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Management of Acute Cough in Children: Where Do We Go From Here?

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The safety of cough and cold products for pediatric use has been a concern of regulatory agencies and advocacy groups for decades. Most recently, the Food and Drug Administration requested input from Pulmonary-Allergy Drugs and Drug Safety and Risk Management advisory committees on the safety of codeine for cough in children aged 18 years and younger. There is little evidence of efficacy for codeine in the treatment of acute cough in children, but mounting evidence for risks of respiratory depression and death. Similarly, dextromethorphan, benzonatate, antihistamines, guaifenesin, and mucolytics lack efficacy in controlled trials or there are no data with which to evaluate efficacy, and dextromethorphan may cause respiratory depression. Honey and topical use of aromatic oils (camphor, menthol, and eucalyptus) have limited evidence of efficacy, but may have the greatest margin of safety for treatment of acute cough in children.

In December 2015, the Food and Drug Administration (FDA) Pulmonary-Allergy Drugs advisory committee and Drug Safety and Risk Management advisory committee met to discuss the safety of codeine for cough (and analgesia) in children less than 18 years old.[1] The meeting was convened due to a recent decision by the European Medicines Agency to contraindicate the use of codeine for cough in children below 12 years of age and to recommend codeine not be used in children 13–18 years who have breathing problems.[2]

The use of cough and cold products in children was last discussed by the FDA in 2007 at a joint meeting of the Nonprescription Drugs and Pediatric Advisory Committees, which resulted in the FDA issuing a statement in 2008 that over-the-counter (OTC) cough/cold medicines not be used in children younger than 2 years of age.[3] The manufacturers of cough and cold products had already recalled these products for children less than 2 years of age shortly before the FDA meeting. Subsequently, the Consumer Healthcare Products Association announced voluntary actions by its members to modify product labels of OTC cough/cold medicines to state ''do not use'' in children less than 4 years of age.

At the most recent meeting on the safety of codeine, the FDA advisory committee members voted to contraindicate (meaning that the risk from use clearly outweighs any possible therapeutic benefit) the use of codeine for cough in children of all ages and to remove OTC use of codeine in all children of all ages. This review will present the issues related to the use of codeine for cough in children leading to these votes, as well as a discussion of alternative cough therapies for children less than the age of 18 years.

In 1962, the Kefauver–Harris Amendment required that new drug applications demonstrate efficacy, as well as safety before market approval. At that time, only 25% of the 100,000–300,000 OTC products had evidence of efficacy.[1] The FDA was tasked to convene advisory panels in 1972 to review existing data on each of ~500 representative OTC active ingredients for safety and efficacy. Each active ingredient was placed into a therapeutic category, and those lists of drugs became OTC monographs (finalized in 1987) that are established in the Code of Federal Regulations. Development of, and change to, monographs for OTC products was (and is) a lengthy multistep process that includes public notice and comment.

Because the standard for OTC monograph inclusion was whether the product was ''generally recognized as safe and effective,'' many of the OTC products and their dosing recommendations have bypassed the current standard process of evaluation through clinical efficacy and safety studies in the intended use population. In 1983, the FDA solicited recommendations from the American Academy of Pediatrics, which issued a warning statement that ''…codeine containing cough syrups can be hazardous…'' and as a result, the monographs established in 1987 had instructions which simply stated ''Children under 6 years of age: consult a doctor.''[1] Although under the monograph process pediatric dosing recommendations were provided to physicians, these instructions were not based upon evidence based data for children, but rather on best practice.

Most of the newly available OTC products were originally available by prescription and, thus, have existing efficacy and safety data. In addition, any new chemical entities for OTC use

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are regulated through the same New Drug Application process as prescription products. The FDA has regulatory authority to require companies to obtain pediatric data for new indications under the Pediatric Research Equity Act. Thus, the majority of newer OTC products with pediatric dosing instructions have safety and efficacy data supporting use in children.

Acute cough is defined as lasting <3 weeks in duration and is typically a consequence of a viral upper respiratory tract infection (URTI).[4] Prospective studies indicate that URTI associated cough resolves in 10 days for 50% of children and in 3 weeks for 90%.[4] Both dry and productive coughs occur as reported by parents.[4] Potential causes for the remaining 10% of children who have prolonged acute cough (3–8 weeks in duration) include acute bronchiolitis, pertussis, postcomplicated acute pneumonia, rhinosinusitis, retained foreign body, and persistent bacterial bronchitis.[4] Children with prolonged acute cough or chronic cough (>8 weeks in duration) should have further evaluation to determine specific etiology and treatment.

Codeine exerts its putative antitussive effects centrally by acting on an involuntary reflex area in the medulla, although this mechanism was identified only in animals and has been called into question.[5] Codeine was ''generally recognized as safe and effective'' and included in the cold, cough, allergy, bronchodilator, and antiasthmatic monograph specifically as an antitussive in the final OTC monographs in 1987. Even at this time (and again in 1997 and 2007), the American Academy of Pediatrics voiced strong concern that codeine-containing cough syrups could be hazardous to young children even at labeled doses.[6,7]

A recent Cochrane analysis[8] identified two controlled trials in adults published in 1992 and 1997 that demonstrated no greater efficacy for codeine than placebo in the treatment of cough. A single study in children published in 2003 evaluating a bedtime dose of codeine for three nights also found no benefit compared with placebo.[8] However, codeine, when in combination with at least one nonnarcotic active ingredient that has medicinal use [such as an antihistamine, decongestant, or expectorant (per the OTC monograph requirements)], is available without a prescription and, thus, can be purchased by consumers in limited quantities for use in children. Currently, 28 states and the District of Columbia permit OTC sale of codeine. Codeine is available by prescription for antitussive use as immediate release products (with promethazine or triprolidine and pseudoephedrine) for children more than 2 years of age and as an extended release product (with chlorpheniramine) that is not approved for children.

Even if codeine had documented efficacy for cough in children, the overriding issue is whether it can be dosed safely. The cause for the many FDA press releases, safety communications, and publications since 2007 is due to the significant risks of respiratory depression or even death in children, and these risks (excluding events due to excessive dosing) are clearly related to the polymorphic pharmacogenetic metabolism of codeine.[1] Codeine is cleared by several metabolic pathways: to morphine by the CYP2D6 enzyme (5%–15%), which is further metabolized to inactive compounds; to norcodeine by CYP3A4 (10%–15%); and to codeine-6-glucuronide by UGT2B7 (50%–70%).[9] The CYP2D6 enzyme is encoded by the polymorphic gene, *CYP2D6*, and impacts the amount of codeine that is ultimately metabolized to morphine. It is the elevated blood levels of morphine that increases the risk of respiratory depression and death associated with codeine use.

CYP2D6 phenotypes include ultrarapid metabolizers (increased risk of morphine formation after codeine ingestion), extensive metabolizers (normal morphine formation), intermediate metabolizers, and poor metabolizers. Intermediate and especially poor metabolizers experience reduced analgesia from codeine due to inadequate conversion to morphine. Cases of severe respiratory depression ($n = 64$) have been voluntarily reported to the FDA[1] in all age groups: 0–1 year (25%), 2–5 years (36%), 6–11 years (17%), and 12–18 years (22%) with intake of as little as a single dose of codeine. Of these, 38% resulted in death. Unfortunately, *CYP2D6* genotype is not convincingly predictive of morphine accumulation after codeine dosing as several reports were of children with the extensive metabolizer phenotype yet had morphine levels typically seen in ultrarapid metabolizers.[1] Thus dosing based on *CYP2D6* genotype is not currently recommended.[1]

Because OTC sales of codeine continue, although it is not known which sales are for children (nearly 170,000 dispensings in 2014), and 1.9 million codeine prescriptions for children were dispensed in 2014 (26% for cough and cold symptoms), there continues to be significant pediatric exposure to the risks of codeine-induced respiratory depression and death. Based upon the data presented to the Advisory committee at the 2015 meeting, the members sent a clear message to the FDA to reduce codeine exposure by voting to remove codeine from OTC use in children and contraindicating its use in children, the latter will primarily affect prescription use. It is not clear if this means codeine would be removed from OTC status completely. In any event, if the FDA heeds the recommendations of the advisory committees, codeine will continue to be available in the near future as the monograph process to remove an OTC product can take years.

Other narcotic products available by prescription that have a current indication for cough in children 6 years and older include hydrocodone with homatropine or with chlorpheniramine. Hydrocodone is metabolized by CYP2D6 to hydromorphone, which is less active than the parent drug. Poor metabolizers thus would be at risk for hydrocodone adverse effects. Respiratory depression and fatalities have also been reported with these products, and given these risks, it would be inadvisable to use these products in children.

Dextromethorphan is the D-isomer of the codeine analog levorphanol, but lacks analgesic and addictive effects, and is believed to exert its antitussive effects similarly to codeine.[10] It is also metabolized by CYP2D6 to inactive metabolites, and poor metabolizers are at risk for adverse effects, including respiratory depression among other adverse effects due to dextromethorphan accumulation.[10] It is available OTC, and in four controlled trials in children, it was found to be no more effective than placebo or diphenhydramine.[8]

Benzonatate is the only nonnarcotic antitussive available by prescription for use in children aged 10 years and older. It was approved by the FDA in 1958—before the Kefauver–Harris Amendment requirement for evidence of efficacy. There have been no published controlled clinical trials of its efficacy. Its mechanism of action in humans is unclear and use is associated with serious adverse effects that include restlessness, seizures, tremors, coma, cardiac arrest, and death.[11,12–14] The number of benzonatate prescriptions has increased in recent years, which may be the result of declining use of codeine and use of benzonatate instead.[14] The shape and size of the product (translucent pearl-shaped gelatin capsule) may be attractive to children and the FDA issued a safety communication in 2010,

which highlighted that all accidental overdoses of benzonatate occurred in children less than the age of 10 years.

First-generation antihistamines, such as diphenhydramine, are included in the OTC monograph as antitussives. The mechanism would be most likely related to a drying effect (anticholinergic properties) on mucus secretions that cause cough due to postnasal drip although both peripheral and central mechanisms on mechanoreceptors are also proposed.[15] A review of five studies that included brompheniramine (in combination with a decongestant), clemastine, chlorpheniramine, diphenhydramine, and promethazine found no benefit on acute cough compared with placebo.[8] Newer nonsedating antihistamines have not been found to be effective in the treatment of acute cough in controlled studies.[15]

There are no well controlled studies of expectorants (guaifenesin) or mucolytics for treatment of acute cough in children.[8]

Honey or other sweet syrups (without alcohol) have also been tried as treatments for acute cough in children.[16] Syrups contain sapid ingredients such as sugar, honey, spicy, or bitter tasting substances (such as lemon), which can initiate reflex salivation and possibly secretion of airway mucus.[16] These effects may be beneficial for both dry and productive coughs, respectively. Honey has been suggested by the World Health Organization as a potential remedy for acute cough in children, but should not be used in infants less than 1 year of age due to the risk contamination with *Clostridium Botulinum*.[17,18]

Honey has been evaluated in a Cochrane review for the treatment of acute cough in three trials in children.[19] In these studies, honey and dextromethorphan were equally effective, and honey was more effective than diphenhydramine or placebo. Given that previous studies have not shown a beneficial effect of dextromethorphan over placebo, the findings for a benefit of honey are unclear. However, honey has few adverse effects and is safer than dextromethorphan, although parents did report increased occurrences of restlessness and difficulty falling asleep in children given honey.[19]

Topical products that include the aromatic oils, camphor, menthol, and eucalyptus, have not been well studied. In a trial that compared Vapor Rub (4.8% camphor, 2.6% menthol, and 1.2% eucalyptus oil) versus petrolatum and no treatment found that Vapor Rub was better than petrolatum or no treatment for reducing frequency and severity of acute cough in children 2–11 years old.[20] Aromatic oils can cause serious toxicity if ingested (e.g., seizures with camphor), thus, parents, not children, should be responsible for applying the product. They are to be applied on the chest and throat and not to the nostrils. They should not be used in children less than 2 years old. The use of these products in steam vaporizers should also be closely monitored to avoid burns in children.

In summary, there is a lack of evidence for efficacy of commonly used antitussive products that include codeine, dextromethorphan, diphenhydramine, or guaifenesin for the treatment of acute cough in children. In addition, codeine and dextromethorphan are considered unsafe in children. Honey, nonalcoholic sweet syrups, or topical aromatic oil products may be beneficial and are likely the same products used by past generations of parents to treat cough in their children due to the common cold.

Author Disclosure Statement

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