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SPECIAL CONTRIBUTION

Pediatrics

Use of antitussive medications in acute cough in young children

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Abstract

Acute cough, a common complaint in young children, is often the result of a viral upper respiratory infection. Cough and cold remedies generate billions of dollars in annual sales in the United States, despite a lack of evidence of their efficacy and multiple warnings by the US Food and Drug Administration. The current article begins with the best available evidence for common over-the-counter (OTC) and prescription antitussive remedies in children. The article concludes with a discussion of the pros and cons for the use of antitussives in children with cough. In general, OTC antitussive medications should not be routinely used in children under 2 years of age. In certain cases, antitussives with minimal adverse profile and some evidence of benefit may be recommended after informed counseling.

KEYWORDS
antihistamines, antitussive, benzonatate, codeine, cough, cough suppression, dextromethorphan, honey

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1 | INTRODUCTION

Cough is a common reason for caregivers to take children to the emergency department. Although chronic cough may suggest serious underlying pathology, acute cough is usually benign. Most adult consensus guidelines define cough as acute (<3 weeks), subacute (3 to 8 weeks) or chronic (>8 weeks).[1] Guidelines and statements for cough in children largely follow the same definitions, though some experts may consider cough lasting longer than 4 weeks as chronic.[2,3]

In pediatrics, acute cough is typically the result of a viral upper respiratory tract infection (URI) or from bronchospasm triggered by illness, allergens, or exercise. As a protective reflex, cough facilitates mucociliary function, helping to clear excessive secretions and debris from the airways. The respiratory tract has cough receptors from the larynx to the segmental bronchi.[4] With mechanical stimulation, cough can be elicited in 10% of 27-week gestational age preterm infants and up to 90% of full-term infants.[5] As many as 50% of school-age children continue to cough up to 10 days after the onset of a common cold, and 10% of preschool children cough for up to 25 days after a respiratory tract infection.[6]

Cough and cold medicines are advertised extensively and sold ubiquitously in pharmacies and stores all over the world. Revenue from over-the-counter (OTC) cough and cold medicine alone in the United States is estimated at $10.3 billion annually, with an average growth of 2.8% per year between 2014 and 2019.[7] Nevertheless, there is little evidence supporting their efficacy, and many are not regulated by the United States Food and Drug Administration (FDA).

This paper aims to inform clinician management of young children with acute cough, for whom the clinician is not concerned about serious disease processes or underlying conditions. We begin with a non-systematic yet extensive review and synthesis of peer-reviewed studies on the effectiveness of common antitussives in children. We include common reported adverse effects, toxicity, and abuse potential. We end with arguments for and against antitussive use in children and implications for clinical practice. The goal of this paper is to provide emergency clinicians with best practice information for a balanced, informed discussion regarding antitussive recommendation in young children presenting with acute cough.

2 | LITERATURE REVIEW

We conducted a structured literature search using PubMed, Medline, Scopus, Cochrane, and Web of Science. Publications were considered for review if they met the following criteria: (1) published between 2001 and 2020, (2) English language, (3) included pediatric subjects (≤18 years of age), and (4) peer-reviewed journal. A combination of MeSH and key terms were used in the searches (Supplemental Table). We manually reviewed references in select articles to identify further studies.

We included an antitussive medicine in our review only if we identified at least 1 study of a given agent as a single ingredient that met these criteria. We extended our literature search window to 20 years because many of the key studies on the topic were published more than a decade ago. Nevertheless, many common antitussives, for example, guaifenesin, pseudoephedrine, hydrocodone, etc. did not have published pediatric data as a *single ingredient* and hence were not included in this review. Similarly, common antitussive formulations, for example, Hyland's Cough n' Cold, were not included for the same reason.

In total we found 10,090 articles matching our initial search criteria. After eliminating duplicates and articles not meeting our inclusion criteria, we were left with 164 articles. Each article was then reviewed by one of the authors (SL) for relevance and inclusion in this review. We did not perform a formal systematic review on the 164 studies included, owing to the existence of several excellent Cochrane reviews on individual antitussive ingredients[8–11] and the lack of high-quality evidence since their publication.

3 | RESULTS

3.1 | Over-the-Counter (OTC)

3.1.1 | Dextromethorphan

There is fairly extensive literature on dextromethorphan, a common OTC medication, to treat cough in children. The mechanism of action is postulated to be suppression of central nervous system cough receptors. Paul et al. compared dextromethorphan, diphenhydramine, and placebo for treatment of 100 children diagnosed with a URI, finding no benefit for dextromethorphan for cough severity or sleep quality.[12] Other pediatric studies yielded similar results.[8,13–19]

Though related to codeine, dextromethorphan does not have analgesic effects or cause respiratory depression at therapeutic doses. The metabolite of dextromethorphan, however, inhibits N-methyl-D-aspartate receptors, and can cause euphoria, dysphoria, and hallucination at high doses. These effects are similar to those of phencyclidine or ketamine. Thus, dextromethorphan has potential for abuse.

Other toxic effects of dextromethorphan include nausea, vomiting, dizziness, ataxia, lethargy, slurred speech, nystagmus, urinary retention, hysteria, stupor, and coma.[20] Because of the hydrobromide salt preparation, some heavy chronic users of dextromethorphan develop bromism, resulting in psychosis, seizures, and delirium. Serotonin syndrome also can result from high doses of dextromethorphan or its interaction with other substances, for example, selective serotonin uptake inhibitors.

3.1.2 | Antihistamines

Antihistamines may theoretically have antitussive effects because of their antimuscarinic, antispasmodic, antiemetic, or sedative properties. We found two published studies on the use of OTC antihistamines to treat cough in children. In the same study by Paul et al. (see discussion of dextromethorphan), diphenhydramine was no more effective than placebo in reducing the frequency of cough, cough severity, or quality of sleep in children with URI.[12] Another pediatric study compared

clemastine, chlorpheniramine, and placebo.[21] In both active treatment groups, cough scores observed by physicians and participants improved in 39.6% of individuals compared with 27.6% in the placebo group, which did not reach statistical significance.

Commonly reported adverse events of antihistamines include tachycardia, hallucinations, somnolence, agitation, and seizures. The abuse potential for antihistamines is relatively low, with substantial negative symptomatology developing before desirable effects.

3.2 | Herbal remedies

3.2.1 | Echinacea purpurea

Echinacea purpurea is a flowering plant in the sunflower family native to North America and is postulated to act via modulation of the immune system and cytokines. Taylor et al. performed a randomized placebo-controlled study comparing *Echinacea purpurea* extract and placebo in the treatment of 407 children with URI.[22] Echinacea was no better than placebo in decreasing the severity or duration of cough. Echinacea is generally well tolerated with few and minor side effects and low potential for abuse.

3.2.2 | Pelargonium sidoides (African geranium) extract

Pelargonium sidoides, or African geranium, is a plant native to South Africa. *Pelargonium sidoides* has been found to have antibacterial, anti-inflammatory, and mucolytic properties.[9] A Cochrane review concluded that *P. sidoides* extract may be effective in relieving symptoms of non-bacterial lower respiratory tract infections in children, with symptoms including sore throat, cough, sputum production, and localized pain, though the quality of evidence is low.[9] Safety concerns include the presence of natural coumarins in *P. sidoides* extract, which could lead to hemorrhagic complications. Hypersensitivity reactions and hepatotoxic reactions have also been described. Potential for abuse is low.

3.3 | Vapor rubs

Vapor rubs are topical preparations that contain a variety of substances, including menthol, camphor, and eucalyptus oils. Vapor rubs theoretically work via various mechanisms on the upper airway. There is, however, a paucity of evidence behind their use. Paul et al. performed a randomized trial of Vicks VapoRub ointment, petroleum ointment, and no treatment for pediatric patients with URI symptoms lasting 7 days or longer. A single application of vapor rub was associated with a decrease in cough and congestion when compared to petroleum ointment or no treatment. Children treated with vapor rub also reportedly had improved sleep. Because of the presence of camphor as an ingredient, seizures can result from vapor rub ingestions, with 20 mL estimated to be the minimum toxic dose in children younger than 6 years.[23] Potential for abuse is low.

3.4 | Honey

Honey has been used as a medicinal treatment for thousands of years. Honey contains several sugars (carbohydrates), amino acids, vitamins, trace elements, and antioxidants. Honey's postulated antitussive effect is via antibacterial, antiviral, and anti-inflammatory properties. In a 2018 Cochrane review, honey was compared to both placebo and other antitussives for the treatment of acute cough caused by URI.[10] The review specifically found that honey was likely superior to placebo or no treatment, may be better than diphenhydramine, and was equal in effect to dextromethorphan in reducing frequency of cough. Nevertheless, the quality of evidence was moderate to weak, hence the authors concluded that there was no strong evidence to support or refute the use of honey for the acute treatment of cough. Honey should not be used in children <1 year of age due to concerns about infantile botulism. Honey generally is well tolerated with low potential for abuse.

3.5 | Prescription medications

3.5.1 | Codeine

Codeine is a prodrug converted to morphine by the hepatic p450 system, with the rate and extent of conversion variable and unpredictable. Patients without CYP2D6 function will not convert codeine to morphine, whereas patients who are CYP2D6 ultra-rapid metabolizers may produce a life-threatening amount of morphine.[24] Similar to dextromethorphan, morphine (as a metabolite of codeine) is postulated to suppress cough via its action on cough receptors in the central nervous system. In April 2015, the European Medicines Agency released a statement that codeine-containing cough and cold medicines should not be used in children under 12 years of age. The statement also recommended against their use in children 12–18 years of age.[25] In 2017, the FDA published strong recommendations against the use of codeine in children. This recommendation was based on a report of 24 deaths and 38 more cases of respiratory depression in children who received codeine-containing medications.[26] The FDA recommends that codeine should not be used to relieve cough in children younger than 12 years of age. The FDA also added a new warning to the drug labels of codeine, recommending against its use in adolescents between 12 and 18 years who have risk factors for respiratory depression, including obesity, obstructive sleep apnea, or compromised respiratory function. Similar to other opioids, the potential for abuse of codeine is high.

3.5.2 | Promethazine

Promethazine exerts its action via both peripheral histamine receptors and central nervous system histamine/dopamine receptors. A randomized controlled trial in India comparing dextromethorphan, promethazine, and placebo in children 1 to 12 years of age with URIs found no significant difference in the frequency of nocturnal cough, post-tussive vomiting, or sleep quality.[27] Promethazine has a similar

side effect profile to antihistamines (see previous section). Promethazine's abuse potential is fairly high, especially among adolescents and young adults.[28]

3.5.3 | Benzonatate

Initially sold under the trade name of Tessalon and now available in generic forms, benzonatate was approved by the FDA in 1958 as a prescription antitussive in patients older than 10 years of age. Benzonatate is an oral anesthetic agent, chemically related to procaine, with a proposed mechanism of cough suppression through inhibition of pulmonary stretch receptors. A single study of capsaicin-induced cough in 30 adult non-smokers with acute URI failed to show any benefit of benzonatate over placebo.[29] In December 2010, the FDA released a safety announcement on the risk of death from accidental ingestion of benzonatate in children younger than 10 years of age. Death has reportedly occurred in children < 2 years of age from as little as 1 or 2 capsules of benzonatate.[30] Symptoms of overdose include restlessness, tremors, seizures, and coma. Symptoms typically manifest within 15–20 minutes after ingestion and death may occur within hours. Information on the symptoms and timing of toxicity was added to the product label of benzonatate-containing products. Potential for abuse is low.

3.5.4 | Inhaled corticosteroids

Inhaled corticosteroids may suppress cough by inhibiting airway inflammation and hyper-reactivity. However, a Cochrane review found no evidence to support the use of inhaled corticosteroids for treatment of subacute (2–4 weeks) cough in children.[11] Although side effects are minimal, prolonged use of high-dose inhaled corticosteroids may lead to cortisol suppression in children. Potential of abuse is low.

4 | COUNSELING CAREGIVERS ON THE USE OF ANTITUSSIVES

Despite a general lack of evidence for their use, parents and caregivers consistently use or request the medications discussed and other agents for young children with acute cough. Most of the existing clinical trials are older and newer trials are unlikely to be performed, at least on existing agents. Clinicians must be prepared to discuss antitussives with caregivers based on the available evidence, including the reasons for and against their use.

4.1 | Reasons for the use of antitussives in children

4.1.1 | Parental concerns

According to a large-scale survey published in 2008, between 1996 and 2006, ≈ 1 in 10 US children were given a cough and cold medication each week, most commonly to children younger than 5-years of age.[31] Cough and associated symptoms can be very disruptive to families, especially to sleep, school attendance, and work.[32,33] Caregivers may also seek medical advice and treatment because they are concerned about potential serious diagnoses and patient suffering related to the cough and sleep disruption. Caregivers may perceive younger children to be vulnerable because of their greater difficulty in communicating and may be concerned about the potential for rapid patient deterioration. Caregivers may be highly motivated to give their child something to stop or to decrease cough.

4.1.2 | Minimal risk

The actual risk of serious adverse events from therapeutic doses of antitussives is very low. In an extensive review of a multisystem surveillance program, the adverse event rate of cough and cold medication in children younger than 12 years of age was 1 case per 1.75 million units sold. Twenty out of 3251 cases (0.6%) resulted in death, none of which involved a therapeutic dose.[34] Additionally, most adverse events resulted from unsupervised ingestion and not therapeutic doses.[35] Although caution is warranted, particularly in children under 2 years of age, the overwhelming majority of antitussives available in the US are safe if given according to manufacturers' directions.

4.1.3 | Placebo effect

The placebo response has been reported to be as high as 85% in some clinical trials of antitussives.[36] These include antitussives trials with younger children as subjects.[37] The placebo effect in these studies might be broken down into 3 components: a physiological effect related to the taste of the medicine, natural recovery, and caregiver/patient belief in the efficacy of the medicine. The physiological effect is enhanced by the many "inactive" ingredients of cough formulations, which stimulate salivation and mucus secretions that soothe and lubricate the airway, and their sweet taste, which may inhibit cough via a brainstem mechanism.

4.2 | Reasons against the use of antitussives in children

4.2.1 | Benign nature of acute cough

Cough, as a reflex response, does not necessarily need to be suppressed and may be beneficial, helping to clear offending irritants from the airway. The majority of illness causing acute cough in children are benign and self-limited. Moreover, for the majority of children with a URI, cough tends to be short lived and usually resolves within 10 days.[6,38,39]

4.2.2 | Lack of evidence

As discussed, there is little evidence for the efficacy of most antitussives. In addition, many agents have a risk of abuse, serious adverse effects, or both, especially with accidental ingestion.[34]

4.2.3 | Recommendations and warnings from government agencies and professional societies

Many governing bodies and professional organizations have issued warning against the use of cough and cold medications in young children. In 2007, the FDA issued a comprehensive recommendation against the use of OTC cough and cold medications in children under 2 years of age, because of concerns about serious and potentially life-threatening adverse effects.[40] Shortly afterwards, the Consumer Healthcare Products Association announced that the leading manufacturers of pediatric OTC cough and cold medicines would voluntarily modify the labels on these products, including a statement that these agents should not be used in children under 4 years of age.[41] Recommendations against use of OTC cough and cold medicines have been issued by Health Canada, the American Academy of Pediatrics, and the American College of Emergency Physicians (ACEP).[42–44]

4.2.4 | Abuse potential

The US Substance Abuse and Mental Health Services Administration reported that, in 2006, 3.1 million people in the United States aged 12–25 years reported using OTC cough and cold medicine to "get high."[45] The National Institute on Drug Abuse has noted an increasing trend in youth drinking of prescription-strength cough syrup containing codeine and promethazine mixed with soda (also known as "Syrup," "Purple Drank," "Sizzurp," or "Lean"). Consumption of such a mixture has been linked to the overdose deaths of some prominent musicians.[46] Eleven million people in the United States struggle with opioid abuse and misuse.[47] Non-prescription use of opioid analgesics, for example, codeine has been shown to increase the lifetime risk for other drug dependency.[48] Moreover, most OTC antitussives are available as combination products, and many are available as elixirs, which may contain up to 20% ethanol by volume.

5 | IMPLICATIONS FOR CLINICAL PRACTICE

Despite multiple reviews attesting to the overall lack of effectiveness of antitussives in acute pediatric cough, caregivers' request for treatment for their children's symptoms likely will never go away. Instead of unyielding and potentially overcautious adherence to statements from governing bodies and professional society guidelines, we advocate for emergency clinicians to take on an educative, supportive position when discussing antitussive recommendations. After serious and life-threatening causes of cough have been rule out, emergency clinicians should focus on parental education on the natural course of acute pediatric cough, while acknowledging their concerns, especially for disruption of sleep, school, and work. When discussing potential treatment with antitussives, parents should be updated on the latest FDA regulations and recommendations, as well as potential risks including misuse and overdose. Prescription antitussives, especially codeine, should not be used in young children. Emergency clinicians may recommend honey for children over 1 year of age. Saline nasal spray/nasal suctioning and vapor rub may also be recommended, and parents should be encouraged to focus on hydration and to use antipyretics, as indicated. "Inactive ingredients" and placebo effect may also contribute to antitussive effectiveness in relieving cough symptoms in some cases. If recommended in selected cases, it is also important to emphasize to parents the need to adhere to dose and age recommendations, and to take precautions to prevent accidental poisoning and misuse by children. If a caregiver is already giving their child an OTC antitussive, emergency clinicians should review the ingredients, dose, and frequency to make sure they are appropriate. Parents also should be counseled that antitussives are indicated for short-term use only.

6 | CONCLUSIONS

OTC antitussive medications should not be routinely used in children under 2 years of age. In certain cases, antitussives with minimal adverse profile and some evidence of benefit may be recommended after informed counseling.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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