Pediatric Fatalities Associated With Over-the-Counter Cough and Cold Medications

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abstract

BACKGROUND AND OBJECTIVES: In 2008, over-the-counter cough and cold medications (CCMs) underwent labeling changes in response to safety concerns, including fatalities, reported in children exposed to CCMs. The objective of this study is to describe fatalities associated with exposures to CCMs in children <12 years old that were detected by a safety surveillance system from 2008 to 2016.

METHODS: Fatalities in children <12 years old that occurred between 2008 and 2016 associated with oral exposure to one or more CCMs were identified by the Pediatric Cough and Cold Safety Surveillance System. An expert panel reviewed all cases to determine the causal relationship between the exposure and death, if the intent of exposure was therapeutic, and if the dose was supratherapeutic. Other contributing factors related to the child's death were also identified as part of a root cause analysis.

RESULTS: Of the 180 eligible fatalities captured during the study period, 40 were judged by the expert panel to be either related or potentially related to the CCM. Of these, the majority (n = 24; 60.0%) occurred in children <2 years old and involved nontherapeutic intent (n = 22; 55.0%). The most frequently involved index ingredient was diphenhydramine (n = 28; 70.0%). In 6 cases (n = 6; 15.0%), the CCM was administered to murder the child. In another 7 cases (n = 7; 17.5%), death followed the intentional use of the CCM to sedate the child.

CONCLUSIONS: Pediatric fatalities associated with CCMs occurred primarily in young children after deliberate medication administration with nontherapeutic intent by a caregiver.

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WHAT'S KNOWN ON THIS SUBJECT: Studies have described the safety profile of cough and cold medications (CCMs) in children, but factors associated with death from CCM exposure have not been described since CCMs underwent major labeling changes in 2008.

WHAT THIS STUDY ADDS: This study provides information about which children are most at risk for dying of CCM exposure and reveals that malicious use of these medications is a common contributor to fatalities from CCMs.

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Over-the-counter cough and cold medication (CCM) use in young children is common; nearly half of parents with children <4 years of age report administering a CCM when their child last had a cold.[1] In 2007, the US Food and Drug Administration (FDA) convened a meeting to review the safety and efficacy of CCMs in children, partially in response to citizen concerns about the safety and efficacy of these products in children <6 years old. Shortly after, drug manufacturers voluntarily withdrew "infant" CCM products from the market.[2,3] In 2008, the FDA released a Public Health Advisory recommending that these products not be used in children <2 years old, and manufacturers subsequently voluntarily changed CCM labeling to state “do not use” in children <4 years old.[2,4] At the same time, additional labeling changes were introduced for CCMs containing certain antihistamines, instructing caregivers not to use the product to sedate or make a child sleepy.[4]

A 2009 review of pediatric fatalities associated with CCMs found that these deaths primarily occurred in children <2 years old, often involved a supratherapeutic dose, and sometimes represented suspected child maltreatment.[5] No subsequent review of pediatric fatalities associated with CCMs has been published. As such, it is unknown whether the characteristics of pediatric fatalities associated with CCMs have changed since 2007–2008, when the withdrawal of infant products and the labeling changes took place. The objective of this study is to describe fatalities due to CCMs in children <12 years old that were detected by a safety surveillance system from 2008 to 2016.

METHODS

Fatalities in children <12 years old associated with CCM exposure were identified by the Pediatric Cough and Cold Safety Surveillance System, which has been described previously.[6,7] In brief, the system collected data from 5 sources: the National Poison Data System (NPDS) of the American Association of Poison Control Centers, the FDA Adverse Event Reporting System, news or media reports, English-language medical literature, and safety reports made to participating CCM manufacturers. Cases were collected from January 1, 2008, to March 31, 2017, based on the report date. Only cases with event dates from January 1, 2008, to December 31, 2016, were included, but given the delay in detection of events inherent to surveillance systems, the detection system remained open for an additional 3 months to capture as many events through the end of 2016 as possible.

The case inclusion criterion for this study of fatalities was oral exposure in the United States to at least 1 of 8 index ingredients: brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, phenylephrine, or pseudoephedrine. Because these index ingredients are also found in prescription products, cases involving both over-the-counter and prescription products were included to augment the analysis of these fatalities. Duplicate cases were identified per the Guideline on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports and were combined to create a single case for review.[8] Autopsy reports were requested from the local medical examiner or coroner.

All case data and documents, including autopsy reports and interpretation of postmortem drug concentrations, were provided to a panel of experts for review. Throughout this study, the panel included the same 5 members with expertise in pediatrics, toxicology, emergency medicine, and forensics. A panelist with expertise in forensic toxicology aided in the interpretation of postmortem drug concentrations. The panel reviewed fatality cases to determine if the causal relationship between each CCM ingredient mentioned and death was related, potentially related, unlikely related, or unable to determine using established definitions.[7] Cases judged related or potentially related were further categorized by intent (therapeutic, nontherapeutic, or unknown intent) and by dose (therapeutic, supratherapeutic, or unknown dose). Therapeutic intent was defined as use for a labeled indication, and nontherapeutic intent was defined as use for any other purpose, including off-label use, accidental exploratory ingestions, and malicious use. Unknown intent was assigned when therapeutic or nontherapeutic intent could not be determined. For NPDS cases, therapeutic intent was informed by the poison center category for exposure reason.[9] Panelists independently reviewed all case information before in-person and teleconference meetings, during which all cases were again reviewed and decisions regarding causality, intent, and dose were made. The panel debated each case until consensus was achieved. The panel additionally documented factors that might have contributed to the child’s death as part of a root cause analysis. Descriptive statistics was used to summarize the data by using SAS software version 9.3 (SAS Institute Inc, Cary, NC).

The Colorado Multiple Institutional Review Board determined this study was non–human subjects research.

RESULTS

Of the 7983 unique cases of adverse events associated with CCM

exposure identified by the Pediatric Cough and Cold Safety Surveillance System during the study period, 188 (2.4%) were fatalities. Eight fatalities were excluded by the expert panel because of lack of exposure to a known index ingredient, intravenous exposure, child age ≥12 years old, and in utero exposure. Of the remaining 180 fatalities, 78 were judged by the panel to be either related or potentially related to an index CCM ingredient, of which 40 had a known event date during the inclusion period. For this analysis, cases judged to be related or potentially related were combined into a single category, at least potentially related, which is subsequently described. The case sources for the 40 included fatalities were the following: news or media reports (n = 15; 37.5%), NPDS (n = 5; n = 12.5%), CCM manufacturer safety records (n = 3; 7.5%), FDA Adverse Event Reporting System records (n = 1; 2.5%), and more than one source (n = 16; 40.0%). Autopsy results were available in 22 (55.0%) of the 40 included fatal cases (Fig 1).

The majority (n = 24; 60.0%) of fatalities occurred in children <2 years old and in boys (n = 26; 65.0%) (Table 1). A parent administered the CCM in 16 cases (40.0%); self-administration by the child (accidental exploratory ingestions) was uncommon (n = 3; 7.5%). The panel's assessment of intent found that more than half (n = 22; 55.0%) of fatalities were nontherapeutic, whereas 6 cases (15.0%) involved therapeutic intent, and intent was unknown in 12 cases (30.0%). The estimated dose in 8 cases (20.0%) was supratherapeutic, and in the rest (n=32; 80.0%), it could not be determined. No fatality was determined to involve a dose that was judged to be therapeutic (Table 2).

A total of 50 CCM products were involved among the 40 fatalities. The most frequently involved index ingredient determined to be at least potentially related to the death was diphenhydramine (n = 28; 70.0%). It was also the most common index ingredient in cases with nontherapeutic intent (n = 19; 86.4%) (Table 3). Seventeen fatalities involved both an index ingredient and at least 1 nonindex ingredient determined to be at least potentially related to the fatality; the most common nonindex ingredients were opioids (n = 11; 64.7%). CCM formulation was unknown for most of those 50 reported products (n = 33; 66.0%); 9 (18.0%) were solid and 8 (16.0%) were liquid formulations. Four cases (10.0%) involved a prescription CCM. All 3 fatalities associated with child self-administration of a CCM occurred with solid adult-formulation diphenhydramine products.

The root cause analysis identified the use of a CCM to sedate the child in 7 cases (17.5%) and to murder a child in 6 cases (15.0%). Murder represented 31.8% (n = 7 of 22) of the nontherapeutic intent cases, and sedation represented another 27.3% (n = 6 of 22). In all 7 sedation cases, the child's caregiver was found to be criminally responsible for the child's death. Among the 18 cases in which the root cause analysis could not determine the contributory factors, 7 cases (38.9%) involved coadministration of an opioid and 5 cases (27.8%) involved coadministration of another nonopioid sedating medication (Table 4).

DISCUSSION

Pediatric fatalities associated with CCMs are rare, accounting for <3% of all reported serious adverse event cases detected by a national multi–data source surveillance system over a 9-year period. We found that in most cases with identifiable characteristics, the child was <2 years old and had been deliberately given a CCM by a caregiver, the majority of which

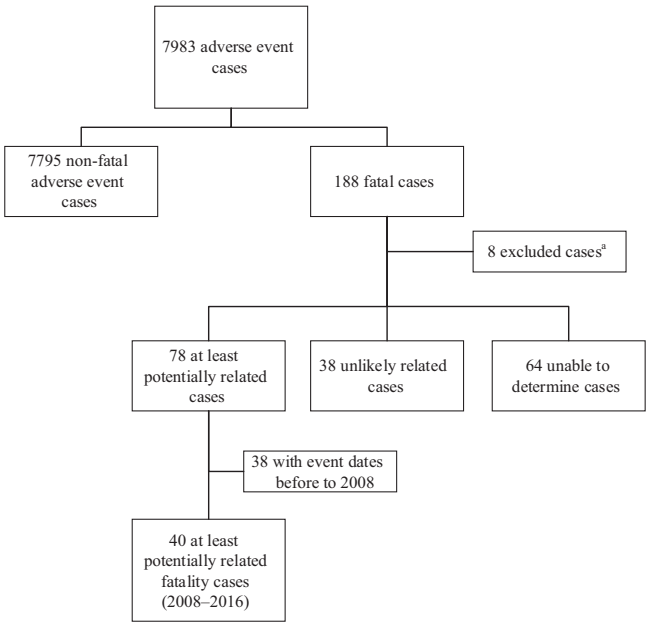

FIGURE 1
Schematic of cases included and excluded for analysis. [a] Cases were excluded because of the following: no index ingredient involved, specific product or active ingredients not identifiable, no oral exposure, child ≥12 years of age, in utero exposure.

TABLE 1 Demographics and Drug Administration in Pediatric Fatalities at Least Potentially Related to Exposure to a CCM

	Fatalities (N = 40) (%)
Age, y	
<2	24 (60.0)
2–<4	5 (12.5)
4–<6	4 (10.0)
6–<8	5 (12.5)
8–<10	0 (0.0)
10–<12	2 (5.0)
Sex	
Male	26 (65.0)
Drug administered by	
Parent	16 (40.0)
Other caregiver	4 (10.0)
Baby-sitter or day care provider	3 (7.5)
Parent and grandparent	3 (7.5)
Self	3 (7.5)
Grandparent	2 (5.0)
Not reported	9 (22.5)

involved nontherapeutic intent. The most common ingredients involved were diphenhydramine, chlorpheniramine, and dextromethorphan, and in several fatalities at least 1 nonindex ingredient contributed to the child's death. There were no fatalities associated with a known therapeutic dose.

These findings mirror those identified in previous work[5]: the preponderance of cases in children <2 years old, the paucity of child self-administrations, the frequent association with nontherapeutic intent, and the lack of fatalities associated with a therapeutic dose remain apparent. A clear at-risk population of young children who are unable to protect themselves is identified. Although the number of fatalities at least potentially related to a CCM in the current study (N = 40) is lower than in previous work (N = 103), this comparison does not consider the longer time period included in previous work or the changes in CCM use rates over time, which are challenging to accurately measure.[5] Previously, pseudoephedrine was the most common ingredient involved in fatal cases, but diphenhydramine is now more common. Our results support an unanticipated benefit of moving pseudoephedrine to "behind the counter" in late 2006.[10] The rise in diphenhydramine-related fatalities may be in part secondary to an increase in health care provider recommendations for antihistamines for children with acute respiratory infections, a trend that has been increasing since 2008 for children, including those <2 years old.[11] Another possibility is that caregivers are increasingly misusing diphenhydramine to induce somnolence in young children. Poison centers report an increase in cases involving diphenhydramine in general and especially those involving intentional, improper exposures.[9,12–16]

TABLE 2 Estimated Dose and Intent of Drug Administration in Pediatric Fatalities at Least Potentially Related to Exposure to a CCM

	Therapeutic Intent (n = 6)	Nontherapeutic Intent (n = 22)	Unknown Intent (n = 12)	Total (N = 40)
Therapeutic dose	0	0	0	0
Supratherapeutic dose	0	6	2	8
Unknown dose	6	16	10	32
Total	0	0	0	40

Several important differences emerge when comparing characteristics of fatalities with characteristics of nonfatal serious adverse events due to CCMs. In a recent analysis of primarily nonfatal serious adverse events due to CCMs from the same surveillance system, children 2 to <4 years old were most commonly involved; children <2 years old had the lowest number of adverse events.[6] The majority of nonfatal serious adverse events in that study were from child self-administrations, particularly unintentional ingestions in young children, whereas child self-administrations were only occasionally associated with fatalities in our analysis. Taken together, these results suggest that although serious adverse events are more common with unintentional ingestions in children >2 years old, these incidents are rarely fatal. In contrast, children <2 years old are disproportionately represented among fatalities, suggesting that deliberate medication administration by a caregiver is usually involved.

Ascertaining a caregiver's intent with medication administration is challenging because the subtlety and nuance of a caregiver's understanding of the risks and benefits of medication administration is not always captured. For example, a caregiver may not recognize that more is not better with respect to medication dosing, or they may not perceive that medication-induced somnolence or sedation is harmful and can result in death. Lack of health literacy has been shown to be associated with errors in medication administration by parents and caregivers.[17] To further complicate

TABLE 3 Index Drug Counts by Intent of Drug Administration in Pediatric Fatalities at Least Potentially Related to Exposure to a CCM

	Therapeutic Intent (n = 6)	Nontherapeutic Intent (n = 22)	Unknown Intent (n = 12)	Total (N = 40) (%)[a]
Diphenhydramine	3	19	6	28 (70.0)
Chlorpheniramine	2	2	2	6 (15.0)
Dextromethorphan	1	1	4	6 (15.0)
Doxylamine	0	0	2	2 (5.0)
Pseudoephedrine	1	0	1	2 (5.0)
Brompheniramine	0	0	0	0 (0.0)
Phenylephrine	0	0	0	0 (0.0)
Guaifenesin	0	0	0	0 (0.0)

Only CCM ingredients determined to be at least potentially related to the death are included in this table.
[a] Totals in column headers refer to the total No. cases with each type of intent and do not reflect the sum of the drug counts in the body of the column. Case counts are also used for the denominator for percentages.

matters, caregivers' self-report of intent is often recorded after harm has already come to the child, which may color the history the caregiver provides (eg, stating that the intent was to help a child sleep when the true intent was malicious) or even lead them to omit the medication from the history entirely. In some cases, the case documents were so sparse that no assessment of intent was possible. As such, our analysis may underestimate the proportion of fatalities that occurred because of a caregiver deliberately attempting harm, which is particularly striking given the relative frequency that injurious intent was identified.

Cases identified as murders or as resulting from sedation were identified because case documents clearly demonstrated the purpose for CCM administration. For example, in 2 murder cases, the caregiver also stabbed the children (although the stab wounds were determined not to have caused the death) and made statements about the children being "better off in heaven." In sedation cases, it was not always clear whether the intent was to help the child sleep because sleep was perceived as beneficial or to chemically sedate the child to ease a caregiver's burden or mask other forms of abuse. For example, in several sedation cases, a sedating CCM was administered by a day care operator or baby-sitter caring for multiple young children who admitted to administering medication to try to induce sleep, although the specific reason was not reported. In all 7 sedation deaths, the child's caregiver was found to be criminally responsible; common convictions included manslaughter and criminally negligent homicide, meaning the caregiver failed to act appropriately for an overtly obtunded child. This suggests that although the caregiver's intent may not have been to kill the child, the caregiver's goal was potentially different from helping a sick child rest.

TABLE 4 Characteristics and Contributing Factors Leading to Pediatric Fatalities Associated With Exposure to CCMs

	Total (N = 40) (%)
Sedation	7 (17.5)
Murder[a]	6 (15.0)
Therapeutic administration[b]	6 (15.0)
Accidental unsupervised ingestion	3 (7.5)
Not reported	18 (45.0)
Age <2 y	12 (66.7)[c]
Coadministration of an opioid[d]	7 (38.9)[c]
Coadministration of a nonopioid sedating medication[d]	5 (27.8)[c]

[a] Defined as a clear intent to kill the child as adjudicated by the panel.
[b] Defined as administration for a labeled indication.
[c] n = 18 "not reported" cases is the denominator for these percentages.
[d] Three cases involved coadministration of both an opioid and a nonopioid sedating medication.

Other authors have demonstrated that children, especially children <2 years old, make up a large proportion of victims of malicious poisoning. A prospective observational cohort study of patients who were poisoned managed by a medical toxicologist found that of 60 confirmed poisoning cases with malicious intent, 21 (35.0%) were children and 17 (28.3%) were children <2 years old.[18] Young children also appear to be particularly susceptible to the most severe outcomes from malicious poisonings. Using death certificate data, Shepherd and Ferslew[19] found that whereas the homicidal poisoning rate over a 7-year period was 0.26 per million deaths (n = 523 homicidal poisonings), the homicidal poisoning rates for children <1 and 1 to 4 years old were 2.05 per million deaths (OR 8.72; 95% confidence interval 6.63–11.49) and 0.49 per million deaths (OR 2.00; 95% confidence interval 1.15–2.65), respectively. Another study using NPDS data found that the mean age of children who died of malicious poisoning was 1.6 years; CCMs were the fourth most common drug class involved in malicious poisonings of children after analgesics, stimulants or street drugs, and sedatives, hypnotics, or antipsychotics.[20] Also noteworthy was the fact that 94.0% of pediatric deaths from malicious poisoning in that study involved exposure to at least 1 sedating agent, and 45.0% of those cases involved an antihistamine, such as those found in some CCMs.

From a childhood poisoning prevention perspective, malicious poisonings are challenging to

prevent because traditional mechanisms designed to decrease accidental exposures or inadvertent overdoses, such as flow restrictors or blister packaging, are not effective in preventing deliberate attempts to sedate or harm a child. Detection and recognition of malicious pharmaceutical poisoning is also challenging because most caregivers are unlikely to provide that history, symptoms can be nonspecific, and many pharmaceuticals are not included as target analytes on urine drug screens. A prospective descriptive study of emergency department patients with an acute life-threatening event found that nearly 5% (13 of 274) of patients who had a comprehensive urine toxicology screen performed had a positive result for a CCM, despite the fact that none of their parents reported having administered a CCM.[21] Another study revealed that up to 7.9% of children suspected of being physically abused also had an occult drug exposure.[22] These results suggest that comprehensive urine toxicology screens may be useful in identifying occult malicious poisoning with pharmaceuticals in children with an acute life-threatening event, unexplained sedation, or signs of physical abuse. Although comprehensive toxicology assays are currently limited by their availability, turnaround time, and expense, there is growing interest in developing comprehensive assays that screen and measure the specific drug(s) and metabolite(s) present for a large number of pharmaceutical agents quickly enough to be clinically relevant.[23] Determining when to refer children with a poisoning for a child abuse evaluation or to social services is also challenging. In a retrospective study of 928 children <6 years old with a diagnosis of poisoning, only 13% were evaluated by a hospital social worker or child protection team, and only 4% were referred to child protective services; although referrals are more common for children with more severe clinical presentations, it is unclear if the severity of presentation is the most appropriate marker for (or is even correlated with) the risk of abuse or neglect.[24]

There were some limitations inherent to our study design. First, using databases that rely on self-reporting may underestimate the true prevalence of an event. Some pediatric fatalities from CCMs were likely not captured because they were not reported to the data sources monitored. When cases were reported, the level of detail provided varied, which affected the panel's ability to determine the causality, intent, dose estimates, and circumstances surrounding the exposure and led to a high number of "unknowns" for several variables. Understanding the intent of CCM administration was generally limited by whatever report the caregiver provided. Poison center data were highly susceptible to misclassification bias, in which the caller misidentifies the exposure, leading to cases being inappropriately excluded.[25] Autopsy reports were similarly not available for all cases. Even when autopsy data were available, the administered dose could be extrapolated from postmortem drug concentrations. Finally, there is no gold standard for assessing the causal association between medication administration and death; in our study, we relied on expert consensus for causality assessments, which is intrinsically imprecise and potentially inconsistent.

CONCLUSIONS

The majority of pediatric deaths associated with exposures to CCMs detected by a multi–data source national surveillance system from 2008 to 2016 occurred in children <2 years old, despite the withdrawal of infant products and the labeling changes that took place during 2007 and 2008. The index ingredient most commonly involved was diphenhydramine, which was most often used with nontherapeutic intent. Given that labeling changes do not appear to have changed the preponderance of young children among CCM fatalities, we recommend that child health providers educate parents and caregivers on avoidance of CCMs, particularly diphenhydramine in children <4 years old as part of routine guidance and during encounters for respiratory complaints. A considerable number of fatalities occurred because of suspected child maltreatment, including attempts to sedate or kill a child. Health care providers must have a high index of suspicion to identify and recognize inappropriate CCM administration as a source of child maltreatment. As comprehensive toxicology testing methods develop faster turnaround times and become more widely available, we recommend testing as a tool in identifying child maltreatment. More research is needed to understand the intersection of child maltreatment and pharmaceutical poisoning so that the medical community and child welfare advocates can develop targeted screening and prevention programs.

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ABBREVIATIONS

CCM: cough and cold medication
FDA: US Food and Drug Administration
NPDS: National Poison Data System

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