Antihistamines for the common cold

Comparison: 5 Subjective severity assessment of nasal obstruction - antihistamines

Outcome: 2 Mean severity score after 3 to 5 days of treatment

| Study or subgroup | Antihistamine sedating N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Gwaltney 1996 | 75 | 1.2 (0.76) | 75 | 1.13 (0.87) | | 48.4 % | 0.07 [ -0.19, 0.33 ] |
| Gwaltney 1997 | 113 | 1.04 (0.85) | 112 | 1.29 (0.95) | | 51.6 % | -0.25 [ -0.49, -0.01 ] |
| **Total (95% CI)** | **188** | | **187** | | | **100.0 %** | **-0.10 [ -0.41, 0.22 ]** |

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 3.18$, df = 1 (P = 0.07); $I^2 = 69\%$

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Not applicable

## Analysis 6.1. Comparison 6 Subjective severity assessment of rhinorrhoea - all trials, Outcome 1 First treatment day.

Review: Antihistamines for the common cold

Comparison: 6 Subjective severity assessment of rhinorrhoea - all trials

Outcome: 1 First treatment day

| Study or subgroup | Anithistamine N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Eccles 1995 | 345 | 2.13 (0.91) | 343 | 2.27 (0.91) | | 27.9 % | -0.14 [ -0.28, 0.00 ] |
| Gaffey 1988 | 119 | 1.8 (0.6) | 115 | 1.9 (0.6) | | 21.8 % | -0.10 [ -0.25, 0.05 ] |
| Gwaltney 1996 | 75 | 0.41 (0.69) | 75 | 0.39 (0.61) | | 11.9 % | 0.02 [ -0.19, 0.23 ] |
| Gwaltney 1997 | 113 | 0.23 (0.43) | 112 | 0.26 (0.53) | | 32.4 % | -0.03 [ -0.16, 0.10 ] |
| Muether 2001 | 29 | 0.17 (0.38) | 24 | 0.17 (0.65) | | 6.0 % | 0.0 [ -0.29, 0.29 ] |
| **Total (95% CI)** | **681** | | **669** | | | **100.0 %** | **-0.07 [ -0.14, 0.00 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.48$, df = 4 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 1.86 (P = 0.063)

Test for subgroup differences: Not applicable

### Analysis 6.2. Comparison 6 Subjective severity assessment of rhinorrhoea - all trials, Outcome 2 Second treatment day.

Review: Antihistamines for the common cold

Comparison: 6 Subjective severity assessment of rhinorrhoea - all trials

Outcome: 2 Second treatment day

| Study or subgroup | Antihistamine N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Eccles 1995 | 345 | 1.77 (0.87) | 343 | 1.92 (0.87) | | 38.4 % | -0.15 [ -0.28, -0.02 ] |
| Gaffey 1988 | 119 | 1.4 (0.8) | 115 | 1.5 (0.7) | | 23.7 % | -0.10 [ -0.29, 0.09 ] |
| Gwaltney 1996 | 75 | 0.67 (0.87) | 75 | 0.97 (0.95) | | 12.4 % | -0.30 [ -0.59, -0.01 ] |
| Gwaltney 1997 | 113 | 0.58 (0.74) | 112 | 0.82 (0.85) | | 21.1 % | -0.24 [ -0.45, -0.03 ] |
| Muether 2001 | 29 | 0.79 (1.02) | 24 | 0.46 (0.89) | | 4.4 % | 0.33 [ -0.18, 0.84 ] |
| **Total (95% CI)** | **681** | | **669** | | | **100.0 %** | **-0.15 [ -0.27, -0.04 ]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.32$, df = 4 (P = 0.26); $I^2 = 25\%$

Test for overall effect: Z = 2.71 (P = 0.0067)

Test for subgroup differences: Not applicable

### Analysis 6.3. Comparison 6 Subjective severity assessment of rhinorrhoea - all trials, Outcome 3 Third treatment day.

Review: Antihistamines for the common cold

Comparison: 6 Subjective severity assessment of rhinorrhoea - all trials

Outcome: 3 Third treatment day

| Study or subgroup | Antihistamine N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Eccles 1995 | 345 | 1.07 (0.98) | 343 | 1.11 (0.98) | | 29.5 % | -0.04 [ -0.19, 0.11 ] |
| Gaffey 1988 | 119 | 1.1 (0.8) | 115 | 1 (0.8) | | 23.9 % | 0.10 [ -0.11, 0.31 ] |
| Gwaltney 1996 | 75 | 0.59 (0.78) | 75 | 0.85 (0.87) | | 19.0 % | -0.26 [ -0.52, 0.00 ] |
| Gwaltney 1997 | 113 | 0.53 (0.74) | 112 | 0.81 (0.95) | | 22.3 % | -0.28 [ -0.50, -0.06 ] |
| Muether 2001 | 29 | 1.24 (1.08) | 24 | 1 (1.3) | | 5.3 % | 0.24 [ -0.41, 0.89 ] |
| **Total (95% CI)** | **681** | | **669** | | | **100.0 %** | **-0.09 [ -0.25, 0.07 ]** |

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.05$, df = 4 (P = 0.06); $I^2 = 56\%$

Test for overall effect: Z = 1.06 (P = 0.29)

Test for subgroup differences: Not applicable

### Analysis 6.4. Comparison 6 Subjective severity assessment of rhinorrhoea - all trials, Outcome 4 Fourth treatment day.

Review: Antihistamines for the common cold

Comparison: 6 Subjective severity assessment of rhinorrhoea - all trials

Outcome: 4 Fourth treatment day

| Study or subgroup | Antihistamine N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Berkowitz 1991 | 48 | 0.75 (0.9) | 48 | 0.77 (0.9) | | 7.9 % | -0.02 [ -0.38, 0.34 ] |
| Gaffey 1988 | 119 | 0.7 (0.8) | 115 | 0.7 (0.8) | | 24.3 % | 0.0 [ -0.21, 0.21 ] |
| Gwaltney 1996 | 75 | 0.51 (0.69) | 75 | 0.64 (0.69) | | 21.0 % | -0.13 [ -0.35, 0.09 ] |
| Gwaltney 1997 | 113 | 0.27 (0.53) | 112 | 0.48 (0.74) | | 36.1 % | -0.21 [ -0.38, -0.04 ] |
| Muether 2001 | 29 | 0.59 (0.81) | 24 | 0.88 (0.23) | | 10.7 % | -0.29 [ -0.60, 0.02 ] |
| **Total (95% CI)** | **384** | | **374** | | | **100.0 %** | **-0.14 [ -0.24, -0.03 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.79$, df = 4 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 2.63 (P = 0.0085)

Test for subgroup differences: Not applicable

## Analysis 7.1. Comparison 7 Subjective severity assessment of rhinorrhoea - non-sedating antihistamines, Outcome 1 Fourth treatment day.

Review: Antihistamines for the common cold

Comparison: 7 Subjective severity assessment of rhinorrhoea - non-sedating antihistamines

Outcome: 1 Fourth treatment day

| Study or subgroup | Antihistamine non-sedat | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Berkowitz 1991 | 48 | 0.75 (0.9) | 48 | 0.77 (0.9) | | 21.1 % | -0.02 [ -0.38, 0.34 ] |
| Gaffey 1988 | 119 | 0.7 (0.8) | 115 | 0.7 (0.8) | | 51.4 % | 0.0 [ -0.21, 0.21 ] |
| Muether 2001 | 29 | 0.59 (0.81) | 24 | 0.88 (0.23) | | 27.4 % | -0.29 [ -0.60, 0.02 ] |
| **Total (95% CI)** | **196** | | **187** | | | **100.0 %** | **-0.08 [ -0.26, 0.09 ]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.47$, df = 2 (P = 0.29); $I^2 = 19\%$

Test for overall effect: Z = 0.93 (P = 0.35)

Test for subgroup differences: Not applicable

## Analysis 8.1. Comparison 8 Subjective severity assessment of rhinorrhoea - sedating antihistamines, Outcome 1 First treatment day.

Review: Antihistamines for the common cold

Comparison: 8 Subjective severity assessment of rhinorrhoea - sedating antihistamines

Outcome: 1 First treatment day

| Study or subgroup | Antihistamine sedat | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Eccles 1995 | 345 | 2.13 (0.91) | 343 | 2.27 (0.91) | | 30.9 % | -0.14 [ -0.28, 0.00 ] |
| Gwaltney 1996 | 75 | 0.41 (0.69) | 75 | 0.39 (0.61) | | 16.0 % | 0.02 [ -0.19, 0.23 ] |
| Gwaltney 1997 | 113 | 0.23 (0.43) | 112 | 0.26 (0.53) | | 34.2 % | -0.03 [ -0.16, 0.10 ] |
| Turner 1997 | 202 | 1.73 (0.95) | 201 | 1.65 (0.98) | | 18.9 % | 0.08 [ -0.11, 0.27 ] |
| **Total (95% CI)** | **735** | | **731** | | | **100.0 %** | **-0.04 [ -0.13, 0.06 ]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.98$, df = 3 (P = 0.26); $I^2 = 25\%$

Test for overall effect: Z = 0.76 (P = 0.45)

Test for subgroup differences: Not applicable

## Analysis 8.2. Comparison 8 Subjective severity assessment of rhinorrhoea - sedating antihistamines, Outcome 2 Second treatment day.

Review: Antihistamines for the common cold

Comparison: 8 Subjective severity assessment of rhinorrhoea - sedating antihistamines

Outcome: 2 Second treatment day

| Study or subgroup | Antihistamine sedat | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Eccles 1995 | 345 | 1.77 (0.87) | 343 | 1.92 (0.87) | | 49.8 % | -0.15 [ -0.28, -0.02 ] |
| Gwaltney 1996 | 75 | 0.67 (0.87) | 75 | 0.97 (0.95) | | 9.9 % | -0.30 [ -0.59, -0.01 ] |
| Gwaltney 1997 | 113 | 0.58 (0.74) | 112 | 0.82 (0.85) | | 19.4 % | -0.24 [ -0.45, -0.03 ] |
| Turner 1997 | 201 | 1.46 (0.96) | 201 | 1.58 (1.09) | | 20.9 % | -0.12 [ -0.32, 0.08 ] |
| **Total (95% CI)** | **734** | | **731** | | | **100.0 %** | **-0.18 [ -0.27, -0.08 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.51$, df = 3 (P = 0.68); $I^2 = 0.0\%$

Test for overall effect: Z = 3.76 (P = 0.00017)

Test for subgroup differences: Not applicable

## Analysis 8.3. Comparison 8 Subjective severity assessment of rhinorrhoea - sedating antihistamines, Outcome 3 Third treatment day.

Review: Antihistamines for the common cold

Comparison: 8 Subjective severity assessment of rhinorrhoea - sedating antihistamines

Outcome: 3 Third treatment day

| Study or subgroup | Antihistamine sedat | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Eccles 1995 | 345 | 1.07 (0.98) | 343 | 1.11 (0.98) | | 30.6 % | -0.04 [ -0.19, 0.11 ] |
| Gwaltney 1996 | 75 | 0.59 (0.78) | 75 | 0.85 (0.87) | | 20.0 % | -0.26 [ -0.52, 0.00 ] |
| Gwaltney 1997 | 113 | 0.53 (0.74) | 112 | 0.81 (0.95) | | 23.4 % | -0.28 [ -0.50, -0.06 ] |
| Turner 1997 | 202 | 1.02 (0.99) | 201 | 1.39 (0.99) | | 26.0 % | -0.37 [ -0.56, -0.18 ] |
| **Total (95% CI)** | **735** | | **731** | | | **100.0 %** | **-0.23 [ -0.39, -0.06 ]** |

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.24$, df = 3 (P = 0.04); $I^2 = 64\%$

Test for overall effect: Z = 2.65 (P = 0.0079)

Test for subgroup differences: Not applicable

## Analysis 8.4. Comparison 8 Subjective severity assessment of rhinorrhoea - sedating antihistamines, Outcome 4 Fourth treatment day.

Review: Antihistamines for the common cold

Comparison: 8 Subjective severity assessment of rhinorrhoea - sedating antihistamines

Outcome: 4 Fourth treatment day

| Study or subgroup | Antihistamine sedat | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Gwaltney 1996 | 75 | 0.51 (0.69) | 75 | 0.64 (0.69) | | 24.7 % | -0.13 [ -0.35, 0.09 ] |
| Gwaltney 1997 | 113 | 0.27 (0.53) | 112 | 0.48 (0.74) | | 40.3 % | -0.21 [ -0.38, -0.04 ] |
| Turner 1997 | 191 | 0.76 (0.88) | 196 | 1.1 (0.95) | | 35.0 % | -0.34 [ -0.52, -0.16 ] |
| **Total (95% CI)** | **379** | | **383** | | | **100.0 %** | **-0.24 [ -0.35, -0.12 ]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.23$, df = 2 (P = 0.33); $I^2 = 10\%$

Test for overall effect: Z = 4.04 (P = 0.000052)

Test for subgroup differences: Not applicable

## Analysis 9.1. Comparison 9 Subjective severity assessment of sneezing - all trials, Outcome 1 First treatment day.

Review: Antihistamines for the common cold

Comparison: 9 Subjective severity assessment of sneezing - all trials

Outcome: 1 First treatment day

| Study or subgroup | Antihistamines N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Eccles 1995 | 345 | 0.93 (0.93) | 343 | 1.04 (0.93) | | 24.4 % | -0.11 [ -0.25, 0.03 ] |
| Gwaltney 1996 | 75 | 0.23 (0.43) | 75 | 0.19 (0.43) | | 24.8 % | 0.04 [ -0.10, 0.18 ] |
| Gwaltney 1997 | 113 | 0.11 (0.32) | 112 | 0.2 (0.53) | | 32.9 % | -0.09 [ -0.20, 0.02 ] |
| Turner 1997 | 202 | 1.17 (0.84) | 201 | 1.32 (0.88) | | 17.8 % | -0.15 [ -0.32, 0.02 ] |
| **Total (95% CI)** | **735** | | **731** | | | **100.0 %** | **-0.07 [ -0.15, 0.00 ]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.75$, df = 3 (P = 0.29); $I^2 = 20\%$

Test for overall effect: Z = 1.87 (P = 0.061)

Test for subgroup differences: Not applicable

### Analysis 9.2. Comparison 9 Subjective severity assessment of sneezing - all trials, Outcome 2 Second treatment day.

Review: Antihistamines for the common cold

Comparison: 9 Subjective severity assessment of sneezing - all trials

Outcome: 2 Second treatment day

| Study or subgroup | Antihistamines N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Eccles 1995 | 345 | 0.62 (0.82) | 343 | 0.84 (0.81) | | 26.1 % | -0.22 [ -0.34, -0.10 ] |
| Gwaltney 1996 | 75 | 0.28 (0.52) | 75 | 0.55 (0.61) | | 18.5 % | -0.27 [ -0.45, -0.09 ] |
| Gwaltney 1997 | 113 | 0.28 (0.53) | 112 | 0.6 (0.64) | | 21.8 % | -0.32 [ -0.47, -0.17 ] |
| Muether 2001 | 29 | 0.14 (0.32) | 24 | 0.17 (0.47) | | 14.7 % | -0.03 [ -0.25, 0.19 ] |
| Turner 1997 | 201 | 0.74 (0.82) | 201 | 1.16 (0.99) | | 18.9 % | -0.42 [ -0.60, -0.24 ] |
| **Total (95% CI)** | **763** | | **755** | | | **100.0 %** | **-0.26 [ -0.37, -0.15 ]** |

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.27$, df = 4 (P = 0.08); $I^2 = 52\%$

Test for overall effect: Z = 4.78 (P < 0.00001)

Test for subgroup differences: Not applicable

## Analysis 9.3. Comparison 9 Subjective severity assessment of sneezing - all trials, Outcome 3 Third treatment day.

Review: Antihistamines for the common cold

Comparison: 9 Subjective severity assessment of sneezing - all trials

Outcome: 3 Third treatment day

| Study or subgroup | Antihistamines N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Eccles 1995 | 345 | 0.36 (0.74) | 343 | 0.54 (0.74) | | 25.9 % | -0.18 [ -0.29, -0.07 ] |
| Gwaltney 1996 | 75 | 0.36 (0.52) | 75 | 0.76 (0.78) | | 18.9 % | -0.40 [ -0.61, -0.19 ] |
| Gwaltney 1997 | 113 | 0.25 (0.42) | 112 | 0.73 (0.74) | | 22.7 % | -0.48 [ -0.64, -0.32 ] |
| Muether 2001 | 29 | 0.52 (0.65) | 24 | 0.46 (0.77) | | 10.1 % | 0.06 [ -0.33, 0.45 ] |
| Turner 1997 | 194 | 0.54 (0.74) | 200 | 0.9 (0.9) | | 22.3 % | -0.36 [ -0.52, -0.20 ] |
| **Total (95% CI)** | **756** | | **754** | | | **100.0 %** | **-0.31 [ -0.46, -0.15 ]** |

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 14.22$, df = 4 (P = 0.01); $I^2 = 72\%$

Test for overall effect: Z = 3.96 (P = 0.000075)

Test for subgroup differences: Not applicable

### Analysis 9.4. Comparison 9 Subjective severity assessment of sneezing - all trials, Outcome 4 Fourth treatment day.

Review: Antihistamines for the common cold

Comparison: 9 Subjective severity assessment of sneezing - all trials

Outcome: 4 Fourth treatment day

| Study or subgroup | Antihistamines N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Berkowitz 1991 | 48 | 0.33 (0.62) | 48 | 0.56 (0.9) | | 6.6 % | -0.23 [ -0.54, 0.08 ] |
| Gwaltney 1996 | 75 | 0.27 (0.43) | 75 | 0.48 (0.69) | | 18.6 % | -0.21 [ -0.39, -0.03 ] |
| Gwaltney 1997 | 113 | 0.16 (0.42) | 112 | 0.42 (0.53) | | 40.2 % | -0.26 [ -0.39, -0.13 ] |
| Muether 2001 | 29 | 0.41 (0.49) | 24 | 0.54 (0.89) | | 4.0 % | -0.13 [ -0.53, 0.27 ] |
| Turner 1997 | 191 | 0.31 (0.59) | 196 | 0.7 (0.83) | | 30.7 % | -0.39 [ -0.53, -0.25 ] |
| **Total (95% CI)** | **456** | | **455** | | | **100.0 %** | **-0.28 [ -0.36, -0.20 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.56$, df = 4 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 7.01 (P < 0.00001)

Test for subgroup differences: Not applicable

## Analysis 10.1. Comparison 10 Subjective severity assessment of sneezing - sedating antihistamines, Outcome 1 First treatment day.

Review: Antihistamines for the common cold

Comparison: 10 Subjective severity assessment of sneezing - sedating antihistamines

Outcome: 1 First treatment day

| Study or subgroup | Antihistamines sedat | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Eccles 1995 | 345 | 0.93 (0.93) | 343 | 1.04 (0.93) | | 24.4 % | -0.11 [ -0.25, 0.03 ] |
| Gwaltney 1996 | 75 | 0.23 (0.43) | 75 | 0.19 (0.43) | | 24.8 % | 0.04 [ -0.10, 0.18 ] |
| Gwaltney 1997 | 113 | 0.11 (0.32) | 112 | 0.2 (0.53) | | 32.9 % | -0.09 [ -0.20, 0.02 ] |
| Turner 1997 | 202 | 1.17 (0.84) | 201 | 1.32 (0.88) | | 17.8 % | -0.15 [ -0.32, 0.02 ] |
| **Total (95% CI)** | **735** | | **731** | | | **100.0 %** | **-0.07 [ -0.15, 0.00 ]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.75$, df = 3 (P = 0.29); $I^2 = 20\%$

Test for overall effect: Z = 1.87 (P = 0.061)

Test for subgroup differences: Not applicable

## Analysis 10.2. Comparison 10 Subjective severity assessment of sneezing - sedating antihistamines, Outcome 2 Second treatment day.

Review: Antihistamines for the common cold

Comparison: 10 Subjective severity assessment of sneezing - sedating antihistamines

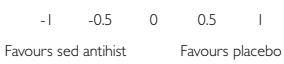
Outcome: 2 Second treatment day

| Study or subgroup | Antihistamines sedat | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Eccles 1995 | 345 | 0.62 (0.82) | 343 | 0.84 (0.81) | | 36.6 % | -0.22 [ -0.34, -0.10 ] |
| Gwaltney 1996 | 75 | 0.28 (0.52) | 75 | 0.55 (0.61) | | 18.8 % | -0.27 [ -0.45, -0.09 ] |
| Gwaltney 1997 | 113 | 0.28 (0.53) | 112 | 0.6 (0.64) | | 25.1 % | -0.32 [ -0.47, -0.17 ] |
| Turner 1997 | 201 | 0.74 (0.82) | 201 | 1.16 (0.99) | | 19.5 % | -0.42 [ -0.60, -0.24 ] |
| **Total (95% CI)** | **734** | | **731** | | | **100.0 %** | **-0.29 [ -0.38, -0.21 ]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.52$, df = 3 (P = 0.32); $I^2 = 15\%$

Test for overall effect: Z = 6.89 (P < 0.00001)

Test for subgroup differences: Not applicable



## Analysis 10.3. Comparison 10 Subjective severity assessment of sneezing - sedating antihistamines, Outcome 3 Third treatment day.

Review: Antihistamines for the common cold

Comparison: 10 Subjective severity assessment of sneezing - sedating antihistamines

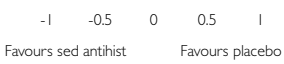
Outcome: 3 Third treatment day

| Study or subgroup | Antihistamines sedat | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Eccles 1995 | 345 | 0.36 (0.74) | 343 | 0.54 (0.74) | | 29.5 % | -0.18 [ -0.29, -0.07 ] |
| Gwaltney 1996 | 75 | 0.36 (0.52) | 75 | 0.76 (0.78) | | 20.5 % | -0.40 [ -0.61, -0.19 ] |
| Gwaltney 1997 | 113 | 0.25 (0.42) | 112 | 0.73 (0.74) | | 25.2 % | -0.48 [ -0.64, -0.32 ] |
| Turner 1997 | 194 | 0.54 (0.74) | 200 | 0.9 (0.9) | | 24.8 % | -0.36 [ -0.52, -0.20 ] |
| **Total (95% CI)** | **727** | | **730** | | | **100.0 %** | **-0.35 [ -0.49, -0.20 ]** |

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 10.84$, df = 3 (P = 0.01); $I^2 = 72\%$

Test for overall effect: Z = 4.57 (P < 0.00001)

Test for subgroup differences: Not applicable



## Analysis 10.4. Comparison 10 Subjective severity assessment of sneezing - sedating antihistamines, Outcome 4 Fourth treatment day.

Review: Antihistamines for the common cold

Comparison: 10 Subjective severity assessment of sneezing - sedating antihistamines

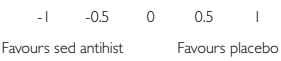
Outcome: 4 Fourth treatment day

| Study or subgroup | Antihistamines sedat | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Gwaltney 1996 | 75 | 0.27 (0.43) | 75 | 0.48 (0.69) | | 23.8 % | -0.21 [ -0.39, -0.03 ] |
| Gwaltney 1997 | 113 | 0.16 (0.42) | 112 | 0.42 (0.53) | | 41.5 % | -0.26 [ -0.39, -0.13 ] |
| Turner 1997 | 191 | 0.31 (0.59) | 196 | 0.7 (0.83) | | 34.6 % | -0.39 [ -0.53, -0.25 ] |
| **Total (95% CI)** | **379** | | **383** | | | **100.0 %** | **-0.29 [ -0.39, -0.19 ]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.81$, df = 2 (P = 0.25); $I^2 = 29\%$

Test for overall effect: Z = 5.69 (P < 0.00001)

Test for subgroup differences: Not applicable



## Analysis 11.1. Comparison 11 Side effects, Outcome 1 All side effects - all trials.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 1 All side effects - all trials

| Study or subgroup | Anthistamines n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Berkowitz 1991 | 6/49 | 5/50 | | 2.4 % | 1.26 [ 0.36, 4.42 ] |
| Bye 1980 | 13/59 | 19/60 | | 8.2 % | 0.61 [ 0.27, 1.39 ] |
| Crutcher 1981 | 14/52 | 15/54 | | 6.0 % | 0.96 [ 0.41, 2.25 ] |
| Gwaltney 1997 | 10/132 | 10/147 | | 4.9 % | 1.12 [ 0.45, 2.79 ] |
| Henauer 1988 | 7/44 | 6/47 | | 2.7 % | 1.29 [ 0.40, 4.20 ] |
| Howard 1979 | 32/133 | 32/138 | | 13.3 % | 1.05 [ 0.60, 1.84 ] |
| MRC (Part 2) 1950 | 121/579 | 111/577 | | 49.0 % | 1.11 [ 0.83, 1.48 ] |
| Muether 2001 | 0/34 | 2/32 | | 1.4 % | 0.18 [ 0.01, 3.83 ] |
| Turner 1997 | 56/202 | 30/201 | | 12.1 % | 2.19 [ 1.33, 3.59 ] |
| **Total (95% CI)** | **1284** | **1306** | | **100.0 %** | **1.18 [ 0.97, 1.44 ]** |

Total events: 259 (Anthistamines), 230 (Control)

Heterogeneity: $Chi^2$ = 10.51, df = 8 (P = 0.23); $I^2$ =24%

Test for overall effect: Z = 1.61 (P = 0.11)

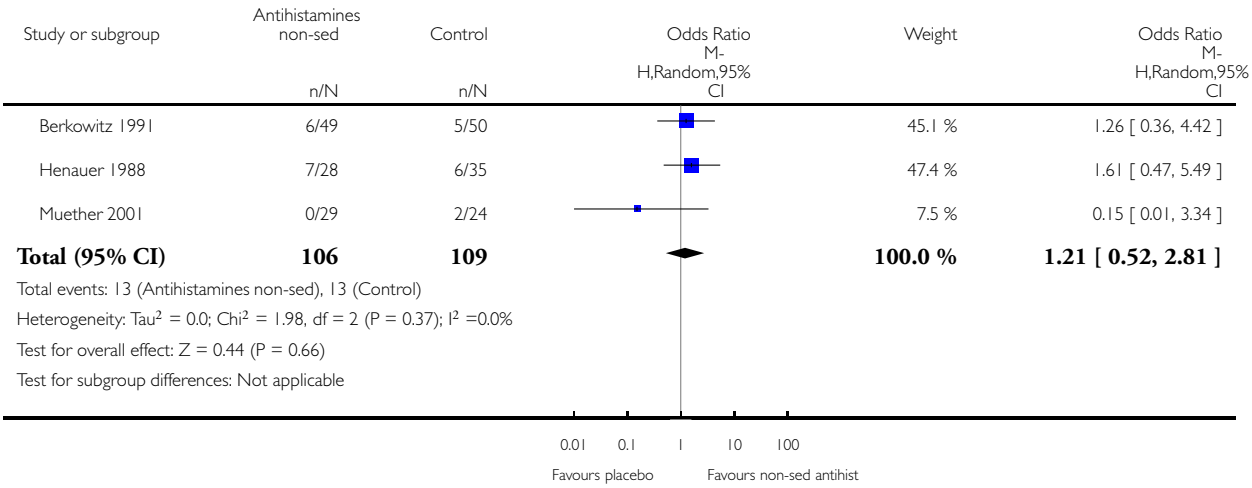
Test for subgroup differences: Not applicable

### Analysis 11.2. Comparison 11 Side effects, Outcome 2 All side effects - non-sedating antihistamines.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 2 All side effects - non-sedating antihistamines

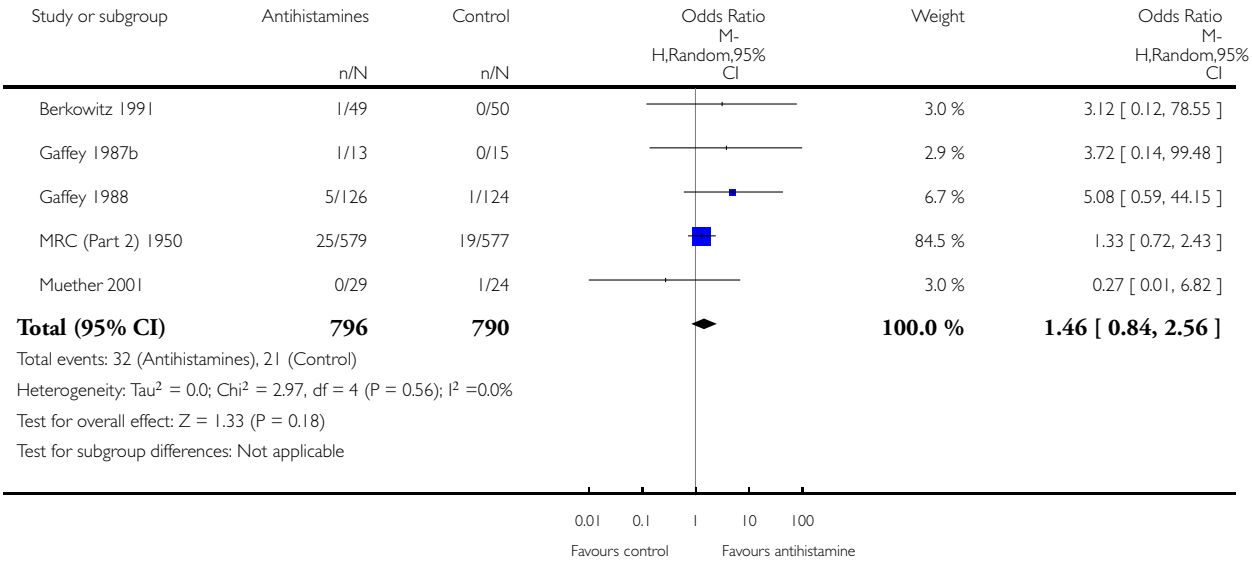


### Analysis 11.3. Comparison 11 Side effects, Outcome 3 Gastrointestinal side effects.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 3 Gastrointestinal side effects

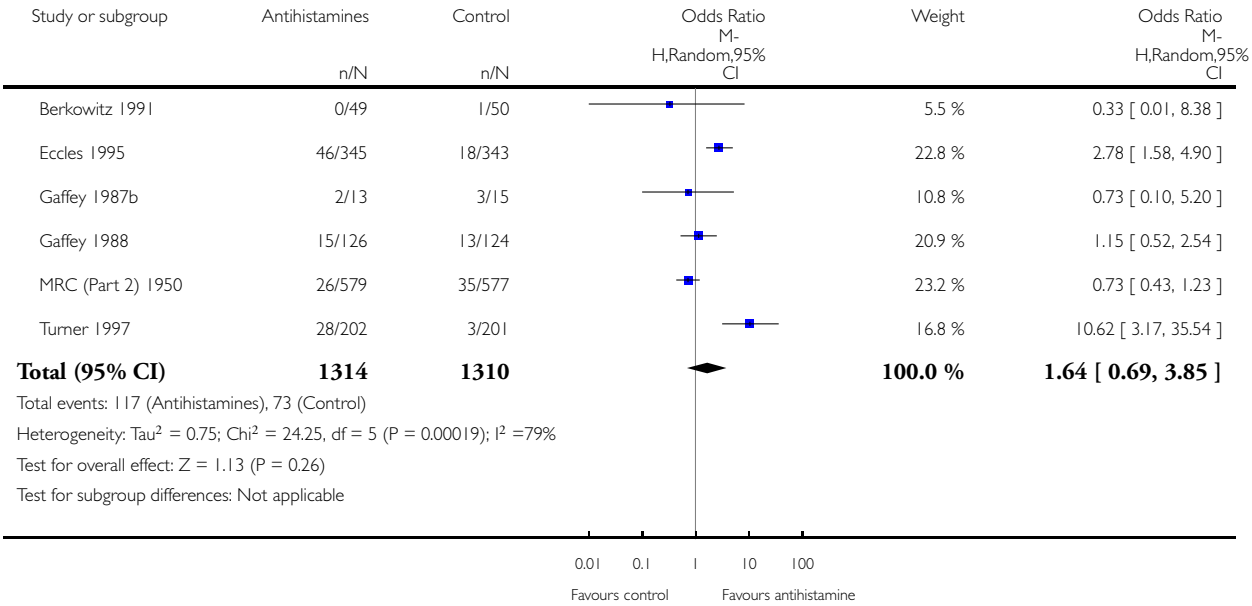


## Analysis 11.4. Comparison 11 Side effects, Outcome 4 Sedation - all trials.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 4 Sedation - all trials

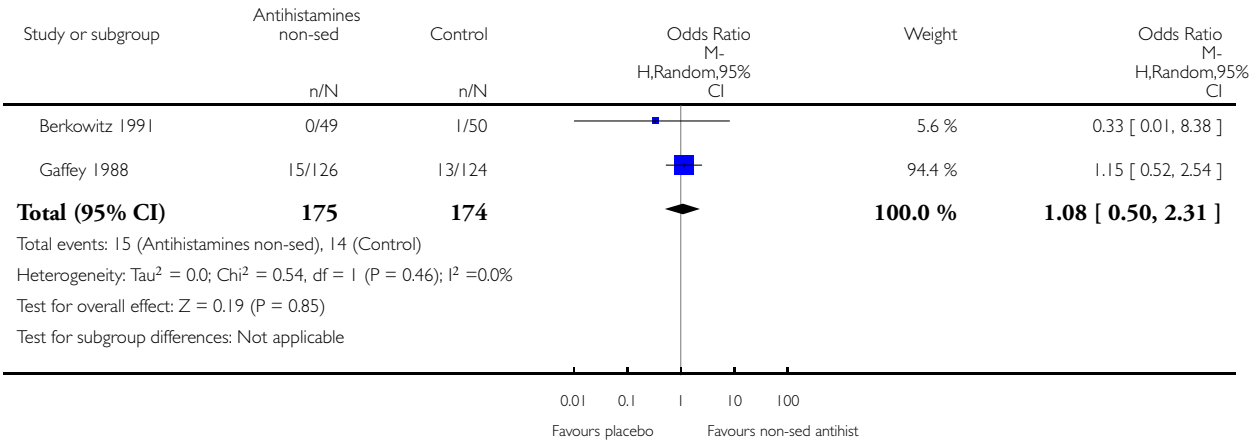


### Analysis 11.5. Comparison 11 Side effects, Outcome 5 Sedation - non-sedating antihistamines.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 5 Sedation - non-sedating antihistamines



### Analysis 11.6. Comparison 11 Side effects, Outcome 6 Sedation - sedating antihistamine.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 6 Sedation - sedating antihistamine

| Study or subgroup | Antihistamines sedat n/N | Control n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Eccles 1995 | 46/345 | 18/343 | | 29.6 % | 2.78 [ 1.58, 4.90 ] |
| Gaffey 1987b | 2/13 | 3/15 | | 16.7 % | 0.73 [ 0.10, 5.20 ] |
| MRC (Part 2) 1950 | 26/579 | 35/577 | | 29.9 % | 0.73 [ 0.43, 1.23 ] |
| Turner 1997 | 28/202 | 3/201 | | 23.7 % | 10.62 [ 3.17, 35.54 ] |
| **Total (95% CI)** | **1139** | **1136** | | **100.0 %** | **2.04 [ 0.64, 6.56 ]** |

Total events: 102 (Antihistamines sedat), 59 (Control)

Heterogeneity: $Tau^2 = 1.11$; $Chi^2 = 22.93$, df = 3 (P = 0.00004); $I^2 = 87\%$

Test for overall effect: Z = 1.20 (P = 0.23)

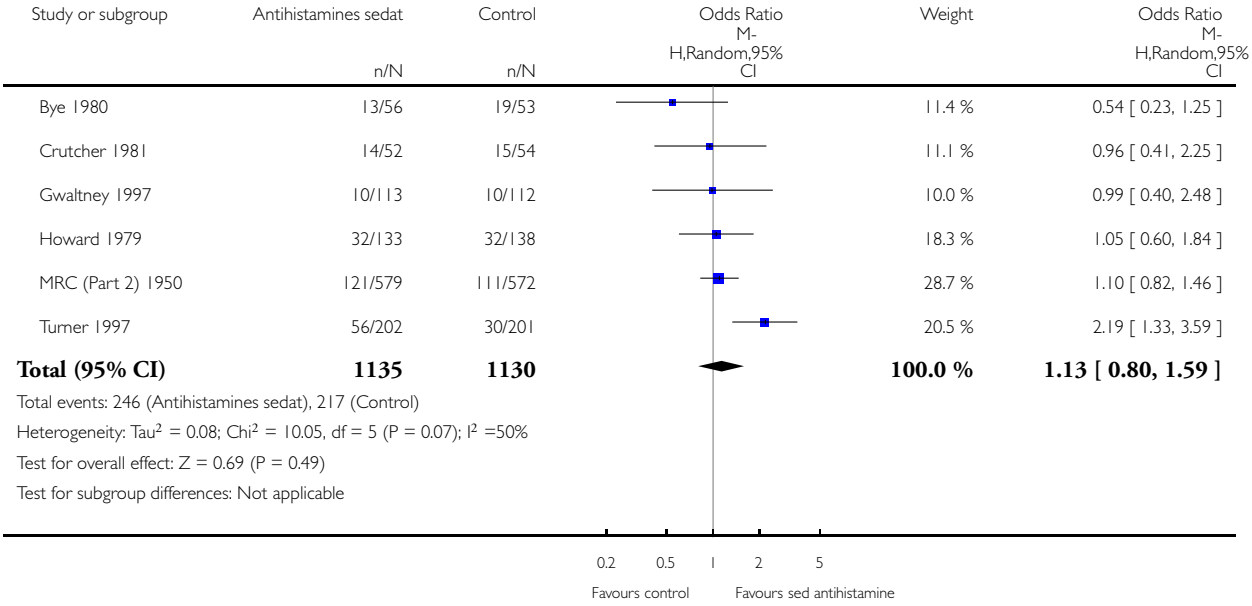
Test for subgroup differences: Not applicable

### Analysis 11.7. Comparison 11 Side effects, Outcome 7 All side effects - sedating antihistamines.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 7 All side effects - sedating antihistamines



### Analysis 11.8. Comparison 11 Side effects, Outcome 8 Sleeplessness.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 8 Sleeplessness

| Study or subgroup | Antihistamines n/N | Control n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Gaffey 1988 | 3/126 | 1/124 | | 49.8 % | 3.00 [ 0.31, 29.24 ] |
| MRC (Part 2) 1950 | 3/579 | 1/577 | | 50.2 % | 3.00 [ 0.31, 28.93 ] |
| **Total (95% CI)** | **705** | **701** | | **100.0 %** | **3.00 [ 0.60, 14.95 ]** |

Total events: 6 (Antihistamines), 2 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.34 (P = 0.18)

Test for subgroup differences: Not applicable


### Analysis 11.9. Comparison 11 Side effects, Outcome 9 Dry nose.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 9 Dry nose

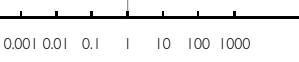
| Study or subgroup | Antihistamines n/N | Control n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Gaffey 1987a | 1/12 | 4/11 | | 41.8 % | 0.16 [ 0.01, 1.73 ] |
| Gwaltney 1996 | 27/75 | 13/75 | | 58.2 % | 2.68 [ 1.25, 5.74 ] |
| **Total (95% CI)** | **87** | **86** | | **100.0 %** | **0.82 [ 0.05, 12.87 ]** |

Total events: 28 (Antihistamines), 17 (Control)

Heterogeneity: $Tau^2 = 3.22$; $Chi^2 = 4.94$, df = 1 (P = 0.03); $I^2 = 80\%$

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable



## Analysis 11.10. Comparison 11 Side effects, Outcome 10 Headache.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 10 Headache

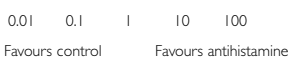
| Study or subgroup | Antihistamines n/N | Control n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Berkowitz 1991 | 3/49 | 2/50 | | 6.4 % | 1.57 [ 0.25, 9.80 ] |
| Gaffey 1988 | 7/126 | 10/124 | | 21.6 % | 0.67 [ 0.25, 1.82 ] |
| MRC (Part 2) 1950 | 32/579 | 22/577 | | 69.9 % | 1.48 [ 0.85, 2.57 ] |
| Muether 2001 | 0/29 | 1/24 | | 2.0 % | 0.27 [ 0.01, 6.82 ] |
| **Total (95% CI)** | **783** | **775** | | **100.0 %** | **1.21 [ 0.76, 1.92 ]** |

Total events: 42 (Antihistamines), 35 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.75$, df = 3 (P = 0.43); $I^2 = 0.0\%$

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable



### Analysis 11.11. Comparison 11 Side effects, Outcome 11 Vertigo/dizziness.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 11 Vertigo/dizziness

| Study or subgroup | Antihistamines n/N | Control n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Berkowitz 1991 | 1/49 | 1/50 | | 5.7 % | 1.02 [ 0.06, 16.79 ] |
| Gaffey 1987b | 0/13 | 1/15 | | 4.1 % | 0.36 [ 0.01, 9.57 ] |
| MRC (Part 2) 1950 | 21/579 | 13/577 | | 90.2 % | 1.63 [ 0.81, 3.29 ] |
| **Total (95% CI)** | **641** | **642** | | **100.0 %** | **1.49 [ 0.77, 2.91 ]** |

Total events: 22 (Antihistamines), 15 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.86$, df = 2 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 1.18 (P = 0.24)

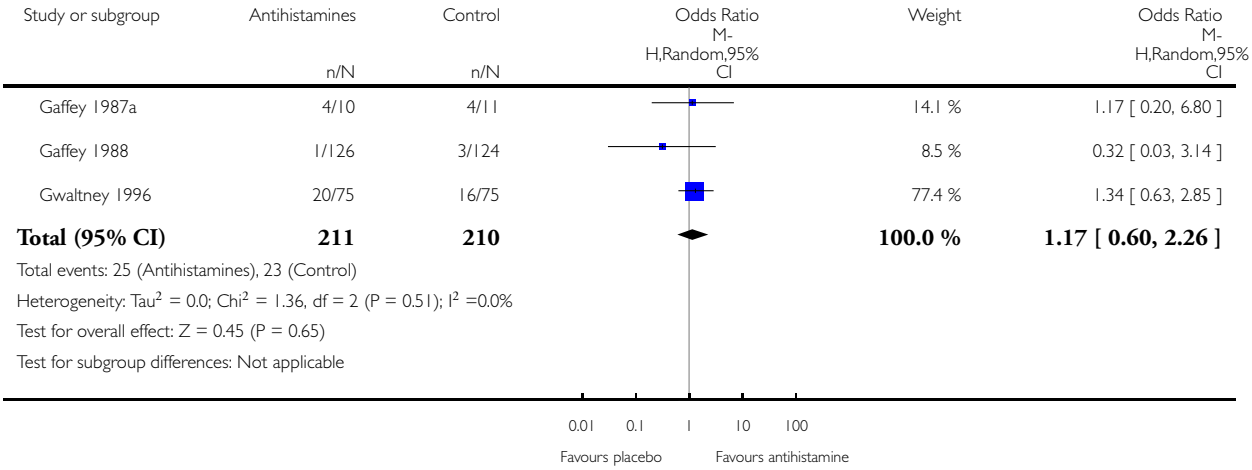
Test for subgroup differences: Not applicable

### Analysis 11.12. Comparison 11 Side effects, Outcome 12 Dry mouth.

Review: Antihistamines for the common cold

Comparison: 11 Side effects

Outcome: 12 Dry mouth




## ADDITIONAL TABLES

**Table 1. Change in severity of overall symptoms**

| Name | Results |
|---|---|
| Crutcher 1981 | Assessments of change in severity of overall symptoms in favour of treatment from 48 hours until day 7 after commencement of treatment; P value = 0.05 (no other data in paper) |
| Gwaltney 1997 | Mean VAS at final evaluation (after 4 days) with active treatment is 6.2/10 and with placebo 5.1/10 (P value < 0. 01) |
| Hugenin 1988 | Number of days until normalisation of general condition is 5.2 (± 2.3) with placebo and 4 (± 2.12) with active treatment (P value = 0.06) |
| Gaffey 1988 | Assessment of severity of overall symptoms score on a 5-point scale with active treatment is 2.2 (± 1.1) and with placebo is 2.1 (± 1.3) (P value = 1) |
| Berkowitz 1991 | Assessment of change in severity of overall symptoms by physician on a 5-point scale at day 4 has no significant differences between treatment groups and no further data are reported in the paper |
| Gwaltney 1996 | No significant difference between treatment groups in daily assessment of severity of overall symptomss |

VAS: visual analogue scale

**Table 2. Subjective severity assessment of nasal obstruction**

| Name | Results |
|---|---|
| Doyle 1988 | (1) Mean sum of severity scores on day 3 to 6 after virus inoculation with chlorpheniramine is 3.2 (± 1.9) and with placebo is 4.7 (± 2.9); (P value = 0.11)<br>(2) Average days with nasal obstruction with chlorpheniramine is 2.4 (± 1.4); (P value = 0.14) |
| Ectors 1994 | Mean change in severity score after 2 days of treatment with cetirizine is from 1.9 to 0.9 and with placebo is from 2. 15 to 1.5 (P value = 0.035) |

**Table 3. Subjective severity assessment of rhinorrhoea**

| Name | Result |
|---|---|
| Doyle 1988 | (1) Sum of score over 4 days of treatment with chlorpheniramine is (3.1 (± 1.7) and with placebo is 4.4 (± 3) , (P value = 0.16)<br>(2) Mean number of days with rhinorrhoea after virus challenge with chlorpheniramine is 2.6 (± 1.3) and with placebo is 2.9 (± 1.4); (P value = 0.6) |
| Bye 1980 | No significant difference in daily severity scores of rhinorrhoea in participants with triprolidine or placebo (numerical data not in paper) |
| Ectors 1994 | Improvement of rhinorrhoea was not significantly larger with cetirizine, although there was a trend in favour of active treatment after 1.5 days of treatment (numerical data not in paper) |
| Henauer 1988 | Rhinoscopy in 16 participants (8 with terfenadine, 8 with placebo) performed 2 hours and 24 hours after the first tablet showed visible nasal secretions were less with terfenadine than with placebo (results only graphically displayed in paper) |
| Howard 1979 | (1) Significantly lower severity score at 18 of 24 time points during 7 days of treatment with chlorpheniramine (numerical data not in paper)<br>(2) Decrease in severity scores (significance not mentioned in paper): at 8 pm on day 1 (this is 10 hours after the first tablet) with chlorpheniramine the decrease is 53.9% and with placebo is 46.4%. At 8 pm on day 2 with chlorpheniramine the decrease is 69.4% and with placebo is 60.7%. At day 7 with chlorpheniramine the decrease is 73.5% and with placebo is 60.7% |
| Hugenin 1988 | (1) Number of days until rhinorrhoea severity score was reduced to 50% of initial value with astemizole is 3. 4 (± 1.7) and with placebo is 5.1 (± 2); (P value = 0.001)<br>(2) Proportion of children with complete disappearance of rhinorrhoea after 7 days of treatment with astemizole is 79% (18/23) and with placebo is 46% (12/27); (P value = 0.015) |
| Sakchainanont 1990 | Amount of nasal discharge is less after 3 days with clemastine in 28/48 children, with chlorpheniramine in 25/48 and with placebo in 22/47; (P value = 0.53) |

**Table 4. Subjective severity assessment of sneezing**

| Name | Result |
|---|---|
| Bye 1980 | Significant larger reduction of mean severity scores in participants with triprolidine (numerical data not in paper) |
| Doyle 1988 | (1) Sum of score over 4 days of treatment with chlorpheniramine is 0.1 (± 0.3) and with placebo is 1.5 (± 1.6); (P value < 0.01)<br>(2) Average number of days with sneezing with chlorpheniramine is 0.1 (± 0.3) and with placebo is 1.3 (± 1.3); (P value < 0.01) |
| Ectors 1994 | Improvement of sneezing was not significantly larger with cetirizine, although there was a trend in favour of active treatment after 1.5 days of treatment (numerical data not in paper) |
| Gaffey 1988 | Severity scores recorded at 7 time points (once every 12 hours during 3.5 days) showed no significant difference between treatment groups (numerical data not in paper) |
| Howard 1979 | (1) Significantly lower severity scores at all 24 time points during 7 days of treatment (numerical data not available)<br>(2) Percentage decrease in severity scores (significance not mentioned in paper): at 10 pm on day 1 (this is 12 hours after the first tablet) with chlorpheniramine the decrease is 66% and with placebo is 56.3%. At 10 pm on day 2 with chlorpheniramine the decrease is 88.4% and with placebo is 69.6% |

# APPENDICES

## Appendix 1. MEDLINE (Ovid) search strategy

1 Common Cold/
2 common cold*.tw.
3 Nasal Obstruction/
4 ((runny or running*) adj2 nose*).tw.
5 ((nasal or nose*) adj3 (block* or discharge* or congest* or dripping)).tw.
6 coryza.tw.
7 (upper adj3 respiratory infection*).tw.
8 (upper adj3 respiratory tract infection*).tw.
9 Sneezing/
10 sneez*.tw.
11 urti.tw.
12 Rhinitis/
13 rhinit*.tw.
14 (rhinorrhea or rhinorrhoea).tw.
15 Nasopharyngitis/
16 (nasopharyngit* or rhinopharyngit*).tw.
17 head cold*.tw.
18 Rhinovirus/
19 rhinovir*.tw.
20 coronavirus/ or coronavirus 229e, human/ or coronavirus nl63, human/ or coronavirus oc43, human/

21 Coronavirus Infections/
22 coronavir*.tw.
23 exp Influenzavirus a/ or exp influenzavirus b/
24 influenza virus*.tw.
25 influenzavirus*.tw.
26 Adenoviridae/
27 Adenovirus Infections, Human/
28 adenovirus*.tw.
29 or/1-28
30 exp Histamine Antagonists/
31 antihistamin*.tw,nm.
32 h1 receptor antagonist*.tw,nm.
33 loratadine.tw,nm.
34 ceterizine.tw,nm.
35 fexofenadine.tw,nm.
36 benadryl.tw,nm.
37 claritin.tw,nm.
38 zyrtec.tw,nm.
39 triaminic.tw,nm.
40 promethazine.tw,nm.
41 brompheniramine.tw,nm.
42 chlorpheniramine.tw,nm.
43 diphehydramine.tw,nm.
44 hydroxyzine.tw,nm.
45 or/30-44
46 29 and 45

## Appendix 2. Embase search strategy

#38. #34 AND #37
#37. #35 OR #36
#36. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti
#35. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#34. #27 AND #33
#33. #28 OR #29 OR #30 OR #31 OR #32
#32. loratadine:ab,ti OR cetirizine:ab,ti OR fexofenadine:ab,ti AND benadryl:ab,ti OR claritin:ab,ti OR zyrtec:ab,ti OR triaminic:ab,ti OR promethazine:ab,ti OR brompheniramine:ab,ti OR chlorpheniramine:ab,ti OR diphenhydramine:ab,ti OR hydroxyzine:ab,ti
#31. 'h1 receptor antagonist':ab,ti OR 'h1 receptor antagonists':ab,ti
#30. antihistamin*:ab,ti OR 'anti-histamine':ab,ti
#29. (histamin* NEAR/2 antagonist*):ab,ti
#28. 'antihistaminic agent'/de OR 'histamine h1 receptor antagonist'/exp
#27. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#26. adenovirus*:ab,ti
#25. 'human adenovirus'/exp OR 'human adenovirus infection'/de
#24. influenzavirus*:ab,ti OR 'influenza virus':ab,ti OR 'influenza viruses':ab,ti
#23. 'influenza virus a'/exp OR 'influenza virus b'/de OR 'influenza virus'/exp
#22. coronavir*:ab,ti
#21. 'coronavirus'/de OR 'human coronavirus nl63'/de OR 'coronavirus infection'/de
#20. rhinovir*:ab,ti
#19. 'human rhinovirus'/de OR 'rhinovirus infection'/de

#18. nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti
#17. 'rhinopharyngitis'/de
#16. 'upper respiratory tract infection':ab,ti OR 'upper respiratory tract infections':ab,ti OR 'upper respiratory infection':ab,ti OR 'upper respiratory infections':ab,ti OR urti:ab,ti
#15. 'upper respiratory tract infection'/de OR 'viral upper respiratory tract infection'/de
#14. 'head cold':ab,ti OR 'head colds':ab,ti
#13. coryza:ab,ti
#12. rhinorrhea:ab,ti OR rhinorrhoea:ab,ti
#11. 'rhinorrhea'/de
#10. rhinit*:ab,ti
#9. 'rhinitis'/de
#8. sneez*:ab,ti
#7. 'sneezing'/de
#6. ((nasal OR nose*) NEAR/3 (blocked OR blockage OR discharg* OR congest* OR dripping)):ab,ti
#5. ((runny OR running) NEAR/2 nose*):ab,ti
#4. 'nose congestion'/de
#3. 'common cold':ab,ti OR 'common colds':ab,ti
#2. 'common cold symptom'/de
#1. 'common cold'/de

## Appendix 3. CINAHL (Ebsco) search strategy

S46 S36 and S45
S45 S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44
S44 (MH "Quantitative Studies")
S43 (MH "Placebos")
S42 TI placebo* OR AB placebo*
S41 TI random* OR AB random*
S40 TI clinic* trial* OR AB clinic* trial*
S39 TI (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or tripl* mask* or trebl* mask* ) OR AB (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or tripl* mask* or trebl* mask*)
S38 PT clinical trial
S37 (MH "Clinical Trials+")
S36 S29 and S35
S35 S30 or S31 or S32 or S33 or S34
S34 TI (loratadine or cetirizine or fexofenadine or benadryl or claritin or zyrtec or triaminic or promethazine or brompheniramine or chlorpheniramine or diphenhydramine) OR AB (loratadine or cetirizine or fexofenadine or benadryl or claritin or zyrtec or triaminic or promethazine or brompheniramine or chlorpheniramine or diphenhydramine)
S33 TI h1 receptor antagonist* OR AB h1 receptor antagonist*
S32 TI antihistamin* OR AB antihistamin*
S31 TI histamin* N2 antagonist* OR AB histamin* N2 antagonist*
S30 (MH "Histamine Antagonists") OR (MH "Histamine H1 Antagonists")
S29 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28
S28 TI adenovir* OR AB adenovir*
S27 TI (influenzavirus* or influenza virus*) OR AB (influenzavirus* or influenza virus*)
S26 (MH "Influenzavirus B+")
S25 (MH "Influenzavirus A+")
S24 (MH "Coronavirus Infections")
S23 TI coronavir* OR AB coronavir*
S22 (MH "Coronavirus")

S21 TI rhinovir* OR AB rhinovir*
S20 TI (rhinopharyngit* or nasopharyngit*) OR AB (rhinopharyngit* or nasopharyngit*)
S19 TI (upper respiratory tract infection* or upper respiratory infection* or urti) OR AB (upper respiratory tract infection* or upper respiratory infection* or urti)
S18 TI (coryza or head cold*) OR AB (coryza or head cold*)
S17 TI (rhinorrhea or rhinorrhoea) OR AB (rhinorrhea or rhinorrhoea)
S16 TI rhinit* OR AB rhinit*
S15 (MH "Rhinitis")
S14 TI sneez* OR AB sneez*
S13 (MH "Sneezing")
S12 TI nose* N2 drip* OR AB nose* N2 drip*
S11 TI nose* N2 congest* OR AB nose* N2 congest*
S10 TI nose* N2 discharg* OR AB nose* N2 discharg*
S9 TI nose* N2 block* OR AB nose* N2 block*
S8 TI nasal N2 drip* OR AB nasal N2 drip*
S7 TI nasal N2 congest* OR AB nasal N2 congest*
S6 TI nasal N2 discharg* OR AB nasal N2 discharg*
S5 TI nasal N2 block* OR AB nasal N2 block*
S4 TI runn* N2 nose* OR AB runn* N2 nose*
S3 (MH "Nasal Obstruction")
S2 TI common cold* OR AB common cold*
S1 (MH "Common Cold")

## Appendix 4. LILACS (Brieme) search strategy

(mh:"Common Cold" OR "common cold" OR "common colds" OR "Resfriado Común" OR "Resfriado Comum" OR mh:"Nasal Obstruction" OR "Obstrucción Nasal" OR "Obstrução Nasal" OR coryza OR mh:"Respiratory Tract Infections" OR "upper respiratory tract infection" OR "upper respiratory tract infections" OR "upper respiratory infection" OR "upper respiratory infections" OR "Infecciones del Sistema Respiratorio" OR "Infecções Respiratórias" OR mh:c01.539.739* OR mh:c08.730* "Infecciones del Tracto Respiratorio Superior" OR "Infecciones de las Vías Respiratorias Superiores" OR "Infecções do Trato Respiratório Superior" OR "Infecções das Vias Respiratórias Superiores" OR "Infecções do Sistema Respiratório Superior" OR mh:sneezing OR sneez* OR estornudo OR espirro OR sneez* OR mh:rhinitis OR rinitis OR rinite OR rhinorrhea OR rhinorrhoea OR mh:nasopharyngitis OR nasofaringitis OR nasofaringite OR rhinopharyngitis OR nasopharyngitis OR mh:rhinovirus OR rhinovir* OR mh:"Coronavirus Infections" OR "Infecciones por Coronavirus" OR "Infecções por Coronavirus" OR mh:coronavirus OR coronavirus OR mh:"Coronavirus 229E, Human" OR mh:"Coronavirus NL63, Human" OR mh:"Coronavirus OC43, Human" OR mh:"Influenzavirus A" OR mh:b04.820.545.405* OR mh:b04.909.777.545.405* OR mh:"Influenzavirus B" OR mh:b04.820.545.407* OR mh:b04.909.777.545.407* OR influenzavir* OR "influenza virus" OR "influenza viruses" OR adenovir* OR mh:"Adenoviridae Infections" OR mh:"Adenovirus Infections, Human") AND (mh:"Histamine Antagonists" OR "Antagonistas de los Receptores Histamínicos" OR "Antagonistas dos Receptores Histamínicos" OR mh:d27.505.519.625.375.425* OR mh:d27.505.696.577.375.425* OR "h1 receptor antagonists" OR "h1 receptor antagonist" OR loratadine OR cetirizine OR fexofenadine OR benadryl OR claritin OR zyrtec OR triaminic OR promethazine OR brompheniramine OR chlorpheniramine OR diphenhydramine OR hydroxyzine) AND db:("LILACS") AND type of study: ("clinical trials")

## Appendix 5. Biosis Previews (Thomson Reuters) search strategy

| | | |
|---|---|---|
| # 5 | 301 | #4 AND #3<br>*Databases=BIOSIS Previews Timespan=All Years* |
| # 4 | 633,263 | Topic=(random* or placebo* or allocat* or crossover* or "cross over" or ((singl* or doubl*) NEAR/1 blind*)) OR Topic=(title)<br>*Databases=BIOSIS Previews Timespan=All Years* |
| # 3 | 673 | #2 AND #1<br>*Databases=BIOSIS Previews Timespan=All Years* |
| # 2 | 35,541 | Topic=((histamin* NEAR/2 antagonist*) or "h1 receptor" or antihistamin*) OR Topic=(loratadine or cetirizine or fexofenadine or benadryl or claritin or zyrtec or triaminic or promethazine or brompheniramine or chlorpheniramine or diphenhydramine or hydroxyzine)<br>*Databases=BIOSIS Previews Timespan=All Years* |
| # 1 | 112,732 | Topic=("common cold" or "common colds" or (runn* NEAR/2 nose*) OR ((nasal or nose*) NEAR/2 (block* or discharg* or congest* or dripping)) or coryza or "head cold" or "head colds" or "acute rhinitis" or nasopharyngit* or rhinopharyngit* or rhinorrhea or rhinorrhoea or sneez* or "upper respiratory tract infection*" or "upper respiratory infection*" or rhinovir* or coronavir* or adenovir* or influenzavir* or "influenza virus*")<br>*Databases=BIOSIS Previews Timespan=All Years* |

## CONTRIBUTIONS OF AUTHORS

AS updated the review and ADS and MVD completed the final update and edits. All authors contributed to writing the review and commented on the drafts.

## DECLARATIONS OF INTEREST

An IM De Sutter: none known.

Avadhesh Saraswat: none known.

Mieke L van Driel: none known.

## SOURCES OF SUPPORT

### Internal sources

- No source of support, Other.

### External sources

- No source of support, Other.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not assess the completeness of reporting for this version of the review by contacting pharmaceutical companies as planned in the protocol.

Due to the limited number of studies eligible to be entered into a meta-analysis and the low risk of bias of many trials, we did not perform the planned sensitivity analysis to assess the impact of high risk of bias on the outcome of the meta-analysis.

We performed subgroup analysis of sedating and non-sedating antihistamines (where possible).

## INDEX TERMS

### Medical Subject Headings (MeSH)

Common Cold [*drug therapy]; Histamine Antagonists [*therapeutic use]; Randomized Controlled Trials as Topic; Time Factors

### MeSH check words

Adult; Child; Humans