Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Review of cough and cold medicines in children

Tabulated summaries of clinical trials prepared by the TGA to accompany the Report by the External Reviewers

May 2009

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Table A1: Dextromethorphan

Reference	Method	Participants	Interventions	Outcomes
1. Smith, et al. 2008	Cochrane Review	25 studies between 1966-2007 (17 in adults, 8 in children) involving 2876 adults and 616 children.	8 studies in children: Antitussives (2) Antihistamines (2) Antihistamine decongestants (2) Antitussive/Bronchodilator combinations (1)	Antitussives, antihistamines, antihistamine decongestants and antitussive/ bronchodilator combinations were no more effective than placebo. The results of one trial favoured active treatment with mucolytics over placebo. One trial tested two paediatric cough syrups and both preparations showed a 'satisfactory response' in 46% and 56% of children compared to 21% of children in the placebo group. Authors' conclusion: There is no good evidence for or against the effectiveness of OTC medicines in acute cough. Studies often showed conflicting results with uncertainty regarding clinical relevance. Higher quality evidence is needed to determine the effectiveness of self-care treatments for acute cough.
2. Gruber, et al. 1961				(Effectiveness of propoxyphene antitussives in children.)
3. Careter. 1963				(Effectiveness of Novrad and acetylsalicylic acid in children with cough.)
4. Paul. 2008				(Dextromethorphan for acute cough: additional data not reported in the subject review.)
5. Korppi, et al. 1991	Double blind parallel group study	78 children aged 1-10 years with cough from respiratory infection	Dextromethorphan HBr (7.5mg for <7 yrs, 15mg for >7 yrs) vs. Dextromethorphan + Salbutamol (1mg for <7yrs, 2mg for >7yrs) vs. Placebo 3x daily for 3 days	No statistically significant difference found between frequency or severity of cough for the 3 groups

Reference	Method	Participants	Interventions	Outcomes
6. Pavesi, et al. 2001	Meta-analysis	6 randomised double-blind placebo controlled studies. Uncomplicated cough due to URTI. Total of 710 adult patients	Dextromethorphan single dose 30mg vs. placebo, 3 hr post-dose evaluation period.	Significantly greater overall reductions in cough bouts, cough components, and cough effort, and an increase in cough latency for patients treated with dextromethorphan hydrobromide, 30 mg, vs. those treated with placebo.
7. Paul, et al. 2004	Single dose	33 patients (19 girls, 14 boys); age range, 2.10-16.50 years)	Dextromethorphan dose: 2-5 yrs, 7.5 mg; 6-11 yrs, 15 mg; 12-18 yrs, 30 mg. This resulted in a range of 0.35 to 0.94 mg/kg per dose. Subjective parental assessments of cough and sleep using a 7-point Likert-type scale, compared symptoms after medication with symptoms during the prior night (without medication). Three dose ranges were compared as a subset analysis of the group that received DXM.	No significant differences were found for any of the outcome measures when comparing the effects of different doses of DM, but observations suggested somewhat more symptomatic relief for patients receiving medium-dose DM (0.45 to <0.60 mg/kg per dose) or high-dose (HD) DM (0.60-0.94 mg/kg per dose) compared with low-dose DM (0.35 to <0.45 mg/kg per dose). Adverse events occurred most often in the HD group.
8. Pender & Parks. 1991	Review of published adverse reactions to dextromethorphan			Although generally considered safe, dextromethorphan has been shown to cause CNS side effects, including hyperexcitability, increased muscle tone, and ataxia. Two deaths have been reported with intentional dextromethorphan overdose.

Reference	Method	Participants	Interventions	Outcomes
9. Bem & Peck. 1992	Review of case reports	Published and database DXM-related adverse drug events		Adverse drug reactions are infrequent and usually not severe. Predominant symptoms are usually dose related and include neurological, cardiovascular and gastrointestinal disturbances. Particular safety concerns arise when monoamine oxidase inhibiting (MAOI) drugs and dextromethorphan are co-administered. The safety profile of DXM is affected by episodic and sporadic abuse. The safety profile of dextromethorphan is reassuring, particularly relating to overdose in adults and children.
10. LoVecchio, et al. 2008	Review of case reports	Poison Centre encounters regarding ingestion of DXM by children. 304 cases over 2 years. Mean age 28.2 months. 72% ≥23 months	All cases co-ingested other products of OTC cough and cold medications (paracetamol, pseudoephedrine, guaifenesin, ibuprofen, and various H_1 receptor antagonists). The mean DXM dose ingested was 35.0 mg (mean of 2.64 mg/kg).	62 (20.4%) patients experienced lethargy as their only neurological sign and no patient had any cardiovascular abnormalities. Only one (a 13 month old) patient, who ingested 3.2 mg/kg and presented with lethargy, was hospitalized and subsequently discharged 14 hours later. No deaths were recorded. No patient required specific treatment for any co-ingestion.
11. Roberg, et al. 1999	Case report	1 x 2-yr old child	Child overmedicated with a pseudoephedrine/dextromethorphan combination cough preparation	Child developed hyperirritability, psychosis, and ataxia

Table A2: Codeine

Reference	Method	Participants	Interventions	Outcomes
1. Amer. Acad. Ped. 1997	Practice Guideline			Numerous prescription and nonprescription medications are currently available for suppression of cough, a common symptom in children. Because adverse effects and overdosage associated with the administration of cough and cold preparations in children have been reported, education of patients and parents about the lack of proven antitussive effects and the potential risks of these products is needed.
2. Smith, et al. 2008	Cochrane review	24 trials (17 in adults, seven in children) involving 3,392 people (2,876 adults and 516 children). Comparison of drug treatment with placebo	OTC oral cough preparations for acute cough in ambulatory settings. A wide range of drugs reviewed.	All cough outcomes (such as frequency and severity, continuous and categorical data, using different ways of measurement) and adverse effects considered. For Codeine: In adults (6 studies) Codeine was no more effective than placebo in reducing cough symptoms. In children (1 study) antitussives were no more effective than placebo (one study).

3. Bolser. 2006	Review	Included 4 studies Codeine vs. placebo in adults. Total 112 patients	Codeine (various dosages) vs. placebo	Mucolytic agents are not consistently effective in ameliorating cough in patients with bronchitis, although they may be of benefit to this population in other ways. Peripheral and central antitussive agents can be useful in patients with chronic bronchitis, but can have little efficacy in patients with cough due to upper respiratory infection. Some protussive agents are effective in increasing cough clearance, but their long-term effectiveness has not been established. Conclusions: Findings suggest that suppressant therapy is most effective when used for the short-term reduction of coughing. Relatively few drugs are effective as cough suppressants

Reference	Method	Participants	Interventions	Outcomes
4. Williams, et al. 2001	Review	Review of pharmacokinetics, metabolism, pharmacology and pharmacodynamics of Codeine	Codeine used as an analgesic	In early life, the immaturity of infant metabolic processes is also likely to reduce the efficacy of codeine. Furthermore, there is evidence that adverse effects may occur in the absence of analgesia in poor metabolisers of the drug. Overall there has been little clinical research into the use of codeine in children. From that which has been done it appears that the popularity of codeine in this patient group is not supported by convincing data of its efficacy or suitability, despite its apparently good safety record. The available evidence implies that codeine may in fact be particularly unsuitable for use in the younger child given the difficulties in pain reporting and assessment in this group and the unpredictable effects of the drug.
5. Jaffe & Grimshaw. 1983	Randomised single-blind study	217 patients, aged between 6 and 12 years	"Pholcolix" (150mg paracetamol, 5mg pholcodine, 12.5mg phenylpropanolamine per 5mL) *vs.* "Actifed" (1.25mg triprolidine HCl, 30mg pseudoephedrine HCl, 10mg codeine phosphate per 5mL)	No significant difference in efficacy was demonstrated. 'Pholcolix' caused significantly fewer side-effects, with 'Actifed' Compound causing markedly more drowsiness after daytime dosage.
6. Lee, et al. 2004	Case report	3-month old infant in Hong Kong	Excessive dosing with codeine phosphate and concomitant use of dexchlorpheniramine, ephedrine and ammonium	Sudden onset cyanosis. Improvements are needed in the prescribing information pertaining to the use of cough and cold formulas containing opioid or opioid-like antitussives among young children, and clear warnings should be included in drug inserts and formularies.
7. Tong & Ng. 2001	Case report	1 neonate	Codeine ingestion	Report of codeine ingestion and apparent life-threatening event in a neonate.

Reference	Method	Participants	Interventions	Outcomes
8. Magnani & Evans. 1999	Case report	29-day old neonate suffering cough and occasional vomiting	Codeine dosage of 0.63mg/kg 6-hourly	Child died during sleep.
9. von Muhlendahl, et al. 1976	Review of case reports	430 children with acute codeine intoxication		Of 234 children who had taken more than 5 mg/kg body-weight, 8 had respiratory arrest necessitating intubation and artificial ventilation; 2 of them died. In all other cases the intoxication produced one or more of the following symptoms: somnolence, ataxia, miosis, vomiting, rash, swelling, and itching of the skin, but no life-threatening side-effects.

Table A3: Pholcodine

Reference	Method	Participants	Interventions	Outcomes
1. Smith, et al. 2008	Cochrane review	Randomised controlled trials of OTC medications vs. placebo between 1966–2004 assessed. 24 trials (17 in adults, seven in children) involving 3,392 people (2,876 adults and 516 children) were included.	OTC medications for acute cough in children and adults in ambulatory settings	In adults, codeine was no more effective than placebo in reducing cough symptoms. In children, antitussives were no more effective than placebo (one study). There is no good evidence for or against the effectiveness of OTC medicines in acute cough. The numbers of studies in each group were small, and studies often showed conflicting results. Effect sizes in many studies were unclear and it is questionable as to whether all of the positive results are clinically relevant.
2. Rose. 1967	Double blind crossover comparison	45 adult patients (35M, 10F) with chronic respiratory disease causing breathlessness and cough	Trial preparation (15mg pholcodine plus 60mg pseudoephedrine) vs. Control (15mg codeine phosphate)	Trial preparation was effective in relieving cough and breathlessness in more patients than the control and produced significantly greater overall clinical improvement.
3. Edwards, et al. 1977	Double blind controlled trial	24 patients with cough	Pholcodine vs. Pholcodine + phenyltoloxamine (antihistamine) vs. placebo,	Pholcodine + phenyltoloxamine reduced cough frequency but Pholcodine without antihistamine had no significant effect

Reference	Method	Participants	Interventions	Outcomes
4. Harboe, et al. 2007		17 patients with previously diagnosed IgE-mediated anaphylaxis towards neuromuscular blocking agents (NMBAs).	1 week's exposure with cough syrup containing either pholcodine or guaifenesin. The primary variables serum IgE and IgE antibodies towards pholcodine, morphine and suxamethonium were measured before and 4 and 8 weeks after start of exposure.	Patients exposed to pholcodine had a sharp rise in levels of IgE antibodies towards pholcodine, morphine and suxamethonium, the median proportional increases 4 weeks after exposure reaching 39.0, 38.6 and 93.0 times that of the base levels respectively. Median proportional increase of IgE was 19.0. No changes were observed in the guaifenesin group. Conclusion: Serum levels of IgE antibodies associated with allergy towards NMBAs increase significantly in sensitized patients after exposure to cough syrup containing pholcodine. Availability of pholcodine should be restricted by medical authorities because of the potential risk of future allergic reactions to muscle relaxants.

5. Florvaag, et al. 2006	Pilot study	Subjects IgE-sensitised and non-sensitised towards neuromuscular blocking agents (NMBAs).	Serum concentrations of IgE and IgE antibodies to pholcodine, morphine and suxamethonium allergens were followed after intake of cough syrup, or exposure to confectionary and other household chemicals containing various amounts of substances cross-reacting with these drugs.	Cough syrup containing PHO gave, in sensitized individuals, within 1–2 weeks, an increase of IgE of 60–105 times and of IgE antibodies to pholcodine, morphine and suxamethonium in the order of 30–80 times. The tested confectionary did not have any similar stimulating effect but seemed to counteract the expected decrease of IgE. No effect was seen in non-sensitised individuals. The PHO stimulated IgE showed a non-specific binding to ImmunoCAP with common allergens and glycine background ImmunoCAP that was up to 10-fold higher than that of monomeric myeloma-IgE at twice the concentration. Conclusions: It seems as cough syrups containing pholcodine have a most remarkable IgE boostering effect in persons IgE-sensitized to pholcodine, morphine and suxamethonium related allergens. Household chemicals containing such allergenic epitopes seem capable of some, minor, stimulation.

Table A4: Dihydrocodeine

Reference	Method	Participants	Interventions	Outcomes
1. Murao, et al. 2008	Case report	35-year old man	Apparent abuse of an OTC tablets containing dihydrocodeine phosphate, methylephedrine, chlorpheniramine, and caffeine.	Patient was referred to hospital with generalized convulsion and mixed acidosis. Although it is difficult to discern which component caused these symptoms, it seems that dihydrocodeine phosphate or methylephedrine was involved in the addiction and chlorpheniramine may have caused the generalized convulsion.
2. Klinder, et al. 1999	Analysis of blood samples	Blood samples from 54 impaired motorists (including 3 fatalities)	Analysis for dihydrocodeine and metabolites	The levels of dihydrocodeine found in impaired individuals and in fatalities show a wide overlap in the ranges. Among other factors, the genetically controlled metabolism of dihydrocodeine should play an important role in dihydrocodeine toxicity. The amount of parent drug always exceeded dihydrocodeine-glucuronide formation and dihydromorphine concentrations ranged from 0.16–0.21 mg/L.

Table A5: Expectorants for acute cough in children

Reference	Method	Participants	Interventions	Outcomes
1. Bolser. 2006	Review	78 references reviewed	Expectorants	Mucolytic agents are not consistently effective in ameliorating cough in patients with bronchitis, although they may be of benefit to this population in other ways. Peripheral and central antitussive agents can be useful in patients with chronic bronchitis, but can have little efficacy in patients with cough due to upper respiratory infection. Some protussive agents are effective in increasing cough clearance, but their long-term effectiveness has not been established. These findings suggest that suppressant therapy is most effective when used for the short-term reduction of coughing. Relatively few drugs are effective as cough suppressants.
2. Wong, et al. 2001	Case report	1 youth	Apparent abuse of OTC cough mixture containing ephedrine and ammonium chloride	Patient developed mixed normal anion gap hyperchloremic metabolic and respiratory acidosis associated with hypokalemia. Metabolic acidosis was likely related to an overdose of ammonium chloride, whereas respiratory acidosis was probably related to the effect of hypokalemia on respiratory muscles, causing hypoventilation.

Reference	Method	Participants	Interventions	Outcomes
3. LoVecchio, et al. 2008	Review of Poison Centre reports	2 years data. 304 cases of children less than 5 years of age (mean age 28.2 months, 72% ≥ 23 months)	Accidental dextromethorphan ingestion. All cases co-ingested other products of over-the-counter cough and cold medications (i.e. acetaminophen, pseudoephedrine, guaifenesin, ibuprofen, and various H1 receptor antagonists).	The mean DXM dose ingested was 35.0 mg (mean of 2.64 mg/kg). 62 (20.4%) patients experienced lethargy as their only neurological sign and no patient had any cardiovascular abnormalities. Only one (a 13 month old) patient, who ingested 3.2 mg/kg and presented with lethargy, was hospitalized and subsequently discharged 14 hours later. No deaths were recorded.
4. Rashid. 2006	Case report	1 Adolescent boy	Surreptitious abuse of ipecac in the context of distress over parental conflict	Extensive medical workup undertaken to evaluate unexplained symptoms of proximal muscle weakness, abdominal pain, and, eventually, cardiomyopathy that are sequelae of ipecac toxicity. Clinicians should be alerted to ipecac ingestion with similar presentation.

Table A6: Antihistamine monotherapy for the common cold and acute cough in children

Reference	Method	Participants	Interventions	Outcomes
1. Sutter, et al. 2003	Cochrane review	32 papers between 1966 and 2003 describing 35 comparisons. A total of 8930 people suffering from the common cold were included	Antihistamines for the common cold. 22 trials studied monotherapy, 13 trials a combination of antihistamines with other medication. Data on general recovery, nasal obstruction, rhinorrhea, sneezing, and side-effects were extracted	There was no evidence of any clinically significant effect - in children or in adults - on general recovery of antihistamines in monotherapy. First generation - but not non-sedating - antihistamines have a small effect on rhinorrhea and sneezing. In trials with first generation antihistamines the incidence of side effects (especially sedation) is significantly higher with active treatment. Two trials, studying a combination of antihistamines with decongestives in small children, both failed to show any effect. Of the 11 trials on older children and adults, the majority show an effect on general recovery and on nasal symptom severity. Authors' conclusions: Antihistamines in monotherapy - in children as well as in adults - do not alleviate to a clinical extent nasal congestion, rhinorrhoea and sneezing, or subjective improvement of the common cold. First generation antihistamines also cause more side-effects than placebo, in particular they increase sedation in cold sufferers. Combinations of antihistamines with decongestives are not effective in small children. In older children and adults most trials show a beneficial effect on general recovery as well as on nasal symptoms. However, it is not clear whether these effects are clinically significant.

Reference	Method	Participants	Interventions	Outcomes
2. West, et al. 1975	Review	45 references from 1947 to 1974 reviewed		Despite their apparent popularity, many cough and cold remedies containing antihistamines have been deemed less than effective by the National Academy of Science, and the Food and Drug Administration has begun an inquiry which may result in action to require manufacturers of these agents to comply with limitations on components and advertising claims. Although there are a number of reports in the literature regarding the effectiveness of antihistamines for the treatment of the common cold, the conflicting nature of the results has led to considerable confusion over the merits of these drugs.
3. Smith, et al. 1993	Review	51 controlled clinical trials between 1950 and 1991 included in review	OTC medications used to treat common cold	Studies were grouped by age into child studies (< 5 years old and < 12 years old) and adolescent (aged 12 years and older)/adult studies. Very few studies have been performed on children. Of those, two done on preschool children demonstrated no symptom relief, whereas two done on older children showed some benefit. In the adolescent/adult studies, chlorpheniramine maleate, pseudoephedrine hydrochloride, oxymetazoline hydrochloride, phenylpropanolamine hydrochloride, ipratropium bromide, and atropine methonitrate all improved nasal symptoms. Combination therapy (using an antihistamine-decongestant mix) was shown to relieve a variety of symptoms. CONCLUSIONS--No good evidence has demonstrated the effectiveness of over-the-counter cold medications in preschool children. Further studies are required to clarify the role of these medications in children. Certain single over-the-counter medications and combinations have been shown to reduce cold symptoms in adolescents and adults.

Reference	Method	Participants	Interventions	Outcomes
4. Luks & Anderson. 1996	Review	Studies published after 1975	Treatment of symptoms of common cold with antihistamines	Three of five studies reporting on sneezing found a statistically significant improvement in the antihistamine group and 3 of 7 studies reporting on nasal discharge found a statistically significant improvement with therapy. No study reported improvement in total symptom score at the level of p<.05. The clinical significance of these improvements was not demonstrated. CONCLUSIONS: The primary literature offers little support for the use of antihistamines in the common cold.
5. Hugenin, et al. 1988	Randomised controlled trial, double-blind	62 patients, aged 2-15	Treatment of common cold with 0.2 mg/kg astemizole vs. placebo once daily for 7 days	Rhinorrhoea severity reduced by 50% 3.4±1.7 days for astemizole and 5.1±days for placebo. After 7 days symptoms cleared in 79% astemizole treated and 46% placebo treated patients.
6. Sakchainanont, et al. 1990	Randomised placebo controlled trial, double-blind	150 children <5yrs of age	Treatment of rhinorrhoea from common cold for 3 days with clemastine fumarate 0.05 mg/kg/d 2x/d vs. chlorpheniramine maleate 0.35mg/kg/d 3x/d vs. placebo	Amount of nasal discharge was less after 3 days in 28/48 children treated with clemastine vs. 25/48 children treated with chlorpheniramine vs. 22/47 placebo

Reference	Method	Participants	Interventions	Outcomes
7. Paul, et al. 2004	Dose response study	33 patients (14M, 19F) aged 2.1-16.5 yrs	Determination of dose response relationship for single nocturnal doses of dextromethorphan in children with cough. The administered doses (per manufacturer recommendations) were as follows: ages 2 to 5 years, 7.5 mg; ages 6 to 11 years, 15 mg; and ages 12 to 18 years, 30 mg. This resulted in a range of 0.35 to 0.94 mg/kg per dose.	No significant differences were found for any of the outcome measures when comparing the effects of different doses of DM, but observations suggested somewhat more symptomatic relief for patients receiving medium-dose DM (0.45 to <0.60 mg/kg per dose) or high-dose (HD) DM (0.60-0.94 mg/kg per dose) compared with low-dose DM (0.35 to <0.45 mg/kg per dose). Adverse events occurred most often in the HD group. CONCLUSIONS: Although no statistically significant differences were detectable for the outcomes studied, observations suggest the potential for improved clinical symptom control with increasing doses of DM.
8. Eccles, et al. 1995	Randomised placebo controlled trial, double-blind	688 adult patients with common cold	Doxylamine succinate 7.5mg/10mL syrup 4x/d (345 patients) vs. placebo (343 patients). Measure: subjective symptom score on day 2 for runny nose and sneezing	A between-group comparison showed that doxylamine-treated volunteers benefited from a significantly greater reduction in runny nose scores (P < 0.01) and sneezing scores (P < 0001), than those volunteers in the placebo group. Doxylamine therapy was well tolerated; the incidence of unexpected side-effects was comparable with placebo. Of the expected side-effects, 13.3% of doxylamine-treated patients reported drowsiness. The incidence of sedative effects was lower than has been reported for other commonly used first-generation antihistamines.

Reference	Method	Participants	Interventions	Outcomes
9. Ten Eick, et al. 2001	Safety review	180 references	Extensive review of safety of first, second and third generation antihistamines in symptomatic treatment of hyperhistaminic conditions in children	Review summarises the particular characteristics and safety profiles of first, second and third generation antihistamines and methods for treating children after overdosing.)
10. Scharman, et al. 2006	Guideline for treatment of poisoning	Review of whole of USA poisons centre data for poisonings with diphenhydramine (28,092 cases in 2003) and dimenhydrinate (2534 cases in children aged <6 yrs in 2000-2004)	Extensive analysis of cases and management of poisoning	Expert panel consensus guideline for assessing , classifying and managing poisonings.
11. McGann, et al. 1992	Case report	19 month old child with varicella	The child's parents had treated her with acetaminophen (paracetamol), diphenhydramine syrup, colloidal oatmeal baths, and frequent applications of Caladryl lotion. T	At the time of presentation the child exhibited dilated pupils, ataxia, urinary retention, and facial grimacing. The results of her immediate laboratory tests were within normal limits, and she was admitted to the hospital for observation. She recovered without therapeutic intervention. Although not available at the time of admission to the hospital, her diphenhydramine serum level was 1948 ng/mL. Diphenhydramine levels above 100 ng/mL have been associated with toxicity.

Reference	Method	Participants	Interventions	Outcomes
12. Baker, et al. 2003	Case reports and literature review	Fatal intoxication in infants 6, 8, 9, 12, and 12 weeks old.	The 5 infants were administered diphenhydramine. Paper summarises post-mortem results and discusses literature on safety of diphenhydramine.	Diphenhydramine is an antihistamine available in numerous over-the-counter preparations. Often used for its sedative effects in adults, it can cause paradoxical central nervous system stimulation in children, with effects ranging from excitation to seizures and death. Reports of fatal intoxications in young children are rare. The paper describes five cases of fatal intoxication in infants 6, 8, 9, 12, and 12 weeks old. Post-mortem blood diphenhydramine levels in the cases were 1.6, 1.5, 1.6, 1.1 and 1.1 mg/L, respectively. Anatomic findings in each case were normal. In one case the child's father admitted giving the infant diphenhydramine in an attempt to induce the infant to sleep; in another case, a day-care provider admitted putting diphenhydramine in a baby bottle. Two cases remain unsolved; one case remains under investigation. The post-mortem drug levels in these cases are lower than seen in adult fatalities.
13. Nine & Rund. 2006	Safety review	One case report and review of infant, paediatric and adult poisonings reported in the literature (33 references) or in poisons centre databases from 1949-2006	Poisonings with the antihistamine diphenhydramine	Combined results from both data sets show the following mean (and range) for age and DPH levels: Adult, 35.6 years (18-84) and 19.53 mg/L (0.087-48.5); pediatric, 8.6 years (1.25-17) and 7.4 mg/L (1.3-13.7); infant, 31 weeks (6 weeks-11 months) and 1.53 mg/L (1.1-2.2), respectively. Most deaths were certified as accident or suicide; however, 6 infant homicides were reported. The most common symptoms for all cases were cardiac dysrhythmias, seizure activity, and/or sympathetic pupil responses. The most common autopsy finding was pulmonary congestion.

Reference	Method	Participants	Interventions	Outcomes
14. Lindsay, et al. 1995	Case report	1 child fatality	Treatment with diphenhydramine	Fatal adult respiratory distress syndrome after diphenhydramine toxicity in a child: a case report.
15. Marinetti, et al. 2005	Case reports	10 infant fatalities	Treatment with OTC cold medications	The Montgomery County Coroner's Office has encountered a series of 10 infant deaths over an 8-month period in infants under 12 months old with toxicology findings that include a variety of drugs commonly found in over-the-counter (OTC) cold medications. The drugs detected were ephedrine, pseudoephedrine, dextromethorphan, diphenhydramine, chlorpheniramine, brompheniramine, ethanol, carbinoxamine, levorphanol, acetaminophen, and the anti-emetic metoclopramide. The majority of these deaths were either toxicity from the OTC cold medications directly or as a contributory factor in the cause of death. Only two of the cases were the result of possible child abuse.
16. Chan, et al. 1991	Case reports	3 children	Ingestion of diphenhydramine HCl by children with varicella zoster infection	The three children developed bizarre behaviour as well as visual and auditory hallucinations following topical applications of large amounts of diphenhydramine to the majority of skin surfaces. In two cases, oral diphenhydramine was also administered. Serum diphenhydramine concentrations approximated or exceeded those previously reported. In each case, a complete resolution of mental status abnormalities occurred within 24 hours after discontinuation of all diphenhydramine-containing products.

Reference	Method	Participants	Interventions	Outcomes
17. Boland, et al. 2003	Case report	1 infant	Administration of pseudoephedrine, brompheniramine, and dextromethorphan. Post-mortem analysis.	Brompheniramine and dextromethorphan were 0.40 mg/L and 0.50 mg/L, respectively, in the blood sample and 0.16 mg/kg and 0.57 mg/kg in the liver sample. The concentration of pseudoephedrine in blood and liver specimens was 14.4 mg/L in the blood and 16 mg/kg in the liver.

Table A7: Antihistamine-decongestant combinations for the common cold and acute cough in children

Reference	Method	Participants	Interventions	Outcomes
1. Sutter, et al. 2003	Cochrane review	32 papers between 1966 and 2003 describing 35 comparisons. A total of 8930 people suffering from the common cold were included	Antihistamines for the common cold. 22 trials studied monotherapy, 13 trials a combination of antihistamines with other medication. Data on general recovery, nasal obstruction, rhinorrhea, sneezing, and side-effects were extracted	There was no evidence of any clinically significant effect - in children or in adults - on general recovery of antihistamines in monotherapy. First generation - but not non-sedating - antihistamines have a small effect on rhinorrhea and sneezing. In trials with first generation antihistamines the incidence of side effects (especially sedation) is significantly higher with active treatment. Two trials, studying a combination of antihistamines with decongestives in small children, both failed to show any effect. Of the 11 trials on older children and adults, the majority show an effect on general recovery and on nasal symptom severity. Authors' conclusions: Antihistamines in monotherapy - in children as well as in adults - do not alleviate to a clinical extent nasal congestion, rhinorrhoea and sneezing, or subjective improvement of the common cold. First generation antihistamines also cause more side-effects than placebo, in particular they increase sedation in cold sufferers. Combinations of antihistamines with decongestives are not effective in small children. In older children and adults most trials show a beneficial effect on general recovery as well as on nasal symptoms. However, it is not clear whether these effects are clinically significant.

Reference	Method	Participants	Interventions	Outcomes
2. Hutton, et al. 1991	Randomised controlled clinical trial	96 young children (6 months to 5 years) with common cold	Antihistamine-decongestant (brompheniramine maleate 4mg/5mL, 0.5-0.75 mg/kg + phenylephrine HCl 5mg/5mL + phenylpropanolamine 5mg/5mL) in 3 divided doses per day for 2 days vs. Placebo vs. no treatment	There were no differences among the three study groups in the proportion of children considered "better" overall by the parent 48 hours after the initial assessment (drug, 67%; placebo, 71%; no treatment, 57%; p = 0.53). There is no clinically significant improvement in symptoms of upper respiratory tract infection, including no significant placebo effect, in young children for whom an antihistamine-decongestant is prescribed.
3. Clemens, et al. 1997	Randomized, double-blind, placebo-controlled trial.	59 children aged 6 months to 5 years with upper respiratory infection of less than 7 days due to common cold	Antihistamine-Decongestant (brompheniramine maleate-phenylpropanolamine hydrochloride) vs. Placebo	Two hours after each dose of study medication, changes in the child's runny nose, nasal congestion, cough, and sleep status were assessed by means of a standardized questionnaire. There were no statistically significant differences in symptom improvement between the ADC and the placebo group (runny nose, p = 0.48; nasal congestion, p = 0.94; cough, p = 0.66). However, the proportion of children asleep 2 hours after receiving the ADC was significantly higher than the proportion receiving placebo (46.6% vs. 26.5%; p = 0.01). Results were unchanged after control for the correlated nature of repeated responses, age, symptom duration, use of acetaminophen, time that the medication was given, and parental desire for medication. CONCLUSIONS: The ADC was equivalent to placebo in providing temporary relief of URI symptoms in preschool children. However, the ADC did have significantly greater sedative effects than did placebo.

Reference	Method	Participants	Interventions	Outcomes
4. Bhambhani, et al. 1983	Randomized double blind	98 children with acute otitis media	Amoxicillin with/without antihistamine and/or decongestant or placebo The effectiveness of a new Dimetapp (DIM) preparation was assessed in comparison with each of its components (brompheniramine maleate [BPM] and phenylephrine hydrochloride [PEH] as well as a placebo (PL) vehicle in the treatment of acute otitis media.	They were evaluated at two weeks by clinical examination, pneumatoscopy, and tympanometry. 58 patients (59%) continued to have evidence of fluid in the middle ear. These patients were continued on the test medications for another two weeks and then re-evaluated. There were significant differences between the treatment groups (DIM, BPM, and PEH) and the control PL group; the patients receiving Dimetapp or placebo fared better than those receiving BPM or PEH. However, there was no difference in the overall response between Dimetapp and placebo. Antihistamine-decongestant therapy does not appear to be necessary in the treatment of acute otitis media in children.
5. Welliver. 1990	Review	16 references relating to infants, children and adults	Antihistamines in treatment of upper respiratory tract infections	Several studies suggest a beneficial effect of antihistamines for URI, and at least an equal number show no beneficial effects. Even in studies with positive results, the effects are comparatively minor and probably not of much clinical benefit. On the basis of current data there does not seem to be a role for antihistamines in the prevention of otitis media.
6. Boland, et al. 2003	Case report	1 infant	Administration of pseudoephedrine, brompheniramine, and dextromethorphan. Post-mortem analysis.	Brompheniramine and dextromethorphan were 0.40 mg/L and 0.50 mg/L, respectively, in the blood sample and 0.16 mg/kg and 0.57 mg/kg in the liver sample. The concentration of pseudoephedrine in blood and liver specimens was 14.4 mg/L in the blood and 16 mg/kg in the liver.

Reference	Method	Participants	Interventions	Outcomes
7. Joseph & King. 1995	Case report	3 year old boy	Child treated for 2 days with conventional doses of an antihistamine/decongestant cold preparation for upper respiratory infection symptoms.	The child was confused and restless, with posturing of limbs. Cranial nerve function was intact. Gastric lavage yielded an aspirate the same colour as the cold syrup the child had ingested. A diagnosis of dystonic reaction was made, and the child was treated with benztropine, which effected resolution of his symptoms.

Table A8: Nasal decongestants for the common cold

Reference	Method	Participants	Interventions	Outcomes
1. Taverner & Latte. 2007	Cochrane review	7 studies in adults between 1951 and 2006	Nasal decongestants for treatment of the common cold.	There was a small but statistically significant 6% decrease in subjective symptoms and nasal airways resistance after a single dose of decongestant compared with placebo. With repeated doses, nasal decongestants produce a very small statistical benefit of 4% over 3-5 days, again supported by a decrease in nasal airways resistance. Authors' conclusion: A single oral dose of nasal decongestant in the common cold is modestly effective for the short term relief of congestion in adults, and these drugs also provide benefit in some individuals after regular use over three to five days. Adverse events in adults are rare and mild. There is insufficient data on the use of these medications in children and therefore they are not recommended for use in children younger than 12 yrs with the common cold.

Reference	Method	Participants	Interventions	Outcomes
2. Eccles, et al. 2008	double-blind, placebo-controlled, study	61 patients with common cold	Patients were treated with xylometazoline 0.1% (n = 29) or placebo (saline solution; n = 32; 1 spray three times a day for up to 10 days).	The decongestant effect of xylometazoline was significantly greater than placebo, as shown by the nasal conductance at 1 hour (384.23 versus 226.42 cm3/s; p ≤ 0.0001) and peak subjective effect (VAS, 20.7 mm versus 31.5 mm; p = 0.0298). Nasal conductance was significantly superior for up to 10 hours (p = 0.0009) and there was a trend in favour of xylometazoline for up to 12 hours (not statistically significant). Xylometazoline significantly improved total and some individual common cold symptoms scores (p < 0.05), leading to significantly greater patient general evaluation and satisfaction with treatment (p < 0.05). Conclusion: Xylometazoline is an effective and well-tolerated decongestant nasal spray that significantly relieved nasal congestion compared with placebo in the common cold and provided long-lasting relief with just 1 spray, helping patients to breathe more easily for a longer period of time.

Reference	Method	Participants	Interventions	Outcomes
3. Pickering, et al. 1999	Nasal flow measurements	54 four healthy children (28M, 26F), median age 9.5 years (range 5.9-16.0),	Study aims were 1) to test the hypothesis that smaller children have relatively larger nasal airways compared to the intrathoracic airways, and 2) to examine the effect of stenting and a decongestant (xylometazoline) on nasal patency and nasal flow.	All subjects performed full forced respiratory manoeuvres through: 1) the mouth, 2) the nose, 3) the nose after application of an external stent (Breathe Right (BR) strip), and 4) the nose following instillation of xylometazoline. Peak inspiratory and expiratory flow (PIF and PEF), and mid-inspiratory and expiratory flow (MIF50 and MEF50) all showed a significant decrease from the oral to the nasal baseline manoeuvre. Mean (SD) %Sup of the nasal baseline was 35.6 (13.7)% and was unrelated to height. PIF and MIF50 increased with the BR strip ($P < 0.05$). Xylometazoline also caused a significant increase in all measured flows ($P < 0.05$). Mean (SD) %Sup of the nasal manoeuvre after application of xylometazoline increased to 53.3 (14.0)%. Authors' conclusion: There is no evidence that relative resistance of nasal and intrathoracic airways change with height.

Reference	Method	Participants	Interventions	Outcomes
4. Hatton, et al. 2007	Review	36 references re efficacy and safety of oral phenylephrine used as an OTC decongestant	Review and meta-analysis of study data	Based on 8 unpublished studies that included 138 patients, phenylephrine 10 mg did not affect nasal airway resistance (NAR) more than placebo; the mean maximal difference in relative change from baseline between phenylephrine and placebo was 10.1% (95% CI -3.8% to 23.9%). Eight unpublished studies on phenylephrine 25 mg showed a significant reduction of maximal NAR compared with placebo of 27.6% (95% CI 17.5% to 37.7%). There was significant heterogeneity among the studies included in this analysis, which was partially attributable to different laboratories and methods used. CONCLUSIONS: There is insufficient evidence that oral phenylephrine is effective for nonprescription use as a decongestant.
5. Turner & Darden. 1996	Randomised double blind placebo controlled trial	44 infants aged 6-18 months with abnormal ear pressures due to common cold	Intranasal phenylephrine drops (n=23) vs. placebo (N=21)	Middle ear pressure remained abnormal after treatment with phenylephrine in 29 of 33 (88%) ears and after treatment with placebo in 26 of 34 (76%). The mean change in middle ear pressure after treatment was +23 mm H2O in the active group and +40 mm H2O in the placebo group. CONCLUSIONS: Treatment of nasal obstruction with topical adrenergic decongestants does not improve abnormal middle ear pressures during the common cold. Clinical Trial. Randomized Controlled Trial. (Ovid #8823858)

Reference	Method	Participants	Interventions	Outcomes
6. Bhambhani, et al. 1983	Randomized double blind	98 children with acute otitis media	Amoxicillin with/without antihistamine and/or decongestant or placebo The effectiveness of a new Dimetapp (DIM) preparation was assessed in comparison with each of its components (brompheniramine maleate [BPM] and phenylephrine hydrochloride [PEH] as well as a placebo (PL) vehicle in the treatment of acute otitis media.	They were evaluated at two weeks by clinical examination, pneumatoscopy, and tympanometry. 58 patients (59%) continued to have evidence of fluid in the middle ear. These patients were continued on the test medications for another two weeks and then re-evaluated. There were significant differences between the treatment groups (DIM, BPM, and PEH) and the control PL group; the patients receiving Dimetapp or placebo fared better than those receiving BPM or PEH. However, there was no difference in the overall response between Dimetapp and placebo. Antihistamine-decongestant therapy does not appear to be necessary in the treatment of acute otitis media in children.
7. Unuver, et al. 2007	Randomised controlled trial	148 patients aged 2 – 12 years with acute nasopharyngitis	Acetaminophen (paracetamol) + diphenhydramine + pseudo-ephedrine vs. acetaminophen	After randomization, Group-1 consisted of cases (n: 86), which used OTC drugs [acetaminophen + diphenhydramine + pseudoephedrine] and Group-2 consisted of cases (n: 62), which used only acetaminophen. After receiving nasal swab for showing the viral aetiology, symptoms were scored clinically on admission and then on 10 days follow-up period, and re-evaluated on the third and fifth days of the drug therapy with the same scoring scale. CONCLUSION: For relieving symptoms of acute nasopharyngitis in children, acetaminophen without any combination is as effective as OTC drugs containing acetaminophen, decongestant, and antihistaminics

Reference	Method	Participants	Interventions	Outcomes
8. Wingert, et al. 2007	Case studies	15 children aged 16 months and below	OTC cold medications causing fatalities	A total of 10 different drugs were detected: pseudoephedrine, dextromethorphan, acetaminophen, brompheniramine, carbinoxamine, chlorpheniramine, ethanol, doxylamine and the anticonvulsants, phenobarbital, and phenytoin. The most predominant drug was pseudoephedrine, which was found in all of the cases (blood concentration, n=14, range=0.10-17.0 mg/L, mean=3.34 mg/L) and was the sole drug detected in three cases. Acetaminophen was detected in blood from each of the five cases with sufficient sample. Other drugs (with frequency of detection) were dextromethorphan (five cases), carbinoxamine (four cases), chlorpheniramine (two cases) and brompheniramine, doxylamine, and ethanol (one case each). This post-mortem study supports previous evidence that the administration of OTC cold medications to infants may, under some circumstances, be an unsafe practice and in some cases may even be fatal.

Reference	Method	Participants	Interventions	Outcomes
9. Marinettio, et al. 2005	Case studies	10 infants under 12 months of age	OTC cold medications causing fatalities	The drugs detected were ephedrine, pseudoephedrine, dextromethorphan, diphenhydramine, chlorpheniramine, brompheniramine, ethanol, carbinoxamine, levorphanol, acetaminophen, and the anti-emetic metoclopramide. The majority of these deaths were either toxicity from the OTC cold medications directly or as a contributory factor in the cause of death. Only two of the cases were the result of possible child abuse. Caregivers may be under the mistaken notion that OTC cold medications formulated for children are also safe for use in infants. These cases demonstrate that not only is administration of some OTC cold medications not safe, but use of OTC cold medications in infants can result in toxicity that can lead to death.
10. Aljazaf, et al. 2003	Single blind placebo controlled trial	8 lactating women	Assessment of effects of 60mg pseudoephedrine vs. placebo on breast milk flow and estimation of infant exposure via breast milk	A single dose of pseudoephedrine significantly reduced milk production. This effect was not attributable to changes in blood flow, but depression of prolactin secretion may be a contributing factor. At the maximum recommended pseudoephedrine doses, the calculated infant dose delivered via milk was < 10% of the maternal dose, and is unlikely to affect the infant adversely. The ability of pseudoephedrine to suppress lactation suggests a novel use for the drug.
11. Roberge, et al. 1999	Case report	2-year old child	Overmedication with pseudoephedrine/dextromethorphan combination cough preparation	Child who developed hyperirritability, psychosis, and ataxia after being overmedicated

Reference	Method	Participants	Interventions	Outcomes
12. van Velzen, et al. 2007	Case reports	101 children aged <6 years		No severe symptoms were observed after exposure to xylometazoline doses reported to be below 0.4 mg/kg (95% confidence interval: 0-6%). CONCLUSION: Less than 6% of children exposed to xylometazoline, at doses reported to be less than 0.4 mg/kg body weight, may develop symptoms that require hospitalization.
13. Bucaretchi, et al. 2003	Case reports	72 children aged 2 months to 13 years	Cases exposed to naphazoline (n = 48), fenoxazoline (n = 18), oxymetazoline (n = 5) and tetrahydrozoline (n = 1), through oral (n = 46), nasal (n = 24) or unknown (n = 2) routes.	No deaths were observed. Patients exposed to naphazoline (n = 47/48) presented a higher frequency of clinical signs of poisoning in comparison with those exposed to fenoxazoline (n = 5/18) ($p < 0.001$). There were no significant differences in the frequency of patients who presented clinical manifestations considering the route of exposure [oral (n = 34/46), nasal (n = 21/24); p = 0.31]. CONCLUSIONS: Most children (especially those younger than 3 years) exposed to imidazoline derivatives (especially naphazoline) presented early signs of poisoning regardless of the exposure route (nasal or oral). The main signs observed were nervous system, cardiovascular and respiratory depression. Most children showed complete resolution of the symptoms within 24 hours.