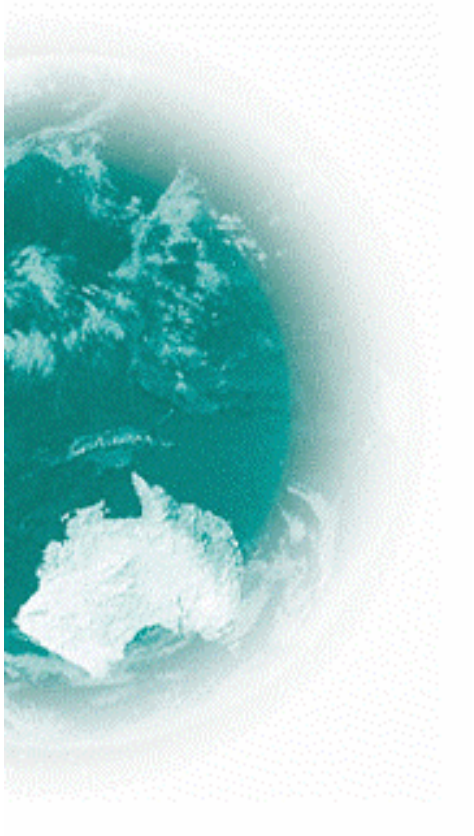
Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Review of cough and cold medicines in children



21 April 2009

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Contents

1. Terms of Reference

The Contractor was requested to review the safety and efficacy of cough and cold medicines currently available in Australia for children aged less than 12 years, using journal articles, documents and other data supplied by the TGA and by sponsors. The report was also required to incorporate all information, facts, issues and opinions that the Contractor considered important and relevant. The TGA determined not to include, in the review, the large number of complementary medicines listed on the Australian Therapeutic Goods Register (ARTG) and marketed in Australia for the symptomatic relief of cough, cold or influenza.

The contractor interprets efficacy to relate to *effectiveness of relief of cough and other symptoms of the common cold*, in accord with the label claims of cough and cold medicines sold for use in children. The contractor interprets safety to include adverse effects of the medicines, either single drugs or a combination of drugs, of any severity, i.e. from minor, to death, in recommended dosages, but including also in non-intentional overdose where this is common.

The search strategy agreed to with the TGA was broad, because of the overlap of the use of drugs for coughs and colds and other conditions. This was to obviate as far as possible missing important references. However, the TGA and the reviewers agreed the report was not intended to extend to the safety and efficacy of cough and cold medicines for *complications* of colds, such as otitis media, otitis media with effusion and pneumonia.

The drug categories and individual drugs which are generally included in cough and cold medicines, and were therefore included in the TGA's search terms included –

Antihistamines:	brompheniramine maleate, chlorpheniramine maleate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, doxylamine succinate, pheniramine maleate, promethazine hydrochloride, triprolidine hydrochloride
Antitussives:	codeine phosphate, dextromethorphan hydrobromide, dihydrocodeine tartrate, pentoxyverine citrate, pholcodine
Mucolytics:	ammonium chloride, bromhexine hydrochloride, guaifenesin, (guaiphenesin), ipecacuanha
Decongestants:	phenylephrine hydrochloride, pseudoephedrine hydrochloride, oxymetazoline hydrochloride, xylometazoline hydrochloride

The TGA conducted searches in Medline and Embase via the Ovid platform and for all available dates as well as information in the worldwide web using Google and Google scholar.

- The basic Ovid search strategy used was as follows: {ingredient} 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).
- Google and Google scholar searches used appropriate combinations of the search key words: {ingredient name or therapeutic class} and (cough or cold or common cold or rhinitis) and (efficacy or effectiveness or clinical trial or safety).

In addition the reviewers examined additional references obtained from other sources including those in industry submissions. Note that, in the report below, the terms 'contractor' and 'reviewers' are used interchangeably. This is because the TGA required there to be only one contractor, requiring the second reviewer to subcontract to the contractor.

2. Conflict of interest and disclaimer

The reviewers declare that neither (the contractor, nor his subcontractor) have any conflict of interest in regard to this report.

The reviewers have carried out this review as objectively as possible. Wherever possible, conclusions are based on evidence, but strong evidence is often not available on the subject of the review. The reviewers believe that evidence-based statements are recognizable as such in the report, as are any statements that are reflective, controversial and/or speculative. The latter have been provided in accordance with the terms of reference, with the intention of providing a comprehensive and useful background to assist the expert committee which will use the report in further advising the TGA.

3. Setting the scene

Almost all cough and cold medicines are S2 (pharmacy medicines). Almost all used in Australia are now, or soon will be, labelled as 'not for use' in children less than 2 years of age. From early 2008, all sedating antihistamines have been categorized as 'prescription only' in this age group. Nevertheless, the market overall for these drugs is very large, with many products for children aged less than 12 years.

Most cough and cold medicines contain combinations of drugs or sometimes a single drug and have been in use for at least 40 years. Indications for the uses of these drugs were accepted at much lower levels of evidence than would now be required, and there is no comprehensive review system for 'grandfathered' uses of drugs. Use in children has usually been extrapolated from adult practice with no specific studies in children at all. The same has applied to doses used in children. The best that can be said is that there has been ample time for post marketing surveillance, and the adverse effects of drugs used in cough and cold medicines are generally well known, both in normal use and over-dosage.

There has been a background level of disquiet over the use of cough and cold medicines in children for many years. Paediatric specialists and academics have long pointed to the lack of evidence of benefit, and advised against use of these drugs. Concern has been expressed over side effects of drugs and drug combinations used in these medicines, both in 'label' doses and in over-dose. A number of controlled trials have been undertaken in the past two decades and more recently three key Cochrane reviews of these agents for symptoms of the common cold have been published.[1-3]

Comprehensive review by the TGA of cough and cold medicines for use in children appears to have been prompted in part by a recent United States (US) Food and Drug Authority (FDA) review following a citizen petition seeking restriction of a wide range of over-the-counter (OTC) drugs for use in children, including but going beyond cough and cold medicines. Related to this, a multinational drug company application led to reconsideration of the scheduling of sedating antihistamines for use in children aged less than two years by the National Drugs and Poisons Schedule Committee (NDPSC).

A comment by an experienced poisons centre pharmacist being interviewed for a medical magazine highlights one aspect of the use of these drugs. 'These drugs do bugger all', she said, 'but people want something to give'. Natural concerns of parents for their sick children and for their own comfort are major factors in the use of drugs in common, discomforting illnesses of childhood. Even if currently available cough and cold medicines have little or no additional benefit over placebos, their extensive use indicates a perceived need for them within the community. This is no

doubt part of a common public attitude of wanting a chemical remedy for every symptom, combined with active and sometimes entrepreneurial research and marketing of the drug manufacture and sales industry. The enormous attraction of self-medication – something you can do for yourself or other family members – is reflected in the enormous annual public spending on over-the-counter pharmaceuticals as well as on alternative medicines.

This review prompts long-stated but unanswered questions. If cough is a normal response to acute respiratory infection, or other airway irritation, secretions, foreign body, etc., might not cough suppression be harmful? The common wisdom is that a non-productive cough such as with the common cold has no benefit and, therefore, attempts to relieve it are justifiable. The 'pain model' is possibly analogous. It is generally accepted that pain usually has a useful function, as an indicator of a problem, but that it is acceptable to relieve pain while simultaneously looking for its cause. However, there do not appear to be readily available antitussive drugs for acute cough with few or no side-effects, and that there is a need for such antitussives where there is an overall net benefit to the sufferer.

The review also prompts questions about the responsibilities of regulatory authorities to Australians generally. How efficacious/effective does a drug or drug combination need to be before it can be labelled as, for instance, for the relief of cough and other symptoms of the common cold in children? If evidence shows only a minimal effect, or an effect only in adults, is such labelling fair and informative? Where a medicine is being used entirely for symptom relief, and does not change the final outcome of any illness, what level of frequent, mild, or rare, severe side-effects can be tolerated?

Both internationally and within Australia, there is a strong emerging viewpoint that drugs should not be used in children without study of efficacy, safety and pharmacokinetics done specifically in children of the age-groups likely to receive those drugs. Applied broadly, this would deprive children of many useful drugs currently used for children, as well as new drugs as they become available. In the current context, the lack of studies done in children is a constantly-recurring feature.

1. Taverner D, Latte J. Nasal decongestants for the common cold. *Cochrane.Database.Syst.Rev.* 2007;CD001953.

2. Sutter AI, Lemiengre M, Campbell H, Mackinnon HF. Antihistamines for the common cold. *Cochrane.Database.Syst.Rev.* 2003;CD001267.

3. Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane.Database.Syst.Rev.* 2008;CD001831.

4. Current product availability and label claims

MIMS Volume 45 No 3 (June/July 2008) and MIMS on-line list over 130 products in the category *expectorants, antitussives, mucolytics and decongestants*. Doses for children aged less than 12 years are supplied on the labels of more than 70 of these medicines, which are mostly scheduled as S2 (pharmacy medicines). After recent changes, all sedating antihistamines are now S4 drugs when used in children aged less than two years.

Far more drugs and drug combinations are used in cough and cold medicines in other countries, and this increases the difficulty in interpreting the literature on the subject, especially side effects of combination products.

The following list shows the active pharmaceuticals used singly or in combination in cough and cold medicines in Australia. For ease of reading, chemical names have been abbreviated where ambiguity is avoidable. The list is not necessarily a complete one. Some medicines contain paracetamol or ibuprofen as well, but such combinations are not listed below. Some may also contain demulcents and other additives.

Codeine

Codeine, pseudoephedrine

Codeine, pseudoephedrine, ammonium chloride, guaifenesin

Dextromethorphan

Dextromethorphan, pseudoephedrine

Dextromethorphan, pseudoephedrine, chlorpheniramine

Dextromethorphan, pseudoephedrine, diphenhydramine hydrochloride

Dextromethorphan, brompheniramine, phenylephrine

Dihydrocodeine

Pentoxyverine

Pholcodine

Pholcodine, chlorpheniramine, ammonium chloride, phenylephrine

Pholcodine, chlorpheniramine, pseudoephedrine

Pholcodine, bromhexine

Pholcodine, pseudoephedrine

Pholcodine, promethazine

Ammonium chloride

Ammonium chloride, diphenhydramine

Bromhexine

Bromhexine, guaifenesin

Bromhexine, pseudoephedrine

Bromhexine, pseudoephedrine, guaifenesin

Guaifenesin

Guaifenesin, pseudoephedrine

Ipecacuanha

Phenylephrine

Phenylephrine, chlorpheniramine

Phenylephrine, brompheniramine

Pseudoephedrine

Pseudoephedrine, chlorpheniramine

A cough or cough and cold medicine, then, could be a sedating antihistamine, or an antitussive, or an expectorant or a decongestant, with a single active, or a combination, such as –

Antihistamine + antitussive

Antihistamine + expectorant

Antihistamine + decongestant

Antihistamine + antitussive + decongestant

Antihistamine + antitussive + expectorant + decongestant

Antitussive + expectorant

Antitussive + decongestant

Antitussive + two expectorants + decongestant

Two expectorants

Expectorant + decongestant

Two expectorants + decongestant

and in addition may contain an analgesic/antipyretic, a demulcent and/or other constituents. Clearly, then, the term 'cough and cold medicines' does not refer to largely similar products, and evidence of efficacy and safety will not be available for many of the combinations listed above.

Label claims vary, even for similar products, not least as most were given approval long ago, prior to current approval mechanisms. We have not done a full review of stated indications on labels, but note that they follow similar patterns e.g. antitussives are often described as 'cough suppressants for unproductive dry cough associated with colds and flu' and combination products as for 'dry raspy cough and cold symptom relief'. Decongestants will often be described as such, as are expectorants, assuming that these terms are commonly understood by the lay public. The term 'chesty cough' in product names is often associated with a mucolytic or an expectorant, i.e. suggesting a productive cough, but the latter is not always specified. The word 'temporary' is increasingly used on labels preceding 'relief'.

5. 'Coughs and colds' – what are we treating?

Cough and cold medicines in children are used for acute or recurrent cough, usually without a definite diagnosis, and for cough and other symptoms believed by a parent to be due to the common cold. The brief discussion to follow refers to causes of these symptoms and to symptom patterns associated with common respiratory illnesses in childhood. This is relevant to the question – does it matter if parents have made the 'wrong diagnosis', and if so is the use of cough and cold medicines a hazard to the child?

Allergy is a common cause of acute cough, often in association with acute allergic rhinitis. This combination of symptoms is often indistinguishable from a mild acute viral respiratory infection – to the sufferer, to a parent, and to an experienced professional. The cough does not necessarily imply the presence of asthma, and presumably results from antigen stimulation of laryngeal, tracheal and other cough receptors.

Acute viral respiratory infection is the commonest cause of cough in childhood. Numerous other infections cause acute or recurrent cough, as do acute asthma, chemical irritation (cigarette smoke), airway foreign body, tumours, structural abnormalities and many rarer causes.

Most acute respiratory infections are self-limiting and require no specific treatment. Acute cough may also herald severe, even potentially life threatening infections, including those that may require specific therapy, such as bronchiolitis, croup, pneumonia, mediastinal obstruction, etc. Does the availability and use of OTC cough and cold medicines delay the diagnosis of these serious conditions and lead to poorer outcomes?

Acute respiratory infection: children suffer an average of 6-8 respiratory infections each year, mostly mild and requiring no treatment. Most of these infections are caused by viruses: rhinovirus, Respiratory syncytial virus, influenza and parainfluenza viruses, metapneumovirus, adenoviruses, some Coxsackie and echoviruses and many others. Most of these can produce some or all of the different patterns of respiratory illness seen in children:

- Coryza (common cold)

- Viral pharyngitis
- Acute otitis media
- Acute sinusitis
- Acute laryngotracheitis (croup)
- Acute bronchiolitis
- Acute viral bronchitis
- Viral pneumonia

Coryza: Mild colds may last only 1-2 days and feature no more than sneezing, nasal obstruction and nasal discharge. Cough and sore throat are variable. More severe colds may be associated with fever, headache, muscle aches and pains, malaise and, in infants, feeding difficulty. Cough may sometimes persist for a few weeks. Nasal obstruction is an early symptom which usually subsides quickly. Colds are quite often followed by otitis media, less often by sinusitis. Most often this is directly due to viral infection, and not complicating bacterial infection. The cough is presumably a direct effect of the virus. With no more than cold symptoms, rhinovirus can be present from nose to smaller bronchi.

Viral pharyngitis: Viral pharyngitis and tonsillitis are seen in children of all ages; bacterial (usually streptococcal) tonsillitis is unusual in children aged less than 4 years. Fever, malaise and sore throat along with pharyngeal inflammation prompt the diagnosis but cough and coryza are often present as well. Cervical lymph nodes are often palpable. Constitutional symptoms vary from mild to severe. Many parents will know from experience that such illnesses are self limiting and appropriately not seek professional advice most of the time. Cough and cold medicines will often be used for such illnesses. Pharyngitis is part of infectious mononucleosis and many less common infections.

Otitis media, acute sinusitis and acute laryngotracheitis all produce symptoms which would suggest more than 'coughs and colds'. The use of cough and cold medicines with prodromal symptoms would not influence the course of these illnesses.

Acute bronchiolitis (a viral infection largely affecting infants aged less than 12 months) and **viral bronchitis** are common illnesses which usually commence with a coryzal prodrome. Treating the cough associated with these infections, and also with **viral pneumonia**, is unlikely to have either beneficial or adverse effects, although this question does not appear to have been systematically examined. It is worth noting that antitussives have not been shown to be effective in pertussis, where paroxysmal cough can be life threatening in infants.

6. Who uses these medicines? What do they expect from them?

There is limited information about patterns of use of cough and cold medicines across the Australian community. What proportion of families use them often, infrequently or never? How much use is based on favourable experience, professional advice, lay advice, promotion, and/or hope of a good night's sleep for everyone? In a paper describing an Australian qualitative study,[1] the authors point out that self-medication (of children, by parents) became a widespread phenomenon in western countries more than 100 years ago. They develop a convincing concept of 'social medication' which in part is aimed at modifying child behaviour to more acceptable patterns, and in part a 'coping strategy'. They found that paracetamol was the commonest 'social medication', followed by cough and cold medicines or sedating antihistamines. They noted that parents may believe in benefits from drugs which go beyond conventional pharmacology. For instance, some parents incorrectly attribute paracetamol as having sedative or calming properties quite separate to any analgesic or antipyretic effect.

A recently published US study[2] showed a remarkably high rate of usage of cough and cold medicines in American children, with approximately 1 in 10 US children under the age of 18 years using cough and cold medicines in a given week. Use was highest in children aged 2-5 years, with children aged <2 years the next highest.

1. Allotey P, Reidpath DD, Elisha D. "Social medication" and the control of children: a qualitative study of over-the-counter medication among Australian children. *Pediatrics* 2004; 114:e378-e383.

2. Vernacchio L, Kelly JP, Kaufman DW, Mitchell AA. Cough and cold medication use by US children, 1999-2006: results from the slone survey. *Pediatrics.* 2008 Aug;122(2):e323-9.

7. Sedation: side-effect or desired effect?

Sedating antihistamines are commonly included in cough and cold medicines for children. Standard reference works e.g. Martindale (Sweetman S [Ed] Martindale: The Complete Drug Reference, London: Pharmaceutical Press. Electronic version, 2008) state the most common adverse effect of these drugs is CNS depression, with effects varying from slight drowsiness to deep sleep, but that paradoxical stimulation may occasionally occur, especially at high doses and in children or the elderly. In some countries these drugs are sold as non-prescription hypnotics.

Sedation of children, either during the day or the night, is generally condemned by health professionals as a poor practice. However, there is clearly a demand from many parents for medicines which will promote sleep in children who have coughs and colds that keep both the child and the parents awake at night. Such drug-induced sleep may not be 'normal' sleep, but perhaps better than no sleep, at least from the parents' point of view. It is believed that some parents may also use sedating antihistamines 'off label' as hypnotics in children aged under the age of two years, and in conditions other than coughs and colds. While health authorities would not approve of such practices, they arise from the fact that sedating antihistamines are readily available without a prescription, there is little evidence that such occasional use is harmful to children, and there must be concern about what parents might use otherwise – for instance, alcohol or drugs prescribed for adult use. However, at least one well designed recent clinical trial does not support the effectiveness of sedating antihistamines for this purpose. The TIRED study was an RCT of diphenhydramine versus placebo for night time wakenings in 6 to 15 month old infants which demonstrated no benefit of diphenhydramine.[2] The study did not demonstrate any harm from diphenhydramine compared with placebo.

Allotey et al quote a parent suggesting that resorting to OTC drugs to promote sleep may protect a child from physical child abuse. We have heard the same concept from some pharmacists. Use of sedating antihistamines is used by some parents in children during air travel. There seems to be a 'common knowledge' of these uses of these drugs, consistent with Allotey and co-authors concept of 'social medication'.

Some evidence suggests that children and parents sleep better when the child is given medicines containing sedating antihistamines, but this is often the same when a placebo is given. Many parents are convinced that cough and cold medicines are effective, and would seek other medicines to give if, for instance sedating antihistamines were to be excluded from available medicines. While public education over self-medication with safe and effective medicines as well as non-drug therapy is laudable, it is one part only of understanding and helping parents with the complex and difficult matter of parenthood.

In deciding the future use of sedating antihistamines in medicines in children, the questions of safety and efficacy remain as key questions, but the following must also be taken into account:

1. There is a strong public demand for non-prescription medicines which can be used short-term to help children sleep when they have short-term intercurrent illnesses.

2. Some parents will give some medicines under these circumstances, possibly choosing other drugs or chemicals including complementary medicines which may be less safe than occasional doses of sedating antihistamines.

1. Martindale: The Complete Drug Reference [electronic version] London: Pharmaceutical Press, 2008.
2. Merenstein D, Diener-West M, Halbower AC, Krist A, Rubin HR. The trial of infant response to diphenhydramine: the TIRED study--a randomized, controlled, patient-oriented trial. *Arch.Pediatr.Adolesc.Med.* 2006; 160:707-712.
3. Allotey P, Reidpath DD, Elisha D. "Social medication" and the control of children: a qualitative study of over-the-counter medication among Australian children. *Pediatrics* 2004; 114:e378-e383.

8. The need for better drugs

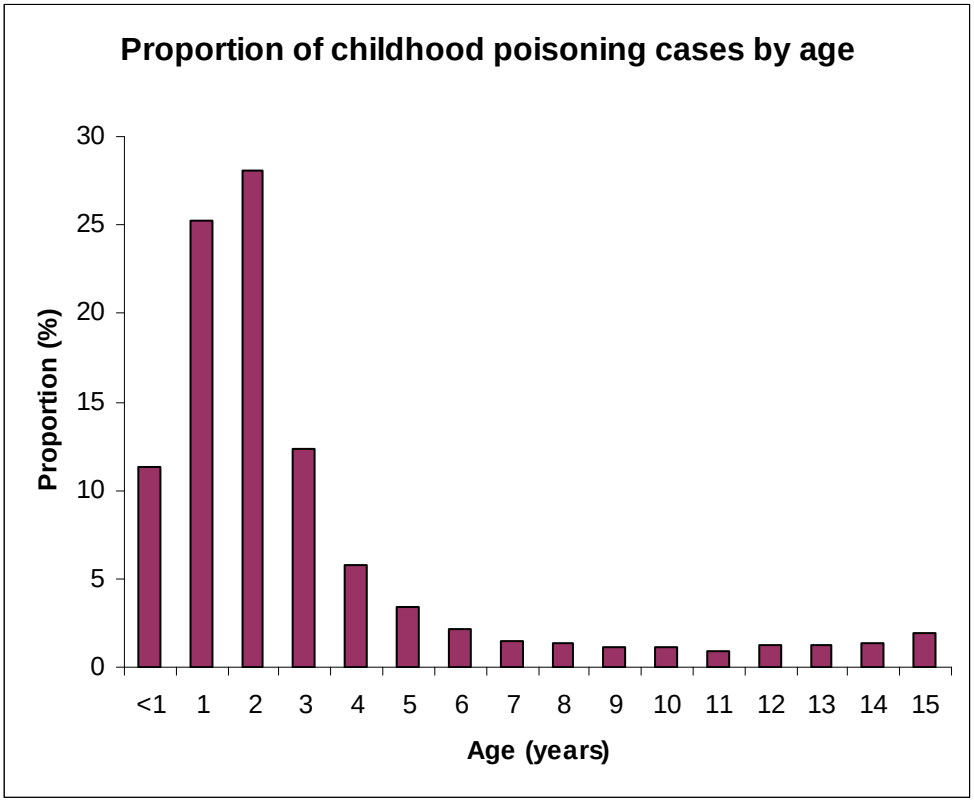
Without pre-empting the discussion below of efficacy of cough and cold medicines for children, it is clear that the currently available drugs for cough and common cold symptoms generally are not highly effective. There is a need for specific novel pharmaceuticals especially to suppress cough safely and effectively.

9. Epidemiology of childhood poisoning

The paragraphs and illustrations under this heading have been adapted from a report by the reviewers written for the February 2008 meeting of the NDPSC, in regard to an application from a sponsor requesting rescheduling of certain sedating antihistamines when used in children of less than 2 years of age. The sponsor's argument generally was that such very young children were more particularly susceptible to toxic effects of these drugs than older children or adults, which generally we thought to be incorrect.

The reviewers proposed different explanations for the higher frequency, morbidity and mortality seen in very young children, set out step-wise below:

Age distribution has shown the same clear and consistent pattern in Western countries over decades. The graph below, from the NSW Poisons Information Centre, shows this typical pattern, for 2006, for children aged <16 years:



The graph is a summary of >50,000 calls, in regard to actual or suspected toxic exposures both from drugs and non-drug chemicals, bites and stings.

A similar pattern is seen in the report of Connor, AIHW, 2001, in this instance showing *hospital separations* of children under <5 years of age in Australia in 1996:

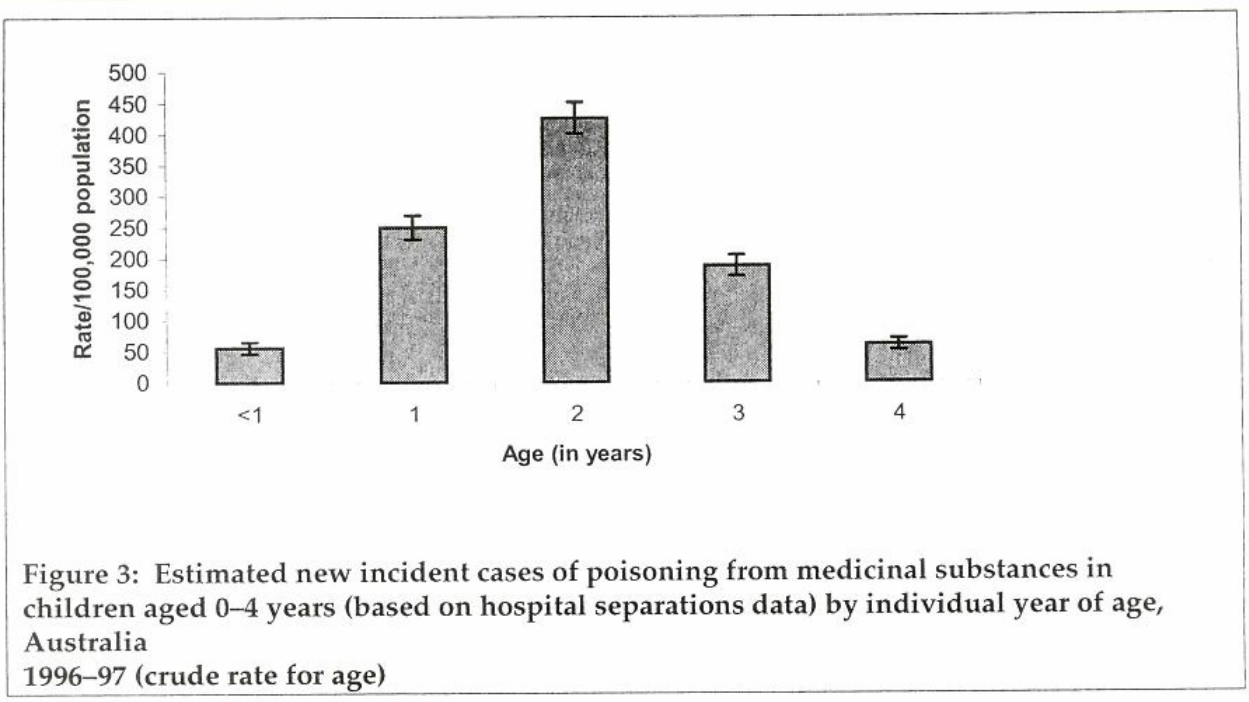


Figure 3: Estimated new incident cases of poisoning from medicinal substances in children aged 0–4 years (based on hospital separations data) by individual year of age, Australia
1996–97 (crude rate for age)

The same pattern was demonstrated in the sponsor's submission, on a literature review of US origin. In that study, most deaths were in children aged <2 years, with only about 1/5 the number of deaths in children 2-5 years and none in children 6-12 years.
This well-described pattern, shown variously above via poison exposures, hospital separations and deaths, as well as further epidemiological information, below, is essential to any proper understanding of childhood poisoning.

1. the peak incidence, in the 2nd and 3rd years of life, is mostly unintentional poisoning via self-ingestion. Some instances relate to unintentional over-dosing by others, and a few to deliberate overdosing by others.
2. Unintentional (commonly referred to as 'accidental') poisoning in young children relates partly to a young child's increasing mobility and explorative behaviour, naivety and willingness to swallow almost anything. It also relates to anything that interferes with maternal awareness and supervision.
3. deliberate ingestion to cause self-harm is seen in children as young as 5 years. Suicidal and experimental use of drugs is seen from the age of 8 years, but becomes much more frequent in teenage years.
4. epidemiological studies show a consistent preponderance of males in all ages up to teenage years, when this is reversed.
5. children ingest liquid and solid forms of drugs and more often than not these will be drugs bought or prescribed for others.
6. there has been one major change in the epidemiology of childhood poisoning over the past 40 years i.e. an enormous reduction in the rate of serious poisonings and deaths. This is almost certainly due to past actions by NDPSC/TGA and similar bodies in other countries, whereby more toxic drugs and other chemicals are required to be sold in child-resistant packaging, and very toxic substances e.g. paraquat are no longer readily available to the general public.

7. childhood poisoning may still differ in some ways, between countries, for instances, as a result of different extents of use child-resistant closures and differing maximum pack sizes commonly available. Thus U.S. experience, especially from past decades cannot be assumed to be necessarily applicable to Australia.

In summary, then, the much higher morbidity and mortality seen in the past in the 1-3 year old age group, especially before the widespread use of child resistant closures, resulted from the combination of the behavioural characteristics of the very young child and unsupervised access to potentially very high doses of drugs – as 'non-intentional' poisoning. In the report by Schaefer,[1] published after the NDPSC meeting of February 2008, the same pattern of high incidence is again seen in young children, albeit some with the much lower morbidity and probably close to zero mortality also experienced over many years in Australia, since child resistant closures have been in widespread use.

1. Schaefer MK, Shehab N, Cohen AL, Budnitz DS. Adverse events from cough and cold medications in children. Pediatrics 2008; 121:783-787.

10. Cough and cold medicines: Australia compared with US

The current US activity over cough and cold medicines, including the incomplete work of the FDA, was predicated on concerns both of efficacy and safety, but we believe that safety concerns, especially excess deaths in very young children, have become the main 'driver'.

In regard to cough and cold medicines, there are many differences between US and Australia. The US has a far greater range of products, with a greater range of 'actives' and a greater range of combination products. Recommendations against use in children aged <2 years has applied to far more products in Australia, until very recently. Whereas the petitioners to FDA suggested these drugs not be used in children <6 years, most drug makers of these products (i.e. members of the US Consumer Healthcare Products Association) have voluntarily agreed (in October 2008) to label their products only for children aged 4 years and older, prior to any FDA policy announcement.

In the US, cough and cold medicines are generally available in drug stores without any requirement for 'pharmacy only' sale or 'pharmacist advice' which is an intrinsic feature of Australian drug regulation, widely considered to be a valuable feature. Records of death with possible attribution to poisoning have been kept in the US for more than 50 years, long before the advent of child resistant packaging both for liquid and solid forms of drugs, which were widely applied much earlier in the US than in Australia. Information based on former decades is now being used to suggest excess mortality from cough and cold medicines. and this information may not altogether reflect the current situation in the US, and even less the situation in Australia. These doubts are supported by a recent paper by Schaefer et al 2008,[1] reporting adverse events from cough and cold medicines in an estimated 14,000 children aged less than 12 years old treated in US emergency departments in 2004 and 2005. Most (82%) were children aged less than 5 years, and 66% were 'unsupervised' ingestions. A much smaller proportion (38%) related to adverse reactions without medication error, and the remainder (12%) to documented error. The great majority of children required little or no treatment. The study did not identify deaths or serious harm from cough and cold medicines, but was not designed to detect those occurring overall in the US. However, it does appear to reflect Australian experience, which is that death or serious injury from children's cough and cold medicines is vanishingly rare. There are substantial numbers of calls to Poisons Centres in regard to these drugs, but very few are considered to be serious enough to refer for assessment and treatment.

Both countries have seen enormous reductions in mortality from poisoning in childhood, and both share the same pattern of occurrence of poisoning, with the largest numbers in children aged 1-3 years. Most of these represent non-intentional, unsupervised poisoning.

1. Schaefer MK, Shehab N, Cohen AL, Budnitz DS. Adverse events from cough and cold medications in children. Pediatrics 2008; 121:783-787.

11. TGA, cough and cold medicines and the general public

Our non-legal-expert reading of the Therapeutic Goods Act 1989 does not suggest that there exists a legislative requirement to re-visit approval of medicines based simply on elapsed time since original approval. Post-marketing surveillance is of course relied upon as the major indicator of problems with a drug and potential need to withdraw or alter approval.

The first stated object of the Act [4: Objects of the Act, (1) (a)] is to provide 'a system of controls relating to the quality, safety, efficacy …… of therapeutic goods…….available in Australia.' This review, then, has been prompted by queries from elsewhere of the efficacy and safety of cough and cold medicines for use in children, and it is clear that TGA has ample scope to review previous decisions it made. The recent changes in scheduling of sedating anti-histamines for children aged under 2 years is an example of this.

A parent who decides to buy a medicine for his or her child with an irritating cough apparently due to a cold will most likely get an S2 product, with, therefore, pharmacist advice available. The TGA website indicates that AUST R medicines are assessed for safety, quality and effectiveness, and that the label on the product will 'tell you what you are buying, what it can do for you and how to get the best results'.

Will not that parent reasonably expect that an S2 medicine labelled for short-term relief of cough and other symptoms of the common cold, containing a number of pharmaceuticals, will have significantly greater effectiveness than a placebo? This is a question for the expert committee evaluating cough and cold medicines for use in children to consider.

12. Dosage considerations

Dosage of almost all cough and cold medicines for children is based on a formula put up by FDA in 1976, i.e. children 6 - 12 years: ½ the adult dose, children 2 - 5 years: ¼ the adult dose and 'ask your doctor' for children aged less than 2 years.

The origin of this system is unclear, but if strictly followed, it will produce more than a 3-fold variation in mg/kg dosage between a normal small girl of just 2 years and a normal big boy of almost 6 years, and up to a 4-fold variation when the same dose is given to a small 6 year old girl and a big boy of almost 12 years.

This dosage variation casts doubt on efficacy claims for these drugs. Is it really likely that cough or nasal congestion, for instance, will respond adequately to such a wide range in dosage?

It is possible that failure to demonstrate symptom relief with coughs and colds in otherwise well-designed studies may have been due to excessively low dosage or inappropriate dosing frequency. This has been demonstrated in a recent dosing analysis of the sub-group of patients who received the active drug in a well-designed clinical trial of dextromethorphan.[1] The main study was unable to demonstrate a significant effect of either dextromethorphan or diphenhydramine versus placebo in the treatment of 100 children with acute cough. The authors undertook a comparison within the 33 patients that received dextromethophan and showed there was a clear trend that the middle and higher doses did have better symptom relief. The study also showed a higher rate of adverse reactions with higher doses. Only further studies can answer the question of appropriate dose and, at least for dextromethorphan, clinical trials of larger doses will be important to assess true efficacy and safety.

1. Paul IM, Shaffer ML, Yoder KE, Sturgis SA, Baker MS, Berlin CM, Jr. Dose-response relationship with increasing doses of dextromethorphan for children with cough. *Clin.Ther.* 2004; **26**:1508-1514.

13. Review of the evidence

All abstracts provided by the TGA and all references from the Cochrane reviews were read and relevant articles were reviewed in full text. Full text articles were reviewed and 64 articles were relevant to this review of the evidence. Relevant clinical trials in children of high quality are included in the attached tables. Additional articles were read and referenced as appropriate in the final review to clarify efficacy and toxicity of the drugs. A summary for each drug and/or drug class is included below.

13.1 Antitussives for acute cough in children

13.1.1 Dextromethorphan

Dextromethorphan is a commonly used cough-suppressant in children and adults. A Cochrane review (2008)[1] found no evidence for its use for acute cough in children. Examination of studies in children and the Cochrane review also supported the view that dextromethorphan did not demonstrate effectiveness in a number of randomised controlled trials (Table 1). However, a letter discussing the systematic review provided information on three other studies and the same author of the letter discussed the importance of dose considerations.4 The two early studies[2,3] suggested that dextromethorphan (with or without salicylic acid) was beneficial for cough but may contain some methodological flaws.[4] A third more recent study compared dextromethorphan with or without salbutamol against placebo and found no benefit for cough symptoms.[5] There are also no paediatric studies assessing objective outcomes for acute cough that compare dextromethorphan and placebo.[4] However a meta-analysis of studies of cough assessing objective data in adults, does suggest benefit of dextropmethorphan.[6]

There is a concern that the dose is insufficient in children and two studies have reported a dose-response effect with dextromethorphan.[2,7] The more recent study provides important evidence.[7] This analysis was a sub-study of one of the negative RCTs 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 (and adults) may be negative because of incorrect and/or insufficient dosing of dextromethorphan. This study is sufficient evidence to suggest that a study should be done of higher doses (0.5mg/kg) of dextromethorphan in a controlled trial with doses in mg/kg and not by age brackets as per the manufacturer. The same study also suggested increased adverse effects (CNS excitation) with larger doses which were also not seen in the controlled trials where adverse effects were similar between placebo and active groups.

Safety

There are a number of case reports and case series providing information on the toxicity of dextromethorphan.[8,9] 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 including with doses exceeding 100 times the normal dose.[9] 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.[10] Mild CNS depression occurred in about 20% of cases.

Toxicity is reported above 10mg/kg and seizures for 20-30mg/kg (see Table 1). 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.[11] There are a number of published deaths either in combination with other agents (more likely to be the causative agents). 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.[8]

1. Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. Cochrane Database Syst Rev 2008;CD001831.
2. Gruber CM, Jr., Carter CH. A measure of the effectiveness of propoxyphene antitussives in children. Am J Med Sci 1961;242:443-7.
3. Careter CH. A clinical evaluation of the effectiveness of Novrad and acetylsalicylic acid in children with cough. Am J Med Sci 1963;245:713-7.
4. Paul IM. Dextromethorphan for acute cough: additional data not reported in the subject review. Archives of Disease in Childhood Fetal & Neonatal Edition 2008;86:170-5.
5. Korppi M, Laurikainen K, Pietikainen M, Silvasti M. Antitussives in the treatment of acute transient cough in children. Acta Paediatr Scand 1991;80:969-71.
6. Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. Chest 2001;120:1121-8.
7. Paul IM, Shaffer ML, Yoder KE, Sturgis SA, Baker MS, Berlin CM, Jr. Dose-response relationship with increasing doses of dextromethorphan for children with cough. Clin Ther 2004;26:1508-14.
8. Pender ES, Parks BR. Toxicity with dextromethorphan-containing preparations: a literature review and report of two additional cases. Pediatr Emerg Care 1991;7:163-5.
9. Bem JL, Peck R. Dextromethorphan. An overview of safety issues. Drug Saf 1992;7:190-9.
10. LoVecchio F, Pizon A, Matesick L, O'Patry S. Accidental dextromethorphan ingestions in children less than 5 years old. J Med Toxicol 2008;4:251-3.
11. Roberge RJ, Hirani KH, Rowland PL3, Berkeley R, Krenzelok EP. Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. J Emerg Med 1999;17:285-8.

13.1.2 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.[1] There are few studies on codeine syrups in children compared to its use in adults.[2] Two studies in adults found that codeine was no more effective than placebo for acute cough,[2] and it is not recommended for acute bronchitis in adults.[3] 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.[4] There is one small comparison of placebo, dextromethorphan and codeine (Table 1) which concludes that codeine syrup was no more effective than placebo. Another comparison study suggests that codeine is more sedative (and less palatable) in children than pholcodeine.[5]

Safety

Codeine appears to cause more adverse effects than other opioid based antitussives based on a comparative study[5] and also the reports of fatal cases due to respiratory depression and cyanosis.[6-9] 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.[6,7] The metabolism of codeine in children and infants is not well understood adding to the uncertainty and unpredictability of adverse effects.

1. American Academy of Pediatrics CoD. Use of codeine- and dextromethorphan-containing cough remedies in children. Pediatrics 1997;99:918-20.
2. Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. Cochrane Database Syst Rev 2008;CD001831.
3. Bolser DC. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. Chest 2006;129:238S-49S.
4. Williams DG, Hatch DJ, Howard RF. Codeine phosphate in paediatric medicine. Br J Anaesth 2001;86:413-21.

5. Jaffe G, Grimshaw JJ. Randomized single-blind trial in general practice comparing the efficacy and palatability of two cough linctus preparations, 'Pholcolix' and 'Actifed' Compound, in children with acute cough. Curr Med Res Opin 1983;8:594-9.

6. Lee AC, Chan R, So KT. A case of probable codeine poisoning in a young infant after the use of a proprietary cough and cold medicine. Hong Kong Med J 2004;10:285-7.

7. Tong TF, Ng KK. Codeine ingestion and apparent life-threatening event in a neonate. Pediatr Int 2001;43:517-8.

8. Magnani B, Evans R. Codeine intoxication in the neonate. Pediatrics 1999;104:E751-E753.

9. von Muhlendahl KE, Scherf-Rahne B, Krienke EG, Baukloh G. Codeine intoxication in childhood. Lancet 1976;2:303-5.

13.1.3 Pholcodine

No studies could be found in children investigating the effectiveness of pholcodine for acute cough. The systematic review of acute cough found no studies of pholcodine.[1] Limited review of previous adult studies provide conflicting evidence and poorly designed studies.[2,3]

Safety

There were no cases of acute toxicity of pholcodine identified in the literature. Recent studies have shown that exposure to pholcodine cough syrup causes a large increase in levels of IgE antibodies towards pholcodine, morphine and suxamethonium increasing the potential future risk of allergic reactions to neuromuscular blocking agents (via these IgE binding to quaternary ammonium ion epitopes).[4,5] The authors of these studies have recommended restriction of pholcodine because of this risk of future allergic reactions to essential drugs.[4]

1. Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. Cochrane.Database.Syst.Rev. 2008;CD001831.

2. Rose JR. Pholcodine plus pseudoephedrine in the treatment of cough. A controlled trial. Practitioner 1967; 198:704-707.

3. Edwards GF, Lewis HE, Stafford D. The effect of pholcodine with and without an antihistamine on cough and expectoration. Br.J.Dis.Chest 1977; 71:245-252.

4. Harboe T, Johansson SG, Florvaag E, Oman H. Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents. Allergy 2007; 62:1445-1450.

5. Florvaag E, Johansson SG, Oman H, Harboe T, Nopp A. Pholcodine stimulates a dramatic increase of IgE in IgE-sensitized individuals. A pilot study. Allergy 2006; 61:49-55.

13.1.4 Dihydrocodeine

There is no efficacy/effectiveness data for dihydrocodeine in children.

Safety

There is limited information on the toxicity of dihydrocodeine and the majority of these are in adults.[1,2] No cases in children were identified in this review although it was not exhaustive.

1. Murao S, Manabe H, Yamashita T, Sekikawa T. Intoxication with over-the-counter antitussive medication containing dihydrocodeine and chlorpheniramine causes generalized convulsion and mixed acidosis. Intern.Med. 2008; 47:1013-1015.

2. Klinder K, Skopp G, Mattern R, Aderjan R. The detection of dihydrocodeine and its main metabolites in cases of fatal overdose. Int.J.Legal Med. 1999; 112:155-158.

13.2 Expectorants for acute cough in children

There is very limited evidence for all of the expectorants in acute cough and acute upper respiratory tract infections. A review of their use in adult respiratory conditions only recommended the use of ipratropium bromide for cough suppression in patients with cough due to an upper respiratory tract infection or chronic bronchitis.[1]

No studies of ammonium chloride as an expectorant in acute cough were identified.

There are no placebo controlled trials demonstrating effectiveness for bromhexine in children. Adult studies are mainly negative for its effects on cough and of marginal benefit at best.[1] The few controlled trials find that bromhexine is no more effective than placebo in a number of conditions.

There are no studies of guaifenesin in children that demonstrate effectiveness and of four studies in adults, mainly with chronic respiratory conditions, there was equivocal evidence.[1]

There are no studies of ipecacuanha for acute cough in children.

Safety

There are a few reports of toxicity from ammonium chloride in cough mixtures, including metabolic acid-base abnormalities with abuse.[2] 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 congested in cough and cold preparations with no reports of major toxicity.[3] Ipecacuanha is occasionally abused by adolescent and young adults with eating disorders.[4]

1. Bolser DC. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. Chest 2006; 129:238S-249S.
2. Wong KM, Chak WL, Cheung CY et al. Hypokalemic metabolic acidosis attributed to cough mixture abuse. Am.J.Kidney Dis. 2001; 38:390-394.
3. LoVecchio F, Pizon A, Matesick L, O'Patry S. Accidental dextromethorphan ingestions in children less than 5 years old. J.Med.Toxicol. 2008; 4:251-253.
4. Rashid N. Medically unexplained myopathy due to ipecac abuse. Psychosomatics 2006; 47:167-169.

13.3 Antihistamine monotherapy for the common cold and acute cough in children

Antihistamines are either used by themselves or in combination with an alpha-adrenocepter agonist for the treatment of the symptoms of the common cold, acute cough, nasal decongestion and allergic rhinitis – antihistamine monotherapy will be considered in this section.

The Cochrane review of antihistamines for the common cold concluded that antihistamine monotherapy did not improve nasal congestion, rhinorrhoea, sneezing or the subjective symptoms of the common cold in children or adults.[1] This was in line with three former critical reviews of the literature.[2-4]

The Cochrane review only identified two studies in children of antihistamine monotherapy for the common cold. One was a study of astemizole[5] and not relevant because it is a second generation antihistamine, and the other of clemastine and chlorpheniramine (Table 2). This study demonstrated no benefit of chlorpheniramine based on subjective and objective assessment.[6]

There is one further study of antihistamines for acute cough (Table 1) which compared diphenhydramine to placebo (a third arm was dextromethorphan) and found no benefit of diphenhydramine over placebo for cough symptoms in children.[7]

There are no studies of dexchlorpheniramine maleate, diphenhydramine hydrochloride, pheniramine maleate, promethazine hydrochloride, doxylamine succinate or triprolidine hydrochloride in children with the common cold or cough. One study in adults showed no difference between doxylamine succinate and placebo for treating the runny nose or sneeze with upper respiratory tract infection.[8]

Safety

There are a number of studies and reviews looking at the effect of the sedating antihistamines on school performance.[9] However, this is less relevant for the short term use of these agents in the treatment of the common cold. The Cochrane review concluded that first generation antihistamines (those included in this review) cause more side-effects than placebo, particularly an increase in sedation for patients with the common cold.[1]

There are numerous cases reports of antihistamines causing severe toxicity or death in infants and young children, and is most likely a reflection of the epidemiology of poisoning. However, there are far more reports of diphenhydramine toxicity in children. There is significant evidence and reports of cases to support diphenhydramine being the most cardiotoxic of the antihistamines.[10] Numerous cases of toxicity have been reported in children.[11] Sodium channel effects and QT prolongation with Torsades de Pointes have been reported in adults. Numerous deaths from diphenhydramine mono-intoxication have been reported in children[12-14] and in series of infant fatalities from OTC medications, diphenhydramine is one of the more common drugs found.[15] Diphenhydramine toxicity has also been reported after topical application for herpes-zoster infection.[16]

Reports of toxicity and deaths from other antihistamines are much less common. This is especially relevant for brompheniramine and chlorpheniramine which also 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 have been reported.[17]

1. Sutter AI, Lemiengre M, Campbell H, Mackinnon HF. Antihistamines for the common cold. Cochrane Database Syst Rev 2003;CD001267.
2. West S, Brandon B, Stolley P, Rumrill R. A review of antihistamines and the common cold. Pediatrics 1975;56:100-7.
3. Smith MB, Feldman W. Over-the-counter cold medications. A critical review of clinical trials between 1950 and 1991. JAMA 1993;269:2258-63.
4. Luks D, Anderson MR. Antihistamines and the common cold. A review and critique of the literature. J Gen Intern Med 1996;11:240-4.
5. Hugenin M, Martin Du PR, Oppikofer-Doody AM. [Astemizole in the treatment of acute rhinopharyngitis (common cold). A double-blind study in pediatrics]. Rev Med Suisse Romande 1988;108:961-6.
6. Sakchainanont B, Ruangkanchanasetr S, Chantarojanasiri T, Tapasart C, Suwanjutha S. Effectiveness of antihistamines in common cold. J Med Assoc Thai 1990;73:96-101.
7. Paul IM, Shaffer ML, Yoder KE, Sturgis SA, Baker MS, Berlin CM, Jr. Dose-response relationship with increasing doses of dextromethorphan for children with cough. Clin Ther 2004;26:1508-14.
8. Eccles R, Van Cauwenberge P, Tetzloff W, Borum P. A clinical study to evaluate the efficacy of the antihistamine doxylamine succinate in the relief of runny nose and sneezing associated with upper respiratory tract infection. J Pharm Pharmacol 1995;47:990-3.
9. Ten Eick AP, Blumer JL, Reed MD. Safety of antihistamines in children. Drug Saf 2001;24:119-47.
10. Scharman EJ, Erdman AR, Wax PM, Chyka PA, Caravati EM, Nelson LS, Manoguerra AS, Christianson G, Olson KR, Woolf AD, Keyes DC, Booze LL, Troutman WG. Diphenhydramine and dimenhydrinate poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2006;44:205-23.
11. McGann KP, Pribanich S, Graham JA, Browning DG. Diphenhydramine toxicity in a child with varicella. A case report. J Fam Pract 1992;35:210, 213-0, 214.
12. Baker AM, Johnson DG, Levisky JA, Hearn WL, Moore KA, Levine B, Nelson SJ. Fatal diphenhydramine intoxication in infants. J Forensic Sci 2003;48:425-8.
13. Nine JS, Rund CR. Fatality from diphenhydramine monointoxication: a case report and review of the infant, pediatric, and adult literature. Am J Forensic Med Pathol 2006;27:36-41.
14. Lindsay CA, Williams GD, Levin DL. Fatal adult respiratory distress syndrome after diphenhydramine toxicity in a child: a case report. Crit Care Med 1995;23:777-81.
15. Marinetti L, Lehman L, Casto B, Harshbarger K, Kubiczek P, Davis J. Over-the-counter cold medications-postmortem findings in infants and the relationship to cause of death. J Anal Toxicol 2005;29:738-43.
16. Chan CY, Wallander KA. Diphenhydramine toxicity in three children with varicella-zoster infection. DICP 1991;25:130-2.
17. Boland DM, Rein J, Lew EO, Hearn WL. Fatal cold medication intoxication in an infant. J Anal Toxicol 2003;27:523-6.

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

Antihistamine-decongestant combinations are frequently used for the treatment of cough and cold symptoms. The Cochrane review of antihistamines for the common cold found no improvement in general condition, nasal obstruction, rhinorrhoea or sneezing in children taking antihistamine-decongestant combinations compared to placebo.[1]

The Cochrane review identified only two studies of antihistamine-decongestant combinations in children (Table 2).[2,3] One study compared a combination of phenylephrine, phenylpropanolamine and brompheniramine, to placebo and no treatment, and found no benefit.[2] In also found no difference in side-effects between active and placebo groups.[2] 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.[3] 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.

A study of brompheniramine versus phenylephrine versus brompheniramine-phenylephrine combination versus placebo for acute otitis media demonstrated no benefit for any of the active treatments.[4] A study of preschool children receiving either placebo or brompheniramine-decongestant mixture at the commencement of upper respiratory tract symptoms of the common cold, had similar frequencies of otitis media.[5]

Safety

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.[6] Dystonic reactions have been reported with cough and cold preparations containing antihistamine-decongestant combinations.[7]

1. Sutter AI, Lemiengre M, Campbell H, Mackinnon HF. Antihistamines for the common cold. Cochrane Database Syst Rev 2003;CD001267.
2. Hutton N, Wilson MH, Mellits ED, Baumgardner R, Wissow LS, Bonuccelli C, Holtzman NA, DeAngelis C. Effectiveness of an antihistamine-decongestant combination for young children with the common cold: a randomized, controlled clinical trial. J Pediatr 1991;118:125-30.
3. Clemens CJ, Taylor JA, Almquist JR, Quinn HC, Mehta A, Naylor GS. Is an antihistamine-decongestant combination effective in temporarily relieving symptoms of the common cold in preschool children? J Pediatr 1997;130:463-6.
4. Bhambhani K, Foulds DM, Swamy KN, Eldis FE, Fischel JE. Acute otitis media in children: are decongestants or antihistamines necessary? Ann Emerg Med 1983;12:13-6.
5. Welliver RC. The role of antihistamines in upper respiratory tract infections. J Allergy Clin Immunol 1990;86:633-6.
6. Boland DM, Rein J, Lew EO, Hearn WL. Fatal cold medication intoxication in an infant. J Anal Toxicol 2003;27:523-6.
7. Joseph MM, King WD. Dystonic reaction following recommended use of a cold syrup. Ann Emerg Med 1995;26:749-51.

13.5 Nasal decongestants for the common cold

The Cochrane review by Taverner and Latte (2007) concludes that there is insufficient evidence for the use of nasal decongestants in children.[1] No studies in children of nasal decongestants for the common cold were identified.[1] Taverner and Latte concluded for 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 in the common cold.[1] Four of these studies included pseudoephedrine as the decongestant either as a single dose or as repeated doses. A very recent

study of xylometazoline in adults also suggests a benefit for symptoms and objective outcomes in patients with the common cold.[2] There is one study of xylometazoline in children which showed it increased nasal flow but there was no control group.[3]

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.[4] It concluded that there was insufficient evidence to support the use of phenylephrine at the recommended dose of 10mg by the FDA and that further research is required.[4] A study in young children (6 to 18 months) with common colds found that topical phenylephrine did not improve abnormal middle ear pressure.[5] A study of phenylephrine vs. placebo (vs. brompheniramine vs. brompheniramine/phenylephrine) in acute otitis media showed no differences between any of the treatments – however it was small and not of high quality.[6]

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.[7]

Safety

There are numerous reports of OTC medications causing toxicity in children which essentially 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.[8] These deaths all occurred in infants where unintentional overdose is unlikely and in most cases this was a therapeutic error.[8] In another series of infant fatalities and OTC medications, pseudoephedrine was one of the more common agents found in post-mortem blood.[9] Pseudoephedrine passes into breast milk and studies have found a proportion of children have irritability with this.[10] Individual cases of pseudoephedrine in combination with other agents in OTC medications have been reported to cause toxicity.[11]

There is limited data on the safety of phenylephrine. The systematic review found no major adverse events but there was considerable heterogeneity between studies making it difficult to determine the safety of phenylephrine.[4]

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.[12]

There are very limited reports on oxymetazoline with one report in Portuguese of 4 cases as part of a study of toxicity of imidazoline derivatives in children.[13]

1. Taverner D, Latte J. Nasal decongestants for the common cold. Cochrane Database Syst Rev 2007;CD001953.
2. Eccles R, Eriksson M, Garreffa S, Chen SC. The nasal decongestant effect of xylometazoline in the common cold. Am J Rhinol 2008;22:491-6.
3. Pickering DN, Beardsmore CS. Nasal flow limitation in children. Pediatr Pulmonol 1999;27:32-6
4. Hatton RC, Winterstein AG, McKelvey RP, Shuster J, Hendeles L. Efficacy and safety of oral phenylephrine: systematic review and meta-analysis. Ann Pharmacother 2007;41:381-90.
5. Turner RB, Darden PM. Effect of topical adrenergic decongestants on middle ear pressure in infants with common colds. Pediatr Infect Dis J 1996;15:621-4.
6. Bhambhani K, Foulds DM, Swamy KN, Eldis FE, Fischel JE. Acute otitis media in children: are decongestants or antihistamines necessary? Ann Emerg Med 1983;12:13-6.
7. Unuvar E, Yildiz I, Kilic A, Toprak S, Aslan SS, Aydin S, Badur S, Oguz F, Sidal M. Is acetaminophen as effective as an antihistamine-decongestant-acetaminophen combination in relieving symptoms of acute nasopharyngitis in children? A randomised, controlled trial. Int J Pediatr Otorhinolaryngol 2007;71:1277-85.

8. Wingert WE, Mundy LA, Collins GL, Chmara ES. Possible role of pseudoephedrine and other over-the-counter cold medications in the deaths of very young children. J Forensic Sci 2007;52:487-90.

9. Marinetti L, Lehman L, Casto B, Harshbarger K, Kubiczek P, Davis J. Over-the-counter cold medications-postmortem findings in infants and the relationship to cause of death. J Anal Toxicol 2005;29:738-43.

10. Aljazaf K, Hale TW, Ilett KF, Hartmann PE, Mitoulas LR, Kristensen JH, Hackett LP. Pseudoephedrine: effects on milk production in women and estimation of infant exposure via breast milk. Br J Clin Pharmacol 2003;56:18-24.

11. Roberge RJ, Hirani KH, Rowland PL3, Berkeley R, Krenzelok EP. Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. J Emerg Med 1999;17:285-8.

12. van Velzen AG, van Riel AJ, Hunault C, van Riemsdijk TE, de V, I, Meulenbelt J. A case series of xylometazoline overdose in children. Clin Toxicol (Phila) 2007;45:290-4.

13. Bucaretchi F, Dragosavac S, Vieira RJ. [Acute exposure to imidazoline derivatives in children]. J Pediatr (Rio J) 2003;79:519-24.

14. Summary and Discussion

14.1 General Considerations

The reviewers agree with the public expectation that a dry, irritating non-productive cough would sometimes be worth treating (with an effective, safe drug, were such available).

A large number of cough and cold medicines are available for children in Australia, for children aged from 2 years. They include antitussives, anti histamines, expectorants, decongestants and other drugs, either singly or in a variety of combinations. Little research of a high modern standard is currently available in regard to these drugs, but what is available does provide sufficient information for discussion for the future.

There is an undoubted strong demand for cough and cold medicines for children, interpreted by some as evidence of efficacy. The reviewers do not agree with this interpretation, but there is no evidence to refute or support the idea. The reviewers do agree that use of cough and cold and other OTC medicines by parents for children represents a complex and very important social phenomenon, not least reflective of the stresses of parenthood, especially during a child's illness, and not something simply to be 'solved' by 'better education' of parents.

The use of OTC cough and cold and other medicines to produce sedation in a sick child is a widely-known but little-studied sociomedical practice. It is in effect supported by OTC availability of sedating antihistamines.

Almost all OTC cough and cold medicines for children are sold with a simple, crude dosage regimen, with two dosage ranges only to cover children from 2 to 11 years. This problem is further exacerbated by the lack of pharmacokinetic studies in this age range.

Ethical concerns are advanced as reasons to accept extrapolation from adult practice, in regard to indications, dosage and usage otherwise. The reviewers note the trend to demand proper and full evaluation of any new drug in all age groups in which it will be used, and believe there may be ethical concerns in regard to continuing to use drugs without now showing them to be effective.

The reviewers note concerns that making cough and cold medicines for children less available may lead to the use of less desirable treatments for coughs and colds. The reviewers agree that this concern is important and must be taken into consideration.

14.2 Efficacy:

It is impossible to make a general statement on the efficacy of cough and cold medicines for children. There are more than 70 products sold in Australia with children's dosages, each containing up to 4 drugs, in 30 different combinations, from a list of about 20 drugs divided into antihistamines, antitussives, expectorants and decongestants. Children include newborn infants to adult-sized young adolescents, i.e. they are not homogenous anatomically, physiologically or in their handling of drugs. There are relatively few high quality studies of efficacy of these medicines

that include children. Extrapolation from adult studies is of limited value. Nevertheless, there is sufficient information to discuss probabilities and to inform decision-making, in regard to at least some of the commoner drugs and combination products.

The relatively few high quality childhood studies show little or no benefit of the medicines over placebo. Inadequacies in these studies have been enumerated (eg as by Lopez in an FDA report[1]) but it is reasonable to conclude that no currently available cough and cold medicines for children could be categorized as 'fairly effective' in terms of label claims.

No antitussive has been shown to be effective for the treatment of acute cough in children. The few available well designed studies are almost all of dextromethorphan (Table 1) except for two small studies codeine (one including pholcodine). All these studies show them to be no more effective than placebo for the treatment of acute cough in children. There is a reasonable possibility that this lack of effect may be due to under-dosing of these drugs and further research is required to determine the appropriate dose in children and whether they are effective at higher doses. The evidence for and against use of dextromethorphan in children is summarized well by a recent from Paul, an academic paediatrician in the United States:

> *"As a practicing pediatrician in the United States, I will continue to follow the guidelines put forth by the American Academy of Pediatrics[2] that concluded that there is no current indication for dextromethorphan as an antitussive. However, these data clearly show a need for further investigations using dextromethorphan to settle this debate over its efficacy once and for all."*[3]

There is no evidence to support the use of expectorants.

There is no evidence to support the use of nasal decongestants in children for acute nasal obstruction from the common cold. There is moderate evidence for their effectiveness in adults but until well-designed studies are undertaken in children there is insufficient evidence for their use in children under the age of 12 years.

Only sedating antihistamines were considered in this review and both studies of antihistamine monotherapy showed no advantage of active over placebo.

A few studies have examined combination therapies (most commonly containing a decongestant and antihistamine +/- another agent) against placebo and against single agents. These studies show no more benefit of the combination agents compared to the individual agents and usually no benefit when compared to placebo or no treatment.

14.3 Safety:

The same great variety and lack of homogeneity both in products and recipient populations described above for efficacy also applies to safety. It is again pointed out that when drugs are being used for symptom relief (as opposed to modifying a disease process and hopefully reducing the duration and severity of an illness) it is not acceptable to have very severe adverse reactions, and even mild side-effects should be infrequent.

Mild, reversible side effects of cough and cold medicines are well known and well described in standard references such as Martindale, as might be expected for drugs which have been in use for decades. The recent paper from Schaefer et al4 refers, with little detail, to a substantial number of 'adverse drug effects' where there was no medication error.

It is possible, though, to make definite conclusions about the safety of cough and cold medicines in children:

- Generally, these medicines are very unlikely to be harmful in label dosages, and in non-intentional overdose in the typical 1-2 year old age group, serious poisoning is rarely seen.

A recent study in the United States demonstrated that OTC cough and cold preparations were only present in toxicology screens in 5% of life-threatening poisonings in children.5

- This may not apply to some drugs in adult doses in solid form, but this is not going to be influenced by any changes that might be made in the nature or availability of cough and cold medicines for children.
- Overseas reports of serious poisoning including deaths from cough and cold medicines are generally not reflected in current Australian experience. Documentation of such deaths is often confounded by co-existing severe illness, multiple drug administration, solid drug forms, the possibility of homicide and other factors.

There are a number of specific comments about some agents in addition to the majority being relative safe in overdose:

- Recent studies have suggested that exposure to pholcodine cough syrup may increase the potential future risk of allergic reactions to neuromuscular blocking agents and the authors of these studies recommend restriction of pholcodine. This demands further study.
- Diphenhydramine is likely to be more toxic in overdose compared to most sedating antihistamines due to its potential to cause cardiac arrhythmias. This is supported by the large number of cases of diphenhydramine toxicity and deaths in children in the literature compared to other antihistamines.
- Nasal decongestant agents are sympathomimetic agents that may be associated with significant morbidity and mortality in large overdoses. There are reports of toxicity with antihistamine-decongestant cough and cold medications.

1. Lolita Lopez, monograph for FDA on cough and cold medicines in children, in - http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4323b1-02-FDA.pdf
2. Paul IM. Dextromethorphan for acute cough: additional data not reported in the subject review. Archives of Disease in Childhood Fetal & Neonatal Edition 2008; 86:170-175.
3. American Academy of Pediatrics CoD. Use of codeine- and dextromethorphan-containing cough remedies in children. Pediatrics 1997; 99:918-920.
4. Schaefer MK, Shehab N, Cohen AL, Budnitz DS. Adverse events from cough and cold medications in children. Pediatrics 2008; 121:783-787.
5. Pitetti RD, Whitman E, Zaylor A. Accidental and nonaccidental poisonings as a cause of apparent life-threatening events in infants. Pediatrics 2008; 122:e359-e362.

15. Possible courses of action:

The expert committee which will report to TGA will determine its own conclusions. Suggestions below of possible courses of action for the committee to consider recommending to TGA are not meant to be directive or exclusive, and the reviewers are certain that the expert committee will consider other options.

15.1 Maintain the 'status quo'

There is currently a strong demand for these drugs. Reducing their availability would leave a 'vacuum' and it is unclear whether this might be lead to the use of other drugs with no proven benefits and/or greater safety concerns. There is currently little evidence in Australia of the safety concerns that appear to have led to further restriction of these drugs in the US (the October 2008 announcement that members of the US Consumer Health Products Association, whose members produce most cough and cold medicines for children, will now label these medicine as not for use in children aged less than 4 years). Much of the concern has been over reports of deaths in infants and young children which have been isolated and simply reflect gross overdose, in accord with the known epidemiology of childhood poisoning and, considering the huge exposure of the agents to children, are relatively unimportant compared to more toxic drugs. Nevertheless, in our opinion, the

TGA would need to be convinced that no individual drug or drug combination has now been identified as a particular hazard, in recommended usage, and that efficacy of cough and cold medicines is sufficient to justify current label claims. This is based on our interpretation of the TGA's legislated responsibilities.

Maintaining the 'status quo' is the stated preference of drug manufacturers that make or distribute cough and cold medicines for children in Australia. It could be argued that strong demand for these drugs has continued over many years, and the onus must be on others to prove the drugs are not effective, and/or unsafe. This would be contrary to the usual decision-making process, where efficacy and safety are a prerequisite for approval of a new medicine. The fact that decision-making here involves re-evaluation of long-used drugs may not justify reversing the usual process.

15.2 Take rigid action based strictly on evidence:

This would be a matter of using the best evidence available to recommend to the TGA whether the efficacy and/or safety of cough and cold medicines for children aged less than 12 years appear to comply with the Therapeutic Goods Act, or whether the TGA now has the responsibility to vary approvals in any particular age groups or other circumstances. This approach would exclude as far as possible considering the use of these drugs where there is little evidence. However, the concern is what would people do if current products were no longer recommended for children aged 2 to 6 years?

The Citizen Petition to FDA (the response to which has not yet been finalised) called for strict labelling changes for cough and cold medicines, including that they should not be given to children aged less than 6 years, and that their efficacy and safety were not assured. This was to be combined with public statements to the same effect. This action was based on the Petitioners' strict interpretation of the evidence, with concern both over safety and efficacy, which is similar to viewpoints previously expressed by the American Academy of Pediatrics, and by paediatric respiratory physicians in the US and elsewhere.

An Australian approach could be to take the same approach on the question of efficacy and safety, and to recommend further reduction of access to cough and cold medicines, for instance in children under the age of 6 years, where the evidence for efficacy is largely absent, and/or where the risks of any medicine outweighs the benefits. Efficacy and safety considerations can be considered separately. Enough concern about either could stand alone, for decision making.

15.3 Take a more evolutionary approach

A third, general approach could be to consider which, if any, actions are immediately required and justifiable and which might be deferred. It would attempt to take into consideration the enormous complexity of the subject, especially the social contexts in which the medicines are used, and the variety of possible consequences from any changes.

This approach might be based on the concept that it would be unfair to children and to the people of Australia generally to continue to have available any cough and cold medicine for children which claims to relieve cough and/or other symptoms of the common cold, *were it true* that any such medicine was no more effective than a placebo. Such unfairness would be increased if the medicine often had side effects. Occasional severe side effects should have the medicine removed, via available regulatory action.

Such an approach might, for instance, include one or more of the following, or a variety of other actions limited only by imagination and practicality.

- Can any current drug or drug combination used in cough and cold medicines in children be identified as being so lacking in efficacy, and/or with serious safety concerns, in both instances on the best information currently available? (Examples of drugs identified above which may fit this description include codeine, pholcodine, diphenhydramine and some decongestants). If yes,

it should be recommended that the drug or drug combination no longer be available for any age-group to which the efficacy and safety concerns apply.

- Are pharmacokinetic studies available in children in the age groups intended for treatment? How much extrapolation is reasonable? Can studies now be carried out in an ethical manner to elucidate questions related to what dose is likely to be efficacious? If it is considered unethical to carry out such studies, is it ethical to continue indefinitely to give drugs with unknown efficacy? TGA cannot commission such studies, but it should have the power to determine better dosage recommendations and set time-lines for these to be required.
- It must be recognised that drug therapy to relieve cough and other symptoms of the common cold is only one part of the care of a child so afflicted, and generally is less important than non-drug therapy (tender loving care by a parent, warmth, hydration, etc). Drug therapy is a 'coping strategy', albeit one much relied upon. While these considerations fall outside the TGA's responsibility, it would still be possible for the TGA to suggest to the NPS, NHMRC, RACP (Paediatrics and Child Health Division), Child Care staff, academics, etc the need for better public health education and instruction, which would include not only simple measures but also balanced information on the use of medicines.
- The studies designed to evaluate efficacy which 'measure up' to current standards, e.g. Cochrane reviews, have been few in number and have largely produced negative results. It is possible that further studies with better study design, different drug doses etc might yet demonstrate efficacy of some cough and cold medicines. While it is not TGA's responsibility to commission research, TGA could set 'time lines' for new and more convincing evidence of efficacy, and defer more final decision-making for a reasonable period of time.

Table 1 Details of relevant and well-conducted controlled trials of antitussives, antihistamines and decongestants for acute cough.

Study	Method	Participants	Interventions	Outcomes	Quality/Comment
Taylor JA 1993	RCT	57 children (19DM, 17Co,13Pl)	Placebo vs. Dextromethorphan vs. Codeine	No differences over 3 days. Improvement related to initial severity	Small study; well conducted
Korppi 1991A	RCT	78 (24DM,25DM+SAL,26Pl)	Placebo vs. Dextromethorphan vs. Dextromethorphan + Salbutamol	No difference	Not blinded
Paul 2004	RCT	100 (33DM,33DP,34Pl)	Placebo vs. Diphenhydramine vs. Dextromethorphan	No difference over 1 night	Good concealment; Letter to Editor about placebo being sucrose, poor cough scores and treatment for 1 night only
Paul 2007	RCT	105(35H,33DM,37Pl)	Placebo vs. Dextromethorphan vs. Honey	No difference for DM, possibly improvement with honey	Well conducted
Yoder 2006	RCT	37 (12DM,12DP,13Pl) >6yrs	Placebo vs. Diphenhydramine vs. Dextromethorphan	No difference - assessed by children >6yrs	From Paul 2004, sub-study of >6yo who could assess own cough.
Jaffe 1983	RCT	217 (107PholMix,110CodMix	Comparison, no placebo; but compared pholcodine mix with codeine mix	Codeine less palatable and causes more drowsiness.	No information on efficacy (comparison), but suggests codeine is more sedative and less palatable.

Table 2: Relevant studies of antihistamines and antihistamine-decongestant combinations for the treatment of the common cold.

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