What is the evidence for the safety and efficacy of over-the-counter cough and cold preparations for children younger than six years of age?

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Over-the-counter (OTC) cough and cold medications have been used by your patients for many years, and now, in light of the recent Food and Drug Administration (FDA) consultation, you wonder what evidence there is for and against the use of these drugs.

OTC cough and cold medications for children, which include antitussives, expectorants, nasal decongestants, antihistamines and combination products, have been available, marketed and used for decades. They have been extremely popular likely due to the high prevalence of cold infections in this age group, estimated at six to eight symptomatic infections per year (1). Furthermore, these products are extensively marketed to the parents of young children. In a 2007 Consumer Healthcare Products Association survey (2), 73% of 648 caregivers with children younger than 18 years of age administered OTC cough medications, regardless of age. In a survey (3) of 310 health care professionals this year, the majority of paediatricians and generalists were in favour of recommending these drugs in the two- to six-year age group and the six- to 12-year age group. However, reports from the FDA meeting of October 18 and 19, 2007, recommended that these medications should not be given to children younger than six years of age. Why is there such a discrepancy between what clinicians and the public believe to be safe and effective and the FDA ruling?

According to the American Academy of Pediatrics (4), part of the reason these drugs are believed to be safe is that they are sold as OTC medications. Numerous evidence-based reports, including several systematic reviews of the literature in this area (5-11), have stated otherwise. In fact, each of the classes of drugs included in these formulations has its own list of associated adverse effects (Table 1) and they often coincide, increasing the danger inherent in combination medications that include many of these preparations (5,6). Furthermore, the active ingredient in these formulations can actually be changed by the manufacturer without any change to the brand name of the product (12), which is often what parents use to differentiate medications.

TABLE 1
Classes of drugs and their associated adverse effects

Active ingredient class	Example(s)	Possible adverse effect(s)
Decongestants	Pseudoephedrine, phenylephrine	Tachycardia, restlessness, insomnia, anxiety, tremors, hypertension, irritability, anorexia, lethargy, headaches, dysrhythmias, hallucinations, dystonic reactions, seizures.
Antitussives	Dextromethorphan	Constipation, dizziness, drowsiness, nausea, vomiting, respiratory ataxia. depression, apnea, palpitations, possible serotonin syndrome with SSRIs.
Antihistamines	Diphenhydramine, chlorpheniramine, brompheniramine	Drowsiness/sedation, dizziness, headache, dry mouth, dry eyes, paradoxic excitability, respiratory depression, hallucinations, tachycardia, arrhythmias, blurred vision
Expectorants	Guaifenesin	Nausea, diarrhea, dizziness, headache but generally well tolerated.

SSRI Selective serotonin reuptake inhibitors

The danger of these medications increases in children younger than six years of age because dosing guidelines for these medications are mostly extrapolated from adult data, and physiology, bioavailability and toxicity may be significantly different between these age ranges (4).

It should be noted that this is not the first time that the FDA has recommended removal of an OTC cough and cold product. Phenylpropanolamine is a decongestant product similar to phenylephrine in its mechanism of action, and used to be present in many cough and cold formulations. However, in 2000, it was removed from all preparations due to concerns of hemorrhagic stroke and transient ischemic attack, as well as reports (6,12) of cardiomyopathy and intracranial hemorrhage in children.

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There have also been several deaths associated with OTC cough and cold products. Between January 1, 2000, and June 30, 2007, there have been 20 reported child deaths in the United States that were thought to be related to ingestion of these preparations (13). Most of the deaths (13 of 20) were in children younger than two years of age, but there were also reports of mortality in children as old as eight years of age. Almost all ingredients present in these compounds were implicated in more than one case, including phenylephrine, dextromethorphan (DM), pseudoephedrine, guaifenesin and diphenhydramine.

Data on efficacy further call these products into question. Several reviews, including the American Academy of Pediatrics guidelines, note that there have been no well-controlled studies that support the efficacy of DM in children; it is the most common antitussive ingredient in OTC cough products (4,10,11). Furthermore, there have been similar results from these reviews for the other active ingredients of most OTC preparations (10,11). Recent original trials (8,14,15) have further supported this claim, finding, respectively, that antihistamine-decongestant combinations, DM and diphenhydramine show no increase in efficacy over placebo on any of the outcome measures studied. These studies further state that while efficacy of the products was uncertain, potential for toxicity was not; for instance, DM carries an adverse events profile at standard doses that includes dystonia, anaphylaxis and bullous mastocytosis (8). Highlighting this issue is a recent study (16) demonstrating that honey was more effective in terms of parental assessment of symptomatic relief of nighttime cough in children compared with DM or placebo.

Given the doubtful efficacy, extrapolation from adult data and the combination nature of many of these products, dosing can be challenging and much of the literature (4,5,12) calls for more research to be done in this area in young children due to uncertainties. There are also factors, aside from adverse effects profiles, that further complicate dosing in children and may contribute to morbidity and mortality. First, caregivers have been found to make dosing errors in attempts to follow 'package guidelines' by misunderstanding the dose required or frequency, using an incorrect measuring device or even giving the wrong preparation (5). Also, the use of several products in an attempt to alleviate symptoms in their child can lead caregivers to overdose their children with certain ingredients due to combination preparations; in some cases, caregivers are not even aware of the active ingredients they are giving, due to small lettering and creative labelling of packages (5). In addition, some combination products contain agents such as ibuprofen or acetaminophen that are also widely available in single-ingredient preparations, increasing the possibility of confusion and inadvertent administration of supratherapeutic doses. These errors have the potential to be more costly in the toddler and preschool populations due to the relative increase in amount per kilogram ingested (5). The uncertainty regarding the safety of these preparations is further compounded by the fact that some children have reduced clearance of these medications that can leave active drugs in their system longer and the potential for abuse of these drugs in older children and teenagers (6). Finally, it is worth noting that the use of these preparations is also associated with cost, the estimated market in North America for children younger than six years of age being approximately $800 million a year, essentially all of which is noninsured and is, thus, a direct cost to families.

In short, there is little to no evidence to support the efficacy of OTC cough and cold preparations in children, but there are several concerns regarding the safety of these products (17). It appears that they have been a market mainstay due to their relative low cost and the perception of parents and clinicians that they improve symptoms and allow for easier tolerance of coughs and colds (2,3), as well as a general perception of safety. However, in light of extensive reports of no objective efficacy coupled with significant adverse events (especially in this age group), a risk-benefit analysis clearly suggests that the use of these products in children younger than six years of age should not be encouraged or supported. Furthermore, parent education about the self-limiting nature of coughs and colds and the lack of efficacy of these drugs is needed (4,17). Supportive therapies, such as humidified air, bulb suctioning, saline nose drops and increased fluid intake continue to receive support in the literature (4,12) and should be used as needed.

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