EVIDENCE-BASED REVIEW

Non-antibiotic treatments for upper-respiratory tract infections (common cold)

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Summary

Objectives: To review the seven Cochrane reviews of non-antibiotic treatment for the common cold.

Methods: Each Cochrane review was read and summarized, and results presented as relative risks and, where possible, numbers needed to treat.

Results: The main theme that runs through these Cochrane reviews is the variable quality of the primary studies. In general, the reviewers are fairly cautious about the benefits of any of the treatments other than first-dose decongestants and antihistamine–decongestant combinations. For antihistamines alone, the reviewers were clear about the lack of efficacy except in the high-quality studies in which a global improvement in symptoms was noted. Some studies were statistically significant, but the Cochrane reviewers were guarded about how clinically significant they were. For Echinacea, problems were found with the quality of the studies and the wide range of different forms of this substance. Heated humidified air seemed to be effective in the UK and Israel, but not the USA, making definitive statements about efficacy difficult. Over-the-counter medication for cough seemed to have no documented benefit in children under the age of 5 years. Letosteine (a mucolytic) may be effective in children but is not available in the UK. Bisolvon (a mucolytic) was found to be effective for cough in only one study. For older children and adults, dextromethorphan may be effective (two out of three studies showed benefit), and guifenesin (an expectorant) showed mixed benefit in two trials. Dextromethorphanamine (a sedating antihistamine)/pseudoephedrine (6 mg/120 mg twice daily for 1 week) was significantly more effective than placebo for severity of cough, whereas, in another study, loratadine (a non-sedating antihistamine)/pseudoephedrine (5 mg/120 mg twice daily for 4 days) did not show any difference between the study groups. Vitamin C may have a small role in preventing the common cold, with possibly a greater role in high-intensity physical activity and sub-arctic conditions. Zinc

Keywords

Non-antibiotic; Over-the-counter; Common cold; Cough; Antihistamine; Echinacea; Nasal decongestant; Heated humidified air; Vitamin C; Zinc

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Please see reference list for Cochrane reviews cited in this evidence-based review.

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Conclusion: Most non-antibiotic treatments for the common cold are probably not effective. The most promising are dextromethorphan, bisolvon and guiaphenesin for cough, antihistamine–decongestant combinations for a wide range of symptoms, nasal decongestants (at least for the first dose) and possibly zinc lozenges.

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Introduction

This paper evaluates the seven Cochrane systematic reviews that deal with non-antibiotic treatments for upper-respiratory tract infection. This was originally intended to include the review of anti-viral treatment for the common cold, but this review has been removed from the library as it was not updated. The treatments in this review are those that may be self-administered in many jurisdictions (e.g. heated humidified air), as well as being recommended in others by clinicians and even subsidized by some health funders. Thus, the term "over-the-counter" (OTC) is not strictly correct. Most of the clinical syndromes in this review fit the definition of the common cold, but, as mentioned in the earlier review in this series on "antibiotics for upper-respiratory tract infections: a review of Cochrane reviews," there is the issue of microbiological aetiology to consider. It is not always clear if an infection is of a viral, bacterial or mixed nature. In this paper, infections are assumed to be mainly viral, but the microbiology is not usually known or sought by clinicians.

In this overview, effects may be reported as the NNTB (number needed to treat for one person to benefit) and the NNTH (number needed to treat for one person to harm). The NNTB is the inverse of the absolute risk reduction (ARR) resulting from a particular treatment in a particular group of patients. It is felt that it is better to report the ARR than the relative risk reduction, as this term refers to the benefit of a treatment without any reference to the baseline risk. Both the ARR and the NNTB (the reciprocal of ARR) take these factors into consideration. The same applies to the NNTH for harm. The NNTB and the NNTH were only reported in this review if they were from statistically significant studies or statistically significant pooled relative risks. The latter is calculated by obtaining a pooled relative risk from the meta-analysis and applying it to the patient expected event rate (PEER). The PEER is the rate of events that occur in the group taking the placebo medication in a randomized trial comparing drug with placebo. Therefore, if the relative risk is less than 1 then the NNTB = 1/((1−RR) × PEER), and if the relative risk is greater than 1 then the NNTB = 1/((RR−1) × PEER).

A number of issues affect the quality of the reviews covered in this paper. These include a wide range of design quality in the studies reviewed. The dose and quality of some of the medicinal components and combination medications are also issues of concern. The latter two of these apply particularly to OTC medications. Issues are also raised by different methods of measuring end points, such as continuous scales compared with dichotomous outcomes (i.e. feeling well or absence of cough). As some of the medications are designed for specific purposes (e.g. cough suppressant), then absence of cough will be appropriate. For decongestants, it will be nasal discharge and stuffiness. This raises the question of what would be the appropriate outcome for an antihistamine for the common cold.

Ideally, the primary outcomes are specified beforehand. However, it is not always possible to tell if the analysis was done on the outcomes of primary interest or on the secondary outcomes. In this particular field, underpowering because of small study size is also an issue. NNTB can only be calculated if dichotomous outcomes are used, but they can be calculated for different symptoms, providing some practical information to guide treatment decisions.

Antihistamines for the common cold

The systematic review on antihistamines for the common cold was undertaken because the use of antihistamines for the common cold is widespread yet there was concern that they may not be effective. The review contained 32 papers with 35 comparisons; 22 trials were of monotherapy and 13 were of a combination of antihistamines with other medication. The number of participants totalled 8930. The authors reported large differences in
study design, participants, interventions and outcomes. For monotherapy, no evidence was found of a clinically significant effect on general recovery with antihistamines as monotherapy for either children or adults.

A benefit for global improvement was found in a subgroup analysis of the higher quality studies of first-generation sedating antihistamines. The relative risk (RR) for benefit was 0.9; 95% confidence interval (CI) 0.82–0.98. On the basis of the range of PEERs in individual studies in this review, the NNTB for a benefit was 12 for a PEER of 0.81 (this means that 81% of patients still had symptoms at the time of analysis) and 17 for a PEER of 0.6. The RR for adverse effects for the sedating antihistamine was 1.20 (95% CI 1.03–1.40). The NNTH for a PEER of 0.05 was 93 and for 0.36 the NNTH was 14. For the non-sedating antihistamines, no sedating adverse effects were found (RR = 1.10; 95% CI 0.55–2.18).

For monotherapy in small children aged 2–5 years, there was little evidence of benefit. One large trial (6 months to 5 years) found no benefit, and one smaller trial found improved rhinorrhea.

Combination antihistamine–decongestant

Similar lack of benefit was seen with combination of antihistamines and decongestants for young children. In older children and adults, evidence of benefit was found, and this was seen in five out of the six included trials. The RR for benefit in terms of global evaluation at 2–4 days was 0.31 (95% CI 0.15–0.65). This is an NNTB of 2.5 for a PEER of 0.58 and an NNTB of 4 for a PEER rate of 0.39. For the only significant harm (dry mouth), the RR was 1.93 (95% CI 1.35–2.75). The NNTH ranged from 2–46 for the PEER rates of 0.023 and 0.54, respectively. This suggests that more patients may experience an adverse event (dry mouth) than will benefit from combination antihistamines and decongestants.

The following interpretation can be made on the basis that (1) combination therapies seem to be effective; (2) monotherapy with antihistamines is not effective; and (3) the systematic review on decongestants (below) shows some benefit: it may be the decongestant component of the combination medications that is providing the effectiveness, and the antihistamine is contributing little or nothing to efficacy.

Echinacea

The systematic review on Echinacea included 16 studies (eight were of prevention and eight of treatment for upper-respiratory tract infections), with a total of 3396 participants. There was such variation in the preparations used and the quality of the study methods, that the authors felt that they could not pool the results.

Prevention in placebo trials

Two of the five prevention trials with a placebo found a statistically significant lower incidence of infection in the treatment group (RR = 0.51 and 0.67), whereas, in the other trials, there were only trends in favour of the treatment groups. The pooled RR was 0.86 (95% CI 0.72–1.02). In assessing the severity and duration of infections, three trials found no clear trends favouring the treatment or the placebo group in the severity of recurring infections.

Prevention trials with no placebo

In all three prevention trials with no treatment controls, the number of children with infection was significantly lower in the group receiving the Echinacea combination compared with the no treatment group. The pooled RR for these studies was 0.56 (95% CI 0.48–0.65). The concern with these trials is that there was no placebo, so caution is needed in interpreting this “positive” result.

Treatment versus placebo

In the six trials comparing treatment with placebo, the outcomes (symptom scores, running nose and duration of illness) was a statistically significant pooled result. They were continuous outcomes, and hence an NNTB could not be calculated. In the four trials of treatment comparing placebo with running nose as the outcome, the pooled result was statistically significant (weighted mean difference [WMD] = −0.65; 95% CI = −0.93 to −0.37). In two trials comparing treatment with placebo for outcomes in terms of duration of symptoms, the pooled result was statistically significant (WMD = −1.0; 95% CI = −1.98 to −0.02). In a recent, large, placebo-controlled trial, Echinacea purpurea, as dosed in this study, was not effective in treating upper-respiratory infection symptoms in children aged between 2 and 11 years, and its use was associated with an increased risk of rash. The authors of the Cochrane review made the following comments: “While overall there is some positive evidence, few recommendations can be made regarding the use of Echinacea products in practice. The heterogeneity
of the available preparations and the limited quality and consistency of the evidence do not allow clear conclusions about which product might be effective in what dose and in what circumstances. Patients and healthcare providers who want to use preparations containing extracts of Echinacea should be aware of the possible extreme differences in the chemical composition and that there is no solid base of evidence concerning their efficacy.5"

Heated, humidified air for the common cold

This systematic review on heated, humidified air for the common cold7 assessed the use of inhaled heated water vapour with the help of a rhinotherm (a machine designed to deliver heated water vapour to a person’s nasal cavity) in the treatment of the common cold. The control group usually received unheated humidified air. Efficacy of this intervention in the studies carried out in UK and Israel differed from those carried out in the USA with similar equipment and methodology. The studies from Israel and UK reported beneficial effect of rhinotherapy in individuals with rhinopharyngitis, whereas three randomized-controlled trials from the USA failed to replicate the findings of these previous investigators. Equipment used to administer the warm vapour differed slightly in the UK (anaesthetic mask) and USA (nozzle). Findings for symptom score, nasal culture washings or a subjective perception of benefit were not significant. The reviewers concluded by stating: ”since the studies reporting use of rhinotherapy have shown only subjective benefit in the symptoms of the common cold in the UK and Israel, this therapy cannot be recommended universally because the results of trials from the US are equivocal.”

Nasal decongestants for the common cold

Five studies were suitable for inclusion in the review on nasal decongestants for the common cold,4 which contained only single component or single-dose studies. For the single-dose studies, four studies were included, and all were statistically significant for a reduction in the nasal symptom of congestion after treatment compared with placebo. The WMD between active and placebo was –0.13 (95% CI –0.19 to –0.06). Discrete outcomes were not reported, hence an NNTB was not able to be calculated. No objective data were available for these studies. Overall, the reduction in nasal airway resistance for active medication compared with placebo was significant. The forms of medication included oxymetazoline nasal drops, oral phenylpropranolamine, oral norphedrine and oral pseudoephedrine.

For the multiple-dose studies, only one study used oral pseudoephedrine 60 mg.8 No significant benefit was found for the symptom of congestion after repeated doses of decongestant over a 5-day period. Again, no discrete data were reported, hence NNTB could not be calculated. Because of the lack of other studies to support this result, no conclusion can be drawn on the efficacy of repeated doses of decongestant.

Over-the-counter medications for acute cough in children and adults in ambulatory settings

Acute cough is a common symptom, and is often associated with the common cold. Many people self-prescribe OTC cough medicines for themselves or their children, and many primary-care clinicians recommend them to their patients as first-line treatment. OTCs are available to the public from pharmacies and shops often without medical prescription, although, in some countries, they can be prescribed (Table 1).

Antitussives in adults

The Cochrane review of OTC medications for acute cough in children and adults in ambulatory settings9 assessed six trials comparing antitussives with placebo. Codeine was no more effective than placebo in reducing cough symptoms in doses of 120 mg per day or as a single dose of 50 mg. Three studies were included, all of which examined dextromethorphan in a single dose of 30 mg. Two studies favoured dextromethorphan over placebo, whereas a third study showed no effect. Moguisteine in doses of 600 mg/day was no more effective than placebo, apart from reducing cough in a subgroup of participants with more severe night cough. Significant adverse effects were found in the intervention group, which consisted mainly of nausea, vomiting and abdominal pain (NNTH = 7).

Expectorants in adults

Two trials compared guaifenesin with placebo. In the larger study, participants taking guaifenesin
200 mg four times a day stated that the medicine was helpful compared with placebo in reducing the cough frequency and intensity, with an NNTB of 2. Four participants (two in each group) reported side-effects, including nausea and hives in the active treatment group, and headaches, drowsiness and excessive perspiration in the placebo group. In another study, sputum thickness was significantly reduced for guaifenesin 480 mg 6 hourly with an NNTB of 2. Adverse effects were not reported in this study.

**Mucolytics in adults**

One trial compared a mucolytic (bisolvon linctus) 5 mg three times daily for an average of 4 days with placebo. Active treatment reduced cough frequency and symptom scores on days 4 and 8. The NNTB was 15 and adverse effects were not reported.

**Antihistamine–decongestant combinations in adults**

Two studies compared antihistamine–decongestant combinations with placebo. Dextrompheniramine (a sedating antihistamine)–pseudoephedrine (6 mg/120 mg twice daily for 1 week) was significantly more effective than placebo for severity of cough. Adverse effects increased, including dizziness and dry mouth. In the other study, loratadine (a non-sedating antihistamine)–pseudoephedrine (5 mg/120 mg twice daily for 4 days) did not show any difference between the study groups. Thirty per cent of the intervention reported dry mouth, headache and insomnia compared with 21% in the placebo group. This translated to an NNTH of 11.

**Other drug combinations in adults**

Three studies compared combinations of drugs other than antihistamine–decongestant with placebo. They contained multiple compounds, such as Vicks Mednite, which contains dextromethorphan, doxylamine, ephedrine and paracetamol. When Vicks Mednite was given as a single dose at bedtime for 2 days, 57.6% of participants in the active treatment group rated the formulation as "good" or better in relieving cough compared with 32.2% in the placebo group, with an NNTB of 4. Seven participants in the active treatment group reported giddiness or drowsiness compared with four participants in the placebo group. Another medication known as EM-VIER was more effective than placebo for reducing cough in adults (reduced coughing fits 25% vs. 11%, NNTB 7 and reduced urge to cough with NNTB of 7). No adverse effects were observed in both groups. Another study compared a dextromethorphan-salbutamol combination, and dextromethorphan alone with placebo. Dextromethorphan-salbutamol was superior to placebo or dextromethorphan alone in relieving cough at night (mean symptom score 0.19 vs. 0.67 and 0.44, respectively, on day 4. The dextromethorphan-salbutamol combination led to more tremor than placebo, and no serious adverse effects were reported.

**Antihistamines in adults**

Three trials compared antihistamines with placebo. Antihistamines were no more effective than placebo in relieving cough symptoms. Adverse events were about equal in the intervention and control groups.

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**Table 1  Potential treatments for the common cold***

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptom</th>
<th>NNTB</th>
<th>NNTH</th>
<th>Cochrane reviewers' assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamine</td>
<td>Global improvement</td>
<td>12–17</td>
<td>14–93</td>
<td>Only for high-quality studies</td>
</tr>
<tr>
<td>Antihistamine decongestant</td>
<td>General improvement</td>
<td>2.5–4</td>
<td>11</td>
<td>Dry mouth. Not effective in under 5-year olds</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>and nasal symptoms</td>
<td>NR</td>
<td>NR</td>
<td>Two out of three studies show benefit</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>NR</td>
<td>NR</td>
<td>Benefit only at 1 day</td>
</tr>
<tr>
<td></td>
<td>Congestion</td>
<td>NR</td>
<td>NR</td>
<td>Both studies had significant results</td>
</tr>
<tr>
<td>Nasal decongestant</td>
<td>Cough, sputum thickness</td>
<td>2</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Guaifenesin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptoms of cold</td>
<td>15</td>
<td>NR</td>
<td>Only one study on this medication</td>
</tr>
<tr>
<td>Bisolvon</td>
<td></td>
<td>4–8</td>
<td>6</td>
<td>Concerns about unblinding</td>
</tr>
<tr>
<td>Zinc lozenges</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Some of these results differ from the conclusions of specific Cochrane reviews, but are presented in a comparative format to give some direction to patients keen on taking a remedy. NNTB, number needed to treat for one person to benefit; NNTH, number needed to treat for one person to harm; NR, not reported.*
Results of studies in children

Antitussives in children

One study of 57 children (mean age 4.7 years; range 18 months to 12 years) with night cough compared a single dose for 3 nights of dextromethorphan and codeine with placebo. No benefit was found for either medication over placebo.

Expectorants in children

No studies using expectorants met the reviewers’ inclusion criteria.

Mucolytics in children

A trial of letosteine (25 mg three times daily for 10 days with placebo) reported symptom score on a four-point scale favouring active treatment from day 4 until day 10. This medication is not currently available in the UK.

Antihistamine–decongestant combinations

Two studies compared antihistamine–decongestant (brompheniramine–phenylpropanolamine) combinations in children aged 6 months to 5 years, and neither was more effective than placebo. In one of the studies, a higher proportion of children were asleep in the active treatment group (46.6%) than in the placebo group (26.5%, \(P = 0.53\)).

Other drug combinations

One trial involving 43 children tested two paediatric cough syrups (Triaminicil syrup and Dorcol paediatric cough syrup). Compared with placebo, 69% of children in both active treatment groups showed a satisfactory response reported by their parents compared with 57% of children in the placebo group, which did not reach statistical significance (\(P = 0.5\)). Adverse effects were not reported.

Another RCT in 51 children compared a combination of dextromethorphan 1.5 mg per ml and salbutamol 0.2 mg per ml 5 ml three times daily for children under the age of 7 years or 10 ml three times a day for older children with placebo. There was no evidence of efficacy.

Antihistamines in children

One trial testing antihistamines in children aged 1.5–5 years found that they were no more effective than placebo.

Vitamin C

The role of oral vitamin C (ascorbic acid) in preventing and treating the common cold has been controversial for many years. Public interest is high, and vitamin C continues to be widely sold and used as a preventive and therapeutic agent for this condition. The systematic review on vitamin C only considered studies of vitamin C 200 mg or more per day.

Prevention of the common cold

Twenty-three studies in "normal people" were included, and the pooled relative risk was of borderline statistical significance (RR 0.98; 95% CI 0.95–1.00). A subgroup of six papers studying marathon runners, skiers and soldiers on subarctic exercises reported another pooled relative risk of borderline statistical significance for prevention of common colds (RR 0.96; 95% CI 0.92–1.00).

The Cochrane reviewers make this comment: “Although these findings point to a definite physiological effect by prophylactic vitamin C on common cold duration, the practical significance of these findings is less convincing. It would not seem reasonable to ingest vitamin C regularly in the mega-dose range throughout the year if the only anticipated benefit is to rather slightly shorten the duration of colds which occur for adults, two or three times per year. Our pooled estimate suggests that long-term supplementation might result in an upper estimate average reduction of annual common cold morbidity from about 12 days (based on Douglas 1979; unpublished Australian data) to about 11 days per year for adults. For children under 12 years who experience colds more frequently, long-term prophylaxis might be associated with an average reduction in 4 symptom days from about 28 days to 24 days per year per child. Such a benefit is not trivial, but is it worth the cost of long-term prophylaxis, and could an equivalent benefit perhaps be achieved in children through therapy alone?” They also make the comment that, in some populations, there may be a low intake of vitamin C and hence explain why some studies find a benefit.
and some do not. Most studies do not take into account regular vitamin C intake.

**Treatment of the common cold with vitamin C**

Seven trials of treatment of the common cold after symptoms have been published, but no significant difference was seen from placebo. However, one large trial reported equivocal benefit from a 4 g therapeutic dose at onset of symptoms.

**Prevention of the common cold with vitamin C**

The failure of vitamin C supplementation to reduce the incidence of colds in the normal population indicates that routine mega-dose prophylaxis is not rationally justified for community use. However, evidence shows that it could be justified in people exposed to brief periods of severe physical exercise, cold environments, or both. Also, the consistent and statistically significant small benefits on duration and severity for people using regular vitamin C prophylaxis indicates that vitamin C plays some role in respiratory defence mechanisms.

**Zinc for the treatment of the common cold**

The systematic review of zinc for the treatment of the common cold\(^\text{11}\) included seven studies examining the use of zinc lozenges for the treatment of the common cold. The reviewers were conservative about the findings, yet an intention-to-treat analysis at 7 days found a statistically significant RR of 0.69 (95% CI 0.56–0.85). The NTNB ranged from 4 to 8 for PEERs at 0.62 to 0.34, respectively. The authors were concerned about the dose of medication and blinding of studies. In four trials, participants treated with zinc complained of altered or bad or unpalatable taste, which suggests zinc lozenges were distinct from placebo lozenges and, in this respect, blinding may have been compromised. In one of the trials, the formulation contained 13.3 mg zinc, about half that used in most other trials; the incidence of nausea in participants treated with zinc (10/49) was significantly increased from that reported for participants taking placebo (2/50). This is an NNTH of 6. Irritation of the oral mucosa and distortion of taste have also occurred at higher incidences in participants treated with zinc.

**Practice points**

- Negotiation about the likely benefits and harms of any of the non-antibiotic treatments is warranted, as few are consistently beneficial.
- First-dose decongestants, either topical or oral, seem to be effective for symptom control
- Antihistamine decongestant combinations seem to be effective for a wide range of symptoms
- Patients need to be reminded that symptoms do linger and that, at 10 days from the onset of illness with the common cold, 25% still have symptoms\(^\text{12}\)

**Research directions**

- A large, high-quality factorial, randomized-controlled trial comparing antihistamines, decongestants and the combination with placebo needs to be undertaken to clarify the effective component(s)
- Large, high-quality, randomized-controlled trials are needed to clarify the efficacy of dextromethorphan, bisolvon and guifenesin

**References**

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