

# Antihistamines for the common cold (Protocol)

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[Intervention Protocol]

## Antihistamines for the common cold

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### ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objectives of this review are to assess:

1. the clinical efficacy of antihistamines in alleviating 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.

## BACKGROUND

### Description of the condition

The common cold is described as “an acute, self-limited 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://ce-preview.bmjknowledge.com/monograph-proof/en-gb/html/252.html>).

The incidence of acute upper respiratory tract infections (URTI), such as the common cold, is difficult to define because of seasonal and location variability. Children younger than one year commonly experience an average of six to eight episodes 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 percent of infected individuals develop a cough, and 20% develop hoarseness, both of which may persist 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 (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 respiratory tract infections (for example, bronchitis, pneumonia) and exacerbations of other respiratory conditions (for example, asthma) (Innes 2006).

### Description of the intervention

H<sub>1</sub>-receptor antagonists are a diverse group of drugs which 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 reactions (a type of allergic reaction, mediated by IgE) along with other chemicals, and acts on the H<sub>1</sub>-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

In this review we will summarise evidence on the efficacy of antihistamines in monotherapy (first-generation and non-sedating) in relieving nasal symptoms of the common cold. As antihistamines are available over the counter in many countries, this review will provide important information for consumers who self treat. In addition, it will assist 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 antihistamines.

## OBJECTIVES

The objectives of this review are to assess:

1. the clinical efficacy of antihistamines in alleviating 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 in monotherapy.

#### Types of participants

Otherwise healthy adults (19 years or older) and children (newborns 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 first-generation or non-sedating) in monotherapy, which is administered either orally or intra-nasally and is compared with a control group. The control group can be either placebo or no treatment. We will also note dosage, frequency of administration, duration of therapy and frequency of assessment.

#### Types of outcome measures

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

#### Search methods for identification of studies

##### Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) latest issue, which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (1950 to present); EMBASE (1974 to present); LILACS (1985 to present) and Biosis Previews (1985 to present).

We will use the following search strategy to search CENTRAL and MEDLINE. We will combine the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (Lefebvre 2011). We will adapt the search strategy to search the other databases.

- 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 drip-ping)).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 rhinorrhea).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 influenza virus a/ or exp influenza virus 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

### Searching other resources

We will search the trials registers. We will also search reference lists of the retrieved articles and contact experts and pharmaceutical companies to find any other potentially relevant published or unpublished data. There will be no language, date or publication restrictions.

## Data collection and analysis

### Selection of studies

Two review authors (AS, MVD) will independently screen the titles and abstracts of citations. We will exclude trials failing to meet the inclusion criteria. We will retrieve articles identified which do not have an abstract or have a limited abstract and assess them for inclusion. A third review author (ADS) will be consulted if disagreements are not resolved by discussion.

### Data extraction and management

Two review authors (AS, MVD) will independently extract data by using a pre-designed data extraction form. We will try to contact trial authors for additional data where necessary. A third review author (ADS) will be consulted if disagreements are not resolved by discussion.

### Assessment of risk of bias in included studies

We will assess 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) will independently assess 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) will be consulted if disagreements are not resolved by discussion. We will report the results in the 'Risk of bias' tables.

### Measures of treatment effect

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

### Unit of analysis issues

We will adjust for clustering if the unit of analysis is not the same as the unit of randomisation, such as is the case for cluster-RCTs,

using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

### Dealing with missing data

We plan to contact trial authors for missing data where possible. Otherwise we will employ intention-to-treat (ITT) analysis, which considers all missing data as treatment failure, when pooling the data. We will compare the results of the ITT analysis with the on-treatment analysis to assess the impact of missing data on the overall outcome.

### Assessment of heterogeneity

We will assess heterogeneity among studies in two ways. First, we will assess heterogeneity at face value by comparing between studies the included population, the interventions and the reported outcomes. Second, we will use the  $I^2$  statistic to assess the presence of statistical heterogeneity (with > 50% as the cut-off value for considerable heterogeneity). We will not pool data if considerable heterogeneity exists at face value. We will use a fixed-effect model for pooling data in the absence of statistical heterogeneity (as described above). We will use a random-effects model whenever statistical heterogeneity is present (Higgins 2011).

### Assessment of reporting biases

We will assess the completeness of reporting of outcomes of each study in order to minimise reporting biases. We will do so by contacting manufacturers to inquire about any unpublished data or studies, if needed. We will also assess any potential conflict of interest of funding and/or authors. We will perform funnel plot analysis to assess potential publication bias if a sufficient number of studies is available (i.e. more than 10).

### Data synthesis

We will include in the meta-analysis the results from studies that meet the inclusion criteria and report any of the selected outcomes. We will summarise data statistically if available, sufficiently similar and of sufficient quality as described in [Measures of treatment effect](#). We will perform statistical analyses according to the statistical guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

### Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis for children compared to adults.

### Sensitivity analysis

We will perform a sensitivity analysis to assess the impact of high risk of bias on the outcome of the meta-analysis by gradually adding studies with a high risk of bias to the pooled studies with low risk of bias.

## ACKNOWLEDGEMENTS

We would like to thank the previous authors (De Sutter AIM, Lemiengre M, Campbell H, Mackinnon HF) of this review for their support and contribution and would like to acknowledge their now withdrawn review ('Antihistamines for the common cold': De Sutter 2003). We would also like to thank Selvakumar DI, Dahiya N, Tambimuttu EG and Gnanasingham AD for their contribution towards the protocol. Finally, we wish to thank the following people for commenting on this draft protocol: Hanan Khalil, Linda Hornbeek, David Rabago, Emin Unuvar, Max Bulsara and Meenu Singh.

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\* Indicates the major publication for the study

**HISTORY**

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**CONTRIBUTIONS OF AUTHORS**

Saraswat A wrote the protocol with assistance provided by van Driel ML and De Sutter A.

**DECLARATIONS OF INTEREST**

None known.