



## Over the Counter but No Longer under the Radar — Pediatric Cough and Cold Medications

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In recent weeks, over-the-counter cough and cold medications for children have received unprecedented attention from regulators, physicians, the media, and parents. This scrutiny represents a

long-overdue reassessment of products that were purchased by 39% of U.S. households during the past 3 years.<sup>1</sup> It also reflects an important evolution in the standard of evidence for medications used in children.

Over-the-counter cough and cold preparations include various combinations of antihistamines, decongestants, antitussives, and expectorants. There is no standard for describing these products; two products marketed similarly may have different types of ingredients (see table). Consumers purchase about 95 million packages of such medication for use in children each year.<sup>1</sup> Within the pediatric com-

munity, however, concern over the effectiveness and safety of such drugs has been growing for more than two decades.

Since 1985, all six randomized, placebo-controlled studies of the use of cough and cold preparations in children under 12 years of age have not shown any meaningful differences between the active drugs and placebo. In 1997, the American Academy of Pediatrics noted in a policy statement on cough medications that “indications for their use in children have not been established.” In 2006, the American College of Chest Physicians found that “literature regarding over-the-counter cough

medications does not support the efficacy of such products in the pediatric age group.”

Meanwhile, poison-control centers have reported more than 750,000 calls of concern related to cough and cold products since January 2000.<sup>2</sup> A recent report from the Centers for Disease Control and Prevention identified more than 1500 emergency room visits in 2004 and 2005 for children under 2 years of age who had been given cough or cold products.<sup>3</sup> Among other concerns are findings in children under six linking decongestants to cardiac arrhythmias and other cardiovascular events, antihistamines to hallucinations, and antitussives to depressed levels of consciousness and encephalopathy. A review by the Food and Drug Administration (FDA) identified 123 deaths related to the use of such prod-

Ingredients and Marketing of Some of the Available Pediatric Cough and Cold Products.*		
Ingredients	Brand Name	Marketed Use
Antihistamine	Pediacare	Nighttime cough
	Triaminic	Cough and runny nose
Antitussive	Robitussin	Long-acting cough
Decongestant	Dimetapp	Decongestant
Antihistamine and antitussive	Robitussin	Long-acting cough and cold
	Tylenol Plus	Cough and runny nose
Antihistamine and decongestant	Dimetapp	Cold and allergy
	Pediacare	Nighttime multisymptom cold
	Triaminic	Nighttime cough and cold
Antitussive and decongestant	Dimetapp	Decongestant plus cough
	Pediacare	Multisymptom cold
	Triaminic	Daytime cough and cold
Decongestant and expectorant	Dimetapp	Cold and chest congestion
	Triaminic	Chest and nasal congestion
Antihistamine, antitussive, and decongestant	Dimetapp	Cold and chest congestion
	Tylenol Plus	Flu
	Tylenol Plus	Multisymptom cold
Antitussive, decongestant, and expectorant	Robitussin	Cough and cold

\* The antihistamines include brompheniramine, chlorpheniramine, and diphenhydramine; the antitussive is dextromethorphan, the decongestant is phenylephrine, and the expectorant is guaifensin. All formulas of Tylenol Plus also contain acetaminophen.

ucts in children under six during the past several decades.<sup>4</sup> Serious adverse effects have been associated with accidental overdose, inadvertent misuse, and drug–drug or drug–host interactions in children given standard doses.

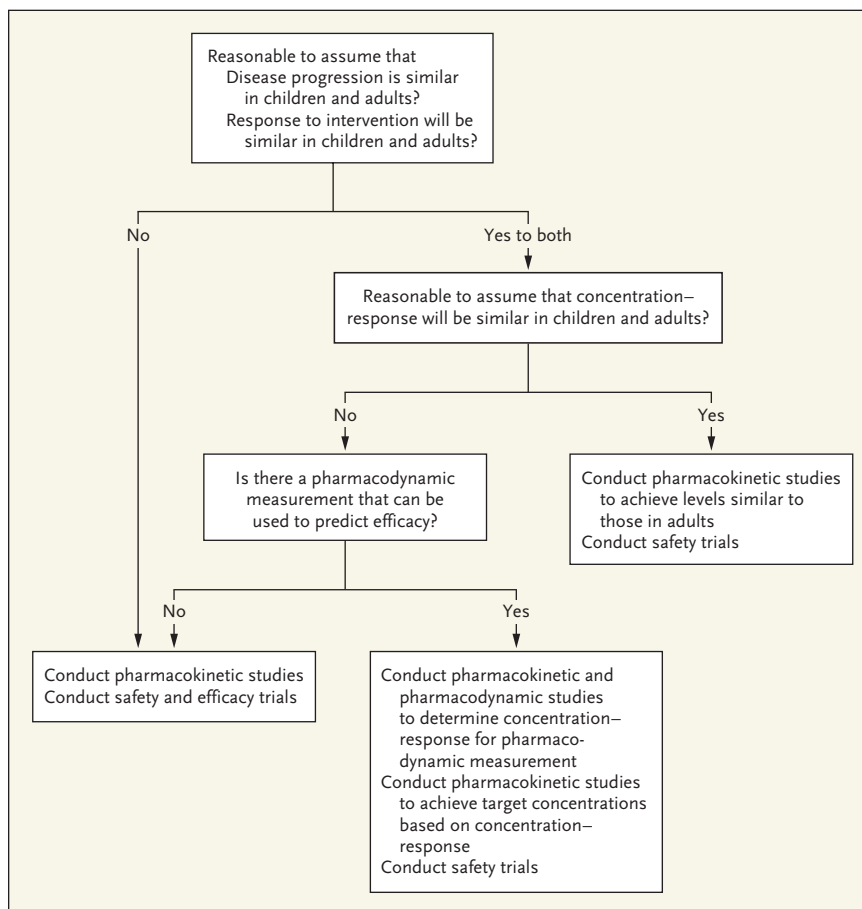
The marketing of these preparations for young children does not reflect the risks or the lack of evidence of efficacy. The Federal Trade Commission, which oversees advertising for over-the-counter products, does not have the FDA's scientific expertise for evaluating

marketing materials and does not require that advertisements show a “fair balance” between risks and benefits. Direct-to-consumer advertisements assert that preparations are safe and effective, and many state that ingredients are “pediatrician-recommended.” A frequent theme is that giving children these products allows parents to relax. In fiscal year 2007, according to data provided by the Prescription Project (a policy-advocacy organization), companies spent more than \$50 million marketing

pediatric over-the-counter cough and cold preparations to parents.

The fact that these medications are widely marketed and used despite the lack of evidence of efficacy can be explained in part by their regulatory history. This class of drugs was first marketed well before 1972, the year that the FDA began a comprehensive review of hundreds of over-the-counter cough and cold preparations. It obtained input from an expert advisory panel, solicited public comment on proposed rules, and prepared a monograph outlining conditions of use. In 1976, the advisory panel endorsed the use of some over-the-counter ingredients for cough or cold symptoms in adults but, in the face of “negligible or nonexistent” data on pediatric use, recommended against their marketing for children under two. For older children, it endorsed the extrapolation of doses from those recommended for adults, using a crude formula: half the adult dose for children between 6 and 11 years of age and a quarter of the adult dose for children between 2 and 5 years. Dose recommendations were calculated for children as young as 6 years for antihistamines and as young as 2 years for all other categories of cough or cold drugs. The FDA adopted these guidelines in its monograph but permitted manufacturers to market the drugs for children below these ages if labeling instructed parents to consult a doctor before use.

In the ensuing 30 years, the FDA never returned to review the effects of these preparations in young children. In March 2007, we, along with 13 other signatories, filed a petition urging the



**FDA's Decision Tree for Determining Whether Pediatric Efficacy Studies of a Drug Are Needed.**

Modified from FDA presentation, "Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications," April 2003.

agency to do so. We asked the FDA to issue a public statement explaining that the products have not been shown to be safe and effective for children under six, to take action against misleading marketing, and to revise its monograph accordingly. The FDA responded by convening a joint meeting of the Pediatric Committee and the Nonprescription Drug Advisory Committee on October 18 and 19, 2007. Ten days before the meeting, major manufacturers voluntarily recalled over-the-counter cough and cold preparations for children under

two and proposed adding the warning "Do not use to sedate children" to the label for antihistamines subject to the monograph.

At the meeting, there was little dispute about the lack of evidence from pediatric efficacy studies. As for safety, the manufacturers claimed that virtually all cases of serious injury or death resulted from overdose, which could be prevented through patient education. The petitioners argued that some serious adverse events have resulted from confusion and unanticipated ef-

fects, which could not be eliminated by labeling or parent education.

More broadly, the committee debated the appropriateness of extrapolating to children data demonstrating modest efficacy in adults. Testifying for the petitioners, Wayne Snodgrass of the University of Texas Medical Branch argued against extrapolation — describing differences between adults and children in the relevant disease processes and physiology and citing recent studies, conducted as a result of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, that indicate that drugs approved for adult use may be ineffective, incorrectly administered, or toxic in children. Examples of prescription drugs include sumatriptan, gabapentin, and pimecrolimus. The American Academy of Pediatrics

concurred, testifying that the results of pediatric drug studies "humble us on a regular basis."

The FDA presented an algorithm (see flow chart) that, in keeping with the current legal standard, permits extrapolation when there is a "similar disease progression" in children and adults and a "similar response to intervention," when it is "reasonable to assume similar concentration-response," when safety trials have been conducted, and when pharmacokinetic studies show that appropriate administration of the drug will achieve

“levels similar to [those in] adults.” Agency scientists, however, stated that pharmacokinetic data were inadequate to support extrapolation for cough and cold preparations. The manufacturers’ trade association promised to conduct additional pharmacokinetic studies and said it would consider conducting efficacy studies in consultation with the FDA.

Advisory committee members expressed concern that these medications have been marketed for decades without good pediatric data, when it has long been feasible to conduct additional studies. The committee rejected the idea that pharmacokinetic data alone would be sufficient. All 22 members agreed that it was unacceptable to extrapolate data for the use of these medications in children under 2, and all but 1 member rejected extrapolation for children between 2 and 11. Instead, the group voted unanimously that pediatric clinical efficacy studies should be required. The committee voted 13 to 9 in favor of immediate action against the use of cough and cold medications in children under six.

After the meeting, the major manufacturers of these products announced that they disagreed with the committee and would continue to market these preparations for children between 2 and 5 years of age. Because the monograph is still in effect, the products and their “toddler” formu-

lations are still being widely advertised to parents in ways that suggest that they are known to be safe, effective, and recommended by most pediatricians. Despite their own proposal that the use of these products for sedation be stopped, companies are



still marketing “nighttime” preparations containing sedating antihistamines. Although the FDA does not need to follow the recommendations of its advisory committees, we believe that it should immediately ask companies to remove these products from store shelves and begin legal proceedings to require them to do so. Rep. Henry A. Waxman (D-CA) and Sen. Edward Kennedy (D-MA) have recently introduced legislation to expedite this process by strengthening the FDA’s oversight of the marketing and advertising of over-the-counter medications.

The agency must also respond

to the broader implications of the committee’s objection to extrapolating efficacy from adults to children. When it is questionable whether a drug’s benefits outweigh its risks, the drug should be studied in children if at all possible. The adoption of this standard would bring benefits far beyond relief of the common cold.

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1. Consumer Healthcare Products Association. Briefing information for the Food and Drug Administration joint meeting of the Nonprescription Drugs Advisory Committee & the Pediatric Advisory Committee. (Accessed November 14, 2007, at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4323b1-01-CHPA.pdf>.)
2. Consumer Healthcare Products Association testimony before the Food and Drug Administration (October 18, 2007). Washington, DC: American Association of Poison Control Centers, 2007.
3. Infant deaths associated with cough and cold medications — two states, 2005. *MMWR Morb Mortal Wkly Rep* 2007;56:1-4.
4. Food and Drug Administration, Division of Drug Risk Evaluation. Nonprescription Drug Advisory Committee meeting: cold, cough, allergy, bronchodilator, antiasthmatic drug products for over-the-counter human use. 2007:29. memorandum. (Accessed November 14, 2007, at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4323b1-02-FDA.pdf>.)

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