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RESTRICTING COUGH AND COLD MEDICINES IN CHILDREN

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“There are probably few, if any, ailments more frequently treated by the sufferer or his friends, without recourse to medical advice, than coughs and colds” (from a BMA publication, 100 years ago)

Secret Remedies – what they cost and what they contain. BMA, 19091
Abstract:

Based on concerns about safety and efficacy, authorities in the United Kingdom and Canada have advised against the use of cough and cold pharmaceuticals in children aged less than 6 years. Authorities in the United States, Australia and New Zealand are considering similar action. For decades cough and cold medicines have been heavily used in children, part of a major social phenomenon of medication for the symptoms of common illnesses, with little evidence of harm, at least in Australia. We systematically reviewed the evidence for the effectiveness and safety of cough and cold medicines in children. There was little support for the effectiveness of these medicines for acute cough or the common cold in children. However, the majority of these medicines do not appear to be highly toxic in children and are not a major cause of severe effects following unintentional poisoning. The common use of these agents does not appear to be responsible for increased deaths in young children. Many cases of toxicity from cough and cold medications in young children are a result of therapeutic error. Particular medications, including diphenhydramine and codeine, appear to be associated with a high frequency of severe adverse effects and toxicity. Restriction of cough and cold medicines in children is supported by currently available evidence.
Introduction

The current interest in restricting cough and cold medicines began with a ‘citizen petition’ to the US Food and Drug Authority (FDA) in 2007. The citizens were mainly academic paediatricians and health administrators. While the FDA is yet to rule on the petition, major drug companies have voluntarily withdrawn cough and cold medicines for children under 4 years old.

Currently available cough and cold pharmaceuticals for children in Australia contain an antitussive, an antihistamine, a decongestant, or an expectorant, or combinations of these (Table 1). Most of these drugs have been used for more than 30 years. There are currently more than 70 medicines in liquid formulations with label doses for children aged over two years. Australian drug regulations restrict most of these medicines to sale in pharmacies. Many parents and health professionals consider them safe and effective in treating cough and cold symptoms, and they are listed in pharmacopoeias for these purposes. However, even rare adverse events could be important if use is common. A recent study revealed the astounding finding that about 1 in 10 children in the USA had used a cough and cold medicine in the previous week, with the highest usage rate in children 2-5 years.²

There have been indisputable reports over decades of serious poisoning including death from the drugs used in cough and cold medicines. Most of the latter occurred in the age group <3 years, with unintentional ingestion of very high doses, often solid formulations intended for adults. In Australia, most cough and cold medicines have been required to be
sold with child-resistant closures for many years, and although ingestion of excess doses of liquid cough and cold medicines in young children is still commonly reported, it is only very rarely serious or requiring of treatment. We undertook a systematic review of the use of cough and cold medicines.
Methods

We conducted a systematic review to identify all articles relating to the use of products to treat symptoms of the common cold, influenza or allergic rhinitis, and any article relating to poisoning or toxicity from unintentional ingestion or overdose in children. The initial search strategy was broad and included the use of these drugs in other conditions and also age groups other than children. However, after review of titles and abstracts, the final review did not include complications of the common cold, such as otitis media and pneumonia, or ages greater than 12 years.

The initial search was of Medline and Embase via the Ovid platform, using the following search strategy: \{ingredient = all individual medications\} and (cough and cold or flu or influenza or antitussive or antihistamine or decongestant or expectorant) and (efficacy or effectiveness or safe or safety or adverse or hazard or warning or mortality or death or toxic or toxicity or toxicology or poison or poisoning or masking or mask or clinical trial or clinical trials). Full details are available from the authors.

One author (GKI) reviewed all the abstracts obtained in the initial search and selected relevant studies for full text review. The authors also cross-checked the references from directly relevant Cochrane review articles\(^3\text{-}^5\) for any further studies and searched reference lists from all articles when full text was obtained. Because the review was to consider both effectiveness and safety of cough and cold medications and the paucity of evidence, no meta-analysis of the information was attempted. The results are presented as a narrative review.
Results

Following the initial search, 295 abstracts were read including relevant references from the Cochrane reviews to identify full text articles for review. Of the full text articles, 72 were relevant. Clinical trials in children of relevance and high quality are included in tables 2 and 3.

Antitussives for acute cough in children

Dextromethorphan

Dextromethorphan is a cough-suppressant commonly used in children and adults. Despite this, there is little evidence to support its effectiveness for acute cough in children, from a Cochrane review\(^3\) and a number of randomised controlled trials (Table 2). A letter discussing the Cochrane review provided information on three further studies and raises the important issue of possible inadequate dosing in children (see below).\(^6\) Two early studies\(^7,8\) suggested that dextromethorphan (with or without salicylic acid) was beneficial for cough, but may contain some methodological flaws.\(^6\) A third more recent study compared dextromethorphan with or without salbutamol against placebo and found no benefit for cough symptoms.\(^9\) There are no paediatric studies assessing objective outcomes for acute cough comparing dextromethorphan with placebo.\(^6\) However, a meta-analysis does suggest dextromethorphan is beneficial for acute cough in adults.\(^10\)

There is a concern that the dose of dextromethorphan is insufficient in children and two studies have reported a dose-response effect with dextromethorphan.\(^7,11\) The more recent study provides important evidence.\(^11\) This analysis was a sub-study of one of the negative
RCTs\textsuperscript{12} and it investigated the effect of dose on outcomes in the clinical trial. Although it did not show a statistically significant difference in response between three dose (mg/kg) ranges in children from the dextromethorphan arm of the trial, there was a clear trend that the middle and higher doses did produce better symptom relief. This raises the question that the RCTs in children may be negative because of incorrect and/or insufficient dosing of dextromethorphan. This study is sufficient evidence to suggest that a controlled trial should be done of higher doses (0.5mg/kg) of dextromethorphan with doses in mg/kg and not by age brackets, the current usual practice. The same study also suggested increased adverse effects (CNS excitation) with larger doses which were also not seen in the other controlled trials where adverse effects were similar between placebo and active groups.

There are a number of case reports and case series providing information on the toxicity of dextromethorphan.\textsuperscript{13,14} The majority focus on abuse which is not relevant for this review. The FDA conducted a review in 1983 of 33 cases in children suggesting that dextromethorphan was relatively safe and mainly causes CNS excitation in overdose. There were no fatalities, even with doses exceeding 100 times the normal dose.\textsuperscript{14} A recent series of 304 cases with a mean ingested dose of 2.64mg/kg, all who co-ingested other agents, reported no deaths and only minor effects.\textsuperscript{15} Mild CNS depression occurred in 20\% of cases.

Toxicity is reported above 10mg/kg and seizures with 20-30mg/kg. There have been a number of case reports of toxicity in children, most focusing on the use of naloxone, with some response to this treatment. One recent case with a large amount (38mg/kg) caused a
dystonic reaction. Combinations of dextromethorphan and pseudoephedrine have caused a number of adverse effects in young children such as irritability, ataxia and psychosis.\textsuperscript{16} There are a number of published deaths with dextromethorphan in combination with other agents, the latter probably the lethal agent. Overall it appears that dextromethorphan is relatively safe in overdose. Poisoning with combinations of dextromethorphan and antihistamines or adrenergic agents is likely to be more toxic.\textsuperscript{13}

**Codeine**

The American Academy of Pediatrics Committee on Drugs made a statement in 1997 that there was insufficient evidence to support the safety or efficacy of codeine in children.\textsuperscript{17} There are few studies on codeine syrups in children.\textsuperscript{18} Two studies in adults found codeine was no more effective than placebo for acute cough,\textsuperscript{3} and it is not recommended for acute bronchitis in adults.\textsuperscript{19} There is a reasonably large literature on the use of codeine as an analgesic in paediatrics and this is reviewed in detail by Williams et al.\textsuperscript{20} There is one small comparison of placebo, dextromethorphan and codeine (Table 2) which concludes that codeine syrup was no more effective than placebo.\textsuperscript{21} Another comparison study suggests that codeine is more sedative (and less palatable) in children than pholcodeine.\textsuperscript{22}

Codeine appears to cause more adverse effects than other opioid type antitussives, based on a comparative study\textsuperscript{22} and reports of fatal cases due to respiratory depression and cyanosis.\textsuperscript{23-26} These cases are mainly reported with the therapeutic (albeit incorrect) use of codeine phosphate and not unintentional overdoses. This would support the view that,
although uncommon, there is a significant risk of death from therapeutic use of codeine, even in children up to the age of 6 years.\textsuperscript{23-25}

The toxic effects of codeine are most likely a result of morphine toxicity, because of the conversion of codeine to morphine by cytochrome P450 2D6 (CYP 2D6). The genetic polymorphic variability of CYP 2D6 is well known for the metabolism of many drugs. Although the significance of this for codeine in terms of its effectiveness in children is not well understood,\textsuperscript{20} CYP 2D6 ultrarapid metabolism of codeine is now recognised as a major cause of codeine toxicity in adults and children.\textsuperscript{27,28} This genetic variability will add to the uncertainty and unpredictability of adverse effects in children. A more significant problem is the use of codeine in breastfeeding mothers which can result in severe adverse effects and death from morphine toxicity in the infants associated with increasing maternal codeine dose and the mother being a CYP 2D6 ultrarapid metaboliser.\textsuperscript{29,30} The use of codeine in all age groups needs review with the increasing understanding of the importance of the genetic variability in the metabolism of codeine.\textsuperscript{30}

\textbf{Pholcodine}

No studies could be found in children investigating the effectiveness of pholcodine for acute cough.\textsuperscript{3} Limited review of previous adult studies provide conflicting evidence and studies were poorly designed.\textsuperscript{31,32} There were no cases of acute toxicity from pholcodine identified in the literature. Recent studies have shown that exposure to pholcodine cough syrup causes a large increase in levels of IgE antibodies to pholcodine, morphine and suxamethonium, raising the potential risk of future allergic reactions to neuromuscular
blocking agents.\textsuperscript{33,34} The authors of these studies have recommended restriction of pholcodine because of the risk of future allergic reactions to essential drugs.\textsuperscript{33}

**Dihydrocodeine**

There are no efficacy/effectiveness data for dihydrocodeine in children. There is limited information on the toxicity of dihydrocodeine, mainly in adults.\textsuperscript{35,36} No cases in children were identified in this review, although it was not exhaustive.

**Expectorants for acute cough in children**

There is limited evidence for any expectorant in acute cough and acute upper respiratory tract infection for any age group. A review of their use in adult respiratory conditions recommended the use of ipratropium bromide only for cough suppression in patients with cough due to an upper respiratory tract infection or chronic bronchitis.\textsuperscript{19} There are no studies of ipecacuanha, ammonium chloride or bromhexine for acute cough in children. Adult studies of bromhexine were mainly negative or of marginal benefit for cough.\textsuperscript{19}

There are a few reports of toxicity from ammonium chloride in cough mixtures, including metabolic acid-base abnormalities with abuse.\textsuperscript{37} Bromhexine appears to have minimal toxicity and there are no reports of major toxicity in children. There are no specific or individual reports of guaifenesin poisoning, although it is often co-ingested in cough and cold preparations with no reports of major toxicity.\textsuperscript{15} Ipecacuanha is occasionally abused by adolescent and young adults with eating disorders.\textsuperscript{38}
Antihistamine monotherapy for the common cold and acute cough in children

Antihistamines are either used by themselves or in combination with an alpha-adrenoceptor agonist for the treatment of the symptoms of the common cold, acute cough, nasal decongestion and allergic rhinitis. A Cochrane review of antihistamines for the common cold concluded that antihistamine monotherapy did not improve nasal congestion, rhinorrhea, sneezing or the subjective symptoms of the common cold in children or adults.5 This was consistent with three former critical reviews of the literature.39-41 There were two studies in children of antihistamine monotherapy for the common cold considered by the Cochrane review, but one was of astemizole, a second generation antihistamine.42,43 (Table 3) The other study demonstrated no benefit of chlorpheniramine based on subjective and objective assessment.43 One further study of antihistamines for acute cough compared diphenhydramine to placebo (a third arm was dextromethorphan) and found no benefit of diphenhydramine over placebo for cough symptoms in children.12 (Table 2)

There are no studies of dexchlorpheniramine maleate, diphenhydramine hydrochloride, pheniramine maleate, promethazine hydrochloride, doxylamine succinate or tripolidine hydrochloride in children with the common cold or cough. One study in adults showed no difference between doxylamine succinate and placebo for treating runny nose or sneeze with upper respiratory tract infection.44

The Cochrane review concluded that first generation antihistamines cause more side-effects than placebo, particularly an increase in sedation for patients with the common
There are numerous case reports of antihistamines causing severe toxicity or death in infants and young children which is most likely a reflection of the epidemiology of poisoning. However, the majority of these are diphenhydramine toxicity in children. There is significant evidence and reports of cases to support diphenhydramine being the most cardiotoxic of the antihistamines, including numerous cases reported in children. Numerous deaths from diphenhydramine mono-intoxication have been reported in children, and in a series of infant fatalities from OTC medications, diphenhydramine is one of the more common drugs found.

Reports of toxicity and deaths from other antihistamines are much less common. This is especially relevant for brompheniramine and chlorpheniramine, both of which have significant use in this age group, but cases of severe toxicity and death from single ingestions of these agents could not be identified in the literature. There are reports of toxicity and death from combinations of brompheniramine and decongestant agents.

**Antihistamine-decongestant combinations for the common cold and acute cough in children**

Antihistamine-decongestant combinations are also frequently used to treat cough and cold symptoms. However, the Cochrane review found no improvement in general condition, nasal obstruction, rhinorrhea or sneezing in children taking antihistamine-decongestant combinations compared to placebo. There were two studies of antihistamine-decongestant combinations in children (Table 3). One study compared a combination of phenylephrine, phenylpropanolamine and brompheniramine, to placebo
and no treatment, and found no benefit.\textsuperscript{52} It also found no difference in side-effects between active and placebo groups.\textsuperscript{52} The other study compared brompheniramine and phenylpropanolamine, to placebo and found no difference except children in the active placebo group were more likely to fall asleep within two hours of treatment.\textsuperscript{53} A difficulty with making any conclusion from these studies is that they both included phenylpropanolamine which has been restricted or withdrawn from the market worldwide and not available in Australia.

Numerous adverse effects have been reported following therapeutic misadventure and poisoning with antihistamine-decongestant combinations in children. The clinical features reflect a combination of antihistamine and sympathomimetic toxicity, and fatalities have occurred.\textsuperscript{51} Dystonic reactions have been reported with cough and cold preparations containing antihistamine-decongestant combinations.\textsuperscript{54}

\textbf{Nasal decongestants for the common cold}

No studies in children of nasal decongestants for the common cold were identified and a Cochrane review concluded that there was insufficient evidence for the use of nasal decongestants in children\textsuperscript{4}. However, the review did conclude from adult studies that there was a small but statistically significant decrease in subjective symptoms and a significant decrease in nasal airways resistance with nasal decongestants when treating symptoms of the common cold.\textsuperscript{4} Four of these studies included pseudoephedrine as the decongestant either as a single dose or as repeated doses. A recent study of xylometazoline in adults suggests a benefit for symptoms and objective outcomes in
patients with the common cold. One study of xylometazoline in children showed it increased nasal flow but there was no control group.

A recent systematic review and meta-analysis of the efficacy and safety of oral phenylephrine found no support for phenylephrine in the common cold by assessing both objective (nasal airways resistance) and subjective (symptoms) measures of efficacy. A study in young children (6 to 18 months) with the common cold found that topical phenylephrine did not improve abnormal middle ear pressure.

One study that compared paracetamol and an antihistamine-decongestant mixture (diphenhydramine + pseudoephedrine) to paracetamol alone, found no difference in children (2 to 12 years old) with acute nasopharyngitis.

There are numerous reports of nasal decongestants (or over-the-counter combinations containing them) causing toxicity in children which again reflects the widespread use of these agents. One series of infant fatalities implicated over-the-counter medications as the cause of death or contributing factor in 8 out of 15 cases with pseudoephedrine being the most prominent single agent. These deaths all occurred in infants where unintentional overdose was unlikely and most cases were the results of a therapeutic error. In another series of infant fatalities and over-the-counter medications, pseudoephedrine was one of the more common agents found in post-mortem blood. Pseudoephedrine passes into breast milk and irritability and disturbed sleep have been reported in infants exposed to pseudoephedrine in breast milk. Individual cases of pseudoephedrine in combination
with other agents in over-the-counter medications have been reported to cause toxicity.\textsuperscript{16} There is limited data on the safety of phenylephrine.

A case series of xylometazoline poisonings in children has been recently reported. This study suggests that the majority of cases cause minimal effects and that severe effects occur with ingestions greater than 0.4mg/kg.\textsuperscript{62} There are very limited reports on oxymetazoline with one Portuguese report of 4 cases as part of a study of toxicity of imidazoline derivatives in children.\textsuperscript{63}
Discussion

This review has found little support for the effectiveness of cough and cold medicines for acute cough or the common cold in children. However, the majority of these medicines do not appear to be highly toxic in children and are not a major cause of severe effects following unintentional poisoning. We cannot support the suggestion that in common usage these agents are responsible for increased deaths in young children. Many cases of toxicity from cough and cold medications in young children are a result of therapeutic error, so education and restriction will play a role in the supply of these medications. Particular medications, including diphenhydramine and codeine appear to be associated with a much high frequency of severe adverse effects and toxicity and their use should be reviewed given the availability of less toxic alternatives.

Reports of severe morbidity and mortality associated with cough and cold medications in children need to be interpreted with care. The aetiology of poisoning in children is complex and simple removal of a group of products may not reduce poisoning in this age group. Statements that deaths or poisoning in children from cough and cold medications peak around the age of 2 years simply reflects the unintentional nature and epidemiology of childhood poisoning and do not suggest that these agents are more toxic than many other medicines. One recent study of children not treated in hospital suggested that a larger proportion of children aged 2 to 11 have moderate to severe toxicity from cough and cold medications compared to the under 2 year old age group. In contrast, a study of fatalities in children associated with cough and cold medications identified age less than 2 years as a contributing factor. Another study of 90 unexpected infant deaths did
find an association with over-the-counter cough and cold medications in 10 of 21 patients where post-mortem toxicology was available.\textsuperscript{66} However, this study may simply reflect the common use of these agents and respiratory illness being a major cause of infant death. Only one of the ten deaths was attributed to cough and cold medication (dextromethorphan) toxicity.\textsuperscript{66}

Regulatory authorities in several countries are taking the unusual route of collectively revisiting cough and cold medicines, i.e. dissimilar drugs being used for similar purposes. Because of their legislated responsibilities, it is difficult for authorities not to act when efficacy/effectiveness and safety are in doubt, even more so when the drugs are used in benign, self-limiting conditions. Self or parent-directed use of non-prescription pharmaceuticals and complementary medicines is an enormous industry, reflecting the importance to people of having some autonomy in treatment. Treating cough and other cold symptoms comprises the largest component of “social medication” in children, and will continue regardless of any changes in availability of some categories of medicines.

Sedation, from drowsiness to deep sleep, is a side-effect of sedating antihistamines, but may be the desired effect for many parents with a miserable sick sleepless young child. Such parents may logically believe sleep will help both the child and themselves. Health professionals would generally condemn this practice because there is no evidence to support it. One controlled trial showed that diphenhydramine was no different to placebo for night-time wakenings.\textsuperscript{67} However, there is little evidence that limited, short-term oral sedation is harmful. Recent research suggests that parents use of cough and cold
medications as a form of “social medication” to give parents more control of the situation. Parents have confidence in these medicines which suggests the strength of the placebo effect and some are certain that paracetamol is a sedative.

Parents might reasonably expect physicians to be a safe source of advice on management of common childhood illnesses. Obviously this should be evidence-based when possible but otherwise simple and honest. For coughs and colds, parental presence, comforting and calming the child come first. Simple ‘soothing’ medicines such as honey and lemon, or an occasional dose of paracetamol or ibuprofen for a miserable child, or saline nose drops for a child suffering from a blocked nose, while largely lacking an evidence-base, give parents options they can consider for their child.

Further restriction of children’s cough and cold pharmaceuticals may lead to off-label use of cough and cold medicines intended for older age-groups, inappropriate use of other medicines, additional use of complementary medicines for which no evidence base exists, and possibly alcohol and methadone. Although there is limited evidence to support substitution of cough and cold medications, one study has shown increased poison centre calls for unintentional paediatric poisoning with ibuprofen when paracetamol was removed temporarily in Australia. It will therefore be important to monitor the frequency of adverse events in young children following the restriction of cough and cold medicines for children aged less than 2 years.
One benefit of restricting these drugs may be the increase in pharmacological studies of cough and cold medications in children which would not otherwise be done, and which may possibly show some to be effective. It should encourage the search for novel, safe and effective antitussives. An example of this is the use of honey for cough. One study suggested that honey improved symptoms and reduced cough frequency compared to no treatment. In addition, it should encourage a re-thinking of the management of common childhood illness and the role parents play in this.
Conclusions

Further restriction of cough and cold medicines in children is supported by currently available evidence. Restriction is accompanied by risk (of what will be used instead) but also the opportunity of re-evaluating the phenomenon of “social medication” and the best care of children with common illnesses. Both require far more study. The use of these drugs should decline, but there remains an unfilled need for proven, effective and safe medicines for acute cough and colds in children.
Key points:

- Children’s cough and cold medicines are highly heterogeneous in categories and varieties of activities, and extensively used by parents in varied circumstances. Decisions on restricting these medicines must be made on current evidence of effectiveness and safety, but also heeding the wider contexts of their use.

- Few available studies of the effectiveness of these medicines reach current scientific standards and for some drugs there are no studies in children. There is only poor evidence for their effectiveness in treating cough and other cold symptoms. None would be accepted for these indications if presented now as new drugs.

- Cough and cold medicines for children are generally safe. Serious harm almost never occurs in normal use or even significant overdose with liquid formulations. The association between deaths or poisoning in children from cough and cold medications peaking around the age of 2 years simply reflects the unintentional nature and epidemiology of childhood poisoning and does not suggest that these agents are more toxic than many other medicines. However, specific safety concerns have now been identified for some drugs.

- Restriction of cough and cold pharmaceuticals formulated for children may lead to increased off-label use of other pharmaceuticals, complementary medicines and other
potentially dangerous treatments. Effective positive information for parents on the optimal care of children with coughs and colds may reduce such risks.
Table 1: Drugs used in Australian cough and cold medicines for children

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihistamines:</strong></td>
<td>brompheniramine maleate, chlorpheniramine maleate,</td>
</tr>
<tr>
<td></td>
<td>dexchlorpheniramine maleate, diphenhydramine hydrochloride,</td>
</tr>
<tr>
<td></td>
<td>doxylamine succinate, pheniramine maleate, promethazine</td>
</tr>
<tr>
<td></td>
<td>hydrochloride, triprolidine hydrochloride</td>
</tr>
<tr>
<td><strong>Antitussives:</strong></td>
<td>codeine phosphate, dextromethorphan hydrobromide,</td>
</tr>
<tr>
<td></td>
<td>dihydrocodeine tartrate, pentoxyverine citrate, pholcodine</td>
</tr>
<tr>
<td><strong>Mucolytics:</strong></td>
<td>ammonium chloride, bromhexine hydrochloride, guaifenesin,</td>
</tr>
<tr>
<td></td>
<td>ipecacuanha</td>
</tr>
<tr>
<td><strong>Decongestants:</strong></td>
<td>phenylephrine hydrochloride, pseudoephedrine hydrochloride,</td>
</tr>
<tr>
<td></td>
<td>oxymetazoline hydrochloride, xylometazoline hydrochloride</td>
</tr>
</tbody>
</table>
Table 2: Details of relevant and well-conducted controlled trials of antitussives, antihistamines and decongestants for acute cough

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Quality/ Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor JA 1993</td>
<td>RCT</td>
<td>49 children</td>
<td>Placebo vs. Dextromethorphan vs. Codeine</td>
<td>No differences over 3 days. Improvement related to initial severity</td>
<td>Small study; well conducted</td>
</tr>
<tr>
<td>Korppi 1991</td>
<td>RCT</td>
<td>75 children</td>
<td>Placebo vs. Dextromethorphan vs. Dextromethorphan+Salbutamol</td>
<td>No difference</td>
<td>Not blinded</td>
</tr>
<tr>
<td>Paul 2004</td>
<td>RCT</td>
<td>100 children</td>
<td>Placebo vs. Diphenhydramine vs. Dextromethorphan</td>
<td>No difference over 1 night</td>
<td>Good concealment; Letter to editor about placebo being sucrose, poor cough scores and treatment for 1 night only</td>
</tr>
<tr>
<td>Paul 2007</td>
<td>RCT</td>
<td>105(35H,33DM,37Pl)</td>
<td>Placebo vs. Dextromethorphan vs. Honey</td>
<td>No difference for DM, possibly improvement with honey</td>
<td>Well conducted</td>
</tr>
<tr>
<td>Jaffe 1983</td>
<td>RCT</td>
<td>217 children</td>
<td>Comparison, no placebo; but compared pholcodeine mixture with codeine mixture</td>
<td>Codeine less palatable and caused more drowsiness.</td>
<td>No information on efficacy (comparison), but suggests codeine is more sedative and less palatable.</td>
</tr>
</tbody>
</table>

RCT – randomised controlled trial; DM – dextromethorphan; Co – Codeine; Pl – placebo; SAL – salbutamol; DP – diphenhydramine; H – honey; PholMix – pholcodeine mixture; CodMix – codeine mixture;
Table 3: Relevant studies of antihistamines and antihistamine-decongestant combinations for the treatment of the common cold.

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Quality/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihistamine Monotherapy</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sakchainanont 1990(^{33})</td>
<td>RCT</td>
<td>95 (Clem 48, Chl 48, Pl 47)</td>
<td>Placebo vs. Chlorpheniramine vs. Clemastine</td>
<td>No difference in nasal discharge, cough or swelling of nasal turbinates</td>
<td>Included a third arm with clemastine; also had no effect.</td>
</tr>
<tr>
<td><strong>Antihistamine/ Decongestant Combination</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hutton 1991(^{32})</td>
<td>RCT</td>
<td>96 (36BPH+Phe+PPA, 27Pl, 33Nil)</td>
<td>Brompheniramine + phenylephrine + phenylpropanolamine vs. Placebo vs. No treatment</td>
<td>No difference between the 3 groups</td>
<td>Well designed. Overall improvement high for all groups and greater improvement if parents requested medication on initial presentation.</td>
</tr>
<tr>
<td>Clemens 1997(^{23})</td>
<td>RCT</td>
<td>59 (28BPH+PPA, 31Pl); 175 responses (90BPH+PPA, 85Pl)</td>
<td>Brompheniramine + phenylpropanolamine vs. Placebo</td>
<td>No difference in runny nose, nasal congestion or cough; proportion asleep greater for active treatment (47% vs 27%)</td>
<td>Well designed. Corrected for multiple responses by the same patient - no change in result.</td>
</tr>
</tbody>
</table>

RCT – randomised controlled trial; Clem – clemastine; Chl – chlorpheniramine; BPH – brompheniramine; Phe – phenylephrine; PPA – phenylpropanolamine; Nil – no treatment;
References


