JPPT | Review

The Use and Safety of Cough and Cold Medications in the Pediatric Population

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Children often experience viral illnesses causing respiratory symptoms. Frequently, nonprescription medications are used in an attempt to decrease the severity and frequency of cough and cold symptoms. Cough and cold medications (CCMs) are not appropriate for all age groups and can have serious adverse effects, including death, especially when used incorrectly. Data surrounding the safety and efficacy of CCMs in patients younger than 6 years are lacking. Currently, the US Food and Drug Administration (FDA) does not recommend the use of cough and cold products that contain an antihistamine or decongestant in children younger than 2 years. Other treatments used by patients for cold symptoms include non-pharmacologic therapies or complementary alternative medications (CAMs), such as zinc or echinacea. Given this is a common ailment for pediatric patients, pharmacists should be knowledgeable about the risks and benefits of each of these therapies to make safe recommendations for patients and their families. This review discusses various cough and cold therapies and the recommendations for their use in pediatric patients.

ABBREVIATIONS AAP, American Academy of Pediatrics; CAM, complementary alternative medication; CCM, cough and cold medication; CHEST, American College of Chest Physicians; CNS, central nervous system; FDA, US Food and Drug Administration; GI, gastrointestinal; KIDs, Key Potentially Inappropriate Drugs in Pediatrics; NSAID, non-steroidal anti-inflammatory drug; WHO, World Health Organization

KEYWORDS antihistamine; cough; common cold; decongestant; medication; nonprescription drugs; pediatrics

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Introduction

Viruses can infect individuals of all ages, thus resulting in an illness. There are more than 200 types of viruses that cause the common cold, which occurs more frequently in the fall and winter months.[1,2] Young children can experience as many as 8 to 10 colds annually.[2] The incidence of infections is similar in developed and developing countries.[3] Sneezing, rhinorrhea, nasal congestion, sore throat, and coughing are symptoms of a cold.[2] Children may also experience malaise and a decreased appetite. Symptoms can last 10 to 14 days, be bothersome for the patient and caregiver, and result in missed school and work days.[1] While there is no cure for the common cold, some medications may decrease symptoms; however, certain medications are not recommended for children of particular ages owing to concerns of serious adverse events and potentially death.

The Slone Survey found that from 1999–2006, 1 of 10 pediatric patients in the United States used a cough and cold medication (CCM) each week.[4] Decongestants (primarily pseudoephedrine), first-generation antihistamines (most common: chlorpheniramine, diphenhydramine, and then brompheniramine), antitussives (primarily dextromethorphan), and then expectorants (primarily guaifenesin) were the most to least common medications used. Cough and cold medications may be single-ingredient formulations or contain multiple ingredients from different medication classes such as antipyretics, antihistamines, decongestants, expectorants, and antitussives. For example, brompheniramine is most commonly found in combination products, often with pseudoephedrine. Multi-ingredient products are more commonly used, 64.2% per the Slone Study.[4] It found a decongestant and first-generation antihistamine combination as the most prevalent and then a combination of an antitussive, decongestant, and first-generation antihistamine.

The US government agencies and professional organizations have published recommendations regarding the use of various medications in the pediatric population for the symptoms of cough and colds. Currently, the US Food and Drug Administration (FDA) does not recommend the use of cough and cold products that contain an antihistamine or decongestant in children younger than 2 years.[5,6] Since 1976, an FDA advisory panel has recommended against marketing cough and cold products for children younger than 2 years.[7] However, at that time dosing for children was extrapolated

from adult dosing with half-doses recommended for 6- to 11-year-olds and a quarter-dose recommended for 2- to 5-year-olds. In 2007, a citizen petition urged the FDA to publicly state these products had not been demonstrated as safe or effective in children younger than 6 years. The FDA's Pediatric Committee and the Nonprescription Drug Advisory Committee met in 2007 and determined a lack of efficacy in pediatric studies and safety concerns. They voted in support of not using CCMs in children younger than 6 years. Ten days before the meeting, manufacturers began voluntarily recalling nonprescription CCMs labeled for children younger than 2 years.

Between 2004 and 2005, a total of 1519 children younger than 2 years were treated in an emergency department owing to CCM adverse events.[8] An FDA review determined there were 54 child deaths due to decongestants and 69 child deaths from antihistamines between 1969 and 2006 in children younger than 6 years, with most deaths occurring in children younger than 2 years.[7] A review of infant deaths in 2005 found 3 infants (1 to 6 months of age) died owing to CCMs.[8] All infants had blood levels of pseudoephedrine, 2 infants also had blood levels of dextromethorphan and acetaminophen, and 1 infant had additional blood levels of doxylamine postmortem. One infant received a prescription CCM, 1 received a nonprescription CCM, and 1 received both a prescription and nonprescription. Owing to these concerns, in January 2008, the FDA issued a Public Health Advisory "recommending that over-the-counter cough and cold medicines not be used to treat infants and children less than two years of age because serious and potentially life-threatening side effects can occur."[9] Regarding CCM for older children, the FDA recommended caregivers "understand that these products are just for symptom relief and will not treat the cause of the symptoms or shorten illness duration." In October 2008, the Consumer Health Products Association stated that manufacturers of nonprescription CCMs would voluntarily change their product labels to note that use under 4 years of age was not recommended.[10] This age limit was increased from younger than 2 years on prior labels.

Cough and cold medications are readily available over the counter and as prescription. Non-pharmacologic and complementary alternative medications (CAMs) are also available and marketed for cough and colds. Medication dosing and common adverse events are noted in Table 1. Potential toxicities from medication classes are noted in Table 2. This review summarizes available evidence for the use and safety of these medications in the pediatric population.

Antitussives

Dextromethorphan, codeine, and benzonatate are used as antitussive medications. Dextromethorphan is classified as an antitussive medication, also commonly referred to as a cough suppressant. Dextromethorphan decreases the sensitivity of cough receptors and suppresses cough in the cough center in the medulla oblongata, most likely via N-methyl-D-aspartate receptor antagonism. Dextromethorphan may also have proserotonergic activity, which can increase the risk of serotonin syndrome in patients receiving other serotonergic agents. At therapeutic doses, adverse effects may include dizziness or drowsiness. In supratherapeutic doses more autonomic and central nervous system (CNS) effects can arise such as tachycardia, mydriasis, ataxia, hallucinations, nystagmus, and irritability or psychosis.

Dextromethorphan has not demonstrated efficacy in any pediatric trials to date. In 1993, Taylor and colleagues[11] studied 49 pediatric patients aged 18 months to 12 years of age and demonstrated neither dextromethorphan plus guaifenesin nor codeine plus guaifenesin to be more efficacious than placebo for cough frequency, sleep quality, or post-tussive emesis when given at bedtime during 3 consecutive nights. In addition, Paul and colleagues[12,13] performed 2 studies with a total of more than 100 patients aged 2 to 18 years, comparing the effects of dextromethorphan, honey, and diphenhydramine with placebo on nocturnal cough and sleep quality, and did not find any significant benefit of dextromethorphan over placebo. The 2006 American College of Chest Physicians (CHEST) Guidelines for Evaluating Chronic Cough in Pediatrics reinforce the recommendation to avoid nonprescription cough medicines in children owing to limited evidence supporting the benefit of medications.[14]

Codeine is still available as a nonprescription medication but has a behind-the-counter status in a few US states.[15] The American Academy of Pediatrics (AAP) recommends educating caregivers and patients regarding the lack of efficacy of cough medications and the concerns of adverse reactions and overdose risks in children.[16] This statement from the Committee of Drugs was reaffirmed in 2006. Specifically, several agencies and organizations recommended against the use of codeine in children. In 2011, the World Health Organization (WHO) removed codeine from its list of essential medications for children owing to questionable safety and efficacy.[17] In 2013, Health Canada recommended against the use of codeine-containing cough medications in children younger than 12 years.[17] In 2015, the European Medication Agency stated that codeine use was contraindicated for cough or colds in children younger than 12 years and not recommended in adolescents with "breathing problems."[18] In 2016, the AAP called for formal restrictions of codeine use in children for safety measures.[17] After a 3-year investigation, in 2018, the FDA changed medication labels on prescription CCMs with codeine or hydrocodone to limit their use to adults.[19] This change was due to the risk of slow

Table 1. Cough and Cold Medication Dosing and Adverse Events in the Pediatric Population

Medication	Ages/Dosing	Common Adverse Events
Antitussive		
Dextromethorphan	Immediate release: 2 to <6 yr: 5 mg every 4 hr 6 to <12 yr: 10 mg every 4 hr ≥12 yr: 20 mg every 4 hr Extended release (dextromethorphan polistirex): 2 to <6 yr: 15 mg every 12 hr 6 to <12 yr: 30 mg every 12 hr ≥12 yr: 60 mg every 12 hr	Dizziness, drowsiness, nausea
Analgesic/antipyretic		
Acetaminophen	Oral 10–15 mg/kg every 4–6 hr Rectal 10–20 mg/kg every 4–6 hr *(not to exceed 5 doses, maximum 75 mg/kg/day or 4000 mg/day, whichever is less)*	Nausea, vomiting, pruritus
Ibuprofen	5–10 mg/kg every 6–8 hr *(maximum 600 mg/dose or 2400 mg/day)*	Anemia, abdominal pain, nausea, dizziness, skin rash
Antihistamine		
First generation		
Diphenhydramine	2 to <6 yr: 6.25 mg every 4–8 hr 6 to <12 yr: 12.5–25 mg every 4–8 hr ≥12 yr: 25–50 mg every 4–8 hr	Sedation, drowsiness, blurred vision, constipation, tachycardia, paradoxical stimulation (excitation, irritability, insomnia, hallucinations, hypotension, hypertension, diarrhea)
Chlorpheniramine maleate	2 to <6 yr: 1 mg every 4–6 hr 6 to <12 yr: 2 mg every 4–6 hr ≥12 yr: 4 mg every 4–6 hr	
Brompheniramine	2 to <6 yr: 1 mg every 4–6 hr 6 to <12 yr: 2 mg every 4–6 hr ≥12 yr: 4 mg every 4–6 hr	
Second generation		
Cetirizine	6 to <12 mo: 2.5 mg once daily 1–5 yr: 2.5 mg once or twice daily ≥6 yr: 5–10 mg once daily	Drowsiness (more common in adolescents than children), headache fatigue, abdominal pain, tachycardia
Loratadine	2 to <6 yr: 5 mg once daily ≥6 yr: 10 mg once daily	
Decongestant		
Pseudoephedrine (oral)	6–11 yr: Immediate release: 30 mg every 4–6 hr (max: 120 mg per 24 hr) ≥12 yr: Immediate release: 60 mg every 4–6 hr (max: 240 mg per 24 hr) Extended release: 120 mg every 12 hr or 240 mg once a day (max: 240 mg per 24 hr)	Tachycardia, bradycardia, palpitations, insomnia, dizziness, rash or urticaria
Oxymetazoline (nasal)	≥6 yr old: 2–3 sprays in each nostril every 12 hr *Therapy not to exceed 3 days*	Hypertension, temporary nasal discomfort (stinging, burning, increased nasal discharge), rebound nasal congestion
Expectorant		
Guaifenesin	Immediate release: 2 to <6 yr: 50–100 mg every 4 hr 6 to <12 yr: 100–200 mg every 4 hr ≥12 yr: 200–400 mg every 4 hr Extended release: ≥12 yr: 600–1200 mg every 12 hr	Nausea, abdominal pain, headache

Table 2. Toxicities of Cough and Cold Medication Classes

Medication	Toxicities
Antitussive	
Dextromethorphan	Serotonin syndrome, CNS effects (ataxia, hallucinations, somnolence, nystagmus, dystonia, hyperexcitability, psychosis), Autonomic effects (tachycardia, mydriasis, hypertension)
Codeine	Severe, life-threatening, or fatal respiratory depression
Benzonatate	Cardiac arrest, torsades de pointes, coma, seizures, hypotension, and metabolic acidosis
Analgesic/antipyretic	
Acetaminophen	Hepatotoxicity
Ibuprofen	GI toxicity (ulceration, perforation, bleeding), anemia, acute kidney injury
Antihistamine	
First and second generation	Anticholinergic effects (tachycardia, mydriasis, urinary retention), hallucinations, cardiac arrhythmias, seizures
Decongestant	
Pseudoephedrine	Psychosis, hypertension, arrhythmias, seizures, delirium, vasospasm leading to myocardial ischemia or cerebrovascular accident
Expectorant	
Guaifenesin	Nephrolithiasis (in high doses)

CNS, central nervous system; GI, gastrointestinal

breathing or breathing difficulties with these medications in infants and children. In the 2020 CHEST Guideline and Expert Panel Report on managing cough in children, the authors recommended avoiding codeine-containing medications in children with acute cough owing to serious adverse reactions including respiratory distress.[20] The Pediatric Pharmacy Association's Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List recommends that codeine be avoided in children unless pharmacogenetic testing is used.[21] This is a strong recommendation based on high-quality evidence.

Although not available over the counter, another antitussive that may commonly be in the family household is benzonatate. Benzonatate is FDA approved for the use of symptomatic relief of cough in patients 10 years or older and desensitizes the pulmonary stretch receptors of the cough reflex.[22] Case reports describe outcomes such as cardiac arrest, narrowing QRS intervals, torsades de pointes, prolonged QT interval, coma, seizures, hypotension, and metabolic acidosis following benzonatate overdose in 4 adolescents.[23–26] All 3 patients recovered from the ingestion but 1 patient had residual blindness. The FDA has released a warning that accidental ingestion of benzonatate by children younger than 10 years can result in death from overdose.[27] Benzonatate is not recommended for use in children younger than 10 years owing to its risks of cardiovascular or neurologic toxicity. As increasing documented cases of benzonatate exposure in children are both from unintentional and intentional use, caregivers should be counseled on the risks of pediatric exposure to benzonatate.[22]

Antipyretic/Analgesic

Some of the most common nonprescription medications used for pediatric ailments are antipyretics and analgesics such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen. These medications can provide symptom relief from pain and fever during pediatric respiratory illness. The FDA recommends the use of acetaminophen or ibuprofen to reduce fever or relieve pain in infants and children.[5] The AAP recommends to only treat a fever in upper respiratory infections if it causes discomfort to the child.[28]

In general, these medications are well tolerated in previously healthy pediatric patients; however, it is important to understand the toxicity associated with each of these medications. In addition, acetaminophen or ibuprofen can be found in various combination CCMs, which can put children at risk for accidental overdose.

A concern for acetaminophen overdose should be considered if a single dose of 150 mg/kg in children or 7.5 g in adults or repeated dosing adding up to 200 mg/kg over 1 day or 150 mg/kg/day over 2 days.[29] Initial signs and symptoms of acetaminophen ingestion are abdominal pain, nausea, vomiting, pallor, diaphoresis, or malaise. Severe acetaminophen toxicity can ultimately result in liver injury and liver failure if not recognized and treated promptly.

Acute toxicity of NSAIDs can include CNS changes, seizures, acute renal failure, and metabolic acidosis. Gastrointestinal (GI) toxicity, such as gastric ulcers, perforation, or GI bleeding is associated with chronic

use of NSAIDs. The risk of acute toxicity in ibuprofen is 400 mg/kg with risk in adults occurring at 3 g.[30] Safety concerns such as GI toxicity and renal dysfunction may limit the use of ibuprofen in ages less than 6 months. However, a large retrospective cohort study found that GI and renal events were similar in infants prescribed ibuprofen who were younger than 6 months (mean ± SD age: 4.5 ± 1.1 months) compared with infants 6 months of age or older (8.8 ± 1.7 months).[31] Yet, infants younger than 6 months who were prescribed ibuprofen and acetaminophen had an increased risk of GI adverse events (OR: 1.68 [1.13–2.50)]) when compared with infants only prescribed acetaminophen.

Aspirin should be avoided in pediatric patients during respiratory infections owing to the potential increased risk of Reye syndrome given the assumed risk is related to aspirin use during viral infections. In addition, aspirin is listed on the KIDs list to use with caution in children with suspicion of viral illness as a weak recommendation and very low evidence.[21]

Antihistamines

H1 antihistamines are used for allergic rhinitis, urticaria, and other allergic diseases. Antihistamines are also commonly used for cold symptoms. H1 antihistamines work as inverse agonists that block actions of H1 receptors found on the surface of vascular endothelial cells, smooth muscle cells, neurons, and the skin and mucosa.[32] H1 antihistamines are divided into first generation and second generation. First-generation antihistamines such as brompheniramine, chlorpheniramine maleate, and diphenhydramine have a shorter half-life and can more easily penetrate the blood-brain barrier, which increases the risk of adverse CNS effects and therefore are more often associated with being more sedating than second-generation agents.[32] In addition, first-generation antihistamines are less selective for H1 receptors and therefore may have higher anticholinergic adverse effects including dry mouth, GI disorders, and tachycardia. Diphenhydramine can also potentially cause paradoxical CNS effects in young children, causing irritability, excitation, and insomnia instead of sedation and drowsiness as more commonly seen in adults.[33] Second-generation antihistamines include cetirizine and loratadine. These medications have longer half-lives and are less likely to cross the blood-brain barrier, causing less CNS effects, if any.

A Cochrane Review of 363 children within 3 studies comparing antihistamines with placebo concluded there is no good evidence for the use of nonprescription antihistamines for acute cough.[34] The first study comparing clemastine or chlorpheniramine with placebo showed all groups had spontaneous improvement in cough scores with no statistical significance.[35] Twenty percent of children experienced drowsiness and sleepiness. Another study looked at a single nighttime dose of diphenhydramine and found it no more effective than dextromethorphan or placebo in reducing cough frequency.[12] Additional trials assessed decongestant-antihistamine combination and found no benefit over placebo, including 2 different trials that similarly compared combination brompheniramine products (one with phenylpropanolamine and the other with phenylpropanolamine and phenylephrine) with placebo in patients aged 6 months to 5 years and found no difference in upper respiratory symptoms as described by the patient's parents 2 hours after each dose of medication or after 48 hours of consistent dosing.[36,37]

Decongestants

Decongestant medications are classified by adrenergic agonism that stimulates vasoconstriction. This mechanism decreases the swelling of the blood vessels in nasal passages and therefore decreases congestion and provides symptomatic relief. Decongestants are often included in combination CCMs. Decongestant medications are formulated as topical intranasal products and oral decongestants.

Oral decongestants include pseudoephedrine and phenylephrine. A trial in 2019 of 568 children aged 6 to 11 years showed oral pseudoephedrine hydrochloride to be more efficacious than placebo for temporary relief of nasal congestion, demonstrated by a decrease in self-reported nasal congestion scores over 8 hours following two 4-hour doses of 30 mg.[38] Somnolence was reported by more patients in the pseudoephedrine group versus placebo. Pediatric patients have experienced adverse events and death from decongestants as stated earlier.[7,8] Data surrounding efficacy and tolerability of pseudoephedrine in pediatric patients younger than 6 years are lacking and therefore should not be recommended in children younger than 6 years.

Phenylpropanolamine was previously studied with brompheniramine and had no benefit in reducing cough, congestion, or runny nose in patients 6 months to 5 years of age.[36,37] The FDA's Nonprescription Drugs Advisory Committee determined phenylpropanolamine to have an association with hemorrhagic stroke and therefore it is not considered to be safe for nonprescription use, and voluntary withdrawal from the market was recommended by the FDA in 2000.[39]

In 2023, the FDA released a statement describing new bioavailability data showing that less than 1% of an oral dose of phenylephrine is systemically available in an active form.[40] A meta-analysis published in 2007 determined there was "insufficient evidence" of efficacy for the FDA-recommended dose of phenylephrine.[41] A 2007 citizen's petition called for the FDA to reevaluate its oral efficacy and remove the approval of use for children <12 years of age because safety data were lacking.[42,43] Another citizen's petition in 2015 called for phenylephrine to be removed from the market because it failed to be efficacious.[42,43] In September 2023, the FDA's Nonprescription Drugs Advisory

Committee voted unanimously that phenylephrine was ineffective.[44] The FDA has not taken action to remove phenylephrine from the market at this time. Therefore, pharmacists must educate patients and caregivers that phenylephrine should not be used for the treatment of nasal congestion at any age owing to lack of efficacy.

Of particular importance is that Dr Leslie Hendeles, a pediatric pharmacist at the University of Florida, played a key role in analyzing data and sharing the lack of phenylephrine's efficacy with the FDA for more than 30 years.[45] He and another pharmacy colleague strongly advocated to the FDA to recognize the lack of efficacy, submitting both citizen's petitions stated above, and publishing about the lack of efficacy in the medical literature. Imidazoline topical decongestant medications include intranasal products like oxymetazoline. These agents are alpha-2 agonists that work peripherally on local vessels to produce vasoconstriction and improvement of nasal congestion. Topical decongestants are not recommended for pediatric nonprescription use owing to a paucity of data in patients younger than 6 years. Nasal agents are known to cause rhinitis medicamentosa also known as rebound congestion, therefore it is important that patients not use this long term with a recommended duration maximum of 3 days. In addition, there are reported cases of acute toxicity in pediatric patients younger than 2 years when left unattended with various ophthalmic topical decongestants.[46]

Expectorants

Guaifenesin is classified as an expectorant and is often found in combination CCMs such as dextromethorphan/guaifenesin combined therapy. Expectorants are thought to reduce the viscosity of respiratory mucus and increase hydration in the airways, helping to stimulate the natural clearance of respiratory mucus. Data surrounding the efficacy of guaifenesin alone in adult and adolescent patients are conflicting and the data in pediatric patients younger than 12 years are limited. Therefore, the FDA does not have specific recommendations for routine use.[34,47] In a 2014 Cochrane review, 3 articles were assessed for acute cough.[34] One adult study found that 75% of participants stated guaifenesin was helpful in reducing cough frequency and intensity at 72 hours, compared with 21% of participants in the placebo group, while another adult study showed guaifenesin had no greater improvement in cough frequency and severity with its use. The third study evaluated extended-release guaifenesin versus placebo in adolescents and adults and found no difference in the total spontaneous symptom severity scores at 7 days. Possible adverse events with the use of guaifenesin include nausea, stomach pain, and headache. No studies in children met criteria for the review. Case reports of nephrolithiasis exist in adult patients who ingested large doses of guaifenesin and dextromethorphan, though this is rare owing to the high doses required to see this toxicity.[48,49] Overall, efficacy and safety data are lacking for guaifenesin use in cough and colds.

Non-pharmacologic Recommendations

Several non-pharmacologic therapies are safe and can ease cough and cold symptoms in children. Fluid intake is important to ensure the child remains hydrated.[1,50] Saline drops or sprays can moisten the nasal passages, loosen mucus, and facilitate clearing the nasal passages. In young infants, using a rubber suction bulb or suction device can assist with this process. A cool mist humidifier or vaporizer can moisten nasal membranes. Steam from a hot shower can facilitate opening the nasal passages but caution should be exercised not to increase the risk of burns to the skin. The WHO does not encourage warm or cool mist therapy owing to the lack of efficacy.[3]

Honey may relieve a cough but should only be used in children 1 year of age or older owing to the risk of botulism.[1] A Cochrane review of 6 randomized trials in 899 children, ages 1 to 18 years, concluded there was no strong evidence supporting or against the use of honey for cough.[51] The authors stated that honey "probably relieves cough symptoms," reduces the cough impact on sleep more than placebo or no treatment, and has little to no difference when compared with dextromethorphan. Most studies evaluated outcomes after 1 night of treatment. Adverse events were similar between active or placebo treatment groups.

Throat lozenges or cough drops may be used but should only be used in children 4 years of age and older owing to the choking hazard.[1] Mentholated rubs should be used with caution owing to the potential to cause irritated skin (redness/rash) and a burning sensation of the eyes, nose, and skin.[52] One study of 144 children who were 2 to 11 years of age with upper respiratory infection symptoms of cough, rhinorrhea, and congestion found that a rub containing camphor, menthol, and eucalyptus provided the greatest improvement in cough frequency and severity, congestion severity, and the ability of the child and caregiver to sleep when compared with petrolatum ointment and no treatment.[52] Caregivers reported these improvements after a single night of therapy. It is important to note that camphor is noted on the KIDs List to be used with caution owing to seizures.[21]

Complementary and Alternative Medicine

Zinc gluconate glycine lozenges were studied in a prospective, phase IV study in 134 adolescents for the prevention and treatment of a cold.[53] Prophylactic dosing was once daily, and treatment dosing was 4 times per day. This zinc preparation reduced the mean number of colds by 25% ($p < 0.05$) in the zinc cohort compared with a control group. Those with a cold experienced a shorter duration when using the zinc lozenges than the control group, 6.9 ± 3.1 days versus

9 ± 3.5 days ($p < 0.001$). The product (Cold-Eeze, Vespyr Brands, Inc, East Windsor, NJ) was well-tolerated. Fifty children, ages 8 to 13 years, who were administered chelated zinc (zinc bis-glycinate) once daily for 3 months experienced no difference in the incidence of a cold or symptoms when compared with placebo.[54] However, the duration of cough and rhinorrhea as well as having 2 or more symptoms with a cold was decreased in the patients taking zinc when compared with placebo ($p < 0.01$). No adverse events were noted with the zinc product. Zinc sulfate (15 mg) has demonstrated efficacy for prophylaxis by decreasing the number of colds per child, compared with placebo, in a group of 200 healthy children whose average age was 5 years, 1.2 versus 1.7 ($p = 0.003$).[55] Patients who were in the zinc group also experienced a shorter duration of cold symptoms than with placebo, 4.7 versus 5.3 days ($p < 0.0001$). Adverse events were similar between groups. Zinc sulfate was assessed in another trial for effectiveness during an acute cold.[56] Children were enrolled within the first 1 to 2 days of initial cold symptoms and were randomly assigned to zinc sulfate or placebo. There were 120 children (average age, 5.2 years) in the final analysis, which found no difference in the duration of the cold when compared with placebo. Three different zinc formulations and dosage forms were used in the clinical trials, and it is important to note that patients with chronic diseases such as asthma were excluded.

A Cochrane review of 14 trials determined the duration of a cold was reduced by 14.2% (7.3% to 21%) in children who prophylactically consumed vitamin C (0.2 g/day or more) on a regular schedule.[57] If children consumed 1 to 2 g/day of vitamin C, the duration was reduced by 18%. The authors stated no trials had evaluated vitamin C for the treatment of a cold in the pediatric population and that individual patients may want to test their outcome to evaluate if chronic supplementation benefits a temporary, acute cold.

Echinacea was found to lack efficacy in treating cold symptoms in children ages 2 to 11 years but did have increased adverse events in the treatment population.[58] Children who used echinacea had a higher incidence of rash (7.1%), compared with 2.7% of patients in the placebo group. However, echinacea use 3 times a day in approximately 200 children (4 to 12 years of age) for the prevention of upper respiratory tract infections did statistically significantly reduce the number of cold days ($n = 429$) when compared with vitamin C ($n = 602$) and prevented 32.5% episodes of illness.[59] Adverse effects were similar between groups including hypersensitivity reactions. Another trial compared a combination of echinacea, propolis, and vitamin C with placebo in 328 children, ages 1 to 5 years, for the prevention of colds.[60] They found the herbal combination decreased the number of illness episodes by 55% (138 versus 308) and demonstrated a 50% reduction in episodes per child (1.8 versus 1.3, $p < 0.001$). The duration of illness was also reduced by 45% (1.6 versus 2.9, $p < 0.001$). Adverse events were similar between groups, consisting of mild gastrointestinal symptoms and palatability issues. These randomized controlled trials used different formulations and dosing forms of echinacea.

It is important to note that CAM products may or may not undergo scientific evaluation, based on the country of origin.

Medication Safety

Additional recommendations have been made to decrease harm from medications. The AAP recommends that all oral liquid medication should be labeled and administered in metric-based units of milliliters and rounded to the nearest 0.1, 0.5, or 1 mL based on safe and effective dosing.[16] Medications should not use dosing instructions of teaspoons or tablespoons because this can encourage the use of household items that do not provide accurate dosing. The AAP also recommends that pharmacies and hospitals dispense dosing devices that match the milliliter markings for oral liquid medications and that manufacturers eliminate non-metric dosing, labels, and devices with products.[16] In 2011, the FDA called for manufacturers to include a standard dosing device with standard measurements that match the label for all nonprescription liquid medications.[61]

After the voluntary labeling changes and FDA Public Health Advisory, several studies have evaluated the impact of these recommendations. One study found that 82% of caregivers stated they would use cough and cold preparations in children younger than 6 years and 58% of caregivers provided inaccurate dosing with the medication label available for consult.[62] Twenty percent of the caregivers stated that health care providers recommended cough medication for their child and 40% of caregivers had administered cough preparations to their child within the last 6 months.

If CCMs are in the house, they should be kept in a safe and secure location and only administered with supervision. A surveillance study examined the Pediatric Cough and Cold Safety Surveillance System (5 data sources) in the United States (2009–2016) for accidental unsupervised ingestions that included CCMs in children younger than 6 years.[63] There were 4756 cases reviewed of which 3314 (65.9%) were determined to be "at least potentially related to a cough and cold medication ingredient." The incidences occurred primarily at home (94.9%) and 43.8% of patients were admitted to a health care facility with 22% admitted to the intensive care unit. Of all cases, most (61.3%) were in children ages 2 to less than 4 years and 96% were a result of diphenhydramine and dextromethorphan (either single or in combination). Diphenhydramine pediatric liquid and dextromethorphan pediatric liquid as single ingredients were 30.1% and 21.4% of cases, respectively. Three

patients died owing to diphenhydramine solid formulations. Another review of cases in the Pediatric Cough and Cold Safety Surveillance System between 2008 and 2016 found 7983 cases of CCM adverse events with 188 (2.4%) resulting in death.[64] Of the 180 included in the study, 40 cases were deemed related or potentially related to CCMs. Deaths occurred mostly in children younger than 2 years (n = 24, 60%) and boys (n = 26, 65%). In 16 cases (40%), caregivers administered the medication. Diphenhydramine was the most common ingredient (70%). Four cases (10%) included a prescription CCM product. The 3 child self-administered deaths involved diphenhydramine in a solid adult formulation. In 7 cases (17.5%), sedation was the caregiver's primary reason for the CCM to be administered to the child. Despite label changes and public warnings to caregivers, pediatric patients continue to use CCMs and adverse events such as death continue to occur.

Nonprescription CCMs continue to have multiple active ingredients and confusion with medication names and ingredients can occur. The brand name of a product does not have to include the generic ingredient as required with prescription medications. For example, with a nonprescription medication, acetaminophen is not required to be in a product labeled as Tylenol (Johnson and Johnson Consumer Inc, Fort Washington, PA). Additionally, liquid medications may be elixirs that contain alcohol. These aspects contribute to patient and caregiver confusion as well as potential unintentional overdoses.

Conclusion

Colds commonly occur in the pediatric population. The illness resolves without treatment, yet medication products are marketed to relieve symptoms. The efficacy and safety of CCMs have not been demonstrated in children younger than 6 years and serious harm such as death has occurred in children younger than 2 years, especially with antihistamines. Respected organizations such as the CHEST, FDA, and AAP recommend against the use of CCMs in children younger than 2 years and caution the use of various CCMs in the older pediatric population. As pharmacists, we must educate our patients, their caregivers, and other providers about the appropriate use and safety of CCMs in the pediatric population as well as the use of proper administration devices and storage.

Article Information

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