Original Article

Prescription practice of antihistamines for acute upper respiratory tract infections in pediatric patients in a local emergency department in Hong Kong

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BACKGROUND: Currently there is very limited data in the literature assessing the prevalence of antihistamine prescription, and there is no local prevalence data about the prescription of antihistamine agents among primary practitioner and emergency physicians. The objectives are 1) to report the prevalence of antihistamine prescription for children less than 6 years old with acute upper respiratory infection and 2) to explore the associated factors for the prescription practice.

METHODS: This is a cross-sectional study. All consecutive cases of paediatric patients aged 6 or below who presented to the emergency department during a study period of one week from April 1 to July 4, 2009 with diagnosis of acute upper respiratory infection were included. Totally 162 patients were included.

RESULTS: Among the 162 cases, 141 (87%) patients were prescribed one antihistamine of any group. Sixty (37%) patients were prescribed two or more antihistamines. In multivariate logistic regression model, age was found to be significantly ($P<0.001$) associated with multiple antihistamine prescription ($OR=1.042$, 95%CI=1.02 to 1.06). Years of graduation of attending physician for more than 5 years was also a strong predictor of multiple antihistamine prescription ($OR=4.654$, 95%CI=2.20 to 9.84, $P<0.001$).

CONCLUSION: In the local emergency department, patients' age and the years of graduation from medical school of the attending physician were predictors of multiple antihistamine prescription for acute upper respiratory infections for children aged less than 6.

KEY WORDS: Upper respiratory infections; Respiratory tract infections; Common cold; Drug prescription; Drug utilization; Prescription practice; Antihistamine; Histamine antagonist; Children

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INTRODUCTION

Acute upper respiratory infections (URI), including common cold, is one of the most prevalent infectious diseases in humans. Although the disease is usually mild and self limiting, symptoms may last for one to two weeks and it is one of the leading causes of doctor visits and missed days from school and work with enormous economic impact. On average, adults suffer from about two to four colds a year, whereas children have about six to ten episodes.^[1] According to the U.S. Centers for

Disease Control and Prevention, 22 million school days are lost annually due to upper respiratory infections.^[1]

Most of the upper respiratory infections are viral in origin. The commonly identified culprit viruses were rhinovirus, adenovirus, coronavirus, influenza virus, respiratory syncytial virus, parainfluenza virus and metapneumovirus.^[2] There is currently no targeted antiviral for URI. Various medications currently available in the market are mainly for alleviation of symptoms but had not been associated with shortening of symptoms.

Commonly used medications include antipyretics, antihistamines and alpha-adrenergic agonist.^[3] The use of antipyretics had evidence of effectiveness in all age groups.^[4] Decongestants and perhaps decongestant/antihistamine combinations in adolescents and adults had scientific evidence to show modest benefit to reduce rhinorrhea, sneezing and nasal obstruction in first 2 days.^[5] First generation antihistamines have shown favorable effects upon nasal symptoms in some of the adult studies, probably because of their anti-cholinergic effects.^[6] However, the use of common cold preparations including antihistamines in children aged younger than 5 is not evidence-based. In the current primary practice in the locality and worldwide, prescription of common cold medications and antihistamines are very common, particularly in the private practice. In a survey by English et al,^[4] 26% of patients younger than age 5 were given a prescription that was not evidence-based and potentially harmful. Most of the prescriptions were extrapolation from the evidence in the adults. The unnecessary medication prescription had also significant cost implication and accounted for 60% of the total prescription cost in a family practice clinic. In Hong Kong, prescription of antihistamine was nearly universal among primary practice, and prescription of double, or even triple antihistaminergic agents for URI was common. The potential adverse side effects, risks and complications may probably be additive or synergistic for multiple simultaneous antihistamine ingestion.

Common cold medication had some evidence for symptomatic relief for adults with URI, through the benefit may be outweighed by the adverse side effects and potential risks. For the paediatric age group, systematic review had shown that use of antihistamine would have modest effect on relief of nasal symptoms in first 2 days but not in mid or long term symptoms.^[5] Furthermore, the use of common cold medications such as codeine may be associated with adverse drug effects and even mortality.^[7,8] The frequency of adverse effects of antihistamines in pediatric patients were not well studied. It may be crucial to evaluate the current prescription practice of the frontline doctors, the prevalence of antihistamine prescription, and explore the associated factors for antihistamine prescription. Currently there is very limited data in the literature assessing the prevalence of antihistamine prescription, and there is no local prevalence data about the prescription of antihistamine agents among primary practitioner and emergency physicians.

The primary objective is to report the prevalence of antihistamine prescription, and prescription of

multiple antihistamines for URI in paediatric age group by emergency physician in a regional hospital. The second objective is to review prescription practice and behavior of emergency physicians about antihistamines and explore the possible associated factors affecting antihistamine prescription.

METHODS

This retrospective study was conducted in the Accident and Emergency Department (AED) of Tuen Mun Hospital, which is a regional hospital in Hong Kong. The regional hospital served a population of above a million people living in the New Territories region of Hong Kong and had a diversified clientele with daily AED attendance of about 600 patients. About a quarter of the patients were in the paediatric age group (aged less than 18). Upper respiratory infections were one of the most commonly encountered clinical problem in the emergency department. In our study, all consecutive cases of paediatric patients aged 6 or below who presented to the AED during a study period of one week from April 1 to July 4, 2009 with diagnosis of acute upper respiratory infection were included. The eligible cases were searched from the hospital electronic record database by the Clinical Data Analysis & Reporting System (CDARS), which is a computerized data retrieval system of the Hospital Authority of Hong Kong utilizing International Classification of Disease Coding, Ninth edition (ICD-9). We searched the diagnosis under the categories of principal and secondary diagnoses. The included ICD-9 codes were 462 (acute pharyngitis), 463 (acute tonsillitis), 381 and 382 (acute otitis media), 460 (acute rhinopharyngitis), 465, 465.9 and 212.9 (non-specific upper respiratory infection). All patients aged more than 6 years were excluded. Patients with diagnosis of acute bronchitis, chronic nasopharyngitis and allergic rhinitis were excluded. Patients who were admitted to hospital in the same attendance and those with labeled history of drug allergy to antihistamines were also excluded. All patients with other medical conditions that justify the use of antihistamines were also excluded. Relevant clinical information were collected from electronic patient record and written clinical record. All case records were retrieved and then reviewed by the principle investigator.

The primary outcome variable was multiple antihistamine prescription which was defined as prescription of more than one antihistamine. Patients

were classified as case group (multiple antihistamine was prescribed) and the control group (multiple antihistamine was not prescribed). The predicting factors variables to examine could be grossly classified into patient and physician factors. The patient factors included age (in months), gender, significant past medical history that warranted long term follow-up by paediatrician or specialist, whether this was a reattendance case (reattendance being defined as reattendance to the AED within 48 hours for similar chief complaint), and the number of antihistamines prescribed by the attending physician. Physician factors included whether the attending physician was a fellow in any specialty and the years of graduation from medical school. Relevant history of drug allergy was reviewed and those with labeled allergy to any antihistamines were excluded.

All variables were first screened through univariate analysis by Chi square test or Fisher's exact test for binary variables, and independent sample *t*-test for continuous variables. They were then included in the model of unconditioned logistic regression analysis with backward stepwise methodology based on likelihood ratios. Age and gender were also included as confounding variables. Likelihood ratio statistic was used to assess the goodness of fit of the model and level of significance was taken at 5%. The statistical package employed was SPSS 16.0.

There is no epidemiological study in the literature to provide suitable reference on sample size planning. We therefore planed our sample size by assuming a power of 90%, a significance level of 5%, baseline response probability as 0.4 to detect a moderate effect size of odds ratio=3 or higher. An adjustment of regression of one independent variable on the other was made and R^2 was assumed to be 0.75. The total sample size (case plus control) required would be 145 as calculated by PASS 2008 Software by NCSS, US.

Ethical approval was exempted with the retrospective study. The study process had been compliant to the principles in the Declaration of Helsinki.

RESULT

A total of 171 eligible cases were retrieved by CDARS. After reviewing the case notes, 8 cases of coexisting medical conditions that warranted antihistamine prescription (eczema, allergic rhinitis) and one case of labeled allergy to chlorpheniramine were excluded. All the remaining 162 cases were included in the final analysis.

Among the 162 cases, 141 (87%) patients were prescribed one antihistamine of any group, while 60 (37%)

patients were prescribed two or more antihistamines (Figure 1).

For analyzing factors associated with multiple antihistamine prescription, the occurrences of studying parameters for both case and control groups were shown in Table 1. For univariate analysis, only patient age and attending physician year of graduation from medical school ≥ 5 years showed statistical significant differences. For the patient group that was prescribed multiple antihistamines, the mean age was 42.7 months compared to the mean age of control group was 29.1 months. For the case group, percentage of attending doctors who graduated from medical school for more than 5 years was 73.3%, compared to the same covariate of 39.2% in the control group.

All of the variables were put into the logistic regression model to adjust for potential confounding (Table 2). Age was found to be significantly ($P < 0.001$) associated with multiple antihistamine prescription ($OR = 1.042$, 95% $CI = 1.02$ to 1.06). There was observed trend of

Figure 1. Prevalence of antihistamine prescription for URI in children aged < 6 .

Table 1. Univariate analysis for predicting factors of prescription of multiple antihistamines in paediatric URI

Predictive factors	Case (antihistamine prescribed) (n=60)	Controls (antihistamine not prescribed) (n=102)	P value (two-tailed)
Chronic diseases, n (%)			0.293
Yes	5 (8.3)	4 (3.9)	
No	55 (91.6)	98 (96.1)	
Reattendance, n (%)			0.613
Yes	2 (3.3)	3 (2.9)	
No	58 (96.7)	99 (97.1)	
Age (mean $\pm$ SD) (months)	42.7 $\pm$ 17.6	29.1 $\pm$ 18.7	<0.001
Attending physician years of graduation ≥ 5 years, n (%)			<0.001
Yes	44 (73.3)	40 (39.2)	
No	16 (26.7)	62 (60.8)	
Attending physician was a fellow, n (%)			0.121
Yes	14 (23.3)	15 (14.7)	
No	46 (76.7)	87 (85.3)	

increasing prevalence of antihistamine prescription with higher age group (Figures 2 and 3). Years of graduation of attending physician for more than 5 years was also a strong predictor of multiple antihistamine prescription ($OR=4.654$, $95\%CI=2.20$ to 9.84 , $P<0.001$).

For the model calibration and goodness of fit, which refers to the agreement in the individual patients between the predicted risks as assigned by the model and the actual observed frequencies, this was evaluated with the Hosmer-Lemeshow test, which if significant indicates poor model fit. In the finalized logistic regression model that integrated patient age and years of graduation of attending physician, the Hosmer-Lemeshow test was insignificant ($P=0.755$), hence indicating good fitting of the model.

DISCUSSION

In Hong Kong, the concept of family doctor and primary care was not yet familiarized by many of the general public and URI remains to be one of the most commonly encountered clinical problem in emergency department in Hong Kong, which accounts up to 10%–20% of the case-mix in the local emergency

departments, including the paediatric age group.^[5,6] In other words, emergency department served as part of the public primary care units in Hong Kong, particularly after opening hours of the General Outpatient Clinics (GOPC). Currently there was no local clinical audit nor quality assurance program about the use of common cold medications including antihistamines for URI within emergency department or primary care clinic in Hong Kong.

Antihistamine and other common cold medications are commonly used for URI in Hong Kong, both in over-the-counter medications and doctors' prescription, including in the primary care clinic and emergency department. A survey conducted by Centers for Disease Control and Prevention in 1994 showed that two-thirds of three-year-old had taken cough or cold medicine in the preceding 30 days.^[9] In a recent review in 2008 in United States, approximately 1 in 10 US children uses a cough and cold medication in a given week. The especially high prevalence of use among children of young age of less than 5 is noteworthy, given concerns about potential adverse effects and the lack of data on the efficacy of cough and cold medications in this age group.^[10] There was no local report or survey in Hong Kong. The problem may be particularly important in Hong Kong because the use of over-the-counter medication, frequent prescription of antihistamines and other common cold medications by general practitioner, frequent doctor-shopping behavior of parents and possible overdosage of

Figure 2. Prevalence of antihistamine prescription among different age groups.

Figure 3. Prevalence of prescription of multiple antihistamine among different age groups.

Table 2. Multivariate logistic regression analysis for multiple antihistamine prescription

Predictive variables	Percent of antihistamine prescription	Number of antihistamine prescription	Odds ratio	95%CI	P value
Age (mean±SD) [months]			1.042	1.02–1.06	<0.001
Cases: 42.7±17.6					
Controls: 29.1±18.7					
Gender					0.161
Male	30.4	24/79	0.56	0.27–1.18	
Female	43.4	36/83	1		
Chronic disease					0.099
Yes	55.6	5/9	3.63	0.75–17.5	
No	35.9	55/153	1		
Reattendance					0.365
Yes	40	2/5	0.445	0.06–3.57	
No	36.9	58/157	1		
Attending physician years of graduation from medical school					<0.001
≥5 years					
Yes	52.3	44/84	4.654	2.20–9.84	
No	20.5	16/78	1		
Attending physician was as fellow					0.711
Yes	48.3	14/29	0.848	0.31–2.33	
No	34.6	46/133	1		

various cold medications.

Although some randomized controlled trials of older first-generation antihistamines have shown positive results for certain end points in adult studies,^[5,6] a Cochrane review concluded that antihistamines had only modest relief of nasal symptoms in first 2 days but not afterwards.^[5] Even if a slight clinical benefit exists, there are risks and adverse effects, especially with first-generation antihistamine.^[11] Table 3 summarizes the efficacy of individual first generation antihistamines in relieving symptoms in paediatric URI in various trials. The Cochrane systematic review also concluded that antihistamines in monotherapy, in children as well as in adults, do not alleviate nasal congestion, rhinorrhoea and sneezing, or subjective improvement of the common cold to a clinically significant extent. First generation antihistamines also cause more side-effects than placebo, in particular they increase sedation in cold sufferers.^[5] Newer-generation non-sedating antihistamines do not have efficacy on relieving cough symptoms.^[12] Currently, no medication available in the market had been shown to effectively treat cough in upper respiratory infection in children.^[13,14]

Antihistamines are heterogeneous groups of compounds with various side effects. Use of antihistaminergic agents is not without risks. As reported by the Centre for Disease Control (CDC), approximately 7 100 patients aged under 12 years were treated in emergency departments for adverse drug events from cough and cold medicines in children in US.^[15–20] Antihistamines are commonly known to have depressant effects on the central nervous system, although occasional paradoxical stimulant effects had been reported, particularly among children. These include tremor, insomnia, irritability, hallucinations and seizure.^[21,22] Although diphenhydramine has been used for treating oculogyric crisis and acute dystonic reactions, dystonia had been reported following use of antihistamine such as chlorpheniramine and diphenhydramine.^[23–29] The exact mechanism is not well defined, but several hypothesis have been

proposed. Diphenhydramine is a phenothiazine derivatives and phenothiazine had antidopaminergic activity, causing imbalance in central cholinergic and dopaminergic neurotransmission.^[30] Other hypothesis include rebound increases in nigral inhibition of the basal ganglia and involvement of the aminobutyric acid neurotransmitter system have been postulated.^[30–32] Furthermore, apparent life-threatening events have been associated with use of common cold medications.^[33] In January 2007, the CDC published a report describing three deaths of infants aged <6 months of age for which cough and cold medications were determined to be the underlying cause of death.^[34] From the Adverse Event Reporting System (AERS) of the US Food and Drug Administration (FDA), 69 fatalities in the paediatric age group was associated with the use of antihistamines were identified: diphenhydramine 33, brompheniramine 9 and chlorpheniramine 27. Of these 69 fatalities, 49 occurred in children aged <2 years and 28 in children aged 2–6 years.^[35] Overdose and drug toxicity were commonly reported adverse events. The reasons given for the overdose occurring included use of multiple cough/cold products, medication errors, accidental exposures and intentional overdoses. There is consensus with expert opinion and evidence-based medicine to support that the risk outweighed the benefit for the use of antihistamines and other common cold medications for treatment of URI in children.^[36] In addition, FDA had issued a black box warning in 2006 against the use of promethazine in children less than 2 years old.

With more evidence of lacking efficacy of antihistamines in children with URI, and more reports of adverse drug events and complications associated with antihistamine use, there is raising concerns in recent years about the safety and efficacy of cough and cold medications in children. In 2006, the American College of Chest Physicians found that "literature regarding over-the-counter cough medications including antihistamines does not support the efficacy of such products in the pediatric age group".^[37] The American Academy of Pediatrics (AAP) considered that there was sufficient

Table 3. Trials evaluating efficacy of antihistamines in treating symptoms of URI in children

Drug	Age group	Study	Conclusion
Brompheniramine + phenylephrine vs. placebo	Less than 6 years old	Hutton et al ^[15]	No significant difference
Brompheniramine + phenylpropanolamine vs. placebo	Less than 6 years old	Clemens et al ^[16]	No significant difference
Chlorpheniramine vs. clematine vs placebo	Less than 6 years old	Sakchainanont et al ^[17]	No significant difference
Diphenhydramine vs. dextromethorphan vs. placebo	2 to 16.5 years old (median 4.5 years old)	Paul et al ^[18]	No significant difference
Diphenhydramine vs. dextromethorphan vs. placebo	2 to 16.5 years old (median 7.5 years old)	Yoder et al ^[19]	No significant difference

available data from paediatric studies to conclude that cough and cold medicines are ineffective in children. In addition, the AAP noted that although these medicines are generally safe when used according to the product labelling, there are two situations that potentially put children at risk of serious adverse events or death when exposed to cough and cold medicines: the first is inappropriate dosing of cough and cold medicines. The AAP considers that the availability of multiple multi-ingredient preparations that may contain the same active ingredients contributes to this risk. Secondly, complete lack of data to support current dosing regimens for paediatric patients. The lack of information available to physicians when the product labeling recommends consulting a physician for dosage advice. In addition there is possible risk with drug interaction between new generation antihistamine and macrolide to cause prolonged QTc-related arrhythmia. The AAP is also concerned that children under 2 appear to have a greater sensitivity to the potentially fatal effects of some of the ingredients in cough and cold medicines. The AAP considered that extrapolation of adult efficacy data for children is not justifiable as available paediatric data do not support the efficacy of these medicines. In addition, there is significant age-related developmental variability in both pharmacokinetics and pharmacodynamics in children such that it is clear that adults and children handle and respond to drugs differently. The AAP expressed considerable concern at the demonstrable lack of efficacy, evidence for considerable misuse, lack of rational basis for dosing, and apparent increased sensitivity to toxicity of these preparations in children under 6 years of age. The AAP recommended that unless clear, evidence-based paediatric dosing guidelines are available for all ages, these products should not be available for over-the-counter use in these age groups. The American Academy of Family Physicians (AAFP) considered that it is inappropriate to extrapolate adult efficacy data to children. The AAFP noted that serious complications are rare when the medications are used correctly, and supported the advice issued by the FDA to parents and caregivers in the Public Health Advisory.

Current advice from the National Health Service (NHS) of United Kingdom on treating colds and coughs in children includes giving fluids and treating fever and pain with paracetamol or ibuprofen, and the use of saline drops to loosen dried nasal secretions or help a stuffy nose in young children and babies. Although steam inhalation is not suitable for children because of the risk of scalding, a child may benefit from sitting in a hot,

steamy bathroom. Simple cough mixtures containing a demulcent, for example glycerin, and syrup can have a soothing effect by coating the throat and relieving the irritation which causes the cough; a child over the age of one may also be helped by a warm drink of lemon and honey.^[38]

In the study, it was demonstrated that younger doctors tend to prescribe less antihistamines for children with URI. We hypothesized that this may be attributable to the emphasis of the risks-benefit ratio of antihistamines in pediatric URI in the undergraduate curriculum in medical schools. This contrasted to the need of change in practice and prescription behaviour for older doctors where they had already developed habits of prescription. This may provide insights on the way on further educational strategies to tackle the problem of overuse of antihistamines.

In Hong Kong, the Department of Health had not issued formal recommendation or advisory statements on the use of cold medications and antihistamine for children with URI. Furthermore, there was no regulation about the labelling of the common over-the-counter cold medications about the caution while using in children. With high rate of doctor shopping behaviour of parents in Hong Kong, children are more likely to expose to various cold medications and multiple antihistamines. Since the effect may be additive or synergistic, this may result in dosing error or overdose, increasing the risk of complications or unexpected death, and cases of unexpected mortality of children with URI were reported to be associated with antihistamine and other cold medication use in Hong Kong. Our study provided a recent review of the prevalence data about antihistamine prescription for URI in children in a local emergency department setting. While for very young infants, the emergency physicians are quite cautious to prescribe antihistamines, but for the toddlers and older children prescription of multiple antihistamines is quite common. More focus should be put on the publication of the concept of higher potential risks of antihistamine use in children aged less than 6. Moreover, doctors who graduated longer from medical schools have higher rate of multiple antihistamine prescription. With further understanding of the factors affecting prescription practice, targeted interventions and educational program could be designed for both primary care physicians, emergency physicians and the public, to reduce the unnecessary prescription of antihistamine and avoid potential risks. A local taskforce for reviewing the current evidence, provide advisory and recommendation, setting up plans for public education,

undergraduate curriculum and postgraduate education of frontline doctors is necessary.

Limitation of the study

The sampling method included pediatric URI patients in one week in first week of April 2009. There is potential selection bias with the sampling method. Furthermore, the antihistamine prescription time from symptom onset were not investigated in the study. There may be potential symptomatic benefit for those presented within 2 days.

CONCLUSION

In the local emergency department, the prevalence of prescription of single and multiple antihistamines for URI in children aged less than 6 were 87% and 37% respectively. Patient's age and the years of graduation from medical school of the attending physician are significant predictors of multiple antihistamine prescription. Further education of the public and recommendations to the emergency physician about cautious prescription of antihistamines and common cold medications for URI in children are necessary.

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REFERENCES

- 1 National Institute of Allergy and Infectious Diseases. Common Cold. Available at: <http://www3.niaid.nih.gov/healthscience/healthtopics/colds>.
- 2 Wat D. The common cold: a review of the literature. *Eur J Intern Med*. 2004;15(2):79–88.
- 3 Mossad SB. Treatment of the common cold. *BMJ*. 1998;317(1):33–6.
- 4 English JA, Bauman KA. Evidence-based management of upper respiratory infection in a family practice clinic. *Fam Med*. 1997;29(1):38–41.
- 5 De Sutter AI, Saraswat A, van Driel ML. Antihistamines for the common cold. *Cochrane Database Syst Rev*. 2015;(11):CD009345.
- 6 Gwaltney JM Jr, Druce HM. Efficacy of brompheniramine maleate for the treatment of rhinovirus colds. *Clin Infect Dis*. 1997;25(5):1188–94.
- 7 Tong TF, Ng KK. Codeine ingestion and apparent life-threatening event in a neonate. *Pediatr Int*. 2001;43(5):517–8.
- 8 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(4):285–7.
- 9 Kogan MD, Pappas G, Yu SM, Kotelchuck M. Over-the-counter medication use among US preschool-age children. *JAMA*. 1994;272(13):1025–30.
- 10 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;122(2):e323–9.
- 11 Montauk SL. Appropriate use of common OTC analgesics and cough and cold medications. Leawood, Kan. American Academy of Family Physicians, 2002.
- 12 Irwin RS, Baumann MH, Bosler DC, Boulet LP, Braman SS, Brightling CE, et al. American College of Chest Physicians. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1 Suppl):1S–23S.
- 13 Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev*. 2004;4:CD001831.
- 14 Paul IM, Yoder KE, Crowell KR, Shaffer ML, McMillan HS, Carlson LC, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics*. 2004;114(5):E85–90.
- 15 Hutton N, Wilson MH, Mellits ED, Baumgardner R, Wissow LS, Bonuccelli C, et al. Effectiveness of an antihistamine-decongestant combination for young children with the common cold: a randomized, controlled clinical trial. *J Pediatr*. 1991;118(1):125–30.
- 16 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(3):463–6.
- 17 Sakchainanont B, Ruangkananasetr S, Chantarojanasiri T, Tapasart C, Suwanjutha S. Effectiveness of antihistamines in common cold. *J Med Assoc Thai*. 1990;73(1):96–101.
- 18 Walburn J. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics*. 2004;114(5):1370.
- 19 Yoder KE, Shaffer ML, La Tournous SJ, Paul IM. Child assessment of dextromethorphan, diphenhydramine, and placebo for nocturnal cough due to upper respiratory infection. *Clin Pediatr (Phila)*. 2006;45(7):633–40.
- 20 Schaefer MK, Shehab N, Cohen AL, Budnitz DS. Adverse events from cough and cold medications in children. *Pediatrics*. 2008;121(4):783–7.
- 21 Garrison JC, Rall TW. Autacoids: Drug therapy of inflammation, in Gilman AG, Rall TW, Nies AS, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 8. Elmsford, New York, Pergamon Press, 1990;574–9.

- 22 Krenzclock EP, Anderson GM, Mirick M. Diphehydramine overdose. *Ann Emerg Med.* 1982;11(4):212–4.
- 23 Joseph MM, King WD. Dystonic Reaction following recommended use of a cold syrup. *Ann Emerg Med.* 1995;26(6):749–51.
- 24 Lavenstein B, Cantor F. Acute dystonia, an unusual reaction to diphendrydamine. *JAMA.* 1976;236(3):291.
- 25 Powers JM. Blepharospasm and orofacial dystonia. *JAMA.* 1982;247(23):3244–5.
- 26 Lewith GT, Davidson F. Dystonic reactions to Dimetapp elixir. *J R Coll Gen Pract.* 1981;31(225):241.
- 27 Sentora J, Samine M. Diphenhydramine-induced dystonia. *Clin Pharm.* 1989;8(7):471.
- 28 Roila F, Donati D, Basurto C, Del Favero A. Diphenhydramine and acute dystonia. *Ann Intern Med.* 1989;111(1):92–3.
- 29 Favis GR. Facial dyskinesia related to antihistamine. *N Engl J Med.* 1976;294(13):730.
- 30 Sentora J, Samine M. Diphenhydramine-induced dystonia. *Clin Pharm.* 1989;8:471.
- 31 Smith RE, Domino EF. Dystonic and dyskinetic reactions induced by H1 antihistamine medications, in Fenn WE (ed): *Tardive Dyskinesia Research and Treatment.* New York, SP Medical & Scientific Book, 1980; 325–332.
- 32 Rupinak NMJ, Jenner P, Marsden CS. Acute dystonia induced by neuroleptic drugs. *Psychopharmacology (Berlin).* 1986;86:403–19.
- 33 Lavonas EJ, Yin S. Apparent life-threatening events and over-the-counter cough and cold medications. *Pediatrics.* 2009;123(1):e170.
- 34 Centers for Disease Control and Prevention (CDC). Infant deaths associated with cough and cold medications—two states, 2005. *MMWR Morb Mortal Wkly Rep.* 2007;56(1):1–4.
- 35 Vassilev ZP, Kabadi S, Villa R. Safety and efficacy of over-the-counter cough and cold medicines for use in children. *Expert Opin Drug Saf.* 2010;9(2):233–42.
- 36 Sweetman, Sean C. *Martindale: The Complete Drug Reference.* Pharmaceutical Press.
- 37 Bolser DC. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. *Chest.* 2006;129(1 Suppl):238S–249S.
- 38 National Health Service. Treating a common cold. assessed at <http://www.nhs.uk/Conditions/Cold-common/Pages/Treatment.aspx>.

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