Safety Profile of Cough and Cold Medication Use in Pediatrics

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BACKGROUND AND OBJECTIVES: The safety of cough and cold medication (CCM) use in children has been questioned. We describe the safety profile of CCMs in children <12 years of age from a multisystem surveillance program.

METHODS: Cases with adverse events (AEs) after ingestion of at least 1 index CCM ingredient (brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, phenylephrine, and pseudoephedrine) in children <12 years of age were collected from 5 data sources. An expert panel determined relatedness, dose, intent, and risk factors. Case characteristics and AEs are described.

RESULTS: Of the 4202 cases reviewed, 3251 (77.4%) were determined to be at least potentially related to a CCM, with accidental unsupervised ingestions (67.1%) and medication errors (13.0%) the most common exposure types. Liquid (67.3%), pediatric (75.5%), and single-ingredient (77.5%) formulations were most commonly involved. AEs occurring in >20% of all cases included tachycardia, somnolence, hallucinations, ataxia, mydriasis, and agitation. Twenty cases (0.6%) resulted in death; most were in children <2 years of age (70.0%) and none involved a therapeutic dose. The overall reported AE rate was 0.573 cases per 1 million units (ie, tablets, gelatin capsules, or liquid equivalent) sold (95% confidence interval, 0.553–0.593) or 1 case per 1.75 million units.

CONCLUSIONS: The rate of AEs associated with CCMs in children was low. Fatalities occurred even less frequently. No fatality involved a therapeutic dose. Accidental unsupervised ingestions were the most common exposure types and single-ingredient, pediatric liquid formulations were the most commonly reported products. These characteristics present an opportunity for targeted prevention efforts.

WHAT’S KNOWN ON THIS SUBJECT: Before 2008, the US Food and Drug Administration became aware of serious and sometimes fatal adverse events related to cough and cold medications (CCMs). Limited data have been available to assess the safety of these products for children.

WHAT THIS STUDY ADDS: This study describes the safety profile and risk factors associated with CCMs from the largest pediatric safety surveillance study on these products. These findings can inform prevention and other safety intervention measures to improve the safety of CCM use in children.


Dr Green drafted the initial manuscript and supervised the data collection, participated in the data analysis, and revised the manuscript; Ms Reynolds supervised the data collection, participated in the data analysis, and reviewed and revised the manuscript; Drs Banner, Bond, Kauffman, Palmer, and Paul participated in the data analysis and reviewed and revised the manuscript; and all authors approved the manuscript as submitted.

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Over-the-counter (OTC) cough and cold medications (CCMs) have been used to treat the symptoms of upper respiratory infection in children for decades. In 2007, concerns were raised via a citizen’s petition that CCMs had not been proven to be safe or effective in children <6 years of age and claimed that the products were not generally recognized as safe and effective by professional organizations and agencies. This led to voluntary relabeling of the dosing instructions to specify “do not use in children less than 4 years old,” withdrawal of the concentrated infant formulations, and reminders from the US Food and Drug Administration (FDA) to never use CCM in children <2 years of age. At the time of these events, little data were available to appropriately assess the efficacy or safety of these products for children. Statements by representatives for the American Academy of Pediatrics noted that these medications should be labeled with warnings that serious adverse events (AEs) have been reported with the use of OTC CCMs, and that OTC CCMs have not been shown to be effective in children.

Before 2007, CCMs were used by an estimated 10% of US children every week, with the highest use in children <5 years of age. Despite these voluntary labeling changes and limited research evaluating efficacy in children, caregivers continue to administer these medications to children, and some physicians may continue to recommend their use, even among children <4 years of age. Although caregivers and physicians continue to use and recommend CCMs, and AEs requiring emergency department visits and hospitalizations continue, there has been some decrease in the volume of reports. Continued use is also demonstrated by the fact that US consumers spend over $5 billion (Information Resources, Inc [multioutlet sales]) annually on these products.

In response to safety concerns associated with these products, the Pediatric Cough and Cold Safety Surveillance System was launched in 2008 and was designed to understand the safety profile of these medications by collecting data on significant AEs associated with pediatric exposures to CCMs, determining the causal relationship of the events to the CCM exposure, and identifying risk factors or root causes to inform prevention and other safety intervention measures.

### METHODS

The Pediatric Cough and Cold Safety Surveillance System continually and systematically collects data from 5 data sources: (1) the National Poison Data System of the American Association of Poison Control Centers, (2) the FDA Adverse Event Reporting System (FAERS), (3) English-language medical literature, (4) US-based news/media reports, and (5) manufacturer postmarketing safety databases (Table 1). Case inclusion criteria from each data source are: patient age <12 years; exposure to at least 1 product that contains ≥1 of the 8 most common active pharmaceutical ingredients in CCMs: brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, pseudoephedrine, and phenylephrine; report of at least 1 significant AE as defined by the case definition for each data source (Table 1); and that the event occurred in the United States. Potential cases were initially reviewed by using the Guideline.

### TABLE 1 Data Sources, Case Definitions, and Case Identification/Acquisition Processes

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Case Definition</th>
<th>Case Identification/Acquisition Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Poison Data System of the American Association of Poison Control Centers</td>
<td>Cases that reported a medical outcome of moderate effect, major effect, or death.</td>
<td>Real-time surveillance software algorithms identified eligible cases by age, index drug, and medical outcome. Standardized data collection sheet included patient information, products involved, dose, duration of use, drug administration technique, clinical course, clinical effects, and outcomes. Deidentified case records were received.</td>
</tr>
<tr>
<td>FAERS</td>
<td>Fatal and nonfatal AEs based on the International Conference on Harmonization definition.</td>
<td>The FAERS database was searched quarterly to identify eligible cases by age and index drug. The deidentified records were obtained from the FDA as MedWatch forms with standardized fields for patient demographics, exposure information, suspect drugs, concomitant medications, AEs, and case narrative.</td>
</tr>
<tr>
<td>Medical literature</td>
<td>Cases that met minimum eligibility criteria.</td>
<td>English-language medical literature was systematically searched weekly to identify eligible cases. Search results were reviewed and the full text of publications that potentially included eligible cases were obtained.</td>
</tr>
<tr>
<td>News/media reports</td>
<td>Cases that met minimum eligibility criteria.</td>
<td>A weekly search using software algorithms was conducted to identify eligible cases in regional or national news and media reports. All reports were publicly available. The full article was retrieved for reports that potentially contained an eligible case.</td>
</tr>
<tr>
<td>Manufacturer postmarketing safety databases</td>
<td>Fatal and nonfatal serious AEs based on the International Conference on Harmonization definition.</td>
<td>Participating manufacturers searched their safety databases quarterly by age and index drug to identify eligible cases. The deidentified record was delivered as either a FDA MedWatch form or World Health Organization’s Council for International Organizations of Medical Sciences form with standardized fields for patient demographics, exposure information, suspect drugs, concomitant medications, AEs, and case narrative.</td>
</tr>
</tbody>
</table>
on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports standards to identify duplicates.\(^{10}\) Key data elements were systematically extracted and reconciled from each case per written work instructions and assembled into standardized summaries. Autopsy reports were sought for all fatal cases and included in the source documents. These summaries were then reviewed by the expert panel in combination with all source documents. The relationship between each AE and reported medication (CCMs as well as any other medications taken) was assigned to 1 of 4 categories: related, potentially related, unlikely related, and unable to determine. The expert panel assigned the intent of CCM administration to 1 of 3 categories: therapeutic (including medication errors), nontherapeutic (including accidental unsupervised ingestion [AUI]), or unknown. Panel members independently reviewed each case, and all final decisions by the panel were formed during face-to-face meetings or conference calls. Decisions were based on the entire body of information available for each case using a priori rules. Cases for which there was initial disagreement among the panel members were re-reviewed and debated by the panel until consensus was reached. Although precise doses could not be determined from the available information, exposures were assigned to 1 of 3 dose categories, therapeutic, supratherapeutic, or unknown, based on established monograph dosing guidelines,\(^{11–16}\) accepted, professional, child-specific dosing guidance, and child-specific research.\(^{17}\)

The expert panel consists of 5 authorities from the specialties of pediatrics, critical care medicine, toxicology, clinical pharmacology, emergency medicine, and forensics.

Using standardized definitions, the expert panel determined whether each event was related, potentially related, unlikely related, or if the relatedness was unable to be determined. These determinations were made based on evaluation of the history of ingestion, drug levels (if available), clinical course, and the likelihood of an alternative cause. For all cases determined to be unlikely related, an alternative cause for the event was determined.

Cases were included for analysis if the expert panel determined that at least 1 AE was potentially related to at least 1 of the 8 most common OTC CCM ingredients. Variables analyzed included age, sex, exposure type, characteristics, clinical effects, and rates of reported events adjusted by product sales. Clinical effects were coded by using the Medical Dictionary for Regulatory Activities (MedDRA; Maintenance and Support Services Organization, McLean, VA) preferred term. CCM unit sales (ie, tablets, gelatin capsules, or liquid equivalent) data from food, drug, and big-box retailers (Information Resources, Inc, Chicago, IL) were used to calculate the rates of reported AE cases per unit of CCM drug sold to adjust for drug availability.

All analyses were performed by using SAS software, version 9.3 (SAS Institute, Inc, Cary, NC). Cases detected as of March 31, 2015, with an event date between January 1, 2009 and December 31, 2014, were included. Although data collection for the multisystem surveillance program launched in 2008, events from 2009 to 2014 were included for these analyses because sales data were not available before 2009.

**RESULTS**

A total of 4202 cases met eligibility criteria for expert panel review. Of these, 3251 (77.4%) were determined to be at least potentially related to an index CCM ingredient and were included in the analysis (Fig 1). The most common exposure types were AUIs (67.1%) and medication errors (13.0%). Forty-six percent (46.0%) of the cases involved a child aged 2 to <4 years, of which the majority (\(n = 1326/1495; 88.7\%\)) were AUIs. Medication errors were relatively more common in children 6 to <12 years of age (44.7%). Sex was similar among AUIs and medication errors, with the slight majority (54.1%) involving boys. The drug was self-administered in almost all (99.8%) of the AUI cases, with 5 (0.2%) involving administration by a sibling <6 years of age. The majority of exposures occurred in the child’s own home (90.3%), which did not differ greatly by exposure reason group. Among medication errors, most cases involved administration by the child’s parent (44.2%) or alternate caregiver, such as another family member or babysitter (42.1%) (Table 2).

More cases involved liquid (67.3%) and pediatric (75.5%) formulations than solid (32.3%) or adult (15.4%) formulations. Single-ingredient products (77.5%) were more likely to be reported than fixed-combination ingredient products (23.3%) (Table 2). CCM mentions were representative of available products on the market with diphenhydramine (\(n = 1892; 58.2\%\)) and dextromethorphan (\(n = 1257; 38.7\%\)) accounting for the majority of mentions. Although diphenhydramine predominated among AUIs (\(n = 1374; 62.9\%\)), dextromethorphan predominated among medication error cases (\(n = 252; 59.6\%\)). The most common AEs reported were tachycardia, somnolence, hallucinations, ataxia, mydriasis, and agitation (Table 3). The most commonly reported events (eg, tachycardia, somnolence, and hallucinations) did not differ between AUI and medication error cases. Twenty (0.6%) fatal cases were reported, of which autopsy...
reports were received for 10 cases (50.0%). Two cases were AUIs, 2 were medication errors, and 9 involved other exposure reasons (6 homicides, 1 use of a CCM as a sleep aid, and 2 unspecified nontherapeutic indication for use). The intent was not reported in the remaining 7 cases. The majority of fatal events occurred in children <2 years of age (n = 14; 70.0%). Exposure characteristics were often not reported among fatal cases, but when information was known, most involved doses administered by a parent (n = 8; 40.0%) and occurred in the child’s own residence (n = 8; 40.0%). Two cases involved self-administration of a CCM, both of which were AUIs. Similar to nonfatal cases, diphenhydramine (n = 13; 65.0%) and dextromethorphan (n = 5; 25.0%) were the most common index ingredients involved, with the addition of chlorpheniramine (n = 4; 20.0%). Seven fatal cases involved only a single-ingredient CCM product. The remaining 13 fatal cases involved 27 nonindex ingredient mentions, including 6 cases involving a prescription opioid combination CCM. Four fatal cases (20.0%) involved a supratherapeutic dose, and in 16 cases (80.0%), the dose could not be determined. Although the dose could not be determined in many cases, no death was determined to be the result of a therapeutic dose of a CCM index ingredient.

The reported AE rate adjusting for sales was 0.573 cases per million units sold (95% confidence interval [CI], 0.533–0.593) or 1 case per 1.75 million units (ie, tablets, gelatin capsules, or liquid equivalent) sold (Table 4). The rate of AUI cases (0.385 [95% CI, 0.369–0.401]) was 5 times that of medication error cases (0.075 [95% CI, 0.068–0.082]). That is, 1 AUI case occurred per 2.60 million units (ie, tablets, gelatin capsules, or liquid equivalent) sold compared with 1 medication error case occurred per 13.33 million units (ie, tablets, gelatin capsules, or liquid equivalent) sold (Table 4). Among all cases, the rate of AEs involving liquid, pediatric formulation, and single-ingredient products was higher than the rate of AEs involving solid, adult formulation, and fixed-combination ingredient products (Table 5).

**DISCUSSION**

Reported AEs from pediatric exposures to CCMs were uncommon, with the majority occurring by self-administration in children <4 years old. Most cases reported transient, non–life-threatening clinical effects consistent with what we know about these medications and their mechanism of action. Also notable was that only 13.0% of cases were associated with medication errors, thus suggesting that medication errors that lead to a significant effect were rare.

Concerns raised at the 2007 FDA Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee were focused on CCM use in children <4 years of age, especially the use of combination CCMs. A previous report described characteristics of fatal cases related to CCMs similar to those
observed in this study, with most involving supratherapeutic doses given by adults or other caregivers to children <2 years of age. Our results confirm the focus on these younger age groups, but suggest that the availability of medication in the home and CCM storage practices that make the medication accessible to toddlers are more readily available than the other index ingredient according to the sales data.

Although these data suggest that CCMs when used as directed are generally safe in children and rates of reported AEs are low, efficacy was not assessed in our study. CCMs are intended to treat the symptoms associated with coughs and colds rather than treating the underlying disease. These symptoms are self-limiting and difficult to measure, particularly in children. Caregivers often report symptom relief and sales data suggest continued use of these products in children. Randomized
controlled trials evaluating the efficacy of these medications are limited. A 2014 Cochrane review evaluated 29 studies (19 adult, 10 pediatric) involving 4835 patients (3799 adults, 1036 children). The small number of trials in each category, the limited quantitative data reported, and the marked variation in patient populations, interventions, and outcome measures prohibited the pooling of data. Hence, the authors’ conclusion was that the available data were inadequate and an evaluation of efficacy was not feasible. Although the safety profile garnered by this large surveillance network provides a reassuring comprehensive risk evaluation, additional well-designed efficacy trials of CCMs are still needed to conduct a true benefit-risk assessment. Understanding what benefit(s) these medications may provide is essential considering that no medication is without risk. Although previous reports suggest that pediatric CCM exposures reported to US poison centers were higher in the period before the launch of this surveillance system, our results suggest that additional efforts are warranted to prevent pediatric CCM AEs and should focus on the prevention of AUIs and medication errors in children <4 years of age. Specifically, there appear to be opportunities with single-ingredient, pediatric liquid products. Child-resistant packaging, proper measuring, and flow-restriction delivery devices may make the biggest impact on decreasing both types of exposures. Manufacturing controls to prevent inappropriate use and reduce medication errors include standardization of units both on the label and dosing devices (ie, milliliters instead of teaspoons), flow restrictors on liquid medication bottles, and limitations in the total medication content in liquid preparations. These initiatives have been developed with the goal of limiting product accessibility, confusion regarding units of measure, inappropriate dose administration, and ultimately toxicity. In addition to packaging, caregiver education on safe storage and proper supervision is always important in preventing AUIs. Poison prevention campaigns from organizations, such as American Association of Poison Control Centers, the Centers for Disease Control and Prevention’s PROTECT Up & Away Campaign, the National Safety Council, and Safe Kids, should continue to be supported and emphasized. The strengths of this study include the use of multiple national data sources and that each case was adjudicated by an expert panel. The size of the study was large and

### TABLE 4 Reported AE Cases per 1 Million Units Sold (ie, Tablets, Gelatin Capsules, Liquid Equivalents) by Exposure Type

<table>
<thead>
<tr>
<th>Case Type</th>
<th>Total Pediatric AE Cases (n = 3251)</th>
<th>Total Rate of Pediatric AE Cases per 1 Million Units Sold (95% CI)</th>
<th>Single Pediatric AE Case per Units Sold</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>3251</td>
<td>0.573 (0.553–0.593)</td>
<td>1 case per 1.75 million units sold</td>
</tr>
<tr>
<td>AUI cases</td>
<td>2183</td>
<td>0.385 (0.369–0.401)</td>
<td>1 case per 2.60 million units sold</td>
</tr>
<tr>
<td>Medication error cases</td>
<td>423</td>
<td>0.075 (0.068–0.082)</td>
<td>1 case per 13.33 million units sold</td>
</tr>
</tbody>
</table>

### TABLE 5 Reported AE Cases per 1 Million Units Sold (ie, Tablets, Gelatin Capsules, Liquid Equivalent) by Product Type

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Total Reported AE Rate per 1 Million Units Sold (95% CI)</th>
<th>Single Pediatric AE Case per Units Sold</th>
<th>Reported AUI AE Rate per 1 Million Units Sold (95% CI)</th>
<th>Single AUI AE Case per Units Sold</th>
<th>Reported Medication Error AE Rate per 1 Million Units Sold (95% CI)</th>
<th>Single Medication Error AE Case per Units Sold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid</td>
<td>4.383 (4.182–4.550)</td>
<td>1 case per 0.23 million units sold</td>
<td>3.012 (2.862–3.168)</td>
<td>1 case per 0.33 million units sold</td>
<td>0.678 (0.608–0.754)</td>
<td>1 case per 1.47 million units sold</td>
</tr>
<tr>
<td>Solid</td>
<td>0.203 (0.191–0.216)</td>
<td>1 case per 4.93 million units sold</td>
<td>0.130 (0.120–0.140)</td>
<td>1 case per 7.69 million units sold</td>
<td>0.016 (0.013–0.020)</td>
<td>1 case per 62.5 million units sold</td>
</tr>
<tr>
<td>Pediatric</td>
<td>1.189 (1.142–1.237)</td>
<td>1 case per 0.84 million units sold</td>
<td>0.820 (0.781–0.860)</td>
<td>1 case per 1.21 million units sold</td>
<td>0.164 (0.147–0.182)</td>
<td>1 case per 6.10 million units sold</td>
</tr>
<tr>
<td>Adult</td>
<td>0.159 (0.127–0.152)</td>
<td>1 case per 7.19 million units sold</td>
<td>0.093 (0.083–0.103)</td>
<td>1 case per 10.75 million units sold</td>
<td>0.009 (0.007–0.013)</td>
<td>1 case per 111.11 million units sold</td>
</tr>
<tr>
<td>Single-ingredient product</td>
<td>1.023 (0.984–1.064)</td>
<td>1 case per 0.98 million units sold</td>
<td>0.723 (0.690–0.758)</td>
<td>1 case per 1.38 million units sold</td>
<td>0.128 (0.114–0.142)</td>
<td>1 case per 7.81 million units sold</td>
</tr>
<tr>
<td>Fixed-combination product</td>
<td>0.236 (0.219–0.253)</td>
<td>1 case per 4.24 million units sold</td>
<td>0.129 (0.116–0.142)</td>
<td>1 case per 7.75 million units sold</td>
<td>0.038 (0.032–0.045)</td>
<td>1 case per 26.32 million units sold</td>
</tr>
</tbody>
</table>
encompassed 6 years of data (2009 to 2014). The data capture system was unique in that it collected real-world consumer experiences, which are data not obtainable from randomized control trials. Reporting to the surveillance system was timely and extended a quarter beyond the study time period to account for the delayed reporting that is common with surveillance systems. The study is limited by reliance on spontaneous, self-reports that were captured after the voluntary product changes. As with any surveillance system that is reliant on spontaneous reporting, not all CCM AE cases are detected, and thus the rates are underestimates of all exposures. However, even if this surveillance system captured only 10% of all cases, the rates of CCM AE exposures would still be low. Finally, not all characteristics surrounding the events of the exposure were consistently reported, which is particularly limiting in the evaluation of dose and related outcomes done for this study.

CONCLUSIONS
Overall, 3251 cases with AEs related to CCMs were reported from 2009 to 2014 in our surveillance system. The overall rate of AEs was equivalent to 1 case per 1.75 million units (ie, tablets, gelatin capsules, or liquid equivalents) sold, indicating these events are rare. The majority of AEs occurred in children <4 years of age (59.7%), involved an AUI (67.1%), and were nonfatal (99.4%). Fatalities were more rare (n = 20) and occurred mostly in children <2 years of age; none were determined to have involved a therapeutic dose. Single-ingredient, pediatric liquid formulations were the most commonly reported formulations and present an opportunity for targeted prevention efforts.

ACKNOWLEDGMENTS
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ABBREVIATIONS
AE: adverse event
AUI: accidental unsupervised ingestion
CCM: cough and cold medication
CI: confidence interval
FAERS: FDA Adverse Event Reporting System
FDA: US Food and Drug Administration
OTC: over-the-counter

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