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Oral antihistamine-decongestant-analgesic combinations for the common cold (Review)

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TABLE OF CONTENTS

[Intervention Review]

Oral antihistamine-decongestant-analgesic combinations for the common cold

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ABSTRACT

Background

Although combination formulas containing antihistamines, decongestants and/or analgesics are sold over-the-counter (OTC) in large quantities for the common cold, the evidence of effectiveness is limited.

Objectives

To assess the effectiveness of antihistamine-decongestant-analgesic combinations in reducing the duration and alleviating the symptoms of the common cold in adults and children.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 4), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, OLDMEDLINE (1953 to 1965), MEDLINE (1966 to November Week 3, 2011) and EMBASE (1990 to December 2011).

Selection criteria

Randomised controlled trials (RCTs) investigating the effectiveness of antihistamine-decongestant-analgesic combinations compared with placebo, other active treatment (excluding antibiotics) or no treatment in children and adults with the common cold.

Data collection and analysis

Two review authors independently extracted and summarised data on general recovery, nasal obstruction, rhinorrhoea, sneezing, cough and side effects. We categorised the trials according to the active ingredients.

Main results

We included 27 trials (5117 participants) of common cold treatments. Fourteen trials studied antihistamine-decongestant combinations; two antihistamine-analgesic; six analgesic-decongestant; and five antihistamine-analgesic-decongestant combinations. In 21 trials the control intervention was placebo and in six trials an active substance. Reporting of methods in most trials was poor and there were

large differences in design, participants, interventions and outcomes. Pooling was only possible for a limited number of studies and outcomes.

Antihistamine-decongestant: 12 trials. Eight trials report on global effectiveness, six could be pooled; n = 309 on active treatment, n = 312 placebo) the odds ratio (OR) of treatment failure was 0.27 (95% confidence interval (CI) 0.15 to 0.50); the number needed to treat for an additional beneficial outcome (NNTB) was four (95% CI 3 to 5.6). On the final evaluation day 41% of participants in the placebo group had a favourable response compared to 66% on active treatment. Of the two trials that were not included in the pooling, one showed some global effect, the other showed no effect.

Antihistamine-analgesic: three trials. Two reported on global effectiveness, data from one study was presented. (n = 290 on active treatment, n = 292 ascorbic acid). The OR of treatment failure was 0.33 (95% CI 0.23 to 0.46) and the NNTB was 6.67 (95% CI 4.76 to 12.5). After six days of treatment 43% were cured in the control group and 70% in the active treatment group. The second study also showed an effect in favour of active treatment.

Analgesic-decongestant: six trials. One trial reported on global effectiveness: 73% benefited compared with 52% in the control group (paracetamol) (OR 0.28, 95% CI 0.15 to 0.52).

Antihistamine-analgesic-decongestant: Five trials. Four trials reported on global effectiveness, two could be pooled: global effect reported (less than one severity point on a four or five-point scale) with active treatment (52%) and placebo (34%); the OR of treatment failure was 0.47 (95% CI 0.33 to 0.67) and the NNTB was 5.6 (95% CI 3.8 to 10.2). Two other trials found no beneficial effect. Two other studies did not show any effect.

Two studies with antihistamine-decongestant (113 children) could not be pooled. There was no significant effect of the active treatment.

Adverse effects: the combination of antihistamine-decongestant had more adverse effects than the control intervention but the difference was not significant: 157/810 (19%) versus 60/477 (13%) participants suffered one or more adverse effects (OR 1.58, 95% CI 0.78 to 3.21). Analgesic-decongestant combinations had significantly more adverse effects than control (OR 1.71, 95% CI 1.23 to 2.37); the number needed to treat for an additional harmful outcome (NNTH) was 14. None of the other two combinations caused significantly more adverse effects. Antihistamine-analgesic: 11/90 with combination suffered one or more adverse effects (12%) versus 9/91 (10%) with control (OR 1.27, 95% CI 0.50 to 3.23). Antihistamine-analgesic-decongestant: in one study 5/224 (2%) suffered adverse effects with active treatment versus 9/208 (4%) with placebo. Two other trials reported no differences between treatment groups but numbers were not reported.

Authors' conclusions

Current evidence suggests that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children. These benefits must be weighed against the risk of adverse effects. There is no evidence of effectiveness in young children.

PLAIN LANGUAGE SUMMARY

Oral antihistamine-decongestant-analgesic combinations for the common cold

The common cold is probably the most common illness known and usually presents with a range of symptoms such as sore throat, nasal stuffiness and discharge, sneezing and cough. On average, young children have six to eight colds per year and adults have two to four. It is caused by viruses (more than 200 viruses have been implicated) and is generally not a serious condition which usually resolves by itself within one to two weeks. However, the common cold has a large impact on time lost from work or school and causes substantial discomfort.

As there is no cure for the common cold, only symptomatic treatment is available. Many people use oral over-the-counter (OTC) medications that contain antihistamines, decongestants, analgesics or a combination to self treat the symptoms of the common cold. Our review of 27 trials with over 5000 participants shows some benefit of these treatments in adults and older children with regards to general recovery and symptoms. The combination of antihistamine-decongestant is the most effective combination but many people experience adverse effects such as drowsiness, dry mouth, insomnia and dizziness. There is no evidence for a beneficial effect in young children. The included trials studied very different populations, treatments and outcomes but overall the methodological quality was acceptable.

BACKGROUND

Description of the condition

The common cold is probably the most common illness known. It is a recurrent, acute respiratory tract infection which affects the whole population. On average, young children have six to eight colds per year and adults have two to four (Gwaltney 2002a; Heikkinnen 2003). The occurrence of the common cold is clearly related to the seasons. In temperate regions of the northern hemisphere, the frequency of respiratory infections increases rapidly in the autumn, remains fairly high throughout the winter, and decreases again in the spring. In tropical areas, most colds occur during the rainy season (Heikkinnen 2003).

Although the common cold is not a serious condition, it has a substantial impact on time lost from work and school, general practitioner consultations and money spent on both prescription and over-the counter (OTC) medications. In the US there is a loss of approximately 22 million school days and 20 million work days, as well as 25 million visits to the family physician annually due to the common cold (Heikkinnen 2003; NIAID 2007).

More than 200 different viruses are known to cause the common cold. Rhinovirus is by far the most frequent cause of the common cold (30% to 50%), although a substantial number are caused by coronaviruses (10% to 15%). Respiratory syncytial virus, influenza, parainfluenza and adenovirus have also been implicated (Wat 2004). The relative proportion of the different virus types depends on several factors such as age, season, virus sampling and detection methods. In 20% to 30% of cases no cause can be found. The recent discovery of a new virus in young children indicates that a number of infectious agents causing colds are yet to be identified (Heikkinnen 2003).

Due to the prevalence of rhinovirus, most studies of common colds are based on this virus (Wat 2004). The infection is transmitted to the nasal epithelium by airborne droplets and by hand from fomites. The initial accumulation of rhinovirus in the eyes and nose leads to attachment of the virus to intercellular receptors at the back of the throat. The detailed mechanisms by which viral infection causes changes in the nasal mucosa are still incompletely understood. The absence of epithelial destruction during rhinovirus infections has led to the idea that the clinical symptoms of the common cold might not be caused by a direct cytopathic effect of the viruses but instead are primarily caused by the inflammatory response of the host. There is evidence of increased concentrations of several mediators which affect the vascular tissues of the nasal epithelium causing engorgement and vascular permeability (Gwaltney 2002a; Heikkinnen 2003; Wat 2004).

The symptoms of the common cold arise after an incubation period that can vary considerably between different viruses. The incubation period for a rhinovirus infection is eight to 12 hours (Gwaltney 2002a). Generally symptom severity increases rapidly, peaking within two to three days after infection, and decreasing soon after. The mean duration of the common cold is seven to 10 days, but in a proportion of patients some symptoms can still be present after three weeks. Rhinovirus infections typically start with a 'scratchy' throat, which is soon accompanied by nasal stuffiness and discharge, sneezing and cough. The soreness of the throat usually disappears quickly, whereas the initial watery rhinorrhoea turns thicker and more purulent. The purulence of the nasal discharge is not associated with changes in the nasopharyngeal bacterial flora. Fever is an infrequent finding during rhinovirus infections in adults, but is fairly common in children (Heikkinnen 2003).

Description of the intervention

Since there is no widely available cure or vaccination for the common cold, treatment is focused on alleviating the symptoms. There is limited evidence that first-generation antihistamines have a limited effect on rhinorrhoea and sneezing (De Sutter 2003). Decongestants can reduce nasal blockage and secretion through vasoconstriction of the nasal vessels (Taverner 2007). Analgesics can relieve headache, muscle ache, sore throat or mild fever, and in the case of non-steroidal anti-inflammatory drugs (NSAIDs), may suppress the inflammatory response caused by the viral infection. NSAIDs have been shown to reduce symptoms in rhinovirus infections (Gwaltney 2002b).

How the intervention might work

Combinations of antihistamines, decongestants and analgesics are used to relieve the broad spectrum of common cold symptoms. The evidence of the effectiveness of these combinations in relieving cold symptoms is summarised in this review.

Why it is important to do this review

Although combination formulas containing antihistamines, decongestants and/or analgesics are prescribed or sold OTC in large quantities for the common cold, their effectiveness is not clear. A previous Cochrane Review that is currently being updated reviewed the evidence for effectiveness of antihistamines in monotherapy in treating the common cold (De Sutter 2003). Our Review complements that work by summarising the evidence on effectiveness of a broader range of therapies containing antihistamines in combination with other active agents such as analgesics and/or decongestants.

OBJECTIVES

To assess the effectiveness of antihistamine-decongestant-analgesic combinations compared with placebo or other active controls (excluding antibiotics) in reducing the duration of symptoms and alleviating symptoms (general feeling of illness, nasal congestion, rhinorrhoea, sneezing and cough) in children and adults with the common cold.

To assess the evidence of adverse effects and hence the risk-benefit of these combination medications for the common cold.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing treatment of the common cold with a combination of antihistamine and/or decongestant and/or analgesic versus placebo or other active treatments (excluding antibiotics) in adults and children.

Types of participants

We included otherwise healthy adults and children with common cold symptoms, who met the case definition for inclusion in the review. The case definition of the common cold comprises symptoms of runny and/or stuffy nose and sneezing, with or without symptoms of headache and cough. We excluded participants if they suffered from allergic rhinitis, had concurrent respiratory infections or other chronic diseases, atopic eczema, asthma, fever (> 38 °C), sinusitis, exudative pharyngitis or had symptoms for more than a week. Source populations were volunteers recruited from the community, hospital or community outpatients. We assessed additional evidence from studies of healthy volunteers challenged with rhinovirus in experimental conditions.

Types of interventions

We included combination therapies containing analgesics and/or decongestants and/or antihistamines administered orally. We permitted other active ingredients with the exception of antibiotics. This treatment was compared with a control. The control was either active, placebo or no treatment.

Types of outcome measures

Primary outcomes

1. Global evaluation of effectiveness (complete relief, marked, moderate, slight or no relief at all).
2. Side effects of treatment.

Secondary outcomes

1. Decrease in the amount, or duration, of individual common cold symptoms (sneezing, nasal congestion, rhinorrhoea or cough). These symptoms can be assessed by means of severity scales (absent, mild, moderate, severe) or by global evaluation of effectiveness (complete relief, marked, moderate, slight or no relief at all).
2. Objective assessments such as rhinometry to assess mean nasal airflow, rhinoscopy to assess redness and swelling of nasal mucosa, nasal secretions and nasal obstruction, counts of number of sneezes and weight of nasal secretions.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 4) www.thecochranelibrary.com (accessed 16 December 2011) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, OLDMEDLINE (1953 to 1965), MEDLINE (1966 to November Week 3, 2011) and EMBASE (1990 to December 2011).

We used the terms in Appendix 1 to search MEDLINE and CENTRAL. We combined the MEDLINE search 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 for EMBASE (see Appendix 2).

Searching other resources

We searched reference lists of the retrieved articles and contacted experts and pharmaceutical companies to find any potentially relevant studies. We imposed no language or publication restrictions.

Data collection and analysis

Selection of studies

Two review authors (ADS, AS) independently screened the titles and abstracts of the search results. We excluded trials failing to meet the inclusion criteria. We retrieved and assessed full papers when we identified articles that did not have an abstract.

Data extraction and management

Two review authors (ADS, AS) independently extracted data. Disagreements were resolved by discussion between the two authors. It was not necessary to include a third author as arbiter. We tried to

contact trial authors for additional data where necessary, but were unsuccessful. We independently analysed trials including young children and trials in older children and adults, where applicable. We divided all trials into four categories:

- combination 1: antihistamine and decongestant;
- combination 2: antihistamine and analgesic;
- combination 3: decongestant and analgesic; and
- combination 4: antihistamine and decongestant and analgesic.

We extracted data on six different outcomes (general recovery, nasal obstruction, rhinorrhoea, sneezing, cough and side effects) for each of these intervention groups.

Assessment of risk of bias in included studies

We assessed the risk of bias of the included trials using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two authors (AK, OL with supervision from MVD) independently assessed the risk of bias by assessing random sequence generation, allocation concealment, blinding, selective reporting and other potential sources of bias. We discussed disagreements with the supervisor and resolved them by consensus. The results are reported in the 'Risk of bias' tables in the Characteristics of included studies section.

Measures of treatment effect

There was a wide variation in the ways outcome was presented across the trials. In most of the studies the outcome measures were a global evaluation of effectiveness (for example, complete relief, marked, moderate, slight or no relief at all), or a decrease in the severity of individual common cold symptoms assessed by severity scales or by global evaluation of effectiveness. We did not extract data where individual severity scores were added up and effectiveness was evaluated by comparing these sum scores, because the clinical meaning of sum scores is unclear. We compared the proportion of patients with treatment failure at the end of the treatment to evaluate the global effectiveness. We used odds ratio (OR) of treatment failure with 95% CI to report the effect estimate for dichotomous data. We used mean difference (MD) or standardised mean difference (SMD) with standard deviation (SD) for continuous variables.

Unit of analysis issues

Individual patients were used as the unit of analysis. If the unit of randomisation was not the same as the unit of analysis, such as in cluster-randomised trials, we had planned to apply the correction for clustering as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We attempted to contact the trial authors in order to obtain the necessary data where original data were missing. We used intention-to-treat (ITT) analysis when pooling the available data in case the information was not available or could not be obtained. ITT assumes that all missing data represent unsuccessful outcomes.

Assessment of heterogeneity

We assessed the presence of heterogeneity using a two-stepped approach. First, we assessed heterogeneity between trials at face value (for example, obviously different populations, settings, treatment regimens). We did not pool data if clinical heterogeneity was clearly present. Secondly, we assessed statistical heterogeneity using the Chi^2 test and the I^2 statistic as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This evaluates whether variations in the results of different trials are attributable to chance alone or whether they were the result of differences in trial design. We considered a Chi^2 test result with a $P < 0.10$ and an I^2 statistical result of 50% or higher as indicative of substantial heterogeneity.

Assessment of reporting biases

We aimed to assess risk of publication bias by using funnel plots if 10 or more studies were available for each of the selected outcomes. In the presence of asymmetry we intended to use the 'trim and fill' method to assess the effect of this asymmetry on the conclusions (Higgins 2011).

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 pooled data only if they were available, sufficiently similar and of sufficient quality as described in Measures of treatment effect. We used a random-effects model for meta-analysis in the presence of statistical heterogeneity (Higgins 2011). We used a fixed-effect model in the absence of heterogeneity.

Subgroup analysis and investigation of heterogeneity

We explored the effects of treatments in children versus adults in a subgroup analysis.

Sensitivity analysis

We did not perform sensitivity analysis as insufficient data were available for pooling of treatment effects.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

We excluded the vast majority of studies found by our electronic searches on the basis of title and/or abstract. We retrieved 51 papers for more detailed evaluation, 27 of which met the criteria for inclusion. There was complete agreement between the review authors assessing the papers. In an updated search in December 2011 one potentially relevant additional trial was identified. This study will be assessed for an update of the review once the full paper has been obtained.

Included studies

The trials showed important differences in study participants, interventions, outcomes and designs. In most reports there was inadequate information to allow pooling of data and requests to trial authors for additional data remained unanswered. Therefore, pooling of data was very limited, and consequently we analysed four different treatment combinations in this review. We have summarised available numerical outcomes of the different trials in the Additional tables section.

Details of included population, setting, inclusion and exclusion criteria, intervention and dosage, outcome measures, and main methodological shortcomings ('Risk of bias' assessment) for the individual studies are summarised in the Characteristics of included studies table.

In total, 27 randomised controlled trials (RCTs) were included. The interventions consisted of combinations of antihistamines (azatadine, pyrilamine, clemastine, diphenhydramine, dexchlorpheniramine, doxylamine, brompheniramine, chlorpheniramine, pheniramine, triprolidine, promethazine, loratadine, dexbrompheniramine, carbinoxamine) with decongestants (ephedrine, pseudoephedrine, phenylpropanolamine, 1,2,3,4-tetrahydro-1-naphtyl imidazoline) and/or analgesics (acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) (acetylsalicylic acid, ibuprofen, ketoprofen, naproxen)).

We divided the trials into four treatment groups. The first group consisted of 14 trials evaluating antihistamine-decongestant combinations; in two of these trials active treatment also contained an antitussive. The second group contained two trials, which evaluated antihistamine-analgesic combinations. The third group comprised of six trials studying analgesic-decongestant combinations. Finally, the fourth group of five studies investigated a combination of the three agents. In one study two different combinations were used: analgesic + antihistamine for night time and analgesic + decongestant for day time. We included the day time combination in the analgesic-decongestant group and the night time combination in the antihistamine-analgesic group.

Nineteen trials compared active treatment with placebo. One trial had a cross-over design. Four trials had more than one active treatment arm (one of the components of the combination, a different dosage of the same combination, or a different combination). In four studies the control group took active treatment (paracetamol (two studies); chlorphenindione + phenylpropanolamine + belladonna; diphenhydramine).

The 27 trials involved 5117 participants suffering from a common cold. Most studies involved adult participants. In eight trials children were included: two trials included very young children (from six months to five years); four included children aged 2 to 16, at least four years old, at least six years old, and 6 to 12 years, respectively. One trial included adults and children aged six to 12 years.

The trials took place in different settings: university clinics, paediatric departments, family medicine departments and general practice surgeries. Seven trials were multi centre trials. In two trials the participants were experimentally infected with cold viruses, and in 25 trials the participants had community-acquired colds. In most studies the recruitment of the participants was not clearly defined. In the vast majority of studies the inclusion criterion was the presence of common cold symptoms. There was a lot of diversity between studies. In general a minimal score on a symptom severity scale was required. This score was calculated by adding the individual severity scores of a number of typical common cold symptoms such as headache, sneezing, chills, sore throat, nasal discharge, nasal obstruction, cough and malaise. In two studies the inclusion criterion was the serum neutralising antibody titre (1:2) to the challenge rhinovirus. In one study the inclusion criterion was the presence of cough attributed to an upper respiratory tract infection (URTI). In another study the inclusion criterion was nasal obstruction assessed by rhinomanometry. In yet another study the inclusion criterion was the presence of congestive rhinitis.

In 15 studies respiratory allergy was an explicit exclusion criterion. One study was conducted outside the pollen season and another study excluded patients with recent hay fever. In 10 studies it is unclear whether or not patients with allergies were excluded.

In the majority of studies the duration of symptoms before inclusion was less than 48 hours. In three trials this was up to three days, in two up to five days, and in two (paediatric trials) up to seven days. In the trials dealing with experimental colds, the therapy started 24 and 30 hours after virus challenge. The majority of trials lasted for five days, but this varied from single administration to eight days of treatment. Diaries were usually kept for the duration of treatment. The longest follow-up period was 14 days.

Only three studies reported independent financial support. All others were fully or partly supported by pharmaceutical companies by means of grants, supply of study drugs or other forms of assistance. In nine studies the source of financial support was not clear.

Excluded studies

We excluded 26 papers after detailed assessment. In nine (Axelsson 1971; Connell 1967; Ghorayeb 2006; Kaminszczik 1983; McLaurin 1966; Mora 1993; Nelson 1970; Taborelli 1975; Todd 1984) the inclusion criteria were not in agreement with the protocol; in nine (Bachert 2005; Bonifaci 1977; Carta 1967; Kuspert 1965; Lea 1984; Mariano 2011; Paul 2004; Peter 1972; Sakchainanont 1990) other interventions were studied; in three (Cantekin 1980; Randall 1979; Virtanen 1982) outcome measures were different; and in five (Chung 1991; Lu 1993; Lu 2010; Pasotti 1966; Yong 1991) the design was not in agreement with the protocol.

Risk of bias in included studies

A summary of the 'Risk of bias' assessment is illustrated in Figure 1 and Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

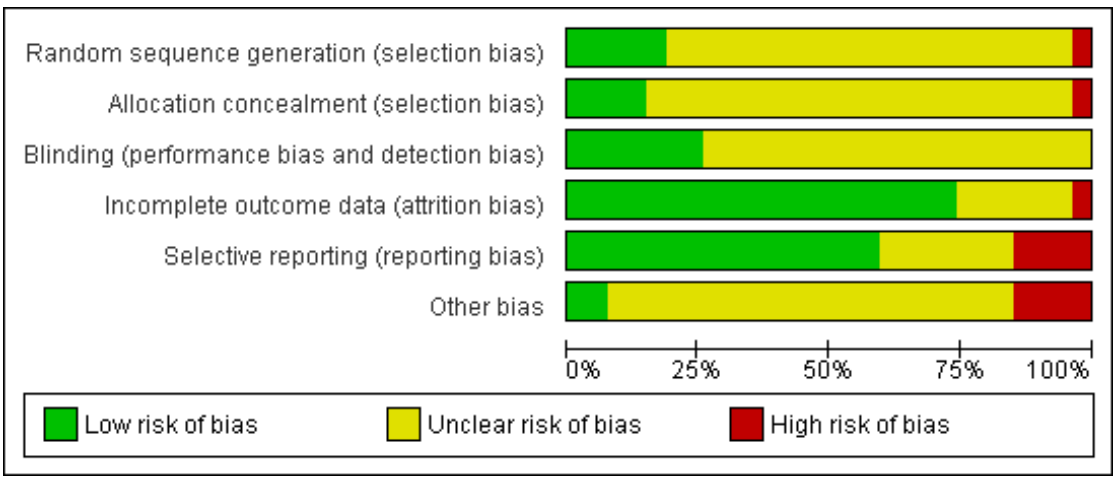
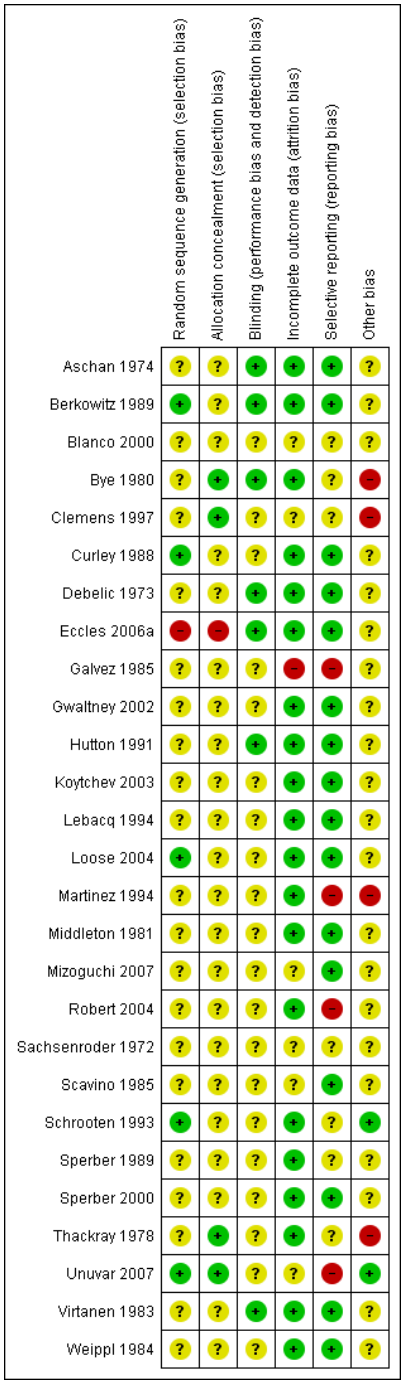


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The method of sequence generation was not described in the majority of studies reviewed. Only a handful (Berkowitz 1989; Curley 1988; Loose 2004; Schrooten 1993; Unuvar 2007) described the sequence generation process, such as the use of a computerised random number generator or envelopes.

There was insufficient information regarding allocation concealment in almost all the studies, with either no description of the method of concealment or insufficient detail provided to allow a definite judgement on how concealment was achieved.

Blinding

Blinding was poorly reported in all the studies. There was insufficient information documented to permit judgement on whether blinding was successful. Blinding of study participants and assessors was not reported in any of the studies with only a few studies stating that their study was double-blinded. Only half of the studies reported that the placebo and active drugs were identical in nature.

Incomplete outcome data

Attrition and exclusion were adequately addressed across most studies. However, the impact of incomplete data is seldom discussed, therefore making interpretation of the results and assessment of their generalisability difficult. Most studies did not carry out intention-to-treat (ITT) analysis for the clinical outcomes, but reported ITT analysis for adverse events.

Selective reporting

Sixteen of the studies documented their study protocol and reported on their prespecified outcomes. Adverse effects were only reported in a small proportion of the studies, some of which failed to clarify if the adverse reactions were seen in the placebo or treatment group(s).

Other potential sources of bias

It was noted that 10 of the studies were either funded by pharmaceutical companies or that the authors of the study were employed by a pharmaceutical company with interests in the trial drug. A majority of studies also failed to document the methods used to recruit participants for their trials, which could introduce selection bias.

Effects of interventions

We included 27 trials involving 5117 participants with the common cold. Fourteen trials studied antihistamine and decongestant combinations (antihistamine-decongestant); two studied antihistamine and analgesic combinations (antihistamine-analgesic); six studied analgesic and decongestant combinations (antihistamine-decongestant); and five studied antihistamine, analgesic and decongestant combinations (antihistamine-decongestant-analgesic). Two trials studied different combinations. The reporting of methods used was poor in most trials and there were large differences in study designs, participants, interventions, control conditions and outcomes.

Overall, most combinations had a significant effect on general recovery in adults and older children. Antihistamine-decongestant odds ratio (OR) of treatment failure was 0.27 (95% confidence interval (CI) 0.15 to 0.50). We could not pool data for other combinations. The combinations containing a decongestant also had some effect on nasal obstruction. Rhinorrhoea and cough improved with antihistamine-decongestant-analgesic, while antihistamine-decongestant combinations may have some effect on severity of sneezing, but not on the first day of treatment. The size of the effect on the specific symptoms, when reported, was less than one severity point on a four- or five-point scale. The combinations containing antihistamine-decongestant and analgesic-decongestant had significantly more adverse effects than placebo. Many different adverse effects are mentioned. There is insufficient evidence for effectiveness in young children.

1. Oral antihistamine-decongestant (AH-D) combinations

A. Oral antihistamine-decongestant combinations in older children and adults

Short description of the studies

Twelve studies evaluated the effectiveness of oral antihistamine-decongestant in combination in adults.

Aschan 1974 studied the effect of promethazine + ephedrine and clemastine + phenylpropanolamine compared to placebo in 60 adult volunteers with nasal blockage due to acute rhinitis. Repeated rhinometric recordings at 30 to 50-minute intervals were performed after one administration of the medication. The recordings took place over a nine-hour period. The effect was evaluated as a positive or negative rhinometric response.

Berkowitz 1989 treated 261 participants with cold-like symptoms with loratadine + pseudoephedrine or placebo. Participants kept a

diary during the five days of treatment and scored daily the overall response and the severity of different symptoms (nasal stuffiness, nasal discharge, sneezing and cough). On day three and five of treatment, the overall response and severity score of the different symptoms were evaluated by the physician.

In the Bye 1980 trial, the effect of triprolidine + pseudoephedrine was studied in 199 cold episodes in adult participants. Some participants were entered several times, having several cold episodes during the course of the study. Participants marked severity of 12 symptoms (for example, runny nose, sneezing, blocked nose, cough) and seven signs (four of which were possible unwanted side effects) on a daily diary card. Treatment was provided for as long as required. An overall assessment was made by the participants eight to 10 days after the start of treatment.

Curley 1988 studied the effect of dexbrompheniramine maleate + pseudoephedrine in comparison with placebo in 86 adults with symptoms of the common cold. Treatment took one week. Symptom severity was scored daily on a five-point scale in a diary kept for 14 days.

Debelic 1973 studied the effect of clemastine + phenylpropanolamine in comparison with belladonna + chlorphenamine + phenylpropanolamine in 40 adult volunteers. There was no placebo or "no treatment" group. The medication was administrated twice daily for eight days. Severity of nasal obstruction, rhinorrhoea (counts of used tissues) and sneezing were assessed daily. The global effectiveness was rated by patients and physicians separately on the last day of treatment.

Galvez 1985 included 60 cold participants aged six years or older. Almost a quarter were lost to follow-up. Active treatment consisted of azatadine + dextromethorphan + pseudoephedrine for five days. Effectiveness was evaluated using a sum score of different symptoms including rhinorrhoea, nasal congestion, cough and sneezing. Individual scores were not provided. Overall therapeutic response was evaluated on day three and five using a five-point scale (exacerbated/poor/fair/good/excellent).

Lebacq 1994 included 36 participants (18 adults and 18 children aged six to 12 years) with acute congestive rhinitis in order to compare the effect of phenylpropanolamine + carbinoxamine and phenylpropanolamine + phenyramine maleate + mepyramine maleate with placebo on bilateral rhinometry results, the subjective evaluation of nasal congestion and the aspect of the nasal mucosa. Participants were kept under standardised circumstances for one day and measurements were performed at different time points after one dose of medication (0.5, 1, 2, 4, 6.5, 11 hours (adults) or 10 hours (children) after medication administration). In the children the treatment was continued over four days and effectiveness of the combination was assessed by the parents. This trial had methodological problems: aetiology of congestive rhinitis and duration of symptoms before the start of treatment are unclear, investigators were not blinded and one of the treatment groups was not masked (combination 2).

Robert 2004 studied the effect of the combination of ebastine + pseudoephedrine compared with placebo in 204 participants with the common cold. The medication was administrated once daily for three days. On the last day a physician evaluated the overall effectiveness, the evolution of the symptoms (runny nose, blocked nose, sneezing), determined nasal peak flow and estimated the likelihood of the patient to take the medication again.

Scavino 1985 (in a trial identical to the trial by Galvez 1985) included 58 participants aged six years or older. Ten were lost to follow-up. Active treatment consisted of azatadine + dextromethorphan + pseudoephedrine. Effectiveness was evaluated in the same way as in the trial of Galvez.

Schrooten 1993 evaluated the effect of a combination of astemizole + pseudoephedrine in comparison with placebo in 83 cold patients aged 12 to 65 years. During seven days of treatment the total nasal symptom severity score (nasal discharge, nasal obstruction, sneezing, postnasal drip), total symptom severity score (nasal symptoms plus coughing, sore throat, headache, myalgia and general discomfort) and side effects were recorded daily by a pharmacist co-investigator. Used nasal tissues were collected and weighed.

Virtanen 1983 studied the effectiveness of dexchlorpheniramine maleate + pseudoephedrine in comparison with placebo in 92 adult volunteers with acute rhinitis. Participants registered the mean severity score of nasal obstruction, secretion, itching and sneezing on a four-point severity scale (absent, mild, moderate, severe) daily for 10 days.

Finally, the Weippl 1984 study included 60 children aged four years and older. Overall therapeutic response of the combination of azatadine maleate + pseudoephedrine + dextromethorphan was compared with an expectorant containing diphenhydramine. The overall therapeutic response and the change in severity score for symptoms of common cold, including rhinorrhoea, nasal congestion, sneezing and cough, were rated by a physician on day three and five of treatment. The time of onset of symptomatic relief was noted.

Results

1. Global effectiveness

Eight trials (Berkowitz 1989; Bye 1980; Debelic 1973; Galvez 1985; Robert 2004; Scavino 1985; Schrooten 1993; Weippl 1984) evaluating 1031 cold episodes assessed the global effectiveness of an oral combination of antihistamine and decongestant on the course of the common cold. Six trials showed some effect.

In the Bye 1980 trial active treatment was significantly more effective for cold symptoms compared to placebo at final evaluation, that is, eight to 10 days after the start of therapy ($P < 0.01$). In the Berkowitz 1989 trial, physicians' scores of overall effectiveness favoured active treatment at both evaluation time points ($P = 0.01$ and $P = 0.02$), but participant diary scores favoured active treatment only on day three ($P = 0.02$). In the Robert 2004 trial the

proportion of patients whom the investigator scored the effectiveness of the treatment received as good or excellent after three days of therapy was significantly higher in the active treatment group (75.8%) than in the placebo group (57.6%; P < 0.001). In the Schrooten 1993 trial the global impression expressed by the patients on day seven was in favour of the combination, with 55% of patients reporting good to excellent results on astemizole-pseudoephedrine versus 35% on placebo (P = 0.013). In the Galvez 1985 trial there was at both evaluation times a significant difference between the total number of participants evaluated by the physician as having a favourable response (fair to excellent), in the active treatment group and in the placebo group (P = 0.014 and P = 0.024). In the Scavino 1985 trial again, at both evaluation times the response was more favourable (fair to excellent) with active treatment compared to placebo (P = 0.010 and P = 0.012). The Debelic 1973 trial comparing two active combinations, showed no difference between the two treatment groups in the number of participants reporting the treatment as good or excellent. In the Weippl 1984 study the overall response was rated at day three and on the final visit (day five) by the physician on a four-point scale. At day three physicians evaluated the response as good or excellent in 83% of the participants in the active treatment group and in 7% of the participants in the control group (P < 0.001). At day five this was 86% and 30% respectively (P < 0.001).

Six studies reported adequate data to include in a meta-analysis (Bye 1980; Galvez 1985; Robert 2004; Scavino 1985; Schrooten 1993; Weippl 1984). The pooled risk ratio of therapy failure at final evaluation was 0.27 (95% CI 0.15 to 0.50) and the number needed to treat to benefit (NNTB) was 4.4. The Berkowitz 1989 trial and the Debelic 1973 trial could not be included in the meta-analysis because numerical data were not reported. However, the results of Berkowitz 1989 were in line with the other trials. Debelic 1973 showed no effect.

Therefore, we can conclude that antihistamine-decongestant combinations have some effect on general recovery compared to placebo treatment.

2. Nasal symptoms and cough

(a) Objective nasal obstruction

Aschan 1974 recorded positive rhinomanometric changes in nasal patency in 24/30 participants after a single dose of active treatment. With placebo there were no positive changes (P < 0.001). In the Lebacq 1994 study phenylpropanolamine + carbinoxamine had some effect on nasal resistance in adult participants 30 minutes to two hours after intake of medication (P < 0.05), but there was no effect in children. The combination of phenylpropanolamine + phenyramine maleate + mepyramine maleate was ineffective. In the Robert 2004 trial participants' peak nasal flow was evaluated before and after three days of treatment. There was no statistically significant difference between active treatment and placebo.

Pooling of results was not possible because different outcome measures were used. Results are presented in Table 1. The two trials showing positive results in objective nasal patency had small sample sizes and took place in an experimental setting (Aschan 1974; Lebacq 1994). One study has serious methodological problems (Lebacq 1994). The third trial took place in a clinical setting and had a much larger sample size (Robert 2004). This trial showed no effect. Therefore, it can be concluded that antihistamine + decongestant combinations probably have no effect on objectively measured nasal patency in clinical circumstances, although there may be some effect in experimental settings.

(b) Subjective severity assessment of nasal obstruction

Seven trials including 677 participants assessed the effect of antihistamine-decongestant combinations on the subjective severity of nasal obstruction (Berkowitz 1989; Bye 1980; Curley 1988; Debelic 1973; Lebacq 1994; Virtanen 1983; Weippl 1984).

In the Lebacq 1994 trial parents assessed severity of nasal congestion in their children. There was no significant difference between treatment groups (P values not mentioned) on any of the four treatment days. Nor was there any significant difference in nasal congestion between the treatment groups in the Virtanen 1982 and Debelic 1973 studies (P values not mentioned).

On the other hand the Bye 1980 trial found significantly less nasal obstruction with active treatment, but only on day one (P value not mentioned).

In the Berkowitz 1989 trial the severity scores for nasal obstruction were significantly lower in the active treatment group from day one to day five (P < 0.05). This was also the case in the Curley 1988 study on days two and three (P < 0.01), four (P < 0.05) and five (P < 0.01).

The Weippl 1984 study showed a significant effect on nasal congestion with active treatment compared with control at both evaluation times (P < 0.001).

We could not pool data from these trials because of differences in outcome measures and lack of adequate data. Results are summarised in Table 1. The trials showing no effect had methodological problems (Lebacq 1994), had a small sample size (Virtanen 1982) or compared two active treatments (Debelic 1973). The trials demonstrating some positive effect are larger and of higher methodological quality. The size of the effect is only reported in the Berkowitz 1989 trial (the difference in mean severity score of nasal congestion between treatment groups being at most 0.3 severity points on a four-point scale). We can conclude that antihistamine + decongestant combinations may have a limited effect on subjective severity of nasal obstruction, but it is not clear whether this is clinically significant.

(c) Effect on results on anterior rhinoscopy

In the Lebacq 1994 trial the condition of the nasal mucosa was assessed at different time points using a four-point scale (normal, red, violet, blue). There was no difference in the aspect of the nasal mucosa between treatment groups (Table 1). In the Berkowitz 1989 study, physicians assessed severity of swelling and hyper-

aemia on day three and five of treatment and found no significant differences.

(d) Rhinorrhoea

Seven trials including 877 cold episodes assessed the effect of an antihistamine-decongestant combination on rhinorrhoea (Berkowitz 1989; Bye 1980; Curley 1988; Debelic 1973; Schrooten 1993; Virtanen 1983; Weippl 1984).

Two trials evaluated rhinorrhoea in an objective way by counting used tissues (Debelic 1973) or by weighing the used tissues (Schrooten 1993). They found no difference between treatment groups.

Five other trials evaluated rhinorrhoea using a subjective severity score. In the Bye 1980 trial no effect of active treatment was noted. In the Berkowitz 1989 trial, severity scores for rhinorrhoea were significantly lower in the active treatment group on day two ($P < 0.05$) and four ($P < 0.05$) but not on days one, three and five. In the Curley 1988 trial this was the case on day two ($P < 0.05$) and three ($P < 0.01$), but not on day one, four and five; and in the Virtanen 1983 trial on day three ($P < 0.05$), but not on the other nine observation days. Finally, in the Weippl 1984 study there was a significant effect on rhinorrhoea with active treatment compared with control at both evaluation times ($P < 0.001$).

Again pooling was not possible. Available results are summarised in Table 1. In only one of the trials with a positive result the size of the effect on nasal discharge was reported: in the Berkowitz 1989 trial the difference in mean severity score between treatment groups is at most 0.3 severity point on a four-point scale. We can conclude that although a small effect on rhinorrhoea on some days of a treatment with a combination of antihistamine + decongestant cannot be excluded, a clinically relevant effect is unlikely.

(e) Sneezing

Sneezing was investigated in five trials including 718 cold episodes (Berkowitz 1989; Bye 1980; Debelic 1973; Virtanen 1983; Weippl 1984). In four trials there is some effect (Berkowitz 1989; Bye 1980; Virtanen 1983; Weippl 1984). In the Berkowitz 1989 trial severity scores for sneezing are significantly lower with active treatment from day two until day five (all $P < 0.05$). In the Bye 1980 trial this was the case on days two, three and four (no P values mentioned) and in the Virtanen 1983 trial on days two to eight (day two: $P < 0.05$; day three: $P < 0.001$; day four $P < 0.01$; day six and seven: $P < 0.01$; and day eight: $P < 0.05$). Weippl 1984 mentions a significant effect on sneezing with active treatment compared with control at both evaluation times ($P < 0.001$). Debelic 1973 compared two active combinations and found no difference.

Pooling of results was not possible. All available data are presented in Table 1. All trials in which this symptom was evaluated found some effect of the active treatment in comparison with placebo. However, in only one trial the size of the effect was reported: in the Berkowitz 1989 trial the difference in mean severity score between treatment groups is at most 0.3 severity point on a four-point scale. We can tentatively conclude that a combination of antihistamine-decongestant has some effect on sneezing, but the effect is small and probably not clinically relevant.

(f) Cough

Four trials including 672 cold episodes evaluated the effect of an antihistamine-decongestant combination on the severity of cough (Berkowitz 1989; Bye 1980; Curley 1988; Weippl 1984). Neither Berkowitz 1989 nor Bye 1980 found any significant difference in severity of cough between the active treatment group and the control group. In the trial of Curley 1988 the mean severity score for cough was significantly less on days three, four and five ($P < 0.05$). In the paediatric trial by Weippl 1984 there was a statistically significant improvement of cough at the interim visit in comparison to control ($P = 0.03$). Pooling was not possible. All available data are represented in Table 1. Results from these four trials are conflicting making it impossible to come to a conclusion about the effectiveness of antihistamine-decongestant combinations on cough.

Adverse effects

In eight trials (Berkowitz 1989; Bye 1980; Debelic 1973; Galvez 1985; Robert 2004; Scavino 1985; Schrooten 1993; Virtanen 1983) including 1149 cold episodes, adverse effects were evaluated. Many different adverse effects were described such as drowsiness, excessive sleepiness, dry mouth, insomnia, dizziness, palpitations, nervousness, headache and gastrointestinal upset.

The numbers of trials mentioning a certain adverse effect are presented in Table 2. Data from different trials are pooled where possible in 'Data and analyses' table Analysis 1.1. Other data are summarised in Table 3.

(a) Total number of patients suffering adverse effects

In the Berkowitz 1989, Bye 1980, Galvez 1985, Robert 2004, Schrooten 1993, Scavino 1985 and Virtanen 1983 trials, the total number of participants with one or more side effect was registered. In total, 842 participants were evaluated for adverse effects: 419 with active treatment, of which 128 or 31% suffered from adverse effects; 423 with placebo, of which 100 or 24% experienced adverse effects (OR 1.58, 95% CI 0.78 to 3.31). In six trials adverse effects were more frequent in the active treatment group. Yet, in the Bye 1980 trial adverse effects were remarkably more frequent in the placebo group causing significant heterogeneity. In the Debelic 1973 trial comparing two active treatments, 19/40 patients suffered adverse effects.

(b) Patients suffering sedation

In the Berkowitz 1989, Robert 2004, Schrooten 1993 and Virtanen 1983 trials, 640 patients were evaluated for sedation (drowsiness, hypersomnia, excessive sleepiness, asthenia) 320 with active treatment, of which 27 or 8% suffered from sedation; and

320 with placebo, of which 17 or 5% suffered from sedation. This difference is not statistically significant (P = 0.25). There is significant heterogeneity between the trials. In the Debelic 1973 trial five participants, all treated with the combination containing belladonna, experienced sleepiness.

(c) Patients suffering dry mouth

In the Berkowitz 1989, Robert 2004, Schrooten 1993 and Virtanen 1983 trials, 713 participants were evaluated for dry mouth: 358 with active treatment, of which 63 or 18% suffered from dry mouth; and 355 with placebo, of which 28 or 8% had dry mouth. This difference is highly statistically significant (P = 0.0001). Likewise, in the Curley 1988 trial an increase in dry mouth on days two to nine with active treatment is mentioned. In the Debelic 1973 trial 11/40 patients suffered from dry mouth.

(d) Patients suffering insomnia

In the trials by Berkowitz 1989 and Schrooten 1993, 344 patients were evaluated for insomnia. Fifteen out of 176 patients from the active treatment group (8.5%) and 5/168 from the placebo group (3%) suffered from insomnia. This difference is statistically significant (P = 0.04). In the Debelic 1973 trial 7/40 patients suffered insomnia.

(e) Patients suffering gastrointestinal upset

In two trials 296 participants were evaluated for gastrointestinal upset (Robert 2004; Virtanen 1983). Six out of 144 participants from the active treatment group (4%) and 2/152 participants from the placebo group (1%) experienced gastrointestinal upset. This difference is not statistically significant (P = 0.91). In the Debelic 1973 trial one participant suffered from nausea, and in the Curley 1988 trial there was no increase in gastrointestinal upset with active treatment.

(f) Patients suffering dizziness

In the trial of Berkowitz 1989, dizziness was evaluated in 261 participants. Five out of 133 patients from the active treatment group (3.8%) and 2/128 from the placebo group (1.6%) suffered from dizziness. This difference is not statistically significant (P = 0.29). In the trial of Curley 1988, an increase in dizziness with active treatment was recorded on days five to seven. In the trial of Debelic 1973, 5/40 participants felt dizzy.

In conclusion, although the total number of adverse effects is not significantly different between antihistamine-decongestant combinations and placebo, dry mouth and insomnia are more frequent with active treatment.

B. Oral antihistamine-decongestant (AH-D) combinations for young children

Two trials evaluated the effect of antihistamine-decongestant combinations in young children (Clemens 1997; Hutton 1991).

Hutton 1991 studied brompheniramine + phenylephrine + phenylpropanolamine in comparison with placebo in 54 children aged six months to five years. Evaluation took place 48 hours after the start of treatment. There was no difference between treatment groups in the number of parents reporting overall improvement (P = 0.74). Congested or runny nose was assessed by the parents by means of a four-point severity scale. There was no difference between the treatment groups in the improvement of symptoms (P = 0.51). Side effects, sleep disturbance, excessive sleepiness and vomiting were also evaluated, but there was no difference between the treatment groups (P > 0.2).

Clemens 1997 included 59 children aged six months to five years in a study comparing brompheniramine + phenylpropanolamine with placebo. Parents were asked to evaluate the cold symptoms two hours after the intake of medication. In total, 175 responses were registered in these 59 children. There was no difference between the treatment groups in the proportion of responses reporting an improvement in runny nose or nasal congestion (P = 0.54 and P = 0.94 respectively). However, children with active treatment were more likely to fall asleep within two hours after the intake (P = 0.01).

In conclusion combinations of antihistamine-decongestant combinations have no effect on common cold symptoms in young children, except maybe increased sleepiness.

2. Oral antihistamine-analgesic (AH-AN) combinations

A. Short description of the studies

Gwaltney 2002 studied the effect of chlorpheniramine + ibuprofen + intranasal interferon and of chlorpheniramine + ibuprofen in comparison with placebo in 150 participants with experimental rhinovirus infection. Participants received treatment for 4.5 days, and effectiveness was evaluated by recording daily subjective severity of nasal symptoms. In this review we considered the comparison between chlorpheniramine + ibuprofen and placebo.

The Koytchev 2003 study included 1167 adult cold patients and assessed the effect of Grippostad®, a combined formulation of acetaminophen + caffeine + chlorpheniramine + ascorbic acid in comparison with two references (chlorpheniramine + ascorbic acid and acetaminophen + caffeine + ascorbic acid) and ascorbic acid. The treatment was given for six days. The participants assessed the severity of their cold symptoms daily, and sum scores were calculated. Data for individual symptoms were not provided. At the end of the treatment period a final global evaluation of effectiveness was made by the patient and the investigator. The proportion of

the participants cured was also assessed. In this review we considered the comparison between Grippostad® and ascorbic acid.
Middleton 1981 evaluated in 191 participants the effectiveness of 'Benylin Day and Night', a combined formulation composed of two different combinations of active substances: Benylin Day (paracetamol + phenylpropanolamine) and Benylin Night (paracetamol + diphenhydramine hydrochloride) in comparison to paracetamol. Participants reported daily during the five days of treatment the severity scores for cold symptoms including runny nose, nasal congestion and cough. On day five a final global evaluation was made by the physicians and by the participants (for day and night separately).

B. Results

Global effectiveness

Two trials evaluating 1358 participants, assessed the global effectiveness of antihistamine + analgesic in the common cold (Koytchev 2003; Middleton 1981).
In the Koytchev 2003 trial, the proportion of participants who were completely cured at the end of the trial with Grippostad® was 70% and with control (ascorbic acid) was 43%. This difference is highly significant (P < 0.0001). In the Middleton 1981 trial overall subjective assessment was measured at the end of the study by asking: "on the whole do you think the tablets have helped you? " Significantly more patients receiving the active night time medication compared with the control group (paracetamol) responded affirmative to the question: 73% versus 52% (P < 0.01).
We did not pool these data because one of the trials used an active control (Koytchev 2003). As both trials had a favourable result we can conclude that antihistamine-analgesic combinations may have a positive effect on subjective general recovery.

Nasal symptoms and cough

Middleton 1981 and Gwaltney 2002 assessed the effect of an antihistamine-analgesic combination on the subjective severity of nasal obstruction, rhinorrhoea and cough. The symptoms were evaluated daily for five days. Both trials failed to show a significant effect of the active treatment compared with placebo or paracetamol on the mean severity scores for nasal obstruction, rhinorrhoea and cough.
Severity of sneezing was studied in the trial of Gwaltney 2002. The baseline adjusted mean severity score was significantly lower with active treatment, but only on the fifth day of therapy.
Pooling of data was not possible. Results are summarised in Table 4. Based on these results we can conclude that a combination of antihistamines and analgesic probably has no effect on nasal symptoms or cough.

C. Adverse effects

All three trials evaluated adverse effects (Gwaltney 2002; Koytchev 2003; Middleton 1981). Many different adverse effects were described: nasal dryness, nasal irritation, blood stained nasal mucus, drowsiness, dry mouth, gastrointestinal upset, loss of appetite, headache, depression and dizziness. Most of the adverse effects were rare and mentioned in only one trial (Table 5; Table 6).

Total number of patients suffering side effects

In the study by Koytchev 2003, 39 out of 1167 participants mentioned a side effect. There were no differences between the different treatment groups. In the trial of Middleton both combinations (day and night) were evaluated together: 11 out of 79 participants taking paracetamol, and nine out of 82 participants taking active treatment mentioned adverse effects (P = 0.57).

Patients suffering drowsiness

In the trial by Gwaltney 2002 five out of 61 participants taking active treatment and zero out of 30 participants taking placebo suffered from drowsiness (P = 0.03). In the trial by Middleton 1981 drowsiness was mentioned by five participants taking paracetamol and by four participants taking the combination therapy (P = 0.68). After pooling, 7% of participants taking the combination therapy and 3% of participants taking placebo or paracetamol suffered from drowsiness. This difference was not significant (P = 0.28).
Other side effects were very rare and there were no differences between treatment groups (Table 6). We can conclude that the combination of antihistamine with analgesics is generally well tolerated.

3. Oral decongestant-analgesic (D-AN) combinations

A. Short description of the studies

The study by Eccles 2006a examined the effectiveness of a combination of pseudoephedrine + paracetamol in comparison to placebo, or pseudoephedrine, or paracetamol in monotherapy (four arms). In total, 305 participants with a natural cold were included. Included participants had symptomatic upper respiratory tract infection with pain of at least moderate intensity and nasal obstruction measurable by rhinomanometry. Effectiveness of treatment on nasal obstruction was assessed during the first four hours after administration of one dose by rhinomanometry, during the next three days of treatment by subjective assessment of nasal congestion, and finally by a global assessment of nasal congestion relief at the follow-up visit after three days of therapy.
Loose 2004 studied the effect of a single-dose acetylsalicylic acid + pseudoephedrine and pseudoephedrine + paracetamol compared

to placebo, in 643 adults with a cold and nasal congestion for five days. Outcomes were the change in nasal congestion score (on an 11-point scale for severity of nasal congestion) and change in the subjective severity of nasal congestion two, four and six hours after the ingestion of the study medication.

Martinez 1994 investigated the effectiveness of naproxen + pseudoephedrine compared to pseudoephedrine and placebo in 65 paediatric participants aged two to 16 years. The treatment was administrated three times daily for five days in different concentrations, depending on the age of the child. The duration of nasal symptoms (nasal oedema and nasal congestion) was evaluated at the end of the study.

The Middleton 1981 study included 191 participants, and studied the effectiveness of 'Benylin Day and Night', a combined formulation composed of two different combinations of active substances: Benylin Day (paracetamol + phenylpropanolamine) and Benylin Night (paracetamol + diphenhydramine hydrochloride) compared to paracetamol. This trial was already described in the previous section. Here we will consider the day combination.

In the Sperber 1989 study, 58 participants developed a cold after experimental virus inoculation. They were kept under observation until six days after inoculation and were treated with a combination of pseudoephedrine + ibuprofen, or pseudoephedrine or placebo. Subjective severity of cold symptoms (runny nose, nasal obstruction, sneezing, cough) were evaluated daily. Rhinorrhoea was further evaluated by weighing used tissues. Nasal congestion was measured by anterior rhinometry. In this review we consider the comparison between pseudoephedrine + ibuprofen and placebo.

In another trial by Sperber 2000 the effectiveness of two doses (the second dose was administrated six hours after the first) of pseudoephedrine + acetaminophen was compared with placebo in 430 adult participants with a natural cold. Participants were evaluated two hours after each administration. Effectiveness of the treatment was measured against the subjective severity of common cold symptoms (nasal obstruction, sneezing, cough, rhinorrhoea) and was assessed using a five-point severity scale.

B. Results

Global effectiveness

Only one trial assessed overall subjective effectiveness at the end of the study by asking "on the whole do you think the tablets have helped you?" (Middleton 1981). Significantly more participants receiving the active day time medication compared with the control group (paracetamol) responded affirmative to the question: 73% versus 52% (RR 0.63, 95% CI 0.48 to 0.83, P < 0.01).

Nasal symptoms and cough

1. Objective nasal obstruction

In the study by Sperber 1989, recipients of the active treatment showed improved nasal patency from the pre-treatment baseline flow rates on day four (P = 0.08) and five (P = 0.06) of treatment. The overall and daily patency tended to be greater in the recipients of pseudoephedrine plus ibuprofen compared to placebo. In the study by Eccles 2006a, the combination treatment was more effective than placebo in increasing nasal airflow conductance (P < 0.001).

2. Subjective severity assessment of nasal obstruction

This symptom was assessed in six trials.

In the trial by Middleton 1981 the severity of nasal obstruction was not significantly different between the treatment group and placebo group. Conversely, in the trial by Martinez 1994, active treatment significantly reduced the duration of nasal congestion.

In the trial by Loose 2004, the differences from baseline of the nasal congestion scores and nasal relief scores were statistically larger (P < 0.05) for all active treatments and at all observation intervals compared to placebo. The peak difference was noted at 120 minutes after dosing. The differences between the different active combinations were not statistically significant.

Sperber 1989 evaluated nasal congestion during five days of therapy on a four-point scale. There was a statistically significant difference in the sum of the day scores between the active treatment (4 +/- 3) and placebo (7 +/- 2, P < 0.05).

In the other trial by Sperber 2000 the mean difference in nasal congestion score at the beginning of the study and after the first and second administration of active medication was evaluated on a five-point scale. Two hours after the first dose there was a statistically significant decrease (P = 0.002) in favour of active treatment. After the second administration the difference was still statistically significant, but smaller (P = 0.03).

In the Eccles 2006a study the sum of nasal congestion differences over three days of treatment was significantly higher with active treatment than with placebo (P = 0.0042) or paracetamol (P = 0.02). The global nasal congestion relief was also greater with active treatment compared to paracetamol or placebo (P = 0.00 4). This was not the case when the combination was compared to pseudo-ephedrine in mono-therapy.

Results of these trials could not be pooled because of differences in outcome measures or lack of adequate data. Results are summarised in Table 7.

From these results we can conclude that decongestant-analgesic combinations are probably effective in alleviating nasal obstruction. In three trials there are some data on the size of the effect: in the trial of Sperber (Sperber 1989) the difference in the sum of the severity scores over five days is three points on a four-point scale. In the second trial of Sperber 2000 the difference is, at most, 1.06 severity points on a five-point scale. In the trial of Eccles 2006a

the mean sum of nasal congestion differences over three days is 0.69 (on a four-point scale) and the difference in global nasal congestion relief is 0.7 (on a five-point scale) .

3. Effect on results on anterior rhinoscopy

In the previously mentioned study of Martinez 1994, the combination significantly reduced the duration of mucosal oedema.

4. Rhinorrhoea

Middleton 1981, Sperber 1989 and Sperber 2000 assessed the effect on the subjective severity of rhinorrhoea. None of these trials showed favourable treatment effect. In the trial of Sperber 1989 there was however a reduction of 30% in nasal mucus weight with active treatment compared with placebo (P = 0.04).
Pooling was not possible. Available data are presented in Table 7. From the above results it can be concluded that decongestant-analgesic combinations are ineffective in subjectively alleviating rhinorrhoea, although there may be an objectively measurable decrease in mucus secretion.

5. Sneezing

Middleton 1981 and Sperber 2000 also assessed the effect of an analgesic-decongestive combination on the subjective severity of sneezing. There was no significant effect. Available data are presented in Table 7.

6. Cough

The same two trials (Middleton 1981; Sperber 2000) also evaluated the effect on cough; there was no effect.

C. Adverse effects

Eccles 2006a, Loose 2004, Middleton 1981, Sperber 1989 and Sperber 2000 evaluated side effects of analgesic-decongestive combinations.
Many different adverse effects were noted, including drowsiness, difficulty sleeping, lethargy, indigestion, nervousness, palpitations, light headiness, nausea, vomiting, dizziness, dry mouth, headache, somnolence, fever, abdominal pain, pharyngitis, loss of appetite, depression, giddiness and diarrhoea.
The number of trials mentioning a particular side effect are presented in Table 8. Data from different trials were pooled where possible in Analysis 3.2, Analysis 3.3, Analysis 3.4, Analysis 3.5 and Analysis 3.6. Other data are summarised in Table 9.

Total number of patients suffering adverse effects

In the five above mentioned trials (Eccles 2006a; Loose 2004; Middleton 1981; Sperber 1989; Sperber 2000), the total number of participants with one or more adverse effects was registered. In total, 1440 participants were evaluated: 162/886 in the active treatment group (18.3%) and 61/554 in the placebo group (11.0%) experienced adverse effects. The OR of a side effect with active treatment is 1.71 (95% CI 1.23 to 2.37). This difference is statistically significant (P = 0.001). The number needed to treat for an additional harmful outcome (NNTH) is 14 (95% CI 9 to 27).

Patients suffering drowsiness, hypersomnia, lethargy, excessive sleepiness

This side effect was reported in four trials including 1287 participants (Loose 2004; Middleton 1981; Sperber 1989; Sperber 2000). In the four trials, 4.4% of participants suffered from sedation with active treatment, 2.7% with control; P = 0.13.

Patients suffering gastrointestinal upset

In the same four trials, 4.1% of participants suffered from some gastrointestinal upset with active treatment, 2.3% with control; P = 0.10.

Patients suffering dizziness

In the four trials (Loose 2004; Middleton 1981; Sperber 1989; Sperber 2000), 3.8% of participants suffered from dizziness when taking active treatment. With control this was 0.8%. This difference is statically significant: P = 0.009. The OR of dizziness with active treatment was 3.49 (95% CI 1.36 to 8.95).

Dry mouth

In three trials dry mouth was noted as a side effect (Eccles 2006a; Middleton 1981; Sperber 2000). It occurred in 2.6% of participants with active treatment and in 1.8% with control; P = 0.49.
In conclusion: adverse effects are, overall, more frequent with a decongestant + analgesic combination than with control treatment. Specifically dizziness is more frequent.

4. Oral antihistamine-decongestant-analgesic (AH-D-AN) combinations

A. Short description of the studies

Blanco 2000 studied a combination of loratadine + pseudoephedrine + acetaminophen in 40 adult participants with a common cold over a five-day period. During the first five hours

after the first administration of treatment, participants were kept under observation. Global assessment of their cold, somnolence and general malaise were observed every 20 minutes. During the next five days the feeling of general malaise and the symptoms of common cold (nasal congestion, rhinorrhoea) were evaluated daily in a diary by the participants and on day three and five by a physician.

Mizoguchi 2007 included 485 adult participants in order to investigate the effectiveness of a single dose of a syrup containing dextromethorphan 15 mg, paracetamol 500 mg, doxylamine 7.5 mg and ephedrine 8 mg administered in the evening. Follow-up data were available for 470 participants. Effectiveness was evaluated by comparing the sum score of different symptoms (nasal congestion, runny nose, cough and pain) and the severity scores of individual symptoms three hours after dosing and within one hour of rising the following morning.

Sachsenroder 1972 studied the effect of cimporhin (tetrahydronaphtylamino imidazolin (a decongestant) + chlorthenoxazin (an anti-inflammatory medication) + chlorphenamine) compared with chlorthenoxazin and with placebo in 165 adult participants suffering rhinorrhoea and flu-like symptoms. The effect on rhinorrhoea was evaluated as "good" or "bad" on day one, two and three of treatment. In this review we considered the comparison between cimporhin and placebo.

Thackray 1978 studied the effect of a combination of doxylamine + ephedrine + paracetamol + dextromethorphan on the night symptoms of the common cold in 70 adult participants. A cross-over design was used. Participants were randomly divided into two groups: the first night one group took the placebo and the other group took the active treatment. At the end of the study, effectiveness was assessed by rating the severity of common cold symptoms including nasal congestion, nasal discharge, sneezing and cough on a six-point scale and by assessing the relief of global cold symptoms. The number of positive ratings after one dose of active or placebo syrup were compared.

Finally, in the study by Unuvar 2007 201 children between 2 and 12 years with an acute respiratory infection were included in order to compare the effect of acetaminophen with diphenhydramine + acetaminophen + pseudoephedrine. Outcome measures were the comparison of the frequency of runny nose, stuffy nose and cough, the comparison of the sum of severity scores (on a four-point scale) of different symptoms and the comparison of clinical recovery ratios on the third and fifth days.

B. Results

Global effectiveness

Four trials including 843 participants assessed the global effectiveness of oral combinations of antihistamine-decongestant-analgesic on the course of the common cold (Blanco 2000; Mizoguchi 2007; Thackray 1978; Unuvar 2007). In two trials the combination showed some effect (Mizoguchi 2007; Thackray 1978).

In the trial by Thackray 1978 the participants received one dose before bedtime and rated their general feeling (useless, almost useless, not very good, good, very good, excellent) in the morning: more participants taking active treatment scored the active syrup as 'good' to 'excellent' compared with the placebo syrup ($P < 0.05$).

In the Mizoguchi 2007 trial overall relief was measured on a five-point severity scale the morning following the night time intake of medication. Severity rating with active treatment was significantly lower than with placebo ($P < 0.0001$). More subjects rated their overall symptom relief during the night as 'good' or 'very good' on rising the following morning (50.2% versus 31.9%).

Two trials showed no effect: in the Blanco 2000 trial, no significant difference was found between treatment groups in the general evolution of the common cold. In the Unuvar 2007 trial, 109 out of 201 included children were evaluated for clinical recovery on day three, and 83 on day five. There was no statistically significant difference in recovery rate.

We pooled data from two trials, Mizoguchi 2007 and Thackray 1978 (Analysis 4.3): significantly more participants evaluated active treatment as beneficial on the morning after an evening dose. Other results are shown in Analysis 4.1, Analysis 4.2 and Table 10.

Nasal symptoms and cough

1. Subjective severity assessment of nasal obstruction

Five trials assessed the effect of the antihistamine-decongestant-analgesic combination on the subjective severity of nasal obstruction and all showed some effect.

In the Blanco 2000 study participants were evaluated on the third and fifth day of treatment using a five-point severity score. In the patients who received active treatment a statistically significant decrease in nasal congestion was observed on the third day of treatment ($P = 0.041$).

In the Thackray 1978 study the participants gave their rating of the effect of the medication on nasal obstruction (useless, almost useless, not very good, good, very good, excellent) in the morning: with active treatment more participants scored the active syrup as good to excellent compared to the placebo syrup ($P < 0.05$).

In the Unuvar 2007 study there was a significant difference in frequency of nasal stuffiness on the fifth day ($P = 0.016$), but not on the third day of therapy. Finally, in the study by Mizoguchi 2007 severity of nasal congestion was evaluated on a five-point scale three hours after intake of medication and the following morning. At both evaluation times severity scores were significantly lower with active treatment ($P = 0.0125$ and $P = 0.0025$)

Pooling of results was not possible. The results are summarised in Table 10. It can be concluded that a combination of decongestant-

antihistamine-analgesic has a favourable effect on nasal obstruction. The size of this effect and its clinical relevance is however not clear. In one trial the effect size was evaluated and the difference in severity score was, at most, 0.29 on a five-point severity scale (Mizoguchi 2007).

2. Effect on results on anterior rhinoscopy

In the Blanco 2000 trial, a favourable effect on oedema of the nasal mucosa was seen on the third treatment day (P = 0.056) (Table 10).

3. Rhinorrhoea

Five trials assessed the effect of an antihistamine-decongestant-analgesic combination on the subjective severity of rhinorrhoea; four showed some effect.

The Blanco 2000 trial found a significantly greater reduction of rhinorrhoea compared with placebo on the third treatment day; in the Thackray 1978 trial more participants evaluated the active syrup as beneficial for rhinorrhoea compared with placebo (P < 0.05); in the trial of Sachsenroder 1972, significantly more participants taking the active treatment rated the effect on rhinorrhoea as "good" compared with placebo treatment (P < 0.0001 on each of the three treatment days. Finally, in the study of Mizoguchi 2007 severity of runny nose was evaluated on a five-point scale three hours after intake of medication and the following morning. At both evaluation times severity scores were significantly lower with active treatment (P = 0.0173 and P = 0.0011).

In contrast, in the trial by Unuvar 2007 there were not significantly more children without rhinorrhoea on day three or five with the combination therapy in comparison with acetaminophen.

Due to differences in outcome measures and lack of adequate data, pooling was not possible. Available results are summarised in Table 10. It can be concluded that a combination containing decongestant-antihistamine-analgesic has a favourable effect on rhinorrhoea in adults. In one trial the effect size can be evaluated (Mizoguchi 2007): difference in severity score was at most 0.33 severity points on a five-point severity scale. In children, however, results are equivocal.

4. Sneezing

Thackray 1978 assessed the effect of an antihistamine-decongestive-analgesic combination on the subjective severity of sneezing. The trial showed no beneficial effect compared with placebo (P = 0.14).

5. Cough

Three trials evaluated the action of an antihistamine-decongestant-analgesic combination on the symptom of cough in the common cold (Mizoguchi 2007; Thackray 1978; Unuvar 2007). Two trials showed some effect (Mizoguchi 2007; Thackray 1978). In the trial by Thackray 1978 there is a statistically significant difference between the number of participants rating the formulation as "good, very good or excellent" on the morning after the dose the night before (P < 0.01). In the study by Mizoguchi 2007 at both evaluation times, severity scores were significantly lower with active treatment (P = 0.0004 and P < 0.0001).

In contrast, the paediatric trial by Unuvar 2007 failed to show any effect on cough.

From these results we can conclude that a combination of antihistamine-decongestant-analgesic may be effective for cough in adults. In one trial the effect size can be evaluated (Mizoguchi 2007): change in severity score was at most 0.42 severity points on a five-point severity scale. In children results are conflicting.

C. Adverse effects

Side effects were reported in four trials and included drowsiness, hypersomnia, insomnia, dizziness, palpitations, giddiness, diarrhoea, headache, abdominal pain and vomiting (Blanco 2000; Mizoguchi 2007; Thackray 1978; Unuvar 2007).

The numbers of trials mentioning a specific side effect are presented in Table 2, Table 5 and Table 8. Data are summarised in Table 11.

Total number of patients suffering adverse effects

In three trials (Mizoguchi 2007; Thackray 1978; Unuvar 2007) the total number of participants with one or more adverse effects was registered. In total, 620 participants were evaluated in these trials: 330 with active treatment and 290 with control. In the trial by Thackray 1978 all patients (70) took active treatment and placebo due to the cross-over design. In one trial no side effects occurred (Unuvar 2007). In the trial by Thackray 1978 19 side effects occurred, of which 11 (16%) could be attributed to the formulations. They were equally distributed between active and control groups. In the trial by Mizoguchi 2007, five (2%) participants taking active medication suffered nine adverse effects and nine (4%) participants taking placebo suffered 10 adverse effects.

Patients suffering drowsiness, somnolence

Thackray 1978, Blanco 2000 and Mizoguchi 2007 looked at the incidence of drowsiness or somnolence. In total 542 participants were included in these three trials: 379 with active treatment, 337 with placebo and 70 who took both placebo and active treatment in a cross-over design. In the trial by Thackray 1978 seven participants felt giddy or drowsy with active treatment and four with placebo. In the trial by Blanco 2000 no more participants

felt sleepy with active treatment compared to placebo. In the Mizoguchi 2007 trial, two patients on active treatment and one participant on placebo suffered from somnolence.

DISCUSSION

Summary of main results

In this review we evaluated the effectiveness of four different combinations of over-the-counter (OTC) treatments for the common cold. All four combinations showed a general benefit in adults and children aged over six years. Where pooling of results was possible we found a number needed to treat to benefit (NNTB) of four (for the combination of antihistamine-decongestant). The combination of antihistamine-analgesic was beneficial in the two trials and the combination of analgesic-decongestant was beneficial in the one trial with data on this outcome. The combination of antihistamine-decongestant-analgesic was more effective than control in two of the four trials, one of which was recent, large and of high methodological quality (Mizoguchi 2007). General improvement is a significant outcome since the literature shows that patients suffering from a common cold find their generalised symptoms and functional impairment more important than specific symptoms (Barret 2005).

All combinations containing decongestants reduced nasal obstruction. Antihistamine-decongestant-analgesic combinations seemed to have some additional effect on cough and rhinorrhoea and antihistamine-decongestant combinations may have some effect on subjective severity of sneezing, but not on the first day of treatment. Yet, when the size of the effect was reported (which was rarely the case), it was invariably small (less that one point on a four- or five-point severity scale).

Adverse effects were not always clearly reported but with the available data we found that adverse effects were usually more frequent with active treatment than with control. Dry mouth and insomnia are more frequent with antihistamine-decongestant and dizziness is more frequent with analgesic-decongestant combinations. The other two combinations, antihistamine-decongestant-analgesic and antihistamine-analgesic, were well tolerated which is rather remarkable as they contain similar products as the two other combinations. It is unclear whether for patients the benefits justify this cost of adverse effects. In a recent study on severity reduction in the common cold Barret 2007 found that a sufficiently important difference meaning "the smallest amount of patient-valued benefit that an intervention would require in order to justify associated costs, risk and other harms" was about 25% for a cheap treatment without adverse effects. The effect found on severity of specific symptoms is much lower than this.

Overall completeness and applicability of evidence

Although the number of studies was small, the majority of the studies included participants suffering from a community-acquired common cold, investigated current combinations of cold medications, and used as outcomes the subjective assessment by the participants. Therefore, the results of this systematic review seem generalisable.

Quality of the evidence

The most striking finding is that in spite of the large number of combination products and formulations on the market and the vast amounts sold, there are only a limited number of studies evaluating their effectiveness, especially in young children. The most studied combination was antihistamines combined with decongestants (eight trials in adults (n = 1091), two in young children (n = 113) and four including older children (n = 214)); the least studied combination was antihistamines with analgesics (three trials in adults (n = 1508)). For analgesics with decongestants we found five trials in adults and one in children (n = 1692), and for the combination of antihistamines with decongestants and analgesics we found four trials in adults and one in children (n = 961). The trials we found differed from each other in every possible aspect: definitions of the common cold, inclusion and exclusion criteria, settings, method of infection (natural (N = 25) or experimental (N = 2)), interventions, control and outcome measures. Pooling of results was very rarely possible and our conclusions are based on a global assessment of the result of each trial (effective/not effective) rather than on numerical data. The overall quality of the included trials was acceptable, although often a clear description of the methods used was missing. In some of the (often older) trials, data required to judge the methodological rigour were not reported at all (mostly information related to the randomisation process). However, the results of these older studies were in line with the more recent higher quality studies and therefore we think that this does not pose a threat to the validity of the meta-analysis.

Potential biases in the review process

Despite our extensive search it is possible that we did not find all relevant trials, because it seems unlikely that so few studies have been performed in view of the vast market for an active preparation. Our results might be over-optimistic and publication bias cannot be excluded.

In most studies it is unclear how the participants were recruited, in other words, it is not clear if the included participants were actively seeking care of their symptoms of the common cold. This may jeopardise the generalisability of the findings. This also raises some ethical issues, as treatments with possible adverse effects may have been given to patients with minor self limiting illnesses.

We have excluded illnesses with a possible bacterial cause or potentially non-self limiting course or conditions which might interfere with the natural course of the common cold (such as allergies). Allergies were also excluded because antihistamines are an effective treatment for them.

We have included studies using active controls because we feel that this makes the review more comprehensive as comparison with an active control allows us to assess the added value of the combination versus a single substance or a current treatment.

As not all studies reported on the occurrence of adverse effects it is possible that the number of adverse effects is underestimated. Some trials evaluated the immediate effect of one dose of active medication; other trials looked at the effectiveness over the duration of the cold. Although these are very different outcomes, both are relevant in view of the goals of the review.

Agreements and disagreements with other studies or reviews

Our results are in line with the results of other reviews. Smith 1993 extensively reviewed the effectiveness of OTC cold medications and concluded that there was very little evidence of effectiveness in young children but that some medications and combinations were effective in adolescents and adults, which is confirmed by our findings. Smith 2008 showed that there was no good evidence of effectiveness of OTC medication for acute cough but that results of studies were conflicting. In our review we found some evidence of effectiveness in cough in adults with the combination of antihistamine-decongestant-analgesic mainly due to the results of one trial not included in the review by Smith (Mizoguchi 2007). Taverner 2007 concluded that a single oral dose of nasal decongestant is modestly effective for short-term relief of congestion in adults and that these medications also provide benefit after regular use over three to five days. This is in accordance with our findings that combinations with decongestants decrease nasal obstruction. A review by Eccles 2006b on the efficacy and safety of OTC analgesics in the treatment of common cold and flu showed that there is little information on the use of analgesics in treating colds. Safety and efficacy data must be related to other pain and fever models. The authors conclude that these medications are effective, which confirms our findings that most combinations showed some general benefit.

As to the possible risks, it has to be noted that in 2005 the Food and Drug Administration (FDA) of the United States issued a warning for OTC nasal preparations containing phenylpropanolamine because of the increased risk of intracranial bleeding (FDA 2005). Moreover, since 2000 the poison-control centres have reported more than 750,000 calls of concern related to cough and cold products. A recent report from the Centres of Disease Control and Prevention identified more than 1500 emergency room visits in 2004 and 2005 for children under two years of age who had been given cough or cold products, and a review by the FDA identified 123 deaths related to the use of such products in children under six years of age over the past few decades (Sharfstein 2007).

AUTHORS' CONCLUSIONS

Implications for practice

The scarce data on the effectiveness of antihistamine-analgesic-decongestant combinations for the common cold shows that there is some general benefit in adults and older children which, however, must be weighed against the risk of adverse events. The effect on individual symptoms is probably too small to be clinically relevant. Combinations containing phenylpropanolamine must be avoided. In young children these combinations should not be used since there is no evidence of effectiveness and they are potentially dangerous. This means that the combinations studied can be used in adults and older children in order to improve general symptoms of the common cold.

Implications for research

Our review shows that there is evidence to support the effectiveness of combinations with antihistamines, decongestants and analgesics compared to placebo. However, it is unclear if the effect is due to the effect of one of the components alone or the combination product. Further trials are needed to explore the added value of combining these individual components in comparison with each in monotherapy. Analgesics and decongestants have some effect in monotherapy (Eccles 2006b; Taverner 2007). Further trials comparing the effectiveness of a single component with a combination may show that the single component is equally effective. Especially, attention should be given to investigating the balance between increased risk of adverse events and clinical benefit. Future studies should report on recruitment of patients, randomisation procedures and include information on the patient perspective. All studies should report patient well-being as the primary outcome, as the benign course of the common cold makes laboratory outcomes or quantification of mucus etc. irrelevant for clinical practice. We do not recommend new studies in small children, given the potentially dangerous adverse effects in children and the benign course of the common cold.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aschan 1974

Methods	RCT, double-blind, placebo-controlled Natural colds 60 patients included 100% follow-up
Participants	Adult volunteers Settings: university department; recruitment: not clear Inclusion: nasal blocking due to acute rhinitis Exclusion: complications (patient with history of pollen allergy not excluded, tests were performed in season without pollen Duration of symptoms before inclusion: 2 to 3 days
Interventions	1. Promethazine chloride 15 mg + ephedrine 10 mg 2. Clemastine 1 mg + phenylpropanolamine 50 mg 3. Clemastine 1 mg + phenylpropanolamine 30 mg 4. Clemastine 1 mg + phenylpropanolamine 50 mg slow release Control: placebo Duration: 1 administration
Outcomes	Rhinomanometric changes in nasal patency (positive or negative changes)
Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	"...the key to each randomisation list was opened and correlated to the rhinomanometric findings only after all had been evaluated"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind investigations were carried out for all drugs tested..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data addressed
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been adequately reported

Aschan 1974 (*Continued*)

Other bias	Unclear risk	Funding source and conflict of interest (COI) not reported

Berkowitz 1989

Methods	RCT, double-blind, placebo-controlled Natural colds 283 patients included 92% follow-up
Participants	Adult volunteers Setting: multi centre; recruitment: not clear Inclusion: moderate rhinorrhoea and stuffiness and a minimum sum score (measured on a 4-point scale for each symptom) of at least 5 for subjective symptoms (nasal discharge, nasal congestion, sneezing, post-nasal drip, cough, earache, sore throat, eye watering/ tearing) and also at least 5 for physical signs (also measured on a 4-point scale for each physical sign: nasal airway patency, eye redness, nasal hyperaemia, rhinorrhoea, mucosal swelling); negative streptococcal screening and pregnancy test Exclusion: presence of fever, exudative tonsillitis, symptoms of allergy, asthma, eczema and sinusitis; use of concomitant medications including steroids, cromolyn, antibiotics or other cold preparations Duration of symptoms before inclusion: at most 48 hours
Interventions	Loratadine 5 mg/ pseudoephedrine 120 mg, 2 x/d Control: placebo Duration: 5 days
Outcomes	1. Overall response according to physician on day 3 and 5 2. Severity score of different signs on day 3 and 5 evaluated by physicians (rhinorrhoea, patency, swelling, cough) 3. Daily overall response score by patients 4. Daily severity score of different symptoms by patients (nasal stuffiness, nasal discharge, sneezing, cough etc) 5. Side effects
Notes	Funding source: not reported, but Claritin-D supplied by Schering-Plough Corporation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were assigned according to a computer-generated randomised schedule ..."
Allocation concealment (selection bias)	Unclear risk	Not reported

Berkowitz 1989 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"This was a double-blind, placebo-controlled, parallel group study..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the total of 283 patients entered into the study, 281 were evaluated for safety (two patients dropped out of the study within hours of beginning the study (reason given)) and 261 for efficacy. Twenty patients were not analysed in the final data due to protocol violations or lost to follow-up (tables show differences between enrolled population and efficacy population)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been adequately reported
Other bias	Unclear risk	Loratadine 5 mg plus pseudoephedrine 120 mg combination used was Claritin-D supplied by Schering-Plough Corporation

Blanco 2000

Methods	RCT, double-blind, placebo-controlled Natural colds 40 patients included 100% follow-up
Participants	Age: 18 to 45 yrs Setting: hospital research centre in Mexico Inclusion: at least 12 on the sum of symptom scores (0 to 3) for rhinorrhoea, nasal congestion, nasal itch, general malaise, odynophagia, headache, conjunctival hyperaemia, lacrimation + at least 5 on the sum of symptom score (0 to 3) for nasal mucosal oedema, retronasal discharge, conjunctival hyperaemia, obstruction of right and left nostrils Exclusion: preceding of present evidence or suffering allergies and/or bacterial infections Duration symptoms before inclusion: 48 hours
Interventions	Loratadine 2.5 mg + pseudoephedrine 60 mg + acetaminophen 500 mg 2 x 2/d for 5 days Control: placebo
Outcomes	1. During 5 hours after the first administration: global assessment of cold, general malaise* 2. Severity assessment by the investigators on a 5-point scale of nasal congestion, rhinorrhoea and general malaise on day 3 and 5 of treatment 3. General evaluation: feeling better or worse 4. Patients' self evaluation of symptoms (anterior rhinorrhoea, nasal congestion, nasal mucosal oedema, obstruction)

Blanco 2000 (*Continued*)

	5. Evaluation of drowsiness
Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The placebo tablets were similar in appearance size and taste to the active tablets and were given with the same timetable. No information on assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No numbers reported, so unclear if all participants were accounted for
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	No information on COI or funding

Bye 1980

Methods	RCT, double-blind, placebo-controlled Natural colds 243 cold episodes 97% follow-up
Participants	Adults Setting: multi centre; recruitment: volunteers of staff of 4 divisions of a pharmaceutical company Inclusion: healthy adults - enrolled before symptoms - developing cold symptoms during study period Exclusion: other medications with possible interference in study, allergic disorders Duration of symptoms before start therapy: on average 20 hours
Interventions	Triprolidine 2.5 mg + pseudoephedrine 60 mg 3 x/day Control: Tripolidine 2.5 mg 3 x/day Placebo Duration of treatment: as long as necessary (maximum 20 tablets or 7 days)

Bye 1980 (*Continued*)

Outcomes	1. Daily scores (4-point scale) of runny nose, sneezing, blocked nose, cough 2. Daily score of 7 possible side effects 3. Overall assessment 8 to 10 days after start of treatment
Notes	Funding source: not reported Unit of analysis is number of colds, not patients (some patients have more than 1 cold entered)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"drugs were allocated from separate randomisation lists for men and women aged below and above 40 years and at each centre (16 lists in all). Balance in numbers was arranged after every eighth person in each list"
Blinding (performance bias and detection bias) All outcomes	Low risk	"...the study is double-blind and the subjects cannot recognise the active drugs from the perception of other, unwanted effects. Table I clearly shows that they did not; more people attributed unwanted effects to placebo than to any of the active drugs." "Drugs were issued to patients in coded bottles containing 20 tablets... All tablets were identical in appearance. All were specially made and differed in appearance from marketed preparations"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Three stopped taking tablets (and completing the diary) because of unwanted effects; two because of excessive drowsiness while taking triprolidine; and 1 because urticaria developed during treatment with pseudoephedrine. No reasons were obtained from the other volunteers who did not complete diaries"
Selective reporting (reporting bias)	Unclear risk	Not clear from methods section
Other bias	High risk	5 of the 7 authors worked for Wellcome (pharmaceutical company that only separated itself from the pharmaceutical indus-

Bye 1980 (*Continued*)

		try in 1995)

Clemens 1997

Methods	RCT, double-blind, placebo-controlled Natural colds 175 "responses" in 59 children Follow-up: unclear
Participants	Age: 6 mo to 5 yrs Setting: 4 private paediatric practices; recruitment: children presenting at these clinics Inclusion: diagnosis of URTI Exclusion: history of asthma or allergies, currently or subsequently taking any prescribed medication Duration of symptoms before therapy: < 7 days
Interventions	Brompheniramine maleate 2 mg/ 5 ml + phenylpropanolamine hydrochloride 12.5 mg/ 5 ml (ADC) Dose: 6 mo to 2 yrs: half a teaspoon, 2 to 5 yrs: 1 teaspoon (as needed, max every 4 hours) Control: placebo
Outcomes	During 48 hours to 2 hours after each intake of medication - registration of: 1. Proportion of patients with improvement on runny nose, nasal congestion, cough* 2. Severity scores of runny nose, nasal congestion, cough*
Notes	Funding source: not reported Unit of analysis is "response" not treated child

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"The child was then randomly assigned in a double-blinded fashion, to receive either the ADC or placebo."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The placebo was formulated to be essentially identical in colour, taste and texture to the ADC." No information on blinding of physicians or assessors

Clemens 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	175 responses recorded for 59 patients - 28 patients (90 responses) received ADC; 31 patients (85 responses) received placebo Attrition/exclusion were not discussed
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were adequately reported No adverse effects reported
Other bias	High risk	"...parents were instructed to give the study medication whenever they thought it was necessary" "With the exception of acetaminophen, not other medication was to be given during the study period." This would introduce the possibility of performance bias

Curley 1988

Methods	RCT, double-blind, placebo-controlled Natural colds 86 patients included 85% follow-up
Participants	Adults > 18 yrs Setting: university hospital, recruitment: unclear - patients kept under observation Inclusion: symptoms and physical signs of nasal passages (e.g. rhinorrhoea, sneezing, nasal obstruction) Exclusion: pregnancy; intake of aspirin, analgesics, antihistamine, decongestants, antibiotics in prior 48 hours; known allergy or vasomotor rhinitis, asthma, eczema, or chronic sinusitis or obstructive pulmonary disease; oral temp > 38 °C; suggestion of allergic or vasomotor rhinitis, sinusitis, pneumonia, acute non respiratory illness, positive throat culture for BHSGA, broncho-provocation consistent with symptomatic asthma Duration of symptoms before inclusion: 12 to 72 hours
Interventions	Dexbrompheniramine maleate 6 mg + pseudoephedrine sulphate 120 mg 2 x/day Control: placebo Duration of treatment: 1 week
Outcomes	1. Daily subjective severity scores of different symptoms (nasal obstruction, nasal discharge, sneezing, cough*) 2. Prevalence of different symptoms 14 days after start treatment (nasal obstruction, nasal discharge, sneezing, cough*)
Notes	Funding source: information about funding not reported
Risk of bias	

Curley 1988 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"With the aid of a computer-generated random number sequence, eligible volunteers were randomised in a double-blind fashion into two treatment groups"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"...identical-appearing placebo..."; double-blinded?
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusion discussed
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been adequately reported
Other bias	Unclear risk	Information on the authors not fully disclosed

Debelic 1973

Methods	RCT, double-blind controlled Natural colds 40 patients included (20 in each group) 90% follow-up
Participants	Adults Setting: hospital, recruitment: unclear Inclusion: symptoms of common cold in early stage Exclusion: vasomotor or allergic rhinitis, rhinitis for more that 48 hours, pathological laboratory results, re-convalescent patients, hypertension, post-myocardial infarction, illnesses requiring chronic treatment Duration of symptoms before inclusion: at most 48 hours
Interventions	Clemastine 1 mg + phenylpropanolamine 50 mg 2 x/day Control: belladonna 0.2 mg, chlorphenamine 4 mg, phenylpropanolamine 50 mg 2 x/day Duration of treatment: 8 days
Outcomes	Daily assessment by the patient of severity of nasal obstruction Daily counts of used tissues Daily assessment by the patient of sneezing Global assessment of efficacy by patient and physician at end of treatment Side effects

Debelic 1973 (*Continued*)

Notes	Funding source: not reported No ITT analysis (only for adverse events)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blinded study; drugs looked alike and were administered 2 x per day for 5 to 8 days; blinding of outcome assessors not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 patients excluded from analysis; 3 because of aggravating symptoms and 1 (control (belladonna/chlorphenamine/phenylpropanolamine) group) due to severe side effect
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	No funding source reported Recruitment of patients: from clinic in Davos (Switzerland), but unclear how recruited

Eccles 2006a

Methods	RCT, double-blinded Natural colds "patients with symptomatic URTI of up to 3 days duration" 384 patients screened; 305 randomised Duration of trial 3 days Outcomes measured after single dose and after multiple doses on day 3
Participants	305 randomised participants Inclusion criteria: nasal congestion (i.e. total nasal airflow resistance of > 0.25 Pa cm^3 as determined by posterior rhinomanometry) and pain of at least moderate intensity at baseline; in general good health and at least 18 years old Exclusion criteria: "history of allergic rhinitis, chronic respiratory disease, anatomical nasal obstruction or deformity, nasal polyps, or a disease which contra-indicated the use of either paracetamol or pseudoephedrine, or patients who had taken certain medications within a given time scale of study entry"

Eccles 2006a (*Continued*)

Interventions	Group 1 (combination): n = 76 Group 2 (paracetamol): n = 76 Group 3 (pseudoephedrine): n = 76 Placebo: n = 77 Initially a single dose administered at the clinic, then as needed at home
Outcomes	Primary: • Nasal airflow conductance • Pain relief of cold and flu like symptoms (composite of sore throat, headache, body aches and pains) was assessed using a 5-point verbal rating scale ('0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete relief') Secondary: • pain intensity (composite of sore throat, headache, body aches and pains) • nasal congestion • global assessment of pain relief and of nasal congestion relief at the follow-up visit
Notes	Funding source: study funded by GlaxoSmithKline (GSK) and 4 authors are employees of GSK Participants were recruited using non-specific advertising campaign for people suffering from 'cold and flu'

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	High risk	Not reported ("...in equal ratio, according to parallel group randomisation schedule")
Blinding (performance bias and detection bias) All outcomes	Low risk	"blinded using double-dummy method"; not described how this was implemented
Incomplete outcome data (attrition bias) All outcomes	Low risk	305 randomised participants No attrition during single-dose phase; 2 participants discontinued multiple-dose phase due to adverse effects (1 each from combination treatment and placebo), not included in the analysis (impact on conclusions are not discussed); high follow-up (only 2/305 not accounted for)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been adequately reported

Eccles 2006a (*Continued*)

Other bias	Unclear risk	Study funded by GSK and 1 author is employee of GSK

Galvez 1985

Methods	RCT, double-blind, placebo-controlled Natural colds 60 patients included 76.6% follow-up on efficacy, 86% for safety evaluation
Participants	6 years or older Setting: not clear, recruitment: not clear Inclusion criteria: a minimum total symptom score of 8 for rhinorrhoea, nasal congestion, cough, sneezing, postnasal drip, lacrimation (scored on 4-point scale); at least mildly severe nasal congestion, rhinorrhoea and cough (score 1 or more for each symptom); and a minimum total sign score of 4 (swelling and hyperaemia of nasopharyngeal mucosa, nasal secretion and obstruction of the left and right nostril, scored on 4-point scale) Exclusion: pregnancy and lactation; known hypersensitive to the study drugs or their respective drug classes; renal, hepatic or serious cardiovascular disease, hypertension, arrhythmias, hyperthyroidism, peptic ulcer, pyloroduodenal obstruction, glaucoma, predisposition for urinary retention, prostatic hypertrophy asthma or a history of asthma, allergic respiratory disease or other serious illness, concomitant pulmonary, nasopharyngeal or sinus bacterial infection, including exudative pharyngitis; purulent nasal secretion, severe sore throat (score > 3) or temperature above 37.8 °C; use of oral corticosteroids within the past 5 days, parenteral corticosteroids within the past 3 weeks, or intranasal corticosteroids within 2 weeks of the trial; use of MAO inhibitors; 12 hours wash out of cold medication, aspirin and antibiotics Duration of symptoms before entry: 24 to 48 hours
Interventions	Intervention: SCH 399 syrup (1 mg azatadine maleate, 60 mg pseudoephedrine sulphate, 20 mg dextromethorphan hydrobromide/5 ml) 1 teaspoon 3 x/day Control: placebo Duration of treatment: 5 days
Outcomes	Sum score at day 3 and 5 of: 1. Overall therapeutic response (proportion of patients with excellent or good response) 2. Symptoms sum scores 3. Side effects
Notes	Funding source: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described

Galvez 1985 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"...in this randomised, double-blind, parallel group study." Method of blinding not discussed
Incomplete outcome data (attrition bias) All outcomes	High risk	"[Patients] lost to the study because of adverse effects, serious illness or concomitant therapy prohibited by the protocol or lost to follow-up, were considered study dropouts." (i.e. no ITT analysis). These patients were not discussed further
Selective reporting (reporting bias)	High risk	"Patients in whom signs and symptoms remained unchanged or were exacerbated by therapy were removed from the study and designated as treatment failures"
Other bias	Unclear risk	The drug studied was SCH 399 (Idulafrin®, Schering, USA)

Gwaltney 2002

Methods	RCT, double-blind, placebo-controlled Experimental colds 150 patients included 100% follow-up
Participants	18 to 51 years Setting: not clear, recruitment: not clear Inclusion criteria: screening serum neutralising antibody titre of <= 2 to type 39 rhinovirus and normal nasal examination results, negative urine pregnancy test in woman Exclusion: cold symptoms 2 weeks before virus challenge; history of allergic rhinitis, bronchial asthma, chronic sinusitis, or chronic lung disease; and allergy to the study medications Treatment started 24 hours after virus challenge
Interventions	lntranasal treatment consisted of lFN (interferon) alpha2b powder (INTRON A) (Scheringl dissolved in PBS containing 0.2% potassium sorbate, 2% glycerin, and 1% human albumin. lntranasal placebo was PBS containing the same ingredients but without IFN Oral medications were commercial ibuprofen (400 rag) and chlorpheniramine maleate (12-rag sustained-release tablets) Chlorpheniramine 12 mg extended release + ibuprofen 400 mg 2 x/day Control: placebo Duration of treatment: 4.5 days

Gwaltney 2002 (*Continued*)

Outcomes	Daily severity scores (5-point scale) of sneezing, runny nose, nasal obstruction, cough* Nasal tissue count Nasal mucus weight Side effects
Notes	Funding source: not reported Declared conflict of interest of authors in the combined treatment used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	"Three groups were randomised in a 2:2: 1 ratio to the following drugs or placebo: intranasal IFN plus oral chlorpheniramine and ibuprofen, intranasal placebo plus oral chlorpheniramine and ibuprofen or intranasal placebo plus oral placebo." No information on concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Oral placebo and active treatment were placed in identical capsules and intranasal treatment and placebo were administered in coarse drops at 0.2 ml per nostril and contained the same ingredients except for IFN in the placebo group Intranasal IFN and placebo was given at 12 h intervals for 3 treatments Oral medication and placebo was given every 12 for 4.5 days No information is provided on blinding of physicians or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study conducted in 2 trials (first trial = 80 participants, second trial = 70 participants) Total of 150 randomised participants challenged with type 39 rhinovirus (full treatment = 59; partial treatment = 61; placebo = 30) Attrition = "1 subject who missed the second oral dose because of malaise and 7 who missed the last oral dose (6 because of drowsiness, 1 because of malaise)"

Gwaltney 2002 (*Continued*)

Selective reporting (reporting bias)	Low risk	Nature of adverse effects and groups they occurred in were reported All prespecified outcomes adequately reported
Other bias	Unclear risk	Information regarding recruitment of participants (possible selection bias) or setting in which trial was conducted was not eluded to

Hutton 1991

Methods	RCT, double-blind, placebo-controlled Natural colds 54 children included 87% follow-up
Participants	Age: children 6 months to 5 yrs Setting: paediatric walk-in clinic and paediatric primary care clinic Inclusion: symptoms of cold and signs of URTI (i.e. nasal congestion and rhinorrhoea) Exclusion: signs or symptoms of a more serious or treatable disease (i.e. temperature > 38.9 °C, vomiting, > 3 loose stools in 24 hours, stridor, wheezing, chest retractions, laboratory tests ordered, antibiotics prescribed); contra-indication to medication (e.g. history of seizures or other neurologic problem) Study carried out in winter period to avoid allergic episodes Duration of symptoms before enrolment: not mentioned
Interventions	Intervention: brompheniramine maleate 4 mg/5 ml + phenylephrine hydrochloride 4 mg/ 5 ml + propanolamine hydrochloride 5 mg/5 ml Dose: calculated by weight to achieve 0.5 to 0.75 mg/kg brompheniramine/day in 3 doses Control: placebo Duration of treatment: 2 days
Outcomes	1. Symptoms severity score change (congested or runny nose, cough*) 2. Number of children (as reported by parents) with overall improvement after 2 days 3. Number of children (as reported by parents) with improvement of congested or runny nose and cough
Notes	Funding source: not reported Duration of symptoms before inclusion not mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described

Hutton 1991 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	"...assign the child randomly to one of three groups: drug, placebo, or no medication." Not discussed
Blinding (performance bias and detection bias) All outcomes	Low risk	"Children randomly assigned to the placebo group received bottles with identical labelling containing placebo prepared by the John Hopkins Hospital Pharmacy" Information regarding blinding of physicians or assessors is not discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusion reported
Selective reporting (reporting bias)	Low risk	"Approximately 20% of the patients in each group reported inappropriately high medicine levels remaining in the bottles, indicating that less than the prescribed amount was given"
Other bias	Unclear risk	Discussion was made about children in the no treatment group receiving other medicines "The outcome measure used was not objective but, rather, depended on parental report of symptoms."

Koytchev 2003

Methods	RCT, double-blind, controlled trial (4 arms) Natural colds 1167 patients tested 97% follow-up
Participants	Age: adults (18 to 70 yrs) Setting: multi centre; recruitment: unclear Inclusion: presence of symptoms of common cold and minimum score of symptoms of 6 points (with a maximum of 12) rated on a 4-point scale before the beginning of treatment. Symptoms rated: headache, throat pain, extremities and joint pain, blocked nose, cough, sleep disturbances) Exclusion: diagnosis of any other infectious disease that produces symptoms of common cold but needed specific treatment with antibacterial or antiviral drugs (e.g. bronchitis, pneumonia, etc.), hypersensitivity to acetaminophen, caffeine, chlorpheniramine hydrogen maleate, ascorbic acid, lactose intolerance, changes in existing concomitant therapy with corticosteroids, or other drug with influence on the immune system any other drug of symptoms of common cold, treatment with any investigational drug within 3 months, legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope and possible consequences of the study, and evidence of an uncooper-

Koytchev 2003 (*Continued*)

	ative attitude Duration of symptoms before treatment: not mentioned
Interventions	Grippostad-C (acetaminophen 200 mg, caffeine 25 mg + chlorpheniramine 2.5 mg + ascorbic acid 150 mg) 3 x 2/day Reference 1: acetaminophen 200 mg + ascorbic acid 150 mg 3 x 2/day Reference 2: chlorpheniramine 2.5 mg + ascorbic acid 150 mg 3 x 2/day Control: ascorbic acid 150 mg 3 x 2/day Duration of treatment/6 days
Outcomes	1. Total score of symptoms rated by the patient on each of the treatment days and a sum of days 2. Sub-score referring to the ratings of headache, throat pain, extremities and joint pain 3. Sub-score referring to the ratings of blocked nose, cough and disturbance of sleeping 4. Percentage of patients cured at the end of the treatment 5. Adverse effects
Notes	Funding source: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	"The patients enrolled were randomly assigned to treatment with 1 or 4 medications at a dose of 3 x 2 capsules a day for 6 days. " No further information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The study does not address this other than stating that "All capsules were identical"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT = 1167 patients (Germany = 182; Poland = 480; Bulgaria = 505) who were allocated into the following groups, varum = 290; placebo/control = 292; reference 1 = 294; reference 2 = 291 1134 participants completed the trial (33 = attrition); 33 participants who did not complete the trial according to protocol, with premature termination from the trial due to adverse events (n = 17), were reported as "deterioration of the disease leading to acute bronchitis or other complications" and withdrawal from the study on patient's request (n = 15). Impact of pre-

Koytchev 2003 (*Continued*)

		mature termination not discussed in study
Selective reporting (reporting bias)	Low risk	"Adverse events in the current trial n=39.. .analysis of adverse events provided no indication of any difference between the 4 treatments administered" All prespecified primary and secondary outcomes have been adequately reported
Other bias	Unclear risk	No information provided as to how patients were recruited for the trial

Lebacq 1994

Methods	RCT, single-blind, placebo-controlled trial (3 arms) Natural colds 36 patients tested 100% follow-up
Participants	Age: adults (25 to 39 yrs) and children (6 to 12 yrs) Setting: hospital, recruitment: unclear; patients are closely followed up during 1 day under standardised circumstances Inclusion: impaired nasal respiration due to acute congestive rhinitis Exclusion: any current disease other than acute congestive rhinitis; insufficiency of any aetiology; drug treatment undertaken within 15 days before the study participation to other clinical trial in the previous 3 months Duration of symptoms before treatment: not mentioned
Interventions	1. Rhinopront (24 mg carbinoxamine + 300 mg phenylpropanolamine/100 g syrup) Adults: 15 g (1 x) ; children 1 g/yr of age 2 x/day) 2. Traminic (tablets: 50 mg phenylpropanolamine hydrochloride, 25 mg pheniramine maleate, 25 mg mepyramine maleate, 10 mg caffeine monohydrate (1 x); drops: 10 mg phenylpropanolamine hydrochloride, 10 mg pheniramine maleate, 10 mg mepyramine maleate/ ml 3 drops/yr of age 3 x/day) Control: placebo Duration: adults: 1 single dose; children: 4 days
Outcomes	1. Nasal resistance at several moments after administration of 1 single dose 2. Clinical score at several moments after administration of 1 dose (nasal congestion, aspect of nasal mucosa) 3. Children: daily nasal congestion severity score during 4 days of treatment 4. Side effects
Notes	Funding source: Pfizer Duration of symptoms before inclusion not mentioned Possible inclusion of allergic patients
Risk of bias	

Lebacq 1994 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	"...each subject was randomly assigned... to receive Rhinopront or placebo...or Triaminic"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"..conducted as a single blind trial with three parallel groups of six patients" "Blinding was imposed to the clinical investigator performing the nasal resistance measurements and the clinical observations" "...measurements and clinical observation were performed by another investigator who was kept unaware of the randomisation scheme" Information on blinding of participants or outcome assessors is not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	36 participants: 18 adults and 18 children (3 parallel groups of: 6 = Rhinopront; 6 = placebo; 6 = Triaminic for adults) "All the patients enrolled in the study completed the treatment"
Selective reporting (reporting bias)	Low risk	"The tolerance was good in each treatment group and no significant adverse events were recorded" The nature of non-significant adverse events was not documented Treatment compliance reported as "100% on day 1 and, 90% on days 2 to 5 in children" All prespecified outcomes have been adequately reported
Other bias	Unclear risk	One of the authors is employed by Pfizer GmbH, who sponsored the study It was unclear how patients were recruited (selection bias)

Loose 2004

Methods	RCT, double-blind, placebo-controlled Natural colds 643 participants included 99.5% follow-up
Participants	Age: adult Setting: bi-central, health centres at university; recruitment: not clear Inclusion: baseline severity score of nasal congestion of at least 6, without spontaneous improvement; the presence of a URTI confirmed by the history of complaints and physical examination Exclusion: use of menthol-containing products in the 2 hours before enrolment; use of local or systemic nasal decongestants, acetylsalicylic acid, paracetamol, ibuprofen or antihistaminic drugs in the 6 h before enrolment; use of long-acting nasal decongestants or NSAIDs in the 12 h before enrolment; use of MAO inhibitors in the 2 weeks before enrolment; the use of any other medications or presence of any other medical condition that might have interfered with the determination of nasal congestion or have compromised the patient's safety Duration of symptoms before inclusion: 5 days
Interventions	Acetylsalicylic acid 1000 mg + pseudoephedrine 60 mg 1 x Acetylsalicylic acid 500 mg + pseudoephedrine 30 mg 1 x Paracetamol 1000 mg + pseudoephedrine 60 mg 1 x Control: placebo Duration: 1 administration
Outcomes	1. Time course of the difference of nasal congestion score from baseline 2. Relief of nasal congestion 3. Adverse effects
Notes	Funding source: not reported, but first author is employee of Bayer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were assigned to two different severity groups according to their baseline score...four separate computer generated randomisation lists ...one for each centre and severity. Study medication was assigned to each patient by giving the patient the next free randomisation number in ascending order"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"All patients were given once the content of four sachets and additionally two capsules", which included one of the 3 treatments or

Loose 2004 (*Continued*)

		placebo No information on blinding of the researchers
Incomplete outcome data (attrition bias) All outcomes	Low risk	645 participants enrolled; ITT population = 643 (ASA 100 mg + PSE 60 mg, N = 161; ASA 500 mg + PSE 30 mg, N = 161, paracetamol 1000 mg + PSE 60 mg, N = 159; placebo, N = 162) Per-protocol population = 609 (3 participants from placebo excluded due to nasal polyps; 3 participants had no data at 0 to 4 h and 0 to 6 h interval (group not specified); 8 participants excluded from 0 to 4 h and 20 patients from 0 to 6 h, "as they took rescue mediation in these intervals" (exact numbers from each group not stated))
Selective reporting (reporting bias)	Low risk	Adverse effects were clearly detailed Both primary and secondary objectives were analysed and reported on An outcome (muscle ache) was reported that was not prespecified
Other bias	Unclear risk	Demographic characteristics of patients is not representative of the general populous, being young university students (selection bias) Author is employee of Bayer

Martinez 1994

Methods	RCT, double-blind, placebo-controlled Natural colds 65 patients included Follow-up 100%
Participants	2 to 16 years Setting: unclear; recruitment: not clear Inclusion criteria: not mentioned Exclusion: bacterial infection or systemic disease Duration of symptoms before inclusion: not mentioned
Interventions	Naproxen sodium + pseudoephedrine 2 to 5 yr: 50 mg naproxen + 15 mg pseudoephedrine every 8 hours 6 to 9 yr: 100 mg naproxen + 30 mg pseudoephedrine every 8 hours 10 to 12 yr: 150 mg naproxen + 45 mg pseudoephedrine every 8 hours Different concentrations, dependent on the age

Martinez 1994 (*Continued*)

	Control: pseudoephedrine syrup (15, 30 or 45 mg) - placebo Duration of treatment: 5 days
Outcomes	1. Number and duration of the symptoms of common cold 2. Adverse effects
Notes	Funding source: not reported Follow-up not mentioned Inclusion criteria not clear Duration of symptoms before inclusion not mentioned Possible inclusion of allergic participants

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"...double-blind clinical trial" Information regarding blinding of patients, physicians or assessors not stipulated (possibility of performance bias)
Incomplete outcome data (attrition bias) All outcomes	Low risk	65 paediatric participants (combination treatment = 20; pseudoephedrine = 15; placebo-combination = 16; placebo-pseudoephedrine = 14) No attrition or exclusion reported 2 to 5 years age group: 5 participants given combination; 1 participant give pseudoephedrine 6 to 9 years age group: 5 participants given combination; 8 participants give pseudoephedrine 10 to 12 years age group: 7 participants given combination; 4 participants give pseudoephedrine 13 to 16 years age group: 3 participants given combination; 3 participants give pseudoephedrine
Selective reporting (reporting bias)	High risk	Not all prespecified outcomes in trial protocol were reported (reporting bias) "No side effects were reported"

Martinez 1994 (*Continued*)

Other bias	High risk	Subject recruitment has not been documented (possibility of selection bias)

Middleton 1981

Methods	RCT, double-blind, controlled Natural colds 191 participants included 92% follow-up
Participants	Age: 18 to 75 yrs Setting: general practice, recruitment: not mentioned Inclusion: symptoms of the common cold or related URTIs Exclusion: pregnancy, hyperthyroidism, hypertension, cardiac dysfunction, diabetes mellitus, hepatic disease, hypersensitivity to any of the trial medications, treatment with MAO inhibitors within 2 weeks Duration of symptoms before inclusion: not specified
Interventions	1. Benylin Day (paracetamol 500 mg + phenylpropanolamine 25 mg) 3 x/day 2. Benylin Night (paracetamol 500 mg + diphenhydramine hydrochloride 25 mg) 1 x/day before sleeping Control: paracetamol 500 mg Duration: 5 days
Outcomes	1. Overall response according to physician on day 5 2. Daily severity score of runny nose, nasal congestion and cough* 3. Assessment of overall response by patients on day 5 4. Side effects
Notes	Funding source: not reported but support from Warner-Lambert Ltd mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	No information provided on allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	All medication was administered 4 times daily over 5 days No reporting of blinding of participants, physicians or outcome assessors

Middleton 1981 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	191 participants admitted to the trial, 95 paracetamol and 96 'Benylin Day and Night' 10 patients did not return their diary cards and were excluded from analysis of the patients with completed cards: 90 paracetamol and 91 'Benylin Day and Night' 6 participants withdrew from the study, 1 stopping treatment for no stated reason, 1 complaining that "the tablets did not help" Remaining 4 patients experienced side effects, 3 of them on paracetamol Impact not discussed in results
Selective reporting (reporting bias)	Low risk	Primary outcome well reported Adverse effects were reported for each group
Other bias	Unclear risk	It was not clear how patients were recruited (selection bias)

Mizoguchi 2007

Methods	RCT, double-blind, placebo-controlled Natural colds 485 participants included 97% follow-up
Participants	Age: 18 to 65 yrs Setting: multi centre across USA - type of centre not specified Inclusion: BMI 30 or less, symptoms of the common cold (present at some point during 24 h before inclusion) moderate or severe nasal congestion, moderate or severe runny nose, at least mild cough, at least mild pain from 1 or more of the following pain symptoms: sore throat, sore chest, headache or body aches/pains: sleep disturbance due to the symptoms Exclusion: known or suspected allergy to any of the study medications, acute symptoms of respiratory allergies, history of chronic aches/pains, chronic fatigue or mood disorders, chronic respiratory illness, or had a significant coexisting illness or medical condition that would compromise their ability to swallow, absorb, metabolise or excrete the study medication. Intake of any medications/supplements within the previous 24 hours for cold symptoms or pain relief or that could produce drowsiness or promote alertness, intake of any antihistamines within the previous 72 hours, of any sedatives within the previous week, of any antidepressants within the previous 3 weeks Duration of symptoms before inclusion: 1 to 5 days
Interventions	Intervention: 1 evening dose of 30 ml containing 15 mg dextromethorphan hydrobromide, 7.5 mg of doxylamine succinate, 600 mg of paracetamol, 8 mg of ephedrine sulphate

	Control: placebo	
Outcomes	Change of severity of nasal congestion, runny nose, cough and pain* rated on a 4-point Likert scale at 3 hours post-dosing and within 1 hour after rising the following morning	
Notes	Funding source: Procter and Gamble ITT described as all participants who dosed and provided at least 1 post-dosing evaluation (inconsistent with standard definition of ITT)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Subjects...were stratified by sex and overall symptom severity at screening and randomised with equal probability (using a block size of 6) to 1 of 2 study product groups". No information on sequence generation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No reporting of blinding of participants, researchers or assessors. However the treatment and placebo was reported to be "identical in appearance"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	485 participants (248 - test group; 237 - placebo group). 15 participants lost to follow-up (no information available). ITT population = 470 (242 - test group; 228 - placebo group) Per-protocol population = 432 (224 - test group; 208 - placebo group) as 38 participants were identified as having major protocol deviations Impact not discussed in results
Selective reporting (reporting bias)	Low risk	Primary outcome well reported Adverse effects reported for each group
Other bias	Unclear risk	The majority of participants were Caucasian (about 80%) All authors but 1 are employed by Procter and Gamble; Study supported by funds from Procter and Gamble

Robert 2004

Methods	RCT, double-blind, placebo-controlled Natural colds 204 patients included 96% follow-up
Participants	Age: 18 to 65 yrs Setting: multi centre (general practice centres), recruitment: not mentioned Diagnosis of common cold; minimum score of 5 and maximum score of 9 for nasal and ocular symptoms (runny nose, blocked nose, tears/itchy eyes, and sneezing/itchy nose); symptoms of runny nose and blocked nose mandatory Exclusion: allergic rhinitis (seasonal or perineal), atopic eczema or asthma; non- allergic rhinitis (vasomotor, drug-related…), influenza, sinusitis, exudative tonsillitis bronchitis, or otitis media; fever; nasal polyps or deviation of the nasal bone; severe chronic illness of any nature; hepatic, renal, cardiac or respiratory impairment; hypersensitivity to the compounds used; fertile woman not using a safe contraceptive method, pregnant or breastfeeding women; previous history of medicine, drug or alcohol abuse; use of compound that could interfere with the study; patients in whom the administration of pseudoephedrine is not advised or is contraindicated (hyperthyroidism, diabetes mellitus, coronary illness, arterial hypertension or prostatic hypertrophy; treatment with other sympathomimetic agents or MAO inhibitors; smokers (> 10 cigarettes/day) Duration of symptoms before inclusion: max 36 hours
Interventions	Intervention: ebastine 10 mg (immediate release) + pseudoephedrine 120 mg (sustained release)/day Control: placebo Duration: 3 days
Outcomes	1. Evaluation of overall efficacy after 3 days of treatment by a physician 2. Evolution of symptoms (runny nose, blocked nose, sneezing*) 4. Disposition of the patient to take the medicine again 5. Variation of nasal peak flow 6. Adverse events
Notes	Funding source: Almirall Prodesfarma, S.A.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly assigned to one of the two possible treatment groups"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Both treatments were administered orally as microgranules as hard gelatin capsules" All medication taken once daily for 3 days No information on blinding of physicians or outcome assessors

Robert 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	204 patients randomised; 8 patients withdrawn: 5 in placebo group and 3 in active treatment group Reasons for withdrawal in placebo group: 3/5 lack of efficacy; 1 violation of protocol; 1 adverse events Reasons for withdrawal in active group: 2 violation of protocol; 1 adverse events Impact not discussed in results, but high follow-up proportion
Selective reporting (reporting bias)	High risk	Primary outcome well reported Secondary outcomes: no numbers provided for nasal peak flow No reporting of the nature of adverse events
Other bias	Unclear risk	It was not clear how patients were recruited (selection bias)

Sachsenroder 1972

Methods	RCT, double-blind, placebo-controlled Natural colds 165 participants included
Participants	Age: adults Setting: unclear Inclusion: rhinorrhoea, cough and signs of flu-like infection Exclusion criteria not mentioned Duration of symptoms before enrolment: 48 hours
Interventions	Z 95 - Rhi (2 mg imidazoline HCl + 6 mg chlorpheniramine maleate + 200 mg chlorthenoxazin) 1 x/day Control: chlorthenoxazin 200 mg Control : placebo Duration: 3 days
Outcomes	Number of patients estimating the effect of the composition as good or bad, on day 1, 2 and 3
Notes	Funding source: unclear, but very likely to be carried out by manufacturer of the studied products Age of patients Flu-like illness = common cold? Setting unclear No exclusion criteria mentioned
Risk of bias	

Sachsenroder 1972 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described, but referred to as "randomised"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blinded, but method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intended outcomes not separately described
Selective reporting (reporting bias)	Unclear risk	Very unclear reporting, no totals reported
Other bias	Unclear risk	Clear explanation of the pharmacological characteristics of the studied drugs and very limited information on the actual trials; report on side effects No information on patient recruitment

Scavino 1985

Methods	RCT, double-blind, placebo-controlled Natural colds 58 patients included 83% follow-up
Participants	Age: 6 yrs or older Setting: university, recruitment: unclear Inclusion: sum of scores on rhinorrhoea, nasal congestion, cough, sneezing, post nasal drip, lacrimation (scale 0 to 3) is minimal 8; rhinorrhoea or nasal obstruction and cough score minimal 2, or rhinorrhoea, cough and nasal obstruction all at least 1 Exclusion: < 6 yrs; pregnancy, lactation, hypersensitivity to study medication; renal, hepatic, cardiovascular disease; hypertension, arrhythmias, hyperthyroidism, peptic ulcers, pyloroduodenal obstruction, glaucoma, predisposition to urinary retention, prostatic hypertrophy, asthma or a history of asthma, allergic respiratory disease or other serious illnesses; concomitant pulmonary, nasopharyngeal or sinus bacterial infection; severe sore throat; exudative pharyngitis, temperature > 37.8 °C; therapy with oral corticosteroids within 5 days, parenteral corticosteroids within 3 weeks, intranasal corticosteroids within 2 weeks of empanelment; treatment with MAO inhibitors or with other medication that might affect the action of study agents Duration of symptoms before inclusion: max 48 hours
Interventions	SCH 339 syrup = azatadine maleate 1 mg, pseudoephedrine sulphate 60 mg, dextromethorphan hydrobromide 20 mg/ 5 cc 3 x/day Control: placebo

Scavino 1985 (*Continued*)

	Duration of therapy: 5 days
Outcomes	Evaluation on day 3 or 4 and 5 or 6 of sum of severity scores for 5 symptoms (rhinorrhoea, nasal congestion, cough, sneezing, postnasal drip, lacrimation, headache, tiredness/drowsiness and general achiness) Global evaluation by physician Side effects
Notes	Funding source: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...randomised... study" Method not discussed
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"...double-blind investigation of SCH 399 syrup and placebo was conducted..." Information regarding blinding of patients, physicians or assessors not stipulated (possibility of performance bias)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Patients who violated protocol were not followed up
Selective reporting (reporting bias)	Low risk	Attrition/exclusions, failures and patients received concomitant therapy were reported
Other bias	Unclear risk	No discussion of how patients were recruited (possible recruitment bias)

Schrooten 1993

Methods	RCT, double-blind, placebo-controlled Natural colds 83 patients included 57% follow-up
Participants	Age: 12 to 65 yrs Setting: community pharmacists. Recruitment: people in the environment of the participating pharmacist Inclusion: symptoms of cold, at least 1 nasal symptom Exclusion: temperature > 39 °C, allergic rhinitis, pregnant or nursing, women without adequate contraception, concomitant treatment with analgesics, antipyretics, corticoids,

Schrooten 1993 (*Continued*)

	sympathomimetics, anticholinergics Duration of symptoms before inclusion: 24 hours or less
Interventions	Astemizole 10 mg + pseudoephedrine 240 mg (controlled release) 1 x/day Control: placebo Duration of treatment: 7 days
Outcomes	Symptom severity score (4-point scale): nasal discharge, nasal obstruction, sneezing, cough, general discomfort) Weight of nasal secretions: weight of used paper tissues General impression Adverse effect
Notes	Funding source: not reported but ethics approval from Janssen Research Foundation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The trial was designed as a double-blind comparison in parallel groups between astemizole-D and placebo. Patients admitted to the study were assigned to one of the two treatment groups according to a computer derived randomisation list"
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The placebo tablets looked identical and had the same taste." Blinding of others not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Sixteen patients were on some kind of concomitant treatment when they were included and during the trial 20 patients committed a protocol violation by taking analgesics, other cough-and-cold preparations or antibiotics". Despite this, they were included in the final findings
Selective reporting (reporting bias)	Unclear risk	Although patients who violated protocol were not considered failures, they were equally spread over both treatment groups All prespecified outcomes reported
Other bias	Low risk	"Authorisation for this trial was obtained from the central ethics committee of the Janssen Research Foundation" However, how patients were recruited to

		study not discussed, possible recruitment bias

Sperber 1989

Methods	RCT, double-blind, placebo-controlled Experimental colds 58 volunteers included 95% follow-up
Participants	Healthy adults Setting: not mentioned; recruitment: not mentioned Inclusion: serum neutralising antibody titre of > 1:2 to the challenge rhinovirus Exclusion: upper respiratory symptoms or fever within week prior to initiation of the study; history of active or chronic sinusitis, asthma or recent hay fever; participants that require use of antihistamines, systemic or topical nasal decongestants, aspirin or other nonsteroidal anti-inflammatory drugs, MAO inhibitors or phenothiazines; participants who had a history of hypersensitivity to aspirin or other anti-inflammatory drugs, pseudoephedrine or other sympathomimetics; pregnant or lactating woman; would be smoking during the study period Treatment initiated 30 hours after virus inoculation
Interventions	Pseudoephedrine hydrochloride 60 mg + ibuprofen 200 mg 1 day: 2 doses; rest of the days: 4 x/day Control: placebo Duration: 5 days
Outcomes	1. Daily evaluation of symptoms severity score (total score, nasal score, etc.) 2. Objective measures including mucus and tissues weight, nasal patency measurements 3. Duration of illness 4. Adverse effects
Notes	Funding source: all medication and placebo supplied by Vicks Research Centre, Shelton, CT

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...[patients] were randomly assigned..." Method not discussed
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo not described. No information on blinding of physicians or assessors "The subjects were isolated in motel rooms for five days beginning 24 hours after rhinovirus challenge..."

Sperber 1989 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusion discussed
Selective reporting (reporting bias)	Unclear risk	"The need for concomitant medications dispensed for cold symptoms was also recorded." This was not discussed further
Other bias	Unclear risk	Method of recruiting patients not discussed

Sperber 2000

Methods	RCT, double-blind, placebo-controlled Natural colds 430 patients included 96% follow-up
Participants	Age: 18 to 65 yrs Setting: multi centre (university clinics), recruitment: not mentioned Inclusion: otherwise healthy with cold symptoms; reported at least moderate symptom severity in response to the question: "Overall, how would you rate the severity of your sinus symptoms?" Absent, mild moderate, moderately severe, severe Exclusion: pregnancy; diastolic pressure > 90 mmHg; underlying illnesses that may be exacerbated by sympathomimetic drugs or that may might affect the assessment of common cold symptoms; receiving drugs that might interact with sympathomimetic drugs Duration of symptoms before inclusion: maximum 48 hours
Interventions	Pseudoephedrine 60 mg + acetaminophen 1000 mg - 2 doses (2nd administered 6 hours after the first) Control: placebo Duration: 8 hours
Outcomes	Evaluation 2 hours after the first dose and 2 hours after the second dose 1. Rating on 5-point scale of efficacy on: nasal obstruction, rhinorrhoea, sneezing cough* 2. Adverse effects
Notes	Funding source: Novartis consumer health

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"..study was a randomised, double-blinded, placebo-controlled clinical trial" Method used to generate allocation sequence not described

Sperber 2000 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"..study subjects were randomly assigned to receive bottles containing either 60 mg of pseudoephedrine plus 100mg of acetaminophen or identically appearing placebo tablets" Blinding of physicians or outcome assessors was not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	430 participants (260 = pseudoephedrine and acetaminophen; 214 = placebo) 18 participants, 10 = pseudoephedrine and acetaminophen and 8 = placebo did not complete the study Active treatment group: 2 withdrew due to adverse effects; 1 was withdrawn due to co-morbidity; 7 were non-compliant with study protocol Placebo group: 8 were non-compliant with study protocol Impact not discussed in results
Selective reporting (reporting bias)	Low risk	51 participants in the active treatment group and 25 participants in the placebo group reported adverse effects Adverse effects were related to the treatment in 41/51 active treatment group participants and 17/25 of the placebo group participants Nature of the adverse effects described
Other bias	Unclear risk	Participants were recruited across the sites, however it has not been stated how this was achieved

Thackray 1978

Methods	RCT, double-blind, placebo-controlled (cross-over) Natural colds 70 patients included 100% follow-up
Participants	Age: 18 to 60 yrs Setting: doctor's surgeries (general practice ?), recruitment: patients seeking help for their cold Inclusion: common cold Exclusion: not mentioned

Thackray 1978 (*Continued*)

	Duration of symptoms before inclusion: not mentioned
Interventions	Active syrup containing: paracetamol 600 mg, dextromethorphan hydrobromide 15 mg, ephedrine sulphate 8 mg, doxylamine succinate 7.5 mg per 30 ml Control: placebo Duration: 1 single dose of 30 ml before bed, evaluation on the next morning
Outcomes	1. Rating on 6-point scale of efficacy of medication on: nasal congestion, nasal discharge, sneezing, cough and generally feeling unwell during the night* 2. Comparison of number of positive rating after 1 dose of active syrup or placebo syrup 3. Side effects
Notes	Funding source: Vick International Division of Richardson-Merrell Ltd

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"Patients were allotted by a random number code to a Treatment Group A or B" "Each (treatment group) was given two bottles... indistinguishable except for the labelling "First Night Medicine" and "Second Night Medicine"""
Blinding (performance bias and detection bias) All outcomes	Unclear risk	""Control" formula was identical but without the active, matched for colour, odour, appearance and taste." Blinding of doctor or outcome assessor not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition or exclusions and all patients followed up on as it was a short 2-day trial
Selective reporting (reporting bias)	Unclear risk	"Only those subjects who had a symptom present on both nights were included in the evaluation of response to therapy for that symptom"
Other bias	High risk	Paper written by the Medical Director of Vick International Division of Richardson-Merrell Ltd. (pharmaceutical company) Inclusion and exclusion criteria not discussed

Unuvar 2007

Methods	RCT, single-blind at inclusion, double-blind at assessment Natural colds 201 participants included 74% follow-up
Participants	Age: 2 to 12 yrs Setting: university hospital, paediatric outpatients department Inclusion: acute respiratory infection with symptoms such as running or stuffy nose, fever and myalgia Exclusion: symptoms for more than 7 days, known chronic disease, use of drugs of the same type as the study drug in the past week, allergy to the medicine, epilepsy, respiratory allergy, cardiac rhythm problem, hypertension, need for hospitalisation Duration of symptoms before inclusion: max 7 days
Interventions	Solution of acetaminophen 120 mg + diphenhydramine 1 mg + pseudoephedrine 15 mg/5 cc. Dose: 10 to 15 mg acetaminophen 4 x/day Control: acetaminophen syrup 120 mg/5 cc. Dose: 10 to 15 mg acetaminophen 4 x/day
Outcomes	Frequency of running nose, cough, nasal stuffiness at day 3 and 5 Clinical recovery ratio at day 3 and 5 Clinical sum scores at day 3 and 5 Complications and side effects
Notes	Funding source: University of Istanbul, Turkey

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation list was acquired from a software and the sequence of the randomisation was prosecuted by using closed envelopes"
Allocation concealment (selection bias)	Low risk	"The case number was shown on the outside of these closed envelopes, and the group number was shown inside...the main researcher was blinded about the group that the next case would belong to"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information regarding the appearance of the two treatments administered by the physician however the assessors were blinded to the group each participant belonged to or the treatment administered Insufficient information regarding blinding of participants

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In Group 1: 16/102 did not return during randomisation. In Group 2: 37/99 did not return during randomisation. Further loss to follow-up of 13 (3 discontinued intervention) in Group 1 and 31 (6 discontinued intervention) in Group 2 respectively. Reasons for discontinuation not discussed
Selective reporting (reporting bias)	High risk	No clinical scores have been reported for the last day of the trial (day 10)
Other bias	Low risk	No problems apparent

Virtanen 1983

Methods	RCT, double-blind, placebo-controlled Natural colds 92 patients included 87% follow-up
Participants	Age: adults, volunteers Setting: university hospital, recruitment: from university population Inclusion: acute rhinitis with common cold Exclusion: fever, allergic manifestations, sinusitis or other disease, use of other cold preparations, steroids, antibiotic during study Duration of cold before enrolment: max 48 hours
Interventions	Slow release dexchlorpheniramine maleate 6 mg, pseudoephedrine sulphate 120 mg 2 x/day Control: placebo Duration of treatment: 5 days
Outcomes	1. Daily score of nose obstruction, secretion, sneezing* 2. Side effects
Notes	Funding source: Medipolar Ltd provided drugs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...patients were randomly allocated to one of two groups" Method not discussed
Allocation concealment (selection bias)	Unclear risk	Not reported

Virtanen 1983 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"The 10 tablets needed for five days treatment were in a numbered package and were identical in appearance." "...and the other, a matching placebo" Although nothing more is written specifically about blinding of patients, researchers and assessors, later in the article, it reads "After analysing the results, it was found that 39 patients had received the drug and 41 patients placebo", implying that there was blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 drop-outs were reported on
Selective reporting (reporting bias)	Low risk	All prespecified outcomes and adverse reactions discussed
Other bias	Unclear risk	Medipolar Ltd was thanked for supplying the drug and placebo. Medipolar is part of the Farmos Group which is a Finnish pharmaceutical company

Weippl 1984

Methods	RCT, double-blind, controlled Natural colds 60 children included 93% follow-up
Participants	Children older than 4 years Setting: university hospital, recruitment: not mentioned Inclusion: upper respiratory symptoms of the common cold and associated cough; at least moderate degree of nasal congestion and/or rhinorrhoea and cough (a rating of 2 or more on each symptom on a 5-point severity scale); ratings of subjective symptoms (all except headache, aching, tiredness/drowsiness and sore throat pain) totaling at least 8; rating for objective signs totaling at least 4; rating of sore throat pain no greater than 3 Exclusion: exudative pharyngitis; allergic respiratory disease; asthma or a history of asthma, pulmonary or nasopharyngeal infection; bacterial sinusitis; renal, hepatic or serious cardiovascular disease; arrhythmias; hyperthyroidism; peptic ulcer; pyloroduodenal obstruction; predisposition for urinary retention; glaucoma, other serious illness; temperature > 37.7 °C; sensitivity to the study drugs or the classes of drugs contained in the study products; patients receiving MAO inhibitors or other medications that might affect the course of study or the action of the test medication; oral corticosteroids within 5 days of the start of the study, or parenteral corticosteroids within 3 weeks, or intranasal corticosteroids within 2 weeks of the start of the study Duration of symptoms before inclusion: at least 24 hours, but not more than 48 hours

Weippl 1984 (*Continued*)

Interventions	1 teaspoon of SCH 399 syrup (azatadine maleate 1 mg , pseudoephedrine sulphate 60 mg, dextromethorphan hydrobromide 20 mg) Control: expectorant containing diphenhydramine Dose: 0.5 teaspoon 3 to 4 x/day Duration: 5 days
Outcomes	1. Overall therapeutic response on day 3 and 5 2. Time of onset of symptomatic relief 3. Side effects
Notes	Funding source: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"A randomised, double-blind design was selected..." Method not discussed
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"A randomised, double-blind design was selected..." Blinding of patients, researchers, assessors not discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patients who completed the study but who violated protocol in some way were excluded from the efficacy analysis. Protocol violations were discussed
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been adequately reported
Other bias	Unclear risk	Method of recruiting patients not discussed

*: In this study more effects on more symptoms were evaluated. The table only mentions outcomes used in the review
x/d: times per day
ASA: acetylsalicylic acid
BHSGA: beta-haemolytic streptococcus group A
BMI: body mass index
COI: conflict of interest
d: day
h: hour
IFN:
INF:

ITT: intention-to-treat
MAO: mono-amine oxidase
mo: months
NSAID: non-steroidal anti-inflammatory drug
PSE: pseudoephedrine
RCT: randomised controlled trial
URTI: upper respiratory tract infection
yr: year

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

Study	Reason for exclusion
Axelsson 1971	Population of participants with vasomotor rhinitis
Bachert 2005	Interventions studied not eligible
Bonifaci 1977	A combination of an analgesic with a NSAID
Cantekin 1980	Only Eustachian tube function evaluated
Carta 1967	Topical medicine used
Chung 1991	Not a RCT
Connell 1967	Population of participants with allergic rhinitis
Ghorayeb 2006	Did not meet inclusion criteria
Kaminszczik 1983	Mixed population of patients with different kinds of rhinitis (common cold, allergy, perennial rhinitis)
Kuspert 1965	Other interventions studied
Lea 1984	Decongestant is phenylpropanolamine, not an antihistamine
Lu 1993	Design does not meet inclusion criteria
Lu 2010	Single-blinded
Mariano 2011	Combination with expectorant, not meeting inclusion criteria
McLaurin 1966	Effects on nasal obstruction Aetiology of nasal obstruction is not clear Common cold not mentioned
Mora 1993	Mixed population of patients with different kinds of rhinitis (common cold, allergy, perennial rhinitis)

(*Continued*)

Nelson 1970	Population of patient with perennial rhinitis
Pasotti 1966	Design does not meet inclusion criteria
Paul 2004	Only mono therapeutic effects of dextromethorphan and diphenhydramine evaluated
Peter 1972	Topical medicine used
Randall 1979	Not looking at symptomatic relief
Sakchainanont 1990	Compares antihistamines only
Taborelli 1975	Mixed population of participants with different kinds of rhinitis
Todd 1984	Patients have purulent nasopharyngitis, not common cold
Virtanen 1982	Only Eustachian tube function evaluated
Yong 1991	Not a RCT

NSAID: non-steroidal anti-inflammatory drug
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Montijo 2011

Methods	Randomised clinical trial, double-blind, placebo-controlled
Participants	100 children < 24 months of any gender, with symptoms associated to common cold
Interventions	Buphenine, aminophenazone and diphenylpyraline hydrochloride versus placebo for 7 days. Both groups received acetaminophen
Outcomes	Change on common cold related symptoms were evaluated
Notes	Spanish paper; to be retrieved from international library

DATA AND ANALYSES

Comparison 1. Combination 1: Antihistamine-decongestant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global evaluation	6	621	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.15, 0.50]
2 Side effects: all - Combination 1: Antihistamine-decongestant	7	842	Odds Ratio (M-H, Random, 95% CI)	1.58 [0.78, 3.21]
3 Side effects: drowsiness, hypersomnia and excessive sleepiness - Combination 1: Antihistamine-decongestant	5	692	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.78, 2.64]
4 Side effects: dry mouth - Combination 1: Antihistamine-decongestant	4	640	Odds Ratio (M-H, Fixed, 95% CI)	3.77 [1.75, 8.14]
5 Side effects: insomnia	2	344	Odds Ratio (M-H, Fixed, 95% CI)	3.02 [1.08, 8.47]
6 Side effects: gastro-intestinal upset - Combination 1: Antihistamine + analgesic	2	296	Odds Ratio (M-H, Fixed, 95% CI)	2.82 [0.64, 12.34]

Comparison 2. Combination 2: Antihistamine-analgesic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global evaluation: Koychev 2003	1	582	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.23, 0.46]
2 Global evaluation: Middleton 1981 night	1	181	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.18, 0.70]
3 Side effects: drowsiness, hypersomnia and excessive sleepiness - Combination 2 : Antihistamine-analgesic	2	272	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [0.59, 6.07]
4 Side effects: all - Combination 2: Antihistamine-analgesic	1	181	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.50, 3.23]

Comparison 3. Combination 3: Analgesic-decongestants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global evaluation	1	181	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.15, 0.52]
2 Side effects: drowsiness, hypersomnia, lethargy and excessive sleepiness - Combination 3: Analgesic-decongestant	4	1287	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [0.86, 3.19]
3 Side effects: dry mouth - Combination 3: Analgesic-decongestant	3	764	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.54, 3.62]
4 Side effects: gastrointestinal side effects Combination 3: Analgesic-decongestant	4	1287	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.89, 3.71]
5 Side effects: dizziness, light headedness - Combination 3: Analgesic-decongestant	4	1287	Odds Ratio (M-H, Fixed, 95% CI)	3.59 [1.37, 9.43]
6 Side effects: all - Combination 3: Analgesic-decongestant	5	1440	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [1.23, 2.37]

Comparison 4. Combination 4: Antihistamine-analgesic-decongestant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global evaluation: after 3 days of treatment - Combination 4: Antihistamine-analgesic-decongestant	1	109	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.31]
2 Global evaluation: after 5 days of treatment	1	83	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.49, 2.77]
3 Global evaluation: on the morning after evening dosing	2	548	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.33, 0.67]

Analysis 1.1. Comparison 1 Combination 1: Antihistamine-decongestant, Outcome 1 Global evaluation.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 1 Combination 1: Antihistamine-decongestant

Outcome: 1 Global evaluation

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Bye 1980	34/61	49/63		21.9 %	0.36 [0.16, 0.78]
Galvez 1985	2/22	9/24		9.4 %	0.17 [0.03, 0.89]
Robert 2004	26/100	43/104		25.9 %	0.50 [0.28, 0.90]
Scavino 1985	0/25	7/23		3.8 %	0.04 [0.00, 0.81]
Schrooten 1993	19/43	26/40		19.8 %	0.43 [0.18, 1.03]
Weippl 1984	23/58	50/58		19.3 %	0.11 [0.04, 0.26]
Total (95% CI)	**309**	**312**		**100.0 %**	**0.27 [0.15, 0.50]**

Total events: 104 (Treatment), 184 (Control)

Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 10.80$, df = 5 (P = 0.06); $I^2 = 54\%$

Test for overall effect: Z = 4.21 (P = 0.000025)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Combination 1: Antihistamine-decongestant, Outcome 2 Side effects: all - Combination 1: Antihistamine-decongestant.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 1 Combination 1: Antihistamine-decongestant

Outcome: 2 Side effects: all - Combination 1: Antihistamine-decongestant

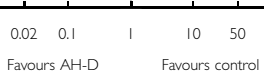
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Berkowitz 1989	42/133	29/128		20.8 %	1.58 [0.91, 2.74]
Bye 1980	6/48	19/53		15.9 %	0.26 [0.09, 0.71]
Galvez 1985	4/25	0/27		4.5 %	11.51 [0.59, 225.67]
Robert 2004	25/100	25/104		20.0 %	1.05 [0.56, 1.99]
Scavino 1985	3/26	0/23		4.4 %	7.00 [0.34, 143.13]
Schrooten 1993	23/43	8/40		16.4 %	4.60 [1.73, 12.25]
Virtanen 1983	25/44	19/48		17.9 %	2.01 [0.87, 4.61]
Total (95% CI)	**419**	**423**		**100.0 %**	**1.58 [0.78, 3.21]**

Total events: 128 (Treatment), 100 (Control)

Heterogeneity: $Tau^2 = 0.54$; $Chi^2 = 20.94$, df = 6 (P = 0.002); $I^2 = 71\%$

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Combination 1: Antihistamine-decongestant, Outcome 3 Side effects: drowsiness, hypersomnia and excessive sleepiness - Combination 1: Antihistamine-decongestant.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 1 Combination 1: Antihistamine-decongestant

Outcome: 3 Side effects: drowsiness, hypersomnia and excessive sleepiness - Combination 1: Antihistamine-decongestant

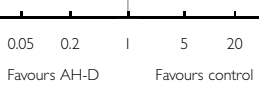
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Berkowitz 1989	7/133	8/128		44.5 %	0.83 [0.29, 2.37]
Galvez 1985	4/25	0/27		2.3 %	11.51 [0.59, 225.67]
Robert 2004	2/100	4/104		22.1 %	0.51 [0.09, 2.85]
Schrooten 1993	3/43	1/40		5.6 %	2.93 [0.29, 29.34]
Virtanen 1983	10/44	6/48		25.5 %	2.06 [0.68, 6.24]
Total (95% CI)	**345**	**347**		**100.0 %**	**1.44 [0.78, 2.64]**

Total events: 26 (Treatment), 19 (Control)

Heterogeneity: Chi^2 = 5.08, df = 4 (P = 0.28); I^2 =21%

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

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Combination 1: Antihistamine-decongestant, Outcome 4 Side effects: dry mouth - Combination 1: Antihistamine-decongestant.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 1 Combination 1: Antihistamine-decongestant

Outcome: 4 Side effects: dry mouth - Combination 1: Antihistamine-decongestant

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Berkowitz 1989	12/133	3/128		35.6 %	4.13 [1.14, 15.01]
Robert 2004	4/100	1/104		12.1 %	4.29 [0.47, 39.08]
Schrooten 1993	10/43	3/40		30.6 %	3.74 [0.95, 14.75]
Virtanen 1983	5/44	2/48		21.7 %	2.95 [0.54, 16.05]
Total (95% CI)	**320**	**320**		**100.0 %**	**3.77 [1.75, 8.14]**

Total events: 31 (Treatment), 9 (Control)

Heterogeneity: $Chi^2 = 0.11$, df = 3 (P = 0.99); $I^2 = 0.0\%$

Test for overall effect: Z = 3.38 (P = 0.00071)

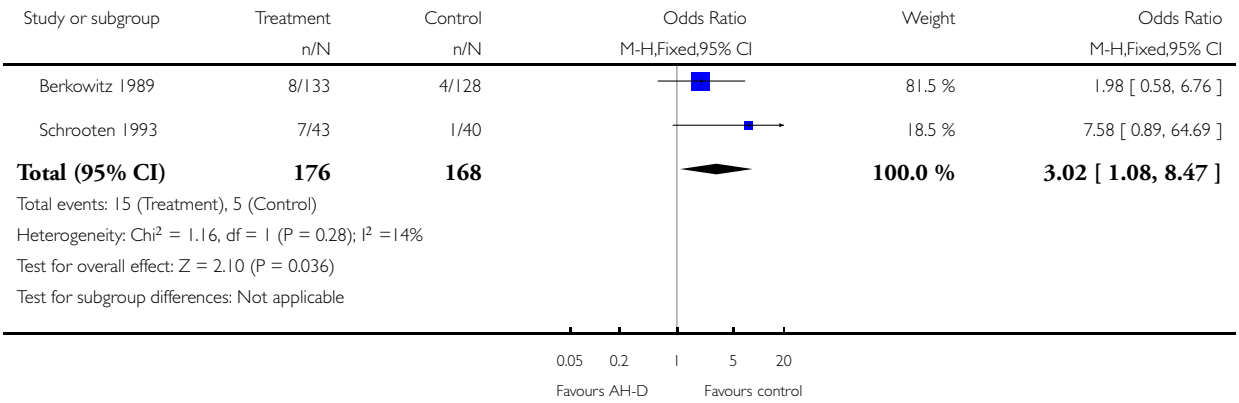
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Combination 1: Antihistamine-decongestant, Outcome 5 Side effects: insomnia.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 1 Combination 1: Antihistamine-decongestant

Outcome: 5 Side effects: insomnia

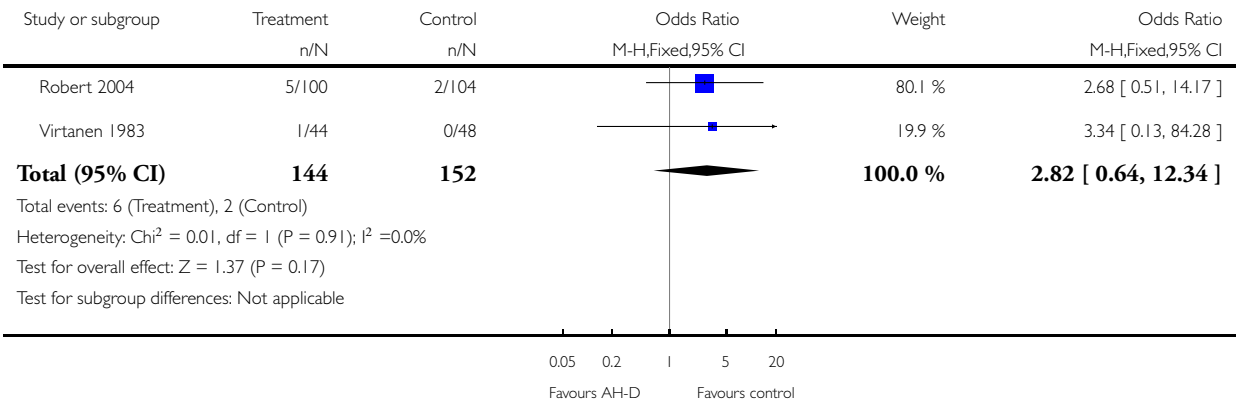


Analysis 1.6. Comparison 1 Combination 1: Antihistamine-decongestant, Outcome 6 Side effects: gastro-intestinal upset - Combination 1: Antihistamine + analgesic.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 1 Combination 1: Antihistamine-decongestant

Outcome: 6 Side effects: gastro-intestinal upset - Combination 1: Antihistamine + analgesic



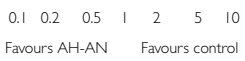
Analysis 2.1. Comparison 2 Combination 2: Antihistamine-analgesic, Outcome 1 Global evaluation: Koychev 2003.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 2 Combination 2: Antihistamine-analgesic

Outcome: 1 Global evaluation: Koychev 2003

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Koytchev 2003	87/290	166/292		100.0 %	0.33 [0.23, 0.46]
Total (95% CI)	**290**	**292**		**100.0 %**	**0.33 [0.23, 0.46]**
Total events: 87 (Treatment), 166 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.44 (P < 0.00001)					
Test for subgroup differences: Not applicable					



Analysis 2.2. Comparison 2 Combination 2: Antihistamine-analgesic, Outcome 2 Global evaluation: Middleton 1981 night.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 2 Combination 2: Antihistamine-analgesic

Outcome: 2 Global evaluation: Middleton 1981 night

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Middleton 1981	16/91	34/90		100.0 %	0.35 [0.18, 0.70]
Total (95% CI)	**91**	**90**		**100.0 %**	**0.35 [0.18, 0.70]**

Total events: 16 (Treatment), 34 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.98 (P = 0.0029)
Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Combination 2: Antihistamine-analgesic, Outcome 3 Side effects: drowsiness, hypersomnia and excessive sleepiness - Combination 2 : Antihistamine-analgesic.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 2 Combination 2: Antihistamine-analgesic

Outcome: 3 Side effects: drowsiness, hypersomnia and excessive sleepiness - Combination 2 : Antihistamine-analgesic

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Gwaltney 2002	5/61	0/30		13.8 %	5.94 [0.32, 111.02]
Middleton 1981	5/91	4/90		86.2 %	1.25 [0.32, 4.81]
Total (95% CI)	**152**	**120**		**100.0 %**	**1.90 [0.59, 6.07]**

Total events: 10 (Treatment), 4 (Control)
Heterogeneity: Chi^2 = 0.95, df = 1 (P = 0.33); I^2 =0.0%
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Combination 2: Antihistamine-analgesic, Outcome 4 Side effects: all - Combination 2: Antihistamine-analgesic.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 2 Combination 2: Antihistamine-analgesic

Outcome: 4 Side effects: all - Combination 2: Antihistamine-analgesic

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Middleton 1981	11/90	9/91		100.0 %	1.27 [0.50, 3.23]
Total (95% CI)	**90**	**91**		**100.0 %**	**1.27 [0.50, 3.23]**
Total events: 11 (Treatment), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.50 (P = 0.62)					
Test for subgroup differences: Not applicable					

Analysis 3.1. Comparison 3 Combination 3: Analgesic-decongestants, Outcome 1 Global evaluation.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 3 Combination 3: Analgesic-decongestants

Outcome: 1 Global evaluation

Study or subgroup	AN-D n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Middleton 1981	25/91	52/90		100.0 %	0.28 [0.15, 0.52]
Total (95% CI)	**91**	**90**		**100.0 %**	**0.28 [0.15, 0.52]**
Total events: 25 (AN-D), 52 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.05 (P = 0.000052)					
Test for subgroup differences: Not applicable					

Analysis 3.2. Comparison 3 Combination 3: Analgesic-decongestants, Outcome 2 Side effects: drowsiness, hypersomnia, lethargy and excessive sleepiness - Combination 3: Analgesic-decongestant.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 3 Combination 3: Analgesic-decongestants

Outcome: 2 Side effects: drowsiness, hypersomnia, lethargy and excessive sleepiness - Combination 3: Analgesic-decongestant

Study or subgroup	AN-D n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Loose 2004	22/481	3/162		28.7 %	2.54 [0.75, 8.60]
Middleton 1981	5/91	4/90		25.5 %	1.25 [0.32, 4.81]
Sperber 1989	0/23	1/10		13.5 %	0.13 [0.01, 3.61]
Sperber 2000	9/216	5/214		32.3 %	1.82 [0.60, 5.51]
Total (95% CI)	**811**	**476**		**100.0 %**	**1.65 [0.86, 3.19]**

Total events: 36 (AN-D), 13 (Control)

Heterogeneity: $Chi^2 = 2.90$, df = 3 (P = 0.41); $I^2 = 0.0\%$

Test for overall effect: Z = 1.50 (P = 0.13)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Combination 3: Analgesic-decongestants, Outcome 3 Side effects: dry mouth - Combination 3: Analgesic-decongestant.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 3 Combination 3: Analgesic-decongestants

Outcome: 3 Side effects: dry mouth - Combination 3: Analgesic-decongestant

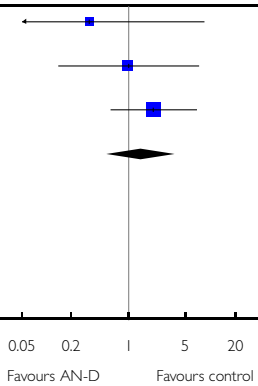
Study or subgroup	AN-D n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Eccles 2006a	0/76	1/77		20.2 %	0.33 [0.01, 8.31]
Middleton 1981	2/91	2/90		26.9 %	0.99 [0.14, 7.18]
Sperber 2000	8/216	4/214		52.9 %	2.02 [0.60, 6.81]
Total (95% CI)	**383**	**381**		**100.0 %**	**1.40 [0.54, 3.62]**

Total events: 10 (AN-D), 7 (Control)

Heterogeneity: $Chi^2 = 1.23$, df = 2 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 0.70 (P = 0.49)

Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3 Combination 3: Analgesic-decongestants, Outcome 4 Side effects: gastrointestinal side effects Combination 3: Analgesic-decongestant.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 3 Combination 3: Analgesic-decongestants

Outcome: 4 Side effects: gastrointestinal side effects Combination 3: Analgesic-decongestant

Study or subgroup	AN-D n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Loose 2004	20/481	4/162		46.7 %	1.71 [0.58, 5.09]
Middleton 1981	7/91	6/90		45.3 %	1.17 [0.38, 3.62]
Sperber 1989	0/23	0/10			Not estimable
Sperber 2000	6/216	1/214		8.0 %	6.09 [0.73, 50.98]
Total (95% CI)	**811**	**476**		**100.0 %**	**1.81 [0.89, 3.71]**

Total events: 33 (AN-D), 11 (Control)

Heterogeneity: $Chi^2 = 1.84$, df = 2 (P = 0.40); $I^2 = 0.0\%$

Test for overall effect: Z = 1.63 (P = 0.10)

Test for subgroup differences: Not applicable

Analysis 3.5. Comparison 3 Combination 3: Analgesic-decongestants, Outcome 5 Side effects: dizziness, light headedness - Combination 3: Analgesic-decongestant.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 3 Combination 3: Analgesic-decongestants

Outcome: 5 Side effects: dizziness, light headedness - Combination 3: Analgesic-decongestant

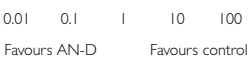
Study or subgroup	AN-D n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Loose 2004	19/481	2/162		48.4 %	3.29 [0.76, 14.28]
Middleton 1981	2/91	2/90		33.1 %	0.99 [0.14, 7.18]
Sperber 1989	2/23	0/10		10.3 %	2.44 [0.11, 55.56]
Sperber 2000	8/216	0/214		8.1 %	17.49 [1.00, 304.94]
Total (95% CI)	**811**	**476**		**100.0 %**	**3.59 [1.37, 9.43]**

Total events: 31 (AN-D), 4 (Control)

Heterogeneity: $Chi^2 = 2.88$, df = 3 (P = 0.41); $I^2 = 0.0\%$

Test for overall effect: Z = 2.60 (P = 0.0093)

Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3 Combination 3: Analgesic-decongestants, Outcome 6 Side effects: all - Combination 3: Analgesic-decongestant.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 3 Combination 3: Analgesic-decongestants

Outcome: 6 Side effects: all - Combination 3: Analgesic-decongestant

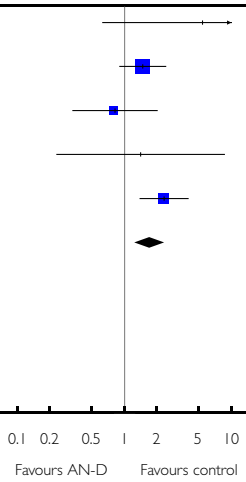
Study or subgroup	AN-D n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Eccles 2006a	5/76	1/77		1.6 %	5.35 [0.61, 46.93]
Loose 2004	91/481	22/162		45.5 %	1.48 [0.90, 2.46]
Middleton 1981	9/90	11/91		16.8 %	0.81 [0.32, 2.06]
Sperber 1989	6/23	2/10		3.5 %	1.41 [0.23, 8.61]
Sperber 2000	51/216	25/214		32.7 %	2.34 [1.39, 3.94]
Total (95% CI)	**886**	**554**		**100.0 %**	**1.71 [1.23, 2.37]**

Total events: 162 (AN-D), 61 (Control)

Heterogeneity: Chi^2 = 5.26, df = 4 (P = 0.26); I^2 =24%

Test for overall effect: Z = 3.23 (P = 0.0013)

Test for subgroup differences: Not applicable



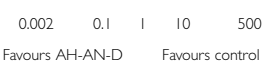
Analysis 4.1. Comparison 4 Combination 4: Antihistamine-analgesic-decongestant, Outcome 1 Global evaluation: after 3 days of treatment - Combination 4: Antihistamine-analgesic-decongestant.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 4 Combination 4: Antihistamine-analgesic-decongestant

Outcome: 1 Global evaluation: after 3 days of treatment - Combination 4: Antihistamine-analgesic-decongestant

Study or subgroup	AH-AN-D n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Unuvar 2007	51/61	45/48		100.0 %	0.34 [0.09, 1.31]
Total (95% CI)	**61**	**48**		**100.0 %**	**0.34 [0.09, 1.31]**
Total events: 51 (AH-AN-D), 45 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.57 (P = 0.12)					
Test for subgroup differences: Not applicable					



Analysis 4.2. Comparison 4 Combination 4: Antihistamine-analgesic-decongestant, Outcome 2 Global evaluation: after 5 days of treatment.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 4 Combination 4: Antihistamine-analgesic-decongestant

Outcome: 2 Global evaluation: after 5 days of treatment

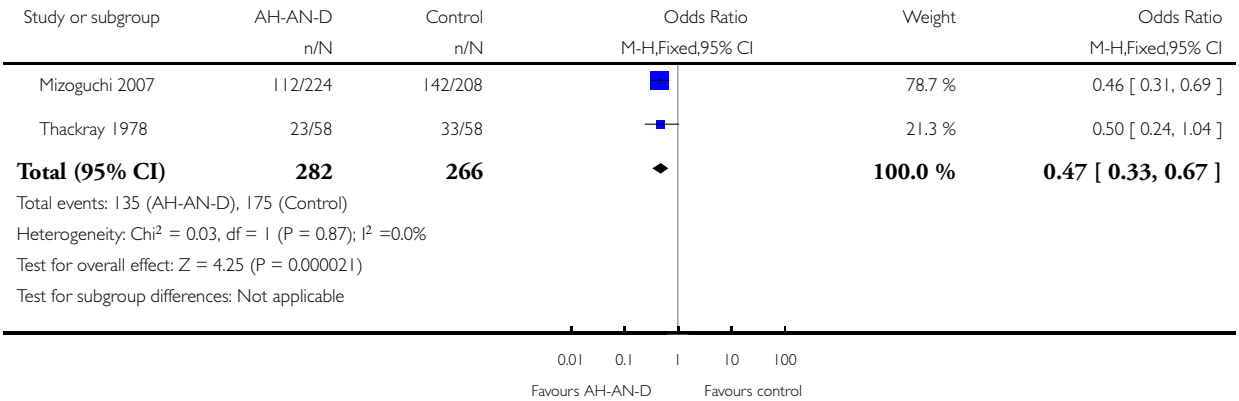
Study or subgroup	AH-AN-D n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Unuvar 2007	21/43	18/40		100.0 %	1.17 [0.49, 2.77]
Total (95% CI)	**43**	**40**		**100.0 %**	**1.17 [0.49, 2.77]**
Total events: 21 (AH-AN-D), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.35 (P = 0.73)					
Test for subgroup differences: Not applicable					

Analysis 4.3. Comparison 4 Combination 4: Antihistamine-analgesic-decongestant, Outcome 3 Global evaluation: on the morning after evening dosing.

Review: Oral antihistamine-decongestant-analgesic combinations for the common cold

Comparison: 4 Combination 4: Antihistamine-analgesic-decongestant

Outcome: 3 Global evaluation: on the morning after evening dosing



ADDITIONAL TABLES

Table 1. Combination 1: Antihistamine-decongestant

ID	Results
Aschan 1974	a. Objective nasal obstruction Promethazine + ephedrine: positive manometric result (pmr) 15/15; placebo: pmr 0/15. P < 0.001 Clemastine + phenylpropanolamine: pmr 14/15; placebo pmr 0/15. P < 0.000001
Berkowitz 1989	a. Global efficacy 1. Overall response evaluated by physicians on a 4-point scale: day 3 P = 0.01, day 5 P = 0.02 in favour of active treatment 2. Overall response evaluated by patients on a 4-point scale: day 3 P = 0.02 in favour of active treatment No further data available b. Subjective severity assessment of nasal obstruction

Table 1. Combination 1: Antihistamine-decongestant (*Continued*)

	Mean scores: active treatment/placebo Day 1: 1.8/2.1 Day 3: 1.7/1.9 Day 3: 1.4/1.7 Day 4: 1.3/1.6 Day 5: 1.2/1.5 P < 0.05 for all presented days c. Rhinorrhoea Mean scores: active treatment/placebo Day 1: 1.8/1.9 Day 2: 1.5/1.9, P < 0.05 Day 3: 1.4/1.5 Day 4: 1.2/1.4, P < 0.05 Day 5: 1.1/1.3 d. Sneezing Mean scores: active treatment/placebo Day 1: 0.9/1 Day 2: 0.6/0.9, P < 0.05 Day 3: 0.5/0.7, P < 0.05 Day 4: 0.3/0.6, P < 0.05 Day 5: 0.3/0.5, P < 0.05 e. Cough Mean scores: active treatment/placebo Day 1: 1.2/1.3 Day 2: 1.2/1.2 Day 3: 1.0/1.1 Day 4: 0.8/1.0 Day 5: 0.8/0.9 No statistically significant difference
Bye 1980	a. Subjective severity assessment of nasal obstruction Severity score significantly reduced on day 1 b. Rhinorrhoea Severity score not significantly reduced with active treatment compared with placebo c. Sneezing Severity score of sneezing significantly reduced on day 2, 3 and 4 in the active group in comparison with the placebo group d. Cough Severity score not significantly reduced with active treatment compared with placebo
Clemens 1997	a. Subjective severity assessment of nasal obstruction Proportion of patients with improvement of nasal congestion 2 hours after intake of: Active treatment 41/84 (48.8%); placebo 40/79 (50.6%); P = 0.94

Table 1. Combination 1: Antihistamine-decongestant (*Continued*)

	b. Rhinorrhoea Proportion of patients with improvement of nasal congestion 2 hours after intake of: Active treatment 42/83 (50.6%); placebo 46/80 (57.5%); P = 0.48 Comparison between scores made on 7-point Likert scale: Active treatment 4.69; placebo 4.76; P = 0.56 c. Cough Proportion of patients with improvement of nasal congestion 2 hours after intake of: Active treatment 24/49 (49.0%); placebo 28/65 (43.1%); P = 0.66 Comparison between scores made on 7-point Likert scale: Active treatment 4.67; placebo 4.57; P = 0.53
Curley 1988	a. Subjective severity assessment of nasal obstruction (1) Graphical display of mean severity score shows a significant difference on: Day 1: P = 0.01 Day 2: P = 0.05 Day 3: P = 0.01 Day 4: P = 0.01 Day 5: P = 0.01 No further data available (2) Prevalence of nasal obstruction after 14 days of treatment: Active treatment 6/38, placebo 20/35. P < 0.001 b. Rhinorrhoea (1) Graphical display of mean severity score shows a significant difference on: Day 2: P = 0.05 Day 3: P = 0.01 No further data available (2) Prevalence of nasal obstruction after 14 days of treatment: Active group: 14/38, placebo group:12/35; P = 0.82 c. Cough (1) Graphical display of mean severity score shows a significant difference on: Day 3: P = 0.05 Day 4: P = 0.05 Day 5: P = 0.05 No further data available
Hutton 1991	a. Subjective severity assessment of nasal obstruction (1) Effect is expressed as "severity score changes" and presented as z-score: negative z-score means "less than average improvement", positive z-score means "more than average improvement". z-score on "congested and runny nose": Active treatment -0.166, placebo +0.194 - difference not significant (2) Number of parents reporting "improvement" of runny or congested nose:

Table 1. Combination 1: Antihistamine-decongestant (*Continued*)

	Active treatment: 16/30; placebo 19/24; P = 0.05 b. Rhinorrhoea (1) Effect is expressed as "severity score changes" and presented as z-score: negative z-score means "less than average improvement", positive z-score means "more than average improvement". z-score on " congested and runny nose": Active treatment -0.166, placebo +0.194 - difference not significant (2) Number of parents reporting "improvement" of runny or congested nose: Active treatment: 16/30; placebo 19/24; P = 0.05 c. Cough (1) Effect is expressed as "severity score changes" and presented as z-score: negative z-score means "less than average improvement", positive z-score means "more than average improvement". z-score on " cough": Active treatment +0.024, placebo -0.058 - difference not significant (2) Number of parents reporting "improvement" of cough: Active treatment 20/30; placebo 14/24, not statistically significant
Lebacq 1994	a. Objective nasal obstruction Nasal resistance as percentage of pre-value P - placebo (n = 6), A1 - combination 1 (n = 6), A2 - combination 2 (n = 6) Adult: 0.5 h post dose: P 116%; A1 61% (P < 0.05)*; A2 106% 1 h post dose: P 96%; A1 52% (P < 0.05)*; A2 96% 2 h post dose: P 100%; A1 58% (P < 0.05)*; A2 81% 4 h post dose: P 103%; A3 77%; A2 83% 6.5 h post dose: P 100%; A1 72%; A2 77% 11 h post dose: P 96%; A1 69%; A2 76% *Significantly different from placebo Children: 0.5 h post dose: P 96%; A1 63%; A2 115% 1 h post dose: 68%; A1 70%; A2 99% 2 h post P 60%; A1 75%; A2 112% 4 h post dose: P 103%; A3 77%; A2 83% 6.5 h post dose: P 64%, A1 78%; A2 97% 11 h post dose: P 65%; A1 72%; A2 99% No significant difference b. Subjective severity assessment of nasal obstruction Severity assessment is presented in 6 scores on a 3-point scale. There was no difference between treatment groups. We show (as an example) results of 1 evaluation point (after 2 hours of intake of medication). Median score 1. adults, 2. children Placebo (n = 6) 2; placebo (n = 6) 2 A1 (n = 6) 2; A1 (n = 6) 1.5 A2 (n = 6) 2; A5 (n = 6) 2

Table 1. Combination 1: Antihistamine-decongestant (*Continued*)

	A1 = combination 1, A2 = combination 2 c. Effects assessed by anterior rhinoscopia Rhinoscopia results are presented as median of 6 scores on a 3-point scale. There was no difference between treatment groups. We show (as an example) results of 1 evaluation point (2 hours after intake of medication) Median score 1. adults 2. children Placebo (n = 6) 2 placebo (n = 6) 1.5 A1 (n = 6) 2; A1 (n = 6) 1 A2 (n = 6) 2; A5 (n = 6) 1.5 A1 = combination 1, A2 = combination
Robert 2004	a. Global efficacy Evaluation of overall efficacy made by the investigators was made on a 4-point scale. Percentage of patients rating "good" or "excellent" for the treatment group was 57.8% (58/100) and for the control group 57.6% (60/104) (P < 0.001). Night Control treatment 56 75 34 26 b. Objective nasal obstruction In the "Results" chapter of the paper it is reported that no differences were observed between the treatment and placebo groups regarding an increase of mean values for nasal peak flow carried out before and after 3 days of treatment
Virtanen 1983	a. Subjective severity assessment of nasal obstruction Graphical presentation of mean severity scores of nasal obstruction register during 10 days (treatment on first 5 days) shows no significant difference between treatment groups. No further data available b. Rhinorrhoea Graphical presentation of mean severity scores of nasal obstruction register during 10 days (treatment on first 5 days) shows no significant difference between treatment groups - except for day 3 (P < 0.05) No further data presented c. Sneezing Graphical presentation of mean severity scores of nasal obstruction register during 10 days (treatment on first 5 days) shows a significant difference between treatment groups on: Day 2, P < 0.05 Day 3, P < 0.001 Day 4, P < 0.01 Day 5, P < 0.001 Day 6, P < 0.01 Day 7, P < 0.01 Day 8, P < 0.05
Weippl 1984	a. Global efficacy Overall therapeutic response was rated by the physician on a 5-point scale (excellent, good, fair, poor, exacerbated) on days 3 and 5:

Table 1. Combination 1: Antihistamine-decongestant (*Continued*)

	Day 3: percentage of "good" or "excellent" responses: therapeutic group 83% (24/29) placebo group 7% (2/27) (P < 0.01) Day 5: percentage of "good" or "excellent" responses: therapeutic group 86% (25/29), placebo group 30%(8/27) (P < 0.01) b. Cough Statistically significant improvement (P < 0.05) at the interim visit c. Significantly greater improvement at both visits (P < 0.001) in rhinorrhoea, nasal congestion and sneezing. No further data presented
Galvez 1985	a. Global efficacy Physician's evaluation of overall therapeutic response on a 6-point scale (difference given by the percentage of patients responding "good" or "excellent" on the medication): Day 3: treatment group 60%, placebo group 8%, P < 0.01 Day 5: treatment group 77%, placebo group 21%, P < 0.01 a. Global efficacy Physician's evaluation of overall therapeutic response on a 6-point scale (difference given by the percentage of patients responding "good" or "excellent" on the medication): Day 3: treatment group 60%, placebo group 8%, P < 0.01 Day 5: treatment group 77%, placebo group 21%, P < 0.01
Scavino 1985	a. Global efficacy Overall therapeutic response evaluated by a physician on a 4-point scale (excellent, good, fair, poor, exacerbated) on days 3 and 5: Day 3: percentage of patients responding "good" or "excellent": therapeutic group 76%, placebo group 17% (P < 0.01) Day 5: percentage of patients responding "good" or "excellent": therapeutic group 88%, placebo group 48% (P < 0.01) b. Cough Evaluation of the percentage of improvement from the baseline score on days 3 and 5: Day 3: active treatment 54%, placebo 24% Day 5: active treatment 90%, placebo 60% a. Global efficacy Overall therapeutic response evaluated by a physician on a 4-point scale (excellent, good, fair, poor, exacerbated) on days 3 and 5: Day 3: percentage of patients responding "good" or "excellent": therapeutic group 76%, placebo group 17% (P < 0.01) Day 5: percentage of patients responding "good" or "excellent": therapeutic group 88%, placebo group 48% (P < 0.01)

h: hour
P: placebo

Table 2. Combination 1: Number of trials reporting specific adverse effects

Side effect	Number
All	8
Drowsiness	7
Dry mouth	6
Gastrointestinal upset	4
Insomnia	4
Dizziness	2
Nervousness	1
Headache	1
Palpitations	2
Rash	1

Table 3. Combination 1: Adverse effects data not in meta analyses

Side effect	ID	Result
Nervousness	Berkowitz 1989	Active treatment 5/133, placebo 3/128; P = 0.51
Dizziness	BerkowitZ 1989	Active treatment 5/133, placebo 2/128; P = 0.45
Dizziness	Curley 1988	Active treatment: 13/38, placebo 10/35; P = 0.06
Rash	Curley 1988	Active treatment 1/38, placebo 0/35; P = 0.33
Palpitations	Virtanen 1983	Active treatment 1/44; placebo 0/48; P = 0.29
Headache	Virtanen 1983	Active treatment 8/44; placebo 11/48; P = 0.25
Debelic (comparison of 2 active treatments)	Clemastine + phenylpropanolamine (= treatment) Side effects: Insomnia 4	Belladonna, chlorpheniramine, phenylpropanolomine (= control) Side effects: Insomnia 3

Table 3. Combination 1: Adverse effects data not in meta analyses (*Continued*)

	Sleepiness 0 Dry mouth 4 Dizziness 3 Palpitations 0 Nausea 0	Sleepiness 5 Dry mouth 7 Dizziness 2 Palpitations 4 Nausea 1

Table 4. Combination 2: Antihistamine-analgesic

ID	Results
Gwaltney 2002	a. Subjective severity assessment of nasal obstruction Comparisons between baseline - adjusted mean daily symptom scores on days 2 to 5 mentioned in a table. The treatment with oral chlorpheniramine and ibuprofen showed no significant effect on nasal congestion scores on any day during therapy Day 2: 1.0 Day 3: 1.0 Day 4: 1.6 Day 5: 1.7 b. Rhinorrhoea Comparisons between baseline - adjusted mean daily symptom scores on day 2 to 5 mentioned in a table. The treatment with oral chlorpheniramine and ibuprofen showed no significant effect on rhinorrhoea scores on any day during treatment Day 2: 1.9 Day 3: 1.1 Day 4: 1.7 Day 5: 1.15 c. Sneezing Comparisons between baseline - adjusted mean daily symptom scores on day 2 to 5 mentioned in a table. The treatment with oral chlorpheniramine and ibuprofen showed significant effect on sneezing scores only on day 5 of treatment Day 2: 2.0 Day 3: 3.2 Day 4: 2.3 Day 5: 6.2 - statistically significant ($P < 0.05$) d. Cough Comparisons between baseline - adjusted mean daily symptom scores on day 2 to 5 mentioned in a table. The treatment with oral chlorpheniramine and ibuprofen showed no significant effect on cough scores on any day during treatment Day 2: 3.0 Day 3: 1.8 Day 4: 2.1 Day 5: 1.8
Koytchev 2003	a. Global efficacy The proportion of patients who were completely cured at the end of the trial:

Table 4. Combination 2: Antihistamine-analgesic (*Continued*)

	Treatment group: 70% Control group and reference 1 group: 43 to 45% b. Subjective severity assessment of nasal obstruction Comparison of the sub-score referring to blocked nose, cough and disturbance of sleep quality was performed between the group of patients receiving the active treatment and the group taking the reference 2. The difference was statistically significant (P < 0.05). No further data available. c. Cough Comparison of the sub-score referring to blocked nose, cough and disturbance of sleep quality was performed between the group of patients receiving the active treatment and the group taking the reference 2. The difference was statistically significant (P < 0.05). No further data available
Middleton 1981	a. Global efficacy Overall subjective assessment was made after asking the patient the question: "On the whole do you think the tablets have helped you?" Daytime: Response Control Treatment Yes 47 66 No 52 25 Compared with the control group a statistically significantly larger number of patients receiving the active medication responded affirmative to the question (P < 0.01) b. Subjective severity assessment of nasal obstruction No significant difference reported in treating nasal congestion with the active substance in comparison with placebo The results are mentioned in the "Results" chapter of the article. No tables or graphics show the data from which the conclusions were drawn c. Rhinorrhoea No significant difference reported in treating rhinorrhoea with the active substance in comparison with placebo The results are mentioned in the "Results" chapter of the article. No tables or graphics show the data from which the conclusions were drawn d. Sneezing No significant difference reported in treating sneezing with the active substance in comparison with placebo The results are mentioned in the "Results" chapter of the article. No tables or graphics show the data from which the conclusions were drawn e. Cough No significant difference reported in treating cough with the active substance in comparison with placebo The results are mentioned in the "Results" chapter of the article. No tables or graphics show the data from which the conclusions were drawn

Table 5. Combination 2: Number of trials reporting a specific adverse effect

Side effect	Number
All	2
Drowsiness	1
Dizziness	1
Gastrointestinal upset	1
Dry mouth	1

Table 6. Combination 2: Adverse effects - data not in meta-analyses

Side effect	ID	Result
Dry mouth	Middleton 1981	Active treatment 2/91, placebo 2/90
Gastrointestinal upset	Middleton 1981	Active treatment 6/91, placebo 5/90
Dizziness	Middleton 1981	Active treatment 1/91, placebo 1/90
All patients reporting	Koytchev 2003	In all trial groups (n = 1167) 39 patients reported an adverse effects

Table 7. Combination 3: Analgesic-decongestant

ID	Results
Gallardo 1994	a. Subjective severity assessment of nasal obstruction The duration of the symptom of nasal congestion was significantly reduced on treatment days 3 and 5. Result mentioned in the "Results" chapter of the text. No further data available d. Objective nasal obstruction The duration of the symptom of mucosal oedema was significantly reduced on treatment days 3 and 5 as compared to placebo. Result mentioned in the "Results" chapter of the text. No further data available
Loose 2004	a. Subjective severity assessment of nasal obstruction (1) Nasal congestion score The nasal congestion score compared with placebo was statistically significantly different ($P < 0.05$) for all active treatment and at all observation intervals (2, 4 and 6 hours after intake). (2) Relief of nasal congestion Relief in nasal congestion was statistically significantly better compared to treatment with placebo for all active treatment and at all observation intervals (2, 4 and 6 hours after intake) Data given in tables but it is not clear what the tables represent

Table 7. Combination 3: Analgesic-decongestant (*Continued*)

Middleton 1981	a. Global efficacy Overall subjective assessment was made after asking the patient the question: "On the whole do you think the tablets have helped you?" Night time: Response Control Treatment Yes 56 75 No 34 26 Compared with the control group a statistically significantly larger number of patients receiving the active medication responded affirmative to the question (P < 0.01) b. Subjective severity assessment of nasal obstruction No significant difference reported in treating nasal congestion with the active substance in comparison with placebo The results are only reported in the "Results" chapter of the article. No tables or graphics show the data from which the conclusions were drawn c. Rhinorrhoea No significant difference reported in treating rhinorrhoea with the active substance in comparison with placebo The results are only written in the "Result" chapter of the article. No tables or graphics show the data from which the conclusions were drawn d. Sneezing No significant difference reported in treating sneezing with the active substance in comparison with placebo The results are only written in the "Result" chapter of the article. No tables or graphics show the data from which the conclusions were drawn e. Cough No significant difference reported in treating cough with the active substance in comparison with placebo The results are only written in the "Result" chapter of the article. No tables or graphics show the data from which the conclusions were drawn
Sperber 1989	a. Objective nasal obstruction Overall and daily nasal patency was greater in the treatment group. The days when this difference was most noticeable were day 4 (P = 0.08) and day 5 (P = 0.06). Analysis of the mean values was confounded by high variability between participants b. Subjective severity assessment of nasal obstruction Reduction of nasal congestion rated on a 4-point scale: Treatment group 4 ± 3; placebo group 7 ± 2, P < 0.05 (significant difference) c. Rhinorrhoea Reduction of nasal congestion rated on a 4-point scale: treatment group 2 ± 2; placebo group 4 ± 3, P < 0.05 (not significant difference)
Sperber 2000	a. Subjective severity assessment of nasal obstruction Mean difference between the nasal congestion scores at the beginning of the study and after the first and second administration of active medication or placebo (nasal congestion evaluated on 5-point scale):

Table 7. Combination 3: Analgesic-decongestant (*Continued*)

	Dose 1: active group -1.06; placebo group -0.67, P = 0.002 - statistically significant Dose 2: active group -1.26; placebo group -0.98, P = 0.03 - not statistically significant b. Rhinorrhoea Mean difference between the rhinorrhoea score at the beginning of the study and after the first and second administration of active medication or placebo (rhinorrhoea evaluated on 5-point scale): Dose 1: active group -0.80; placebo group -0.71, P = 0.12 - not statistically significant Dose 2: active group -1,15; placebo group -0,86, P = 0,09 - not statistically significant c. Sneezing Mean difference between the sneezing score at the beginning of the study and after the first and second administration of active medication or placebo (sneezing evaluated on 5-point scale): Dose 1: active group -0.84; placebo group -0.79, P = 0.71 - not statistically significant Dose 2: active group -0.98; placebo group -0.85, P = 0.15 - not statistically significant d. Cough Mean difference between the cough score at the beginning of the study and after the first and second administration of active medication or placebo (cough evaluated on 5-point scale): Dose 1: active group -0.61; placebo group -0.51, P = 0.27 - not statistically significant Dose 2: active group -0.78; placebo group -0.58, P = 0.06 - not statistically significant Trend suggestive of greater reduction in cough score
Eccles 2006	Nasal congestion Area under nasal airflow conductance curve 0 to 4 h (rhinomanometry) Mean difference 120.3, 95% CI 66.18 to 174.37, P = 0.0001 Sum of nasal congestion differences 0 to 3 days (4-point scale) Mean difference 0.69, 95% CI 0.219 to 1.162, P = 0.0042 Global nasal congestion relief (5-point scale) Paracetamol + pseudoephedrine: 1.7 +/- 1.2 P = 0.0004 Placebo: 1.0 +/- 0.9

Table 8. Combination 3: Number of trials reporting a specific adverse effect

Side effect	Number
All	5
Gastrointestinal upset	4
Dizziness	4
Drowsiness	4
Dry mouth	4
Headache	1

Table 8. Combination 3: Number of trials reporting a specific adverse effect (*Continued*)

Difficulty sleeping	1
Fever	1
Pharyngitis	1

Table 9. Combination 3: Adverse effects - data not in meta-analyses

Side effect	ID	Result
Dry mouth	Middleton 1981	Active treatment 2/91, paracetamol 2/90
Gastrointestinal upset	Middleton 1981	Active treatment 6/91, paracetamol 5/90
Dizziness	Middleton 1981	Active treatment 1/ 91, paracetamol 1/90
Drowsiness and sleepiness	Middleton 1981	Active treatment 5/91, paracetamol 4/90
Loss of appetite	Middleton 1981	Active treatment 0/91, paracetamol 1/90
Depression headache	Middleton 1981	Active treatment 0/91, paracetamol 1/90
Giddy, dizzy	Middleton 1981	Active treatment 1/91, paracetamol 1/90
Abdominal pains, diarrhoea	Middleton 1981	Active treatment 1/91, paracetamol 0/90
Headache	Loose 2004	Active treatment 17/481, placebo 9/162
Fever	Loose 2004	Active treatment 8/481, placebo 2/162
Pharyngitis	Loose 2004	Active treatment 4/481, placebo 2/162
Nervousness	Sperber 2000	Active treatment 8/216, placebo 0/214
Difficulty sleeping	Sperber 1989	Active treatment 1/23, placebo 1/10
CNS	Eccles 2006a	Active treatment 4/76, placebo 0/76
dry mouth	Eccles 2006a	active treatment 1/76, placebo 1/76

Table 10. Combination 4: Antihistamine-decongestant-analgesic

ID	Results
Blanco 2000	a. Global efficacy Comparison of severity ratings on the third day of treatment between treatment groups: results are graphical displayed and summarised in a table. It is not clear what is presented in the table On the graphs, P values are mentioned when there is a statistical significant difference: for general unwell feeling: there is no significant difference b. Subjective severity assessment of nasal obstruction Comparison of severity ratings on the third and fifth day of treatment between treatment groups: results are graphical displayed and summarised in a table. It is not clear what is presented in the table In the graphs, P values are mentioned when there is a statistical significant difference: for nasal congestion P = 0.041 c. Effect on results on anterior rhinoscopy Comparison of severity ratings on the third and fifth day of treatment between treatment groups: results are graphical displayed and summarised in a table. It is not clear what is presented in the table In the graphs, P values are mentioned when there is a statistical significant difference: for anterior rhinoscopy P = 0.0456, on the third day d. Rhinorrhoea Comparison of severity ratings on the third day of treatment between treatment groups: results are graphical displayed and summarised in a table. It is not clear what is presented in the table. In the graphs, p- values are mentioned when there is a statistical significant difference: for anterior rhinorrhoea P = 0.012
Sachsenroder 1972	a. Rhinorrhoea Number of patients rating the efficacy of the product "good" or "bad" in treating the symptom of nasal congestion on day 1, 2 and 3 of taking medications. Ap 67 (n = 52), Z 95-Rh1 (n = 52), placebo (n = 55). Difference: Day 1: good 18, 27, 9; bad 34, 25, 46 significant Day 2: good 30, 34, 18; bad 22, 18, 37 not significant Day 3: good 36, 40, 20; bad 16, 10, 35 not significant a. Rhinorrhoea Number of patients rating the efficacy of the product "good" or "bad" for treating the symptom of nasal congestion on days 1, 2 and 3 of taking medications Ap 67 (n = 52), Z 95-Rh1 (n = 52), placebo (n = 55). Difference: Day 1: good 18, 27, 9; bad 34, 25, 46 significant Day 2: good 30, 34, 18; bad 22, 18, 37 not significant Day 3: good 36, 40, 20; bad 16, 10, 35 not significant
Mizogushi 2007	a. Overall relief (scale: 0 = very poor, 1 = poor, 2 = fair, 3 = good, 4 = very good) Day 2 morning: T 2.4 +/- 1.01; P 1.98 +/- 1.11, P < 0.0001 b. Nasal congestion (0 = much worse, 1 = somewhat worse, 2 = about the same, 3 = somewhat better, 4 = much better) Hour 3, day 1: T 2.59 +/-0.72, P 2.43 +/- 0.68, P = 0.0124

Table 10. Combination 4: Antihistamine-decongestant-analgesic (*Continued*)

	Day 2 morning: T 2.29 +/-0.98, P 2.00 +/- 1.10, P = 0.0025 c. Runny nose (0 = much worse, 1 = somewhat worse, 2 = about the same, 3 = somewhat better, 4 = much better) Hour 3, day 1: T 2.73 +/- 0.78, P 2.56 +/- 0.75, P = 0.0173 Day 2 morning: T 2.49 +/- 0.97, P 2.16 +/- 1.12, P = 0.0011 d. Cough (0 = much worse, 1 = somewhat worse, 2 = about the same, 3 = somewhat better, 4 = much better) Hour 3, day 1: T 2.72 +/- 0.77, P 2.46 +/- 0.82, P = 0.0124 Day 2 morning: T 2.50 +/ -0.97, P 2.08 +/- 1.11, P = 0.0025 Percentage (%) of subjects improved (no P values provided) 1) Hour 3, day 1: Nasal congestion: T 55.4, P 44.7 Runny nose: T 58.9, P 51 Cough: T 56.7, P 43.3 2) Day 2 morning: Nasal congestion: T 45.2, P 36.2 Runny nose: T 54.3, P 40.6 Cough: T 52.3, P38
Thackray 1978	a. Global efficacy Number of patients rating the formulation as "good, very good or excellent" on the morning after the dose of the night before: n = 58 Active treatment: 35/58 Placebo: 25/58 P < 0.05 b. Subjective severity assessment of nasal obstruction (Number of patient defining as good, very good, excellent next morning after administration) Number of patients rating the formulation as "good, very good, excellent" on the morning after the dose the night before: n = 58 Active treatment: 35/58 Placebo 25/58 P < 0.05 c. Rhinorrhoea Number of patients rating the formulation as "good, very good, excellent" on the morning after the dose the night before: n = 55 Active treatment: 35/55 Placebo 21/55 P < 0.05 d. Sneezing Number of patients rating the formulation as "good, very good, excellent" on the morning after the dose the night before:

Table 10. Combination 4: Antihistamine-decongestant-analgesic (*Continued*)

	n = 30 Active treatment: 25/30 Placebo 20/30 P = 0.14 e. Cough Number of patients rating the formulation as "good, very good, excellent" on the morning after the dose the night before: Active treatment: 57.6% Placebo 32.2% P < 0.01
Unuvar 2007	Clinical score Day 3: Treatment: 4.0 +/- 2.8 Acetaminophen: 4.1 +/- 2.6 P = 0.81 Day 5: Treatment: 1.7 +/- 1.4 Acetaminophen: 2.0 +/- 1.6 P =0.39 Unuvar (treatment = acetaminophen + diphenhydramine + pseudoephedrine) Nasal stuffiness Day 3 Treatment: 27/86 Acetaminophen 21/62 P = 0.75 Day 5: Treatment: 0/86 Acetaminophen: 4/62 P = 0.016 Runny nose Day 3 Treatment: 28/86 Acetaminophen: 25/62 P = 0.33 Day 5 Treatment: 7/86 Acetaminophen: 8/62 P = 0.49 Cough Day 3 Treatment: Acetaminophen Day 5 Treatment

Table 10. Combination 4: Antihistamine-decongestant-analgesic (*Continued*)

	Acetaminophen: 13/8614/622/864/62 P = 0.24, P = 0.29 Unuvar (treatment = acetaminophen + diphenhydramine + pseudoephedrine)

Table 11. Combination 4: Adverse effects - data not in meta-analyses

Side effect	ID	Result
Side effects: all	Thackray 1978	Cross-over design: all participants took active formulation; 19 side effects occurred, equally distributed between active and control formulation. No further numbers reported
Side effects: all	Mizoguchi 2007	5 participants with active treatment report 9 side effects 9 participants with control treatment report 10 side effects
Drowsy or sleepy	Blanco de la Mora 2000	Not more frequent with active treatment - numbers not mentioned
Giddiness/drowsiness	Thackray 1987	Cross-over design: side effect reported by 7 patients when taking active treatment, and by 4 when taking placebo
Diarrhoea	Mizogushi 2007	T 2/224, P 1/208
Headache	Mizogushi 2007	T 2/224, P 1/208
Abdominal pain	Mizogushi 2007	T 1/224, P 0/208
Dizziness	Mizogushi 2007	T 1/224, P 1/208
Vomiting	Mizogushi 2007	T 1/224, P 1/208

APPENDICES

Appendix 1. MEDLINE and CENTRAL search strategy

MEDLINE (Ovid)
1 Common Cold/
2 common cold*.tw.
3 Respiratory Tract Infections/
4 respiratory tract infection*.tw.
5 Cough/
6 cough*.tw.
7 Nasal Obstruction/
8 nasal obstruction*.tw.
9 Sneezing/
10 sneez*.tw.
11 Rhinovirus/
12 rhinovirus infection*.tw.
13 or/1-12
14 exp Histamine H1 Antagonists/
15 exp Histamine H1 Antagonists, Non-Sedating/
16 exp Anti-Allergic Agents/
17 histamine-h1-antagonist*.tw.
18 anti-allerg*.tw.
19 (antazoline* or methapyrilene* or pyrilamine* or tripelennamine* or clemastine* or dimenhydrinate* or diphenhydramine* or doxylamine* or brompheniramine* or chlorpheniramine* or dimethindene* or pheniramine* or triprolidine* or promethazine* or cetrizine* or meclizine* or hydroxyzine* or astemizole* or cyproheptadine* or loratadine* or terfenadine* or acrivastine* or fexofenadine* or dexbrompheniramine* or carbinoxamine*).tw,nm.
20 exp Nasal Decongestants/
21 decongestant*.tw.
22 Ephedrine/
23 Pseudoephedrine/
24 (ephedrine* or pseudoephedrine* or phenylephrine* or naphazoline* or oxymetazoline* or tramazoline* or xylometazoline* or phenylpropanolamine*).tw,nm.
25 exp Analgesics/
26 Acetaminophen/
27 paracetamol*.tw.
28 Aspirin/
29 acetylsalicylic acid.tw,nm.
30 Ibuprofen/
31 Ketoprofen/
32 Naproxen/
33 (analgesic* or acetaminophen* or aspirin* or ibuprofen* or ketoprofen* or naproxen*).tw,nm.
34 or/14-33
35 13 and 34

Appendix 2. EMBASE search strategy

EMBASE (Ovid)
1 Common Cold/
2 common cold*.tw.
3 Respiratory Tract Infection/
4 respiratory tract infection*.tw.
5 Coughing/
6 cough*.tw.
7 Nose Obstruction/
8 nasal obstruction*.tw.
9 sneezing/
10 sneez*.tw.
11 rhinovirus/
12 rhinovirus infection*.tw.
13 or/1-12
14 exp Histamine H1 Receptor Antagonist/
15 exp Antiallergic Agent/
16 (acrivastine* or fexofenadine* or dexbrompheniramine* or carbinoxamine* or antazoline* or methapyrilene* or pyrilamine* or tripelennamine* or clemastine* or dimenydrinate* or diphenhydramine* or doxylamine* or brompheniramine* or chlorpheniramine* or dimethindene* or pheniramine* or triprolidine* or promethzine* or cetrizine* or meclizine* or hydroxyzine* or astemizole* or cyproheptadine* or loratadine*).tw.
17 histamine-h1-antagonist*.tw.
18 anti-allerg*.tw.
19 exp Decongestive Agent/
20 (decongestant* or decongestive*).tw.
21 Ephedrine/
22 Pseudoephedrine/
23 (ephedrine* or pseudoephedrine* or phenylephrine* or naphazoline* or oxymetazoline* or tramazoline* or xylometazoline* or phenylpropanolamine*).tw.
24 exp Analgesic Agent/
25 Paracetamol/
26 (acetaminophen* or paracetamol*).tw.
27 Acetylsalicylic Acid/
28 (aspirin* or acetylsalicylic acid).tw.
29 Ibuprofen/
30 Ketoprofen/
31 Naproxen/
32 (analgesic* or ibuprofen* or ketoprofen* or naproxen*).tw.
33 or/14-32
34 33 and 13
35 random.tw. or placebo.mp. or double-blind.tw.
36 35 and 34

WHAT'S NEW

Last assessed as up-to-date: 16 December 2011.

Date	Event	Description
16 March 2010	Amended	Three new authors joined the review team to write this review

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 2, 2012

Date	Event	Description
14 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

An IM De Sutter (ADS) contributed to the data extraction and performed the data analyses, wrote the first draft, based on the protocol for antihistamines.

Lousie Kenyon (LK) and Mieke van Driel (MVD) commented on the draft and contributed to the final version.

Alja Skrt (AS) contributed to the data extraction and data analyses. Anna Kumar (AK) and Olivia Lesslar (OL) performed the 'Risk of bias' assessment under the supervision of MVD.

DECLARATIONS OF INTEREST

The authors have no conflict of interest to declare.

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- Department of General Practice and Primary Health Care, Belgium.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Analgesics [administration & dosage; *therapeutic use]; Common Cold [*drug therapy]; Drug Combinations; Histamine Antagonists [administration & dosage; *therapeutic use]; Nasal Decongestants [administration & dosage; *therapeutic use]

MeSH check words

Adult; Child; Humans