

# Emergency Department Visits for Overdoses of Acetaminophen-Containing Products

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**Background:** Limited national data on the circumstances of acetaminophen overdoses have hindered identification and implementation of prevention strategies.

**Purpose:** To estimate the frequency of and characterize risks for emergency department visits for acetaminophen overdoses that were not related to abuse in the U.S.

**Methods:** Data were collected from two components of the National Electronic Injury Surveillance System from January 1, 2006, through December 31, 2007, and analyzed from 2009 to 2010 to estimate the annual number of emergency department visits for non-abuse-related acetaminophen overdose by patient demographics, treatments, and type and amount of acetaminophen-containing product ingested.

**Results:** There were an estimated 78,414 emergency department visits (95% CI=63655, 93172) annually for non-abuse-related overdoses of acetaminophen-containing products. Most emergency department visits for acetaminophen overdose were for self-directed violence (69.8%, 95% CI=66.4%, 73.2%), with the highest rate among patients aged 15–24 years (46.4 per 100,000 individuals per year). Unsupervised ingestions by children aged <6 years accounted for 13.4% (95% CI=11.0%, 15.9%) of visits for acetaminophen overdoses (42.5 per 100,000 individuals per year). Therapeutic misadventures accounted for 16.7% (95% CI=14.0%, 19.5%) of visits and most involved overuse for medicinal effects (56.1%, 95% CI=50.6%, 61.6%) rather than use of multiple acetaminophen-containing products or dose confusion.

**Conclusions:** Non-abuse-related overdoses of acetaminophen products lead to many emergency department visits each year, particularly emergency department visits for self-directed violence. Acetaminophen overdose prevention efforts will likely need to be multidimensional.

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## Introduction

Acetaminophen has been used to treat pain and fever for more than 50 years. It is sold over the counter (OTC) as a single-ingredient product or in combination with other ingredients to treat symptoms of allergies, colds and upper respiratory tract infections, migraines, sleep disorders, and other conditions. To treat more severe pain, acetaminophen is combined with opioid analgesics in numerous prescription products. A

1-week prevalence survey found that acetaminophen, taken either as a single ingredient or in a combination product, was the most commonly used drug among adults in the U.S.<sup>1</sup> Combination acetaminophen/hydrocodone products have been the most frequently dispensed prescription drugs in the U.S. since 1997.<sup>2</sup>

Acetaminophen is considered to be safe and effective when used as directed; however, because of its relatively narrow therapeutic index, exceeding the maximum recommended dose can lead to liver toxicity. For adults, a single dose of 10–15 g can cause hepatic necrosis, and for some the toxicity threshold may be lower.<sup>3,4</sup> Manifestations of toxicity range from abnormal liver function tests to acute liver failure (ALF) and death,<sup>5</sup> and the U.S. Food and Drug Administration (FDA) convened an advisory committee meeting in June 2009 to review data on liver injury related to use of acetaminophen and to suggest potential harm-reduction strategies.<sup>6</sup>

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Previous assessments of acetaminophen-related overdoses and liver injury in the U.S. have been based on data from single institutions,<sup>7</sup> tertiary care centers,<sup>8,9</sup> or surveillance systems that are no longer operational.<sup>10</sup> Data on the context of and risk factors for acetaminophen overdoses and the specific type of acetaminophen-containing products involved are limited.<sup>11</sup> Therefore, nationally representative public health surveillance data were analyzed to characterize emergency department visits for non-abuse-related acetaminophen overdoses in the U.S.

## Methods

### Data Source

National estimates of the number of emergency department visits for overdoses involving acetaminophen-containing products were based on data from two components of the National Electronic Injury Surveillance System (NEISS)—the Cooperative Adverse Drug Event Surveillance project (NEISS-CADES) and a special study of the All Injury Program (NEISS-AIP) on self-directed violence.

Both NEISS-CADES and NEISS-AIP use the same national stratified probability sample of 63 hospitals with a minimum of six beds and a 24-hour emergency department in the U.S. and its territories and have been described in detail elsewhere.<sup>12–16</sup> For NEISS-CADES, trained coders at each participating emergency department review clinical records of every visit and report data to identify adverse drug events (ADEs) based on the verbatim clinical diagnoses and supporting information.<sup>13,14</sup> Clinical narratives, diagnoses, testing, treatments, and up to two implicated medications are reported. The NEISS-AIP special study on self-directed violence characterizes self-directed violence-related emergency department visits by analyzing additional data reported by NEISS coders, including (1) whether the emergency department visit resulted from suicidal behavior or self-harm behavior; (2) existing medical and psychiatric conditions of the patient (e.g., clinical depression, alcohol abuse, or substance abuse) as reported by relatives or friends; and (3) alcohol or drug use at the time of the injury as determined by hospital staff members or laboratory reports.<sup>15</sup> For ingestions involving self-directed violence, up to four implicated products and the amount ingested are reported.

### Case Definition

A case was defined as an emergency department visit by a patient from January 1, 2006, to December 31, 2007, for an overdose of an acetaminophen-containing product. A medication overdose was defined as ingestion of supra-therapeutic amounts or inadvertent exposure. Acetaminophen-containing products were identified based on verbatim names of implicated medications. When non-specific brand names were reported, cases were included only if all available formulations contained acetaminophen. Cases in which the emergency department chart described abuse/recreational use of acetaminophen products or in which there was insufficient information to characterize the event were not included.

## Measures

An emergency department visit for acetaminophen overdose was the primary outcome measure. Unintentional overdoses were categorized as unsupervised ingestions or therapeutic misadventures. Unsupervised ingestions included consumption of medication by a child aged  $\leq 10$  years without adult supervision. Therapeutic misadventures included overuse of a drug for medicinal effects (e.g., ingestion of greater-than-recommended quantities for control of pain or fever, or intentional use of a medication prescribed for someone else) and medication errors (e.g., unintentional ingestions of greater-than-recommended quantities because of mistakes in administration, prescribing, or dispensing). Secondary measures included patient age; gender; emergency department treatments; disposition from the emergency department; and type, dose form, and number of acetaminophen-containing pills ingested.

## Statistical Analysis

Each NEISS-CADES and NEISS-AIP visit was assigned a sample weight based on the inverse probability of selection, and adjusted annually for nonresponse, population changes, hospital closures, and mergers.<sup>12</sup> National estimates of emergency department visits from 2006 to 2007 and the corresponding 95% CIs were calculated in 2009–2010 using the Surveymeans procedure in SAS, version 9.2, to account for weighting and the complex sample design. To obtain annual estimates, frequency estimates and 95% CIs were divided by 2 for the period 2006–2007. Population rates were calculated using 2006 and 2007 population estimates from the U.S. Census Bureau.<sup>17</sup> National estimates based on  $< 20$  cases or with a coefficient of variation  $> 30\%$  were considered statistically unstable and are not reported.<sup>16</sup>

## Results

Based on 2717 total cases, an estimated 78,414 emergency department visits (95% CI=63655, 93172 visits) occurred annually for overdoses of acetaminophen-containing products, excluding overdoses related to recreational drug use or abuse. Most emergency department visits for overdoses of acetaminophen-containing products (69.8%, 95% CI=66.4%, 73.2%) involved self-directed violence; the remaining visits (30.2%, 95% CI=26.8%, 33.6%) involved unintentional overdoses. Unintentional overdoses included unsupervised ingestions by a child (13.4% of the total, 95% CI=11.0%, 15.9%) and therapeutic misadventures (16.7% of the total, 95% CI=14.0%, 19.5%).

The median age of individuals treated for self-directed violence involving acetaminophen was less than the median age for therapeutic misadventures (29 years, range=10–85 years, vs 35 years, range= $< 1$ –93 years). For unsupervised child ingestions, the median age was 2 years (range= $< 1$ –10 years). Most visits for self-directed violence and therapeutic misadventures were made by women/girls (65.9% and 63.5%, respectively); most visits for unsupervised ingestions were by men/boys (55.6%; Table 1). Nearly three fourths of self-

**Table 1.** Emergency department visits for overdoses involving acetaminophen-containing products, U.S., 2006–2007

Patient and case characteristics	Emergency department visits for intentional overdose			Emergency department visits for unintentional overdose					
	Self-directed violence <sup>a</sup>			Unsupervised ingestion <sup>b</sup>			Therapeutic misadventures <sup>b,c</sup>		
	Cases	Annual national estimate		Cases	Annual national estimate		Cases	Annual national estimate	
No.	No.	% (95% CI)	No.	No.	% (95% CI)	No.	No.	% (95% CI)	
<b>Age (years)</b>									
<6	NA	NA	NA	439	10,463	99.2 (98.4, 100.0)	10	—	—
6–14	105	2,440	4.5 (3.1, 5.8)	6	—	—	23	—	—
15–24	716	19,641	35.9 (31.6, 40.1)	NA	NA	NA	111	3,418	26.0 (21.0, 31.1)
25–39	555	16,424	30.0 (26.7, 33.4)	NA	NA	NA	109	3,517	26.8 (22.0, 31.6)
40–49	291	9,217	16.8 (14.9, 18.8)	NA	NA	NA	45	1,335	10.2 (6.8, 13.6)
50–64	157	5,812	10.6 (8.0, 13.2)	NA	NA	NA	67	2,313	17.6 (13.0, 22.2)
>64	33	1,211	2.2 (1.4, 3.1)	NA	NA	NA	50	1,912	14.6 (9.5, 19.7)
<b>Gender<sup>d</sup></b>									
Women/girls	1225	36,071	65.9 (62.1, 69.6)	203	4,680	44.4 (37.6, 51.2)	265	8,340	63.5 (56.4, 70.7)
Men/boys	632	18,672	34.1 (30.4, 37.9)	242	5,866	55.6 (48.8, 62.4)	149	4,721	36.0 (28.8, 43.1)
<b>Disposition<sup>e</sup></b>									
Admitted, admitted for observation, or transferred to another acute care facility	781	24,722	45.2 (37.7, 52.6)	64	—	—	111	3,540	27.0 (19.9, 34.1)
Admitted to psychiatric facility or service	556	15,830	28.9 (23.3, 34.5)	NA	NA	NA	NA	NA	NA
Treated and released or left against medical advice	518	14,171	25.9 (19.6, 32.2)	381	9,603	91.1 (85.2, 96.9)	304	9,585	73.0 (65.9, 80.1)
<b>Other implicated medications</b>									
Non-acetaminophen products also involved	955	28,860	52.7 (46.5, 59.0)	45	—	—	114	3,949	30.1 (24.1, 36.1)
Only acetaminophen products involved	902	25,883	47.3 (41.0, 53.5)	400	9,953	94.4 (91.4, 97.3)	301	9,175	69.9 (63.9, 75.9)
<b>Number of acetaminophen products</b>									
One acetaminophen product involved	1753	51,361	93.8 (92.2, 95.4)	439	10,429	98.9 (97.7, 100.0)	393	12,543	95.6 (93.3, 97.8)
≥2 acetaminophen products involved	104	3,383	6.2 (4.6, 7.8)	6	—	—	22	—	—
<b>Acetaminophen product classes</b>									
Single-ingredient acetaminophen	821	20,885	38.2 (33.1, 43.2)	305	7,099	67.3 (61.3, 73.3)	123	3,378	25.7 (19.4, 32.1)
Opioid analgesic combination	729	24,371	44.5 (39.5, 49.5)	69	1,625	15.4 (10.1, 20.7)	205	7,258	55.3 (48.4, 62.2)

(continued on next page)

**Table 1.** Emergency department visits for overdoses involving acetaminophen-containing products, U.S., 2006–2007 (continued)

Patient and case characteristics	Emergency department visits for intentional overdose				Emergency department visits for unintentional overdose			
	Self-directed violence <sup>a</sup>		Unsupervised ingestion <sup>b</sup>		Therapeutic misadventures <sup>b,c</sup>			
	Cases No.	Annual national estimate % (95% CI)	Cases No.	Annual national estimate % (95% CI)	Cases No.	Annual national estimate % (95% CI)	Cases No.	Annual national estimate % (95% CI)
Non-opioid analgesic combination	81	2,383 4.4 (2.8, 5.9)	26	—	30	848 6.5 (3.9, 9.0)	—	—
Cough/cold/antihistamine combination	162	5,129 9.4 (7.1, 11.6)	40	1,112 10.5 (6.3, 14.8)	42	1,319 10.1 (7.3, 12.8)	—	—
Two or more different acetaminophen product classes	64	1,976 3.6 (2.5, 4.7)	5	—	15	—	—	—
Total	1857	54,743 100.0	445	10,546 100.0	415	13,125 100.0	—	—

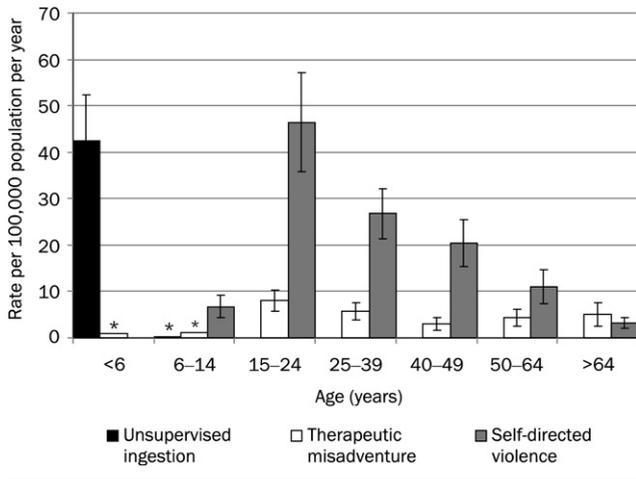
<sup>a</sup>Estimates based on the National Electronic Injury Surveillance System—All Injury Program, 2006–2007. Estimates based on <20 cases, a total estimate <1200, or with a coefficient of variation >30% are not shown (—).  
<sup>b</sup>Estimates based on the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance project, 2006–2007. Estimates based on <20 cases, a total estimate <1200, or with a coefficient of variation >30% are not shown (—).  
<sup>c</sup>Therapeutic misadventures includes intentional ingestion of greater than recommended quantities for therapeutic effects and unintentional ingestions of greater than recommended quantities because of medication errors. Cases of abuse (recreational use or use for euphoric effects) are not included.  
<sup>d</sup>Unknown for one case of therapeutic misadventure  
<sup>e</sup>Unknown for two cases of self-directed violence

directed violence visits involving acetaminophen required admission/observation in an acute care facility (45.2%) or admission to a psychiatric service or facility (28.9%). Most emergency department visits for unsupervised ingestion and therapeutic misadventures involving acetaminophen did not require admission/observation, but 28.0% (95% CI=21.8%, 34.1%) of children treated for unintentional ingestion of an acetaminophen product were treated with *N*-acetylcysteine (NAC) or received gastrointestinal decontamination.

Acetaminophen-containing products were the only drugs implicated in most emergency department visits for unsupervised ingestions and therapeutic misadventures (94.4% and 69.9%, respectively); however, half (52.7%) of visits for self-directed violence involved at least one additional non-acetaminophen-containing drug. Visits in which more than one acetaminophen product was implicated were infrequent across all intent types. For intentional overdoses, more than one acetaminophen-containing product was implicated in only 6.2% of emergency department visits (104 cases). More than one acetaminophen-containing product was implicated in only six cases of unsupervised child ingestion and 22 cases of therapeutic misadventure. Of the emergency department visits for unsupervised ingestion, consumption of a pill or tablet form of acetaminophen (56.4%, 95% CI=50.8%, 62.0%) was most commonly reported. Consumption of a liquid acetaminophen product was reported in 37.0% (95% CI=31.6%, 42.3%) of emergency department visits for unsupervised ingestions, and the formulation consumed was unknown in 6.7% (95% CI=3.3%, 10.1%) of visits.

Population rates of self-directed violence visits involving acetaminophen were highest among patients aged 15–24 years (46.4 per 100,000 individuals per year) and declined with increasing age (Figure 1). The second highest population rate of emergency department visits was for unsupervised ingestions among children aged <6 years (42.5 per 100,000 individuals per year). The population rates for emergency department visits attributed to therapeutic misadventures were 2.5- to 6.9-fold lower than the rates for self-directed violence for all age groups except among individuals aged >64 years.

Population rates of self-directed violence visits were significantly higher for women/girls (27.2 per 100,000 individuals per year, 95% CI=21.9, 32.6) compared to men/boys (14.4 per 100,000 individuals per year, 95% CI=11.4, 18.0). The difference between men/boys and women/girls narrowed with increasing age (Figure 2). Disposition from the emergency department, involvement of non-acetaminophen products, and number and type of implicated acetaminophen-containing products did not differ significantly between men/boys and wom-

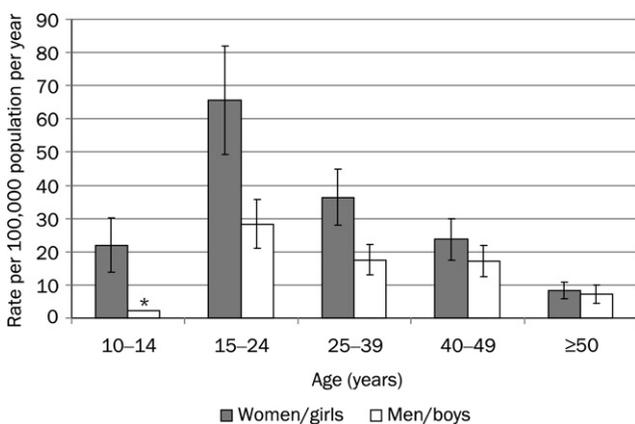


**Figure 1.** Estimated rates of emergency department visits for overdoses involving acetaminophen-containing products, by age category and intent—U.S., 2006–2007

Note: Population rate estimates based on the average of 2006 and 2007 mid-year U.S. Census estimates from the National Center for Health Statistics, CDC; bars represent 95% CIs; asterisk denotes estimates with coefficient of variation >30%

en/girls. Single-ingredient acetaminophen products were involved in most self-directed violence visits involving patients aged  $\leq 24$  years, whereas opioid analgesic combination products were most commonly implicated in self-directed violence visits involving patients aged  $\geq 25$  years (Appendix A, available online at [www.ajpmonline.org](http://www.ajpmonline.org)).

The amount of acetaminophen ingested was documented in 69.8% of the emergency department visits for self-directed violence. Among the self-directed violence



**Figure 2.** Estimated rates of emergency department visits for self-directed violence involving acetaminophen-containing products, by age category and gender—U.S., 2006–2007

Note: Population rate estimates based on the average of 2006 and 2007 mid-year U.S. Census estimates from the National Center for Health Statistics, CDC; bars represent 95% CIs; asterisk denotes estimates with coefficient of variation >30%

**Table 2.** Number of acetaminophen-containing pills ingested in cases resulting in emergency department visits for self-directed violence involving acetaminophen-containing products—U.S., 2006–2007

Number of pills	Annual national estimate <sup>a</sup>	
	%	(95% CI)
$\leq 10$	39.0	(34.3, 43.7)
11–20	24.0	(20.7, 27.4)
21–30	14.7	(12.1, 17.3)
31–40	4.8	(3.2, 6.4)
41–50	3.8	(2.6, 5.1)
$\geq 51$	8.6	(6.8, 10.3)
$\geq \frac{1}{2}$ bottle	5.1	(3.1, 7.0)

<sup>a</sup>Percents are based on 69.8% of visits in which the amount of acetaminophen product ingested was documented.

visits in which the amount of acetaminophen product ingested was documented, 39.0% (95% CI=34.3%, 43.7%) involved ingestion of  $\leq 10$  acetaminophen-containing pills; 24.0% (95% CI=20.7%, 27.4%) involved ingestion of 11–20 pills; and 31.9% (95% CI=28.1%, 35.8%) involved ingestion of 21 or more pills (Table 2). In approximately 5% of self-directed violence visits, at least half a bottle of acetaminophen-containing product was consumed; however, the exact number of pills was not reported. Number of pills ingested did not vary significantly by age (Appendix A, available online at [www.ajpmonline.org](http://www.ajpmonline.org)).

Among emergency department visits for therapeutic misadventures, the type of acetaminophen product most commonly implicated differed significantly by age. In younger patients (those aged 15–24 years), the rate of visits for overdoses of non-opioid-containing acetaminophen products was three times higher than the rate for opioid-containing acetaminophen products (6.0 per 100,000 individuals per year, 95% CI=4.0, 7.9, vs 1.9 per 100,000 individuals per year, 95% CI=0.9, 2.9). For older patients (aged  $\geq 40$  years), the rate of emergency department visits related to use of opioid-containing acetaminophen products was four times higher than the rate of visits from non-opioid-containing products (3.3 per 100,000 individuals per year, 95% CI=2.1, 4.5, vs 0.8 per 100,000 individuals per year, 95% CI=0.3, 1.2).

More than half of emergency department visits for therapeutic misadventures (56.1%, 95% CI=50.6%, 61.6%) resulted from overuse of an acetaminophen-containing product for medicinal effects (e.g., for added symptom relief), whereas only 16.3% (95% CI=21.6%, 33.5%) were attributed to medication errors. The specific

circumstances were unknown for the remaining 27.6% of visits. Among those aged 15–24 years, overuse for medicinal effects was documented in 75.0% (95% CI=66.1%, 83.8%) of emergency department visits attributed to therapeutic misadventures.

## Discussion

This is the first study that we are aware of that uses nationally representative surveillance data to describe non-abuse-related overdoses involving acetaminophen-containing products by patient intent, patient demographics, and type of acetaminophen product.

### Self-Directed Violence

The finding that 70% of emergency department visits for non-abuse-related acetaminophen overdoses involved intentional self-harm and that nearly 75% of these visits resulted in medical or psychiatric hospitalization suggests that addressing self-directed violence has large potential for public health impact. Indeed, based on an annual estimate of 206,981 emergency department visits,<sup>18</sup> one of every four emergency department visits for intentional self-poisoning involved an acetaminophen product.

Adolescents and young adults, particularly women/girls, had the highest rate of self-directed violence visits for acetaminophen overdose, and OTC products were most commonly involved. Previous studies have found that ingestion of medications is a common method of suicide attempt among adolescents,<sup>19</sup> impulsivity is an important factor in self-poisoning by adolescents,<sup>20</sup> and that acetaminophen self-poisonings are often impulsive acts.<sup>21</sup> There is some evidence that restrictions on the amount of acetaminophen that may be purchased at one time have reduced acetaminophen-related self-harm in some localities,<sup>22,23</sup> but there is variable adherence to purchasing restrictions,<sup>24</sup> and the long-term effectiveness of these measures in reducing acetaminophen-related harm continues to be debated.<sup>25,26</sup> Another option that has been suggested to discourage impulsive self-poisonings is packaging acetaminophen products in blister packs, and in at least one study of self-poisoning with acetaminophen, individuals who had taken medication from blister packs ingested substantially fewer pills.<sup>21</sup>

### Unsupervised Ingestion

The population rate of emergency department visits for unsupervised ingestions among children aged <6 years was second to only the rate of emergency department visits for self-directed violence by those aged 15–24 years, and nearly one third of unsupervised ingestions were treated with NAC or gastrointestinal decontamination. Similar to previous studies,<sup>27,28</sup> most of these unsuper-

vised ingestions were by children aged <6 years, and slightly more than half of emergency department visits for unsupervised ingestions of acetaminophen were attributed to ingestion of pills. These findings suggest that to eliminate morbidity from child ingestions, interventions will need to include liquid and pill formulations.

Incorporating flow restrictors could reduce the amount of liquid medication that children are able to drink directly from the bottle and unit-dose packaging can limit the amount of product consumed in unsupervised ingestions.<sup>29</sup> Targeted education campaigns focusing on limiting child access to medicines could complement packaging innovations.

### Therapeutic Misadventure

Therapeutic misadventures accounted for 16.7% of emergency department visits for acetaminophen overdoses, and most therapeutic misadventures (56.1%) involved overuse of an acetaminophen product for a medicinal effect. Previous studies of patient knowledge and practices have found that oftentimes, individuals are not aware of the potential harm from taking or administering acetaminophen improperly.<sup>30,31</sup> Among adolescents and young adults, overuse of an acetaminophen product for more potent medicinal effects was documented in three fourths of emergency department visits attributed to therapeutic misadventures, and three fourths of therapeutic misadventures involved OTC formulations. On the other hand, among older adults, more than four fifths of therapeutic misadventures involved acetaminophen-opioid combination products. Thus, these data suggest that to reduce the incidence of emergency department visits for therapeutic misadventures, interventions should target safe practices in the use of OTC medications by adolescents and young adults and safe use of acetaminophen-opioid combination products by older adults.

### Limitations

The current findings should be interpreted in the context of the limitations of emergency department-based public health surveillance data. First, the current estimates likely underestimate the number of medication overdoses involving acetaminophen. Both NEISS-CADES and NEISS-AIP capture only those overdoses that are treated in a hospital emergency department and do not capture overdoses that are not treated in emergency departments or that result in death prior to an emergency department visit. A narrow definition for acetaminophen product exposure was used and included only cases in which an acetaminophen product was explicitly mentioned. Products that are available in non-acetaminophen-containing formulations (e.g., DayQuil®, hydrocodone) were not in-

cluded. Emergency department visits related to abuse/recreational drug use are not included.

Second, case identification relies on patients and caregivers to provide accurate accounts of the circumstances surrounding the overdose, physicians to correctly diagnose and document the medication overdose and to identify an acetaminophen product, and NEISS coders to correctly interpret and transcribe supporting case information. Although the number of pills ingested was collected for self-directed violence patients, the exact milligram dose was not collected. There also was potential for misclassification of intent, particularly when the circumstances surrounding the overdose are sensitive matters (e.g., intentional ingestions may have been reported by patients as mistakes or errors and inappropriately coded as unintentional ingestions).

Third, when acetaminophen combination products or non-acetaminophen-containing products were implicated, it is possible that the pharmacologic effects of the non-acetaminophen drug precipitated the emergency department visit. Lastly, emergency department record-based surveillance data were used to estimate the public health burden of acetaminophen overdose but these data do not directly assess liver injury. Emergency department-based surveillance data, including data from NEISS, are not ideal for measuring the burden of acetaminophen-induced liver toxicity because acetaminophen may be implicated only after admission; reporting of diagnostic testing is not always complete; and although a patient may have sustained a serious overdose, toxicity may be averted by prompt treatment.

## Conclusion

Non-abuse-related overdoses of acetaminophen-containing products are involved in many emergency department visits each year, particularly emergency department visits for self-directed violence. Nationally representative data on acetaminophen-related emergency department visits can help target interventions to have the greatest potential for minimizing harms while preserving options for pain management and symptom relief.

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## Appendix

### Supplementary data

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