

# Ingestion of Over-the-Counter Liquid Medications: Emergency Department Visits by Children Aged Less Than 6 Years, 2012–2015



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**Introduction:** Unintentional medication ingestions by young children lead to nearly 60,000 emergency department visits annually; 15% involve oral liquid medications. Safety packaging improvements have been shown to limit liquid medication ingestions. Estimated rates of emergency department visits for pediatric ingestions by product were calculated to help target interventions.

**Methods:** Frequencies and rates of emergency department visits for unintentional pediatric ingestions were estimated using adverse event data from the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance project and retail sales/pharmacy dispensing data from Information Resources, Inc. and QuintilesIMS (collected 2012–2015; analyzed 2017). Rates of emergency department visits for ingestions of over-the-counter liquid medications were compared with those for prescription solid medications.

**Results:** From the results of 568 cases, an estimated 6,427 emergency department visits (95% CI=4,907, 7,948) were made annually after a child aged <6 years accessed one of the four most commonly implicated over-the-counter liquid medications without caregiver oversight. Nearly two thirds (63.8%) of these visits were made by children aged  $\leq 2$  years and 9.0% resulted in hospitalization. Acetaminophen was the most commonly implicated over-the-counter liquid medication (2,515 estimated emergency department visits annually). Rates of emergency department visits for liquid diphenhydramine and acetaminophen ingestions (8.1 and 7.4 emergency department visits per 100,000 bottles sold) were higher than rates for other common over-the-counter liquids and comparable to high-rate prescription solid medications (clonidine and buprenorphine/naloxone: 11.1 and 10.5 emergency department visits per 100,000 dispensed prescriptions, respectively).

**Conclusions:** Product-specific rates of emergency department visits for unintentional ingestions can help prioritize preventive interventions, such as enhancing safety packaging with flow restrictors.

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## INTRODUCTION

Child-resistant (CR) packaging has contributed to significant declines in pediatric deaths from medication ingestions.<sup>1</sup> However, unintentional medication ingestions by children aged less than 6 years continue to lead to approximately 450,000 poison center calls and 60,000 emergency department (ED) visits each year in the U.S.<sup>2,3</sup> Oral liquid medications are involved in approximately 15% of ED visits for pediatric medication ingestions<sup>2</sup> and, although rare, life-threatening ingestions of over-the-counter (OTC) and prescription liquid

products continue to occur.<sup>3,4</sup> Because the rate of these ingestions relative to units of medication sold has not been assessed previously, rates of ED visits for unintentional ingestions of common oral liquid

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**Table 1.** ED Visits for Unintentional Ingestions Involving Commonly Implicated Oral Medications, Children <6 Years, 2012–2015<sup>a</sup>

Characteristics	ED visits involving the top four commonly implicated liquid medications <sup>b</sup>			ED visits involving the top four commonly implicated prescription solid medications <sup>c</sup>		
	Cases, n	Annual national estimate		Cases, n	Annual national estimate	
		n	% (95% CI)		n	% (95% CI)
Age, years						
<2	124	1,693	26.3 (21.7, 31.0)	166	1,771	39.5 (30.5, 48.4)
2	217	2,405	37.4 (32.2, 42.7)	129	1,646	36.7 (30.8, 42.5)
3	148	1,657	25.8 (20.4, 31.2)	45	736	16.4 (9.7, 23.1)
4–5	79	672	10.5 (6.5, 14.4)	34	335	7.5 (4.7, 10.2)
Sex						
Female	283	3,161	49.2 (41.9, 56.4)	194	2,460	54.8 (46.0, 63.6)
Male	285	3,267	50.8 (43.6, 58.1)	180	2,029	45.2 (36.4, 54.0)
Number of implicated medications						
1	555	6,311	98.2 (96.5, 99.8)	305	3,659	81.5 (74.9, 88.1)
2 or more	13	—	—	69	830	18.5 (11.9, 25.1)
Disposition						
Hospitalized	81	578	9.0 (5.2, 12.8)	189	1,883	41.9 (31.6, 52.3)
Treated and released or left against medical advice	487	5,850	91.0 (87.2, 94.8)	185	2,606	58.1 (47.7, 68.4)
Total	568	6,427	100.0 (N/A)	374	4,489	100.0 (N/A)

<sup>a</sup>Estimates of ED visits for unintentional pediatric medication ingestions based on data from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project (2012–2015). Estimates based on <20 cases are not shown.

<sup>b</sup>Most commonly implicated (top four) oral over-the-counter liquid medications: single-ingredient acetaminophen, diphenhydramine allergy products, and ibuprofen, and single- or multi-ingredient cough and cold medicines.

<sup>c</sup>Most commonly implicated (top four) oral prescription solid medications: clonidine, clonazepam, lisinopril, and buprenorphine/naloxone. ED, emergency department; N/A, not applicable.

medications are calculated and compared with rates for commonly ingested solid medications.

## METHODS

The numbers of ED visits for unintentional pediatric medication ingestions were estimated using data from the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance project, a stratified probability sample of hospitals in the U.S and its territories with at least six beds and 24-hour EDs.<sup>5,6</sup> Trained abstractors at the 60 participating hospitals review all ED medical records to identify and record clinician-diagnosed adverse drug events, including pediatric medication ingestions. Data collection from the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance project hospitals has been deemed a public health surveillance activity by Centers for Disease Control and Prevention human subject oversight bodies and did not require IRB approval.

Cases included ED visits from January 1, 2012 through December 31, 2015 in which a child aged <6 years ingested or was suspected of ingesting acetaminophen, diphenhydramine, ibuprofen, or cough and cold medicines (CCMs), as previous analyses found that >75% of ED visits for unintentional ingestions of liquid medications involved one of these four medications.<sup>2</sup> Dosage form, prescription status, and intended age group for each product were categorized by a study pharmacist based on case narratives, drug

databases, and manufacturer websites.<sup>7,8</sup> The four prescription solid medications most commonly implicated in ED visits for unintentional ingestions were identified for comparison.

National estimates of OTC liquid medication bottles sold were obtained from Information Resources, Inc. The Information Resources, Inc. data include complete point-of-sale data for mass merchandise, club, dollar, and military stores and estimated sales for drug and food stores (based on 92% and 75% coverage, respectively). National estimates of prescriptions dispensed from outpatient retail pharmacies were obtained from QuintilesIMS National Prescription Audit. QuintilesIMS uses proprietary methods to estimate dispensed prescriptions based on data from nearly 48,000 retail pharmacies (representing  $\cong$ 80% of prescriptions from drug, food, and mass merchandise stores).

Annual national estimates of ED visits and corresponding 95% CIs were calculated in 2017 using the SURVEYMEANS procedure in SAS, version 9.3, to account for sample weights and complex sample design.<sup>9</sup> Rates were calculated by dividing the estimated number of ED visits by the estimated numbers of bottles sold or prescriptions dispensed.

## RESULTS

From the results of 568 cases, an estimated 6,427 ED visits (95% CI=4,907, 7,948) were made annually for unintentional ingestions of one of the four most commonly

**Table 2.** ED Visits for Unintentional Ingestions Involving Commonly Implicated Oral Medications, by Product, Children <6 Years, 2012–2015<sup>a</sup>

Medications	Annual national estimate, n (95% CI)	Rate (95% CI)
Liquid drug products <sup>b,c</sup>		
Acetaminophen	2,515 (1,532, 3,498)	7.4 (4.5, 10.3)
Diphenhydramine allergy products <sup>d</sup>	1,200 (817, 1,583)	8.1 (5.5, 10.7)
Ibuprofen	1,197 (862, 1,531)	3.3 (2.4, 4.2)
Cough and cold medicines	1,561 (1,025, 2,096)	0.9 (0.6, 1.1)
Pediatric products	914 (450, 1,378)	2.3 (1.1, 3.5)
Family/adult/unspecified age products	653 (349, 956)	0.5 (0.2, 0.7)
Total	6,427 (4,907, 7,948)	N/A
Prescription solid drug products <sup>e</sup>		
Clonidine	1,417 (1,011, 1,824)	11.1 (7.9, 14.3)
Clonazepam	1,232 (799, 1,664)	4.7 (3.0, 6.3)
Lisinopril	979 (516, 1,442)	1.1 (0.6, 1.7)
Buprenorphine/naloxone	861 (423, 1,299)	10.5 (5.1, 15.8)
Total	4,489 (3,307, 5,670)	N/A

<sup>a</sup>Estimates of ED visits for unintentional pediatric medication ingestions based on data from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project (2012–2015). The sum of estimates for individual products may be greater than the total because ED visits may involve >1 commonly implicated medication.

<sup>b</sup>Pediatric formulations were implicated in nearly all ED visits attributed to single-ingredient acetaminophen (one case involved a product with unspecified age group) and diphenhydramine (two cases involved a family product), and in all visits attributed to ibuprofen.

<sup>c</sup>Rate per 100,000 bottles sold. Estimates of bottles sold based on data from Information Resources, Inc. (2012–2015).

<sup>d</sup>Excludes one case involving an OTC liquid diphenhydramine adult sleep aid.

<sup>e</sup>Rate per 100,000 dispensed retail prescriptions. Estimates of dispensed oral retail prescriptions based on data from the QuintilesIMS National Prescription Audit (2012–2015).

ED, emergency department; OTC, over-the-counter; N/A, not applicable.

implicated OTC liquid medications from 2012 through 2015 (Table 1). During this time, 4,489 estimated visits (95% CI=3,307, 5,670) were made for unintentional ingestions of one of the four most commonly implicated prescription solid medications. The top four OTC liquid medications were implicated in an estimated 10.7% (95% CI=9.3%, 12.1%) of all ED visits for unintentional medication ingestions and the top four prescription solid medications were implicated in 7.5% (95% CI=6.2%, 8.8%).

Acetaminophen was the most commonly implicated OTC liquid medication in ED visits for pediatric ingestions, accounting for an estimated 2,515 ED visits annually (Table 2). Although nearly all ED visits for ingestions of OTC liquid acetaminophen (98.7%, 95% CI=96.2%, 100.0%), diphenhydramine (98.1%, 95% CI=95.2%, 100.0%), and ibuprofen (100.0%) involved pediatric formulations, there were fewer visits attributed to CCMs that definitively involved pediatric formulations (58.5%, 95% CI=41.2%, 75.9%). There were an additional 920 annual ED visits (95% CI=392, 1,448) for ingestion of the top four OTC medications for which the dosage form was not specified, but even if all were oral liquid products, there were no significant changes in the proportion of estimated visits by patient or case characteristics, or by implicated medication (Appendix Table 1, available online).

Estimated rates of ED visits for liquid diphenhydramine and acetaminophen ingestions (8.1 and 7.4 ED visits per 100,000 bottles sold) were significantly higher than rates of ED visits for ibuprofen and CCM ingestions (Table 2). The rate of ED visits involving pediatric CCMs was more than four times the rate involving family or adult CCMs or those for which the age group was not specified (2.3 vs 0.5 ED visits per 100,000 bottles sold). Estimated rates of ED visits for pediatric ingestions per bottle sold for diphenhydramine and acetaminophen were comparable to the rates per prescription dispensed for clonidine and buprenorphine/naloxone (11.1 and 10.5 ED visits per 100,000 dispensed prescriptions).

## DISCUSSION

One reason unintentional ingestions of liquid medications by young children persist despite CR packaging is that most CR packaging in the U.S. uses safety closures/caps on multidose bottles, which requires that parents/caregivers immediately and fully re-secure CR closures after every use. To mitigate this limitation, restricted delivery systems, such as flow restrictors—adapters that narrow bottle openings or create re-closable seals—have been added to some liquid medications.<sup>10–13</sup> These devices add an automatic, passive

safety barrier and were voluntarily added to infants' acetaminophen in 2011 and subsequently added to some children's acetaminophen products.<sup>13</sup> From the number of calls to poison centers, when bottles had flow restrictors, pediatric ingestions of liquid acetaminophen were found to be significantly less likely to involve clinically meaningful doses.<sup>14,15</sup>

A 2015 U.S. Food and Drug Administration voluntary guidance recommends adoption of container features, such as flow restrictors, to reduce the incidence and magnitude of pediatric ingestions on all pediatric OTC liquid products containing acetaminophen.<sup>16</sup> Recommendations to use such restricted delivery systems for other medicines is currently under consideration by U.S. Food and Drug Administration<sup>17</sup> and recommended by other professional and standards organizations.<sup>12,18</sup> An ASTM Standard Test Method to help manufacturers assess optimal flow restrictors for specific products is under development.<sup>19</sup>

Which products might be candidates for enhanced safety features? ED visits for pediatric ingestion of liquid diphenhydramine products and liquid acetaminophen products occurred at two to four times the estimated rate compared with ibuprofen and pediatric CCM products, and at rates comparable to the prescription solid medications clonidine and buprenorphine/naloxone.<sup>20,21</sup> Although voluntary U.S. Food and Drug Administration guidelines already recommend such features for pediatric liquid acetaminophen-containing products, acute toxicity of diphenhydramine may be greater than acetaminophen after ingestion of comparable volumes. From the current guidelines, a child aged less than 5 years would likely be referred for emergency evaluation only after ingesting a full 120-mL bottle of children's acetaminophen, but would be referred after just one half of a 120-mL bottle of children's diphenhydramine.<sup>22,23</sup> Flow restrictors could be expected to prevent ingestion of such volumes and need for subsequent ED visits, as in a randomized trial, only 6% of preschool-aged children were able to empty bottles with flow restrictors and no children aged less than 3.5 years removed even 5 mL.<sup>24</sup>

### Limitations

Public health surveillance data have limitations. First, the number of pediatric medication ingestions was likely underestimated because only ingestions resulting in ED visits were included. Second, only outpatient retail pharmacy data were included in the analysis. Prescription solid medications obtained from other settings (e.g., mail order/specialty pharmacies) were not included. Similarly, OTC medication sales data from Information

Resources, Inc., did not include Internet sales or sales from retail locations with low volumes of medication purchases (e.g., gas stations, airports). Third, this study focused on four OTC liquid medications previously identified as leading to the majority of ED visits for liquid medication ingestions.<sup>2</sup> While prescription liquid medications lead to fewer ED visits, pediatric ingestions involving some prescription medications (e.g., liquid opioids) may lead to significant harm, including death, and future studies might assess improved safety packaging for these products.<sup>25</sup> Further investigation of such products for improved safety packaging may be justified based on severity of harm rather than frequency of ED visits.

### CONCLUSIONS

Product-specific rates of emergency department visits for unintentional liquid medication ingestions can help prioritize preventive interventions, such as enhancing safety packaging with flow restrictors. Additionally, improvements in safety packaging should be combined with reminding parents/caregivers to store medications up and away and out of children's reach and sight.<sup>26,27</sup>

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## SUPPLEMENTAL MATERIAL

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