Abstract:
Young children have cold symptoms multiple times per year, which are usually part of a viral upper respiratory illness. Fever is commonly associated with these viral upper respiratory infections and is one of the most frequent chief complaints for children presenting to an emergency department. Cold and cough medications (CCMs) are widely marketed and used for the relief of cold symptoms. Studies have not found the ingredients in CCM to be beneficial for symptom relief. Both the Food and Drug Administration and American Academy of Pediatrics have recommended against the use of CCM in young children younger than 2 years, citing a lack of efficacy and potential for harmful side effects. Clinical toxicity and death have been reported both with therapeutic use, misuse, and overdose. In addition to unintentional harm, CCM can be misused and/or abused. The purpose of this article is to review the classes of medications found in over-the-counter CCM, the epidemiology of their use, the pharmacology and clinical toxicity of specific medications, dextromethorphan abuse, and the management of children presenting with overdose or adverse effects.

Keywords:
cough and cold medications; dextromethorphan; antihistamine; decongestant; antitussive

Cold and Cough Medications for Children: Dangerous and Over the Counter!

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A 2-year-old boy arrives to the emergency department (ED) with flushed, dry skin, hallucinations (picking in the air for things), dilated pupils with horizontal nystagmus, and drowsiness. Upon examination, pupils were 6 mm, heart rate was 180 beats per minute, and the skin was flushed and dry. An electrocardiogram showed a prolonged corrected QT interval of 500 milliseconds. A urine drug screen is positive for tricyclic antidepressants (TCAs) and phencyclidine (PCP). The family states that the child ingested an unknown amount of an over-the-counter (OTC) cough and cold product in the last 2 hours.

Exposure history revealed that the parents found the child somewhat drowsy playing on the bed. An empty cough and cold medicine bottle was found on the bathroom floor with a small amount of spillage and a purple stain on a hand towel where the child supposedly tried to wipe it up. The mother called the poison control center (PCC) for advice. Because of the potential toxic amount (up to 4 ounces) and the presence of symptoms, the child was referred into the ED.

Because a medication is over the counter, can it really be dangerous? What medications are in these OTC cough and cold products? What is their mechanism of action? What side effects
and toxic effects may they cause? Are these medications even efficacious?

The average child will have anywhere from 3 to 10 colds per year with an expected duration of 10 to 14 days. These colds are usually viral in etiology, self-limited, and cause symptoms including cough, nasal congestion, sneezing, and low-grade fever. Nasal secretions have the highest concentration of viruses and are spread by sneezing, nose blowing, and nose wiping. Children tend to spread viruses to one another more easily than adults because their nasal secretions contain higher viral concentrations; they shed virus for longer periods; wash hands infrequently; and in general, have more close contact with one another than do adults. Viral upper respiratory infections are commonly associated with cold symptoms and fever and are a very frequent cause for parents seeking evaluation in the ED as well from their primary health care providers.

Over-the-counter cough and cold medications (CCMs) are widely marketed in the United States for relief of cold symptoms. There are estimated to be at least 800 different formulations. The various constituents of OTC CCMs and the numerous product formulations available for purchase are ever changing. The latter leads to confusion and “mistaken” administration of various formulations for the expected symptom relief. It is important for pediatric emergency care providers to understand the various ingredients and their purported effects as well as the lack of evidence to support their use, especially in young children. The purpose of this article is to review the classes of medications found in OTC CCM, the pharmacology and clinical toxicity of specific medications, dextromethorphan (DM) abuse, and the evaluation and treatment of children presenting with overdose or adverse effects. In addition, the epidemiology of CCM use and its associated mortality will be presented.

**EPIDEMIOLOGY**

Pediatric cold and cough preparations are readily available and regularly used. In 1988, 1.5 billion dollars was spent on antihistamine-decongestant combination products (both prescription and over the counter). The Slone Survey randomly surveyed 4297 individuals between February 1998 and April 2007 in the contiguous 48 states and District of Columbia and revealed that, in any given week, 1 in 10 US children had used a cough and cold preparation. Many members of the Consumer Healthcare Products Association voluntarily added statements to cough and cold products stating “Do Not Use” in children younger than 4 years and announced the introduction of new child-resistant packaging and updated measuring devices for OTC CCM. In 2008, the Food and Drug Administration (FDA) issued a public health advisory regarding pediatric cough and cold preparations recommending that OTC CCMs not be used in children younger than 2 years due to potential serious adverse effects. The advisory also included statements for parents and caregivers that chose to use these products in children between 2 and 11 years old. These recommendations include: (1) check the active ingredients on the label; (2) take caution when administering more than 1 CCM product due to similar ingredients; (3) follow directions on labels carefully; (4) use measuring spoons or cups only; (5) select products with child-resistant closures; (6) OTC CCMs treat symptoms only and are not curative; (7) these products are not intended to be used for sedation; and (8) contact a physician or pharmacist with any questions regarding CCM. The FDA is continuing to review data regarding children aged 2 to 11 years and plans to issue more recommendations when the review is complete.

The American Academy of Pediatrics also has recommended that CCM not be used in children younger than 6 years, citing a lack of data supporting efficacy and potentially harmful side effects.

**FORMULATIONS AND PRODUCTS**

Parents often turn to OTC CCMs with the goal of relieving symptoms of the common cold. Antihistamines and decongestants are given with the aim of helping to reduce nasal secretions and congestion, and antitussives are used with the goal of relieving cough, especially at night. The ingredients of these product formulations include decongestants, antihistamines, antitussives, expectorants, and/or acetaminophen, either as single agents or more commonly as combination products.

For example, one particular brand, Triaminic™, has at least 11 different formulations on the market, which include the word “cold” and/or “cough” in the product name. On their Web site, they even have a Triaminic™ product selector to guide parents in choosing the particular formulation for their child’s
Impairment, nystagmus, but with diaphoresis.

Mia, mydriasis, agitation, delirium, seizures, warm skin, and vomiting.

Adverse and toxic effects: DM indicates dextromethorphan.

Antihistamines' therapeutic activity in cold preparations is secondary to their anticholinergic effects, which reduce secretions in the nasal passages. Histamine does not play any pathophysiologic role in the common cold. The anticholinergic effects reduce the production of secretions and attenuate rhinorrhea, but have minimal effect on nasal congestion. The most common OTC antihistamines in cough and cold products are brompheniramine maleate, chlorpheniramine maleate, and diphenhydramine hydrochloride. Diphenhydramine, an ethanolamine, has a marked sedation effect, whereas chlorpheniramine and brompheniramine, alkylamines, are mildly sedating. The older antihistamines, diphenhydramine and chlorpheniramine, have been in use since the 1950s and are smaller water-soluble chemicals. When not protein bound, they may enter the brain causing central nervous effects such as drowsiness, anxiety, and hallucinations. The onset and duration of action for regular release formulations of diphenhydramine, chlorpheniramine, and brompheniramine are similar at 15 minutes to 1 hour and 4 to 6 hours, respectively. The lack of effectiveness of antihistamines in reducing nasal congestion has resulted in them being combined with decongestants. Diphenhydramine has dual purposes in cough and cold preparations, both as an antihistamine and as an antitussive. Diphenhydramine is a centrally acting antitussive with an unclear mechanism of action. Many coughs are not histamine mediated, and antihistamines may be ineffective. Coughs secondary to postnasal drip may benefit from diphenhydramine's drying action.

Nasal decongestants fall into the class of sympathomimetic agents. These sympathomimetic agents work by stimulating the α-adrenergic receptors, which cause vasoconstriction in the blood vessels of the nasal mucosa. The vasoconstriction leads to increased airflow through the nasal passages. The only 2 oral decongestants available without a prescription in the United States are pseudoephedrine (usually behind the counter requiring a signature to stem abuse) and phenylephrine. Phenylephrine is not considered an effective decongestant agent due to its extensive first-pass metabolism. Pseudoephedrine (an isomer of ephedrine) relieves nasal congestion for 4 to 6 hours at therapeutic doses and up to 12 hours if an extended release product. At therapeutic doses, decongestants may cause increased heart rate and blood pressure, nervousness, dizziness, insomnia, headache, and tremors.

Dextromethorphan (DM) is a widely used nonopioid antitussive that has been in existence for 50 years. Dextromethorphan is the d-isomer of levorphanol, a codeine analog. It exhibits its antitussive activity by centrally increasing the

**TABLE 1. Selected OTC cough and cold products and their ingredients.**

<table>
<thead>
<tr>
<th>Product</th>
<th>Ingredients</th>
<th>Pharmacological Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimetapp Cold &amp; Allergy®</td>
<td>Brompheniramine, Phenylephrine</td>
<td>Antihistamine a</td>
</tr>
<tr>
<td>Dimetapp Cold &amp; Cough®</td>
<td>Brompheniramine, Phenylephrine</td>
<td>Antihistamine a</td>
</tr>
<tr>
<td>Dimetapp Multi-symptom</td>
<td>Acetaminophen</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Cold &amp; Flu®</td>
<td>Phenylephrine</td>
<td>Decongestant b</td>
</tr>
<tr>
<td>Robitussin Children's Cough &amp; Cold</td>
<td>Chlorpheniramine</td>
<td>Antihistamine a</td>
</tr>
<tr>
<td>Robitussin Children's Long-Acting®</td>
<td>DM</td>
<td>Antitussive c</td>
</tr>
<tr>
<td>Triaminic Day Time Cold &amp; Cough®</td>
<td>DM</td>
<td>Antitussive c</td>
</tr>
<tr>
<td>Triaminic Night Time Cold &amp; Cough®</td>
<td>Diphenhydramine</td>
<td>Antihistamine a</td>
</tr>
<tr>
<td>Triaminic Chest &amp; Nasal Congestant®</td>
<td>Phenylephrine</td>
<td>Decongestant b</td>
</tr>
<tr>
<td>Triaminic Cough &amp; Sore Throat®</td>
<td>Acetaminophen</td>
<td>Analgesic</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>Antitussive c</td>
</tr>
</tbody>
</table>

DM indicates dextromethorphan.

Adverse and toxic effects:
- **a** Antihistamine—tachycardia, hypertension, hyperthermia, flushed warm skin, dry mucous membranes, mydriasis, hallucinations, lethargy, sedation, acute psychosis, seizures.
- **b** Decongestant—tachycardia, hypertension, hyperthermia, mydriasis, agitation, delirium, seizures, warm skin, but with diaphoresis.
- **c** Antitussive—hallucinations, slurred speech, memory impairment, nystagmus.
- **d** Acetaminophen—hepatic injury.
- **e** Expectorant/guaifenesin—minimal, possible nausea and vomiting.
cough threshold as effectively as codeine. The antitussive effect onset is 15 to 30 minutes and may last for 5 to 6 hours.\textsuperscript{18,19} Dextromethorphan is metabolized by the liver to dextrophan, which also exhibits cough suppressing properties.\textsuperscript{17}

Guaifenesin is the only OTC expectorant approved by the US FDA.\textsuperscript{20} It achieves its expectorant properties by thinning the mucus, thus increasing mucus elimination, although objective evidence is lacking.\textsuperscript{21,22} Guaifenesin may also increase mucus volume due to hydrating and thinning mucus, thus easing expectoration and possibly inducing a cough.\textsuperscript{23}

**ADVERSE EFFECTS AND TOXICITY**

The use and misuse of CCM in children have led to significant morbidity and mortality. Reports in the literature have shown adverse events related to both appropriate dosing and overdosing of CCM. Children have been unintentionally given overdoses of these medications in many different scenarios: administration of multiple medications by multiple caregivers, administration of multiple medications with the same ingredient, administration of adult medications to children, dosing administration mistakes due to confusion and different measuring devices, and unsupervised ingestions of medications left in easy accessible locations for children. Malevolent and/or intentional overdose can be seen when parents seek to sedate the child by giving high doses of these medications or in cases of intentional harm or abuse. Unfortunately, child abuse may be one of these scenarios with intentional administration to children.

Adverse events with therapeutic CCM use have been frequently reported in the literature and include mild symptoms such as sedation to more serious events necessitating hospitalization such as coma, transient left ventricle dysfunction, and even death. A case series describes a toddler who was given medication by the caregiver containing phenylpropanolamine (removed from U.S. market in 2000) and brompheniramine and subsequently developed vomiting and lethargy. He had symptoms including bradycardia, tachypnea, and hypertension and required intensive care monitoring. Another toddler in this series was found to have left ventricle dilation and dysfunction after being treated for weeks with "Tylenol" per his caregivers. Upon further investigation, the preparation was "Children's Tylenol Cold\textsuperscript{®}," which contained acetaminophen, chlorpheniramine, DM, and pseudoephedrine. Repeat echocardiogram 2 weeks later showed resolution of the left ventricle dilation and dysfunction. The last case involved a 9-month-old who presented to the ED in full cardiopulmonary arrest. Toxicology testing revealed concentrations of acetaminophen, chlorpheniramine, phenylpropanolamine, DM, and pseudoephedrine. Cause of death was attributed to use of multiple OTC CCM.\textsuperscript{24} Another report discusses a 30-month-old child who presented with a dystonic reaction including ataxia and nystagmus after ingestion of DM. Most of her symptoms resolved after treatment with diphenhydramine, but the nystagmus persisted.\textsuperscript{25}

### TABLE 2. Cough and cold preparations exposures in pediatrics (5 years) reported to PCC in the United States from 2001 to 2010.\textsuperscript{30}

<table>
<thead>
<tr>
<th>Year</th>
<th>Number (Does Not Include Single Entity Antihistamines)</th>
<th>Percent of All Pediatric Calls to PCCs</th>
<th>Deaths Reported to the AAPCC (Does Not Include Single Entity Antihistamines or Opiate Containing CCM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>59949</td>
<td>5.1</td>
<td>0</td>
</tr>
<tr>
<td>2002</td>
<td>62107</td>
<td>5.1</td>
<td>3</td>
</tr>
<tr>
<td>2003</td>
<td>68493</td>
<td>5.5</td>
<td>4</td>
</tr>
<tr>
<td>2004</td>
<td>67494</td>
<td>5.4</td>
<td>1</td>
</tr>
<tr>
<td>2005</td>
<td>70398</td>
<td>5.7</td>
<td>1</td>
</tr>
<tr>
<td>2006</td>
<td>69645</td>
<td>5.7</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>65044</td>
<td>5.1</td>
<td>4</td>
</tr>
<tr>
<td>2008</td>
<td>52723</td>
<td>4.1</td>
<td>1</td>
</tr>
<tr>
<td>2009</td>
<td>45033</td>
<td>3.36</td>
<td>0</td>
</tr>
<tr>
<td>2010</td>
<td>38410</td>
<td>3.06</td>
<td>0</td>
</tr>
</tbody>
</table>

AAPCC indicates American Association of Poison Control Centers.
In children younger than 12 years, there have been 103 reported fatalities potentially related to the use of OTC CCM. Most of these fatalities involved unintentional overdose in children younger than 2 years. In Arizona, the investigation of unexpected deaths in infants over a 1-year period showed 10 deaths that may have been related to recent CCM use. Similarly, over an 8-month period in Ohio, the coroner’s office has linked deaths of 10 infants younger than 12 months to the use of CCM. The Consumer Healthcare Products Association issued a voluntary recall of OTC CCM marketed to infants in 2007. Since that time, CCM-related ED visits for children younger than 2 years have decreased by 50%, but overall, the number of visits in children younger than 12 years has not changed.

The prevalence of pediatric exposures resulting in a call to a Poison Center is summarized in Table 2 with data from the American Association of Poison Control Centers’ annual reports. Adverse effects of these medications with therapeutic use may be similar to clinical toxicity seen with supratherapeutic use and/or overdose, with the latter being more severe and/or sometimes lasting a longer period. The most common adverse effect from an antihistamine is drowsiness. Antihistamines, due to their anticholinergic effects, can also produce a toxic syndrome or toxidrome characterized by tachycardia, hypertension, hyperthermia, flushed warm skin, dry mucous membranes, mydriasis, and hallucinations/acute psychosis. Severe cases have resulted in seizures, hyperthermia, and QTc prolongation. Dystonic reactions have also been reported after antihistamine use.

Adverse effects of decongestants include palpitations, anxiety, and tremor. Toxicity of the decongestants usually presents with the sympathomimetic toxiayed characterized by tachycardia, hypertension, hyperthermia, flushed warm skin, dry mucous membranes, mydriasis, and hallucinations/acute psychosis. Severe cases have resulted in seizures, hyperthermia, and QTc prolongation. Dystonic reactions have also been reported after antihistamine use.

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Dextromethorphan has become a popular drug of abuse, especially among teenagers. It is found in various OTC formulations either as a single agent or in combination with other agents including Robitussin DM®, Coricidin®, Delsym®, Nyquil®, and Benylin®. Dextromethorphan when abused is often called “red devils,” “robo,” “skittles,” “triple C,” “dext,” or “DXM.” It is an attractive drug among the teenage population for several reasons: OTC formulations are easily accessible within their home or in retail stores, it can be shoplifted or bought at a lower price than most street drugs, and it is perceived to be a “safe” drug by many of those who abuse it. Coricidin is the most frequently abused form of DM. There have been reports of several different “plateaus” that DM abusers reach, which are shown in Table 3. These effects can be affected by a person’s body weight and ability to metabolize DM as discussed above.

Decongestants and antihistamines are not frequently abused in isolation, but cold medications containing DM in addition to these medications can cause several symptoms. Dextromethorphan with pseudoephedrine can cause paranoia and mania; with chlorpheniramine, can cause agitations, hallucinations, confusion, or sedation; and with diphenhydramine, can lead to delirium, altered

<table>
<thead>
<tr>
<th>DM Dose</th>
<th>Effects</th>
</tr>
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<tbody>
<tr>
<td>100-200 mg</td>
<td>Mild stimulation, hyperexcitability</td>
</tr>
<tr>
<td>200-400 mg</td>
<td>Intoxication, hallucinations, slurred speech, memory impairment</td>
</tr>
<tr>
<td>300-600 mg</td>
<td>“Out-of-body” sensations/effects, altered senses, nystagmus</td>
</tr>
<tr>
<td>600-1500 mg</td>
<td>Full dissociative effect</td>
</tr>
</tbody>
</table>
level of consciousness, and disorientation.\textsuperscript{42} Dextromethorphan can lead to serious injury or death from overdose leading to central nervous system depression or pulmonary edema or as a result of psychoses or hallucinations that lead abusers to violent behaviors.\textsuperscript{42,43}

**EFFICACY**

There have been numerous studies addressing the efficacy of CCM use in children. When comparing the treatment of febrile nasopharyngitis, an acetaminophen-diphenhydramine-pseudoephedrine combination vs acetaminophen alone showed no benefit in regard to improvement or duration of symptoms.\textsuperscript{44} These results are consistent with earlier studies performed with decongestants that are no longer in use.\textsuperscript{45-47} Studies by Paul and Yoder have investigated the use of OTC medication in young children on sleep quality and relief of nighttime cough. Neither diphenhydramine nor DM has been shown to alleviate nocturnal cough or improve sleep quality for the sick child or for the caregiver when compared with placebo groups.\textsuperscript{48,49} In a more recent study by Paul et al,\textsuperscript{50} DM as compared with placebo did not alleviate nocturnal cough or help with sleep, but honey was shown to significantly improve nocturnal symptoms and sleep quality as compared with placebo. Similarly, in a study by different researchers when both diphenhydramine and DM are compared with honey in regard to sleep quality, cough frequency, and severity, the honey group was superior. However, in contrast to Paul, this study did demonstrate some benefit in the diphenhydramine and DM group compared with a control group.\textsuperscript{51} One important finding in many of the studies is that symptoms tend to improve with time regardless of whether the study participants are in treatment or control groups. The most recent evidence seems to indicate that the most common ingredients in CCM are not effective for the treatment of cough in children, but honey may be beneficial. In addition, other than the risk of botulism in children younger than 1 year, honey does not seem to carry the potential toxicity and side effects of CCM.

**CASE SCENARIO CONTINUATION**

In the ED, the PCC was contacted. No gastrointestinal decontamination was recommended due to the presence of symptoms, specifically lethargy, in the child as well as the increased time since exposure.\textsuperscript{52,53} The PCC discussed that symptoms may continue due to slowed gastric absorption, skewed kinetics in overdose exposures, and recommended that the patient be monitored until asymptomatic. The child was observed in the ED with cardiopulmonary monitoring and returned to baseline over the course of 12 hours.

At discharge, the physician reviewed dangers of OTC CCM and recommended to the parents to always read labels and use the appropriate measuring device, because a silverware teaspoon may be anywhere from 3 to 7 mL.\textsuperscript{54} When traveling, the parents were encouraged to store medications in locked boxes and have the telephone number for poison control programmed into their cell phones.

**EVALUATION AND TREATMENT FOR OTC CCM TOXICITY**

Differential diagnosis for the child in this case scenario—altered mental status, dilated pupils, and tachycardia—must include infectious etiologies such as meningitis, brain trauma or masses, and electrolyte abnormalities. In the scenario given, there is a known ingestion, and therefore, supportive care and continued assessment is appropriate so long as the patient returns to baseline. In the absence of an ingestion history or if the patient does not have resolution of symptoms after an observation period, the ED physician must consider further testing to rule out other causes.

Many preparations of CCM include antipyretics, and therefore, obtaining an acetaminophen concentration should be considered in acute overdoses, cases of chronic OTC medication use, and when multiple OTC medications have been given. Urine drug screens can be confirmatory in the case of suspected ingestions but cannot predict toxicity nor can a negative result rule out an ingestion. In addition, the ingredients in CCM can have significant cross reactivity in a urine drug screen. Diphenhydramine may cross-react with various TCA assays; DM, with PCP assays; and pseudoephedrine and phenylephrine may give false-positive results for amphetamines.

Certain antidotes may be considered for selected toxic effects. Dystonic reactions can be treated with benzotropine (Cogentin), especially if the culprit is diphenhydramine. Seizures or severe agitation can be treated with benzodiazepines. Physostigmine may be used cautiously to treat pure anticholinergic toxicity when there is no concern for coinestion of a TCA and usually only after a consultation with a medical toxicologist. Treatment should be guided
by the suspected ingredients of the ingested substance and by presenting symptoms of the patient. Poison control information is available 24 hours a day at 1-800-222-1222 and can help guide the ED care providers regarding ingredients, toxicity, and treatment.

**SUMMARY**

Over-the-counter CCMs are widely used by parents seeking symptomatic relief for their child. Cold and cough medications have theoretical benefits, but to date, there is no clear evidence that they help relieve symptoms or shorten duration of a cold in children. The multiple ingredients in CCM have the potential for dangerous side effects and significant toxicity. Therapeutic/supratherapeutic use and overdose have been implicated in numerous pediatric deaths. Dextromethorphan is a popular hallucinogenic and dissociative effects. Treatment and toxicity of these medications and should not be routinely advocating their use, especially in children younger than 2 years.

**REFERENCES**


