U.S. Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases

Preventing Pediatric Medication Overdose:
Strategies, Challenges, and Innovations

Nonprescription Analgesic/Antipyretic Drug Development in Children 2 to Less Than 12 Years Workshop

November 15, 2024

Jennifer Lind Lyles, PharmD, MPH, MBA and Maribeth Sivilus, MPH
Medication Safety Program, Medical Product Safety Branch

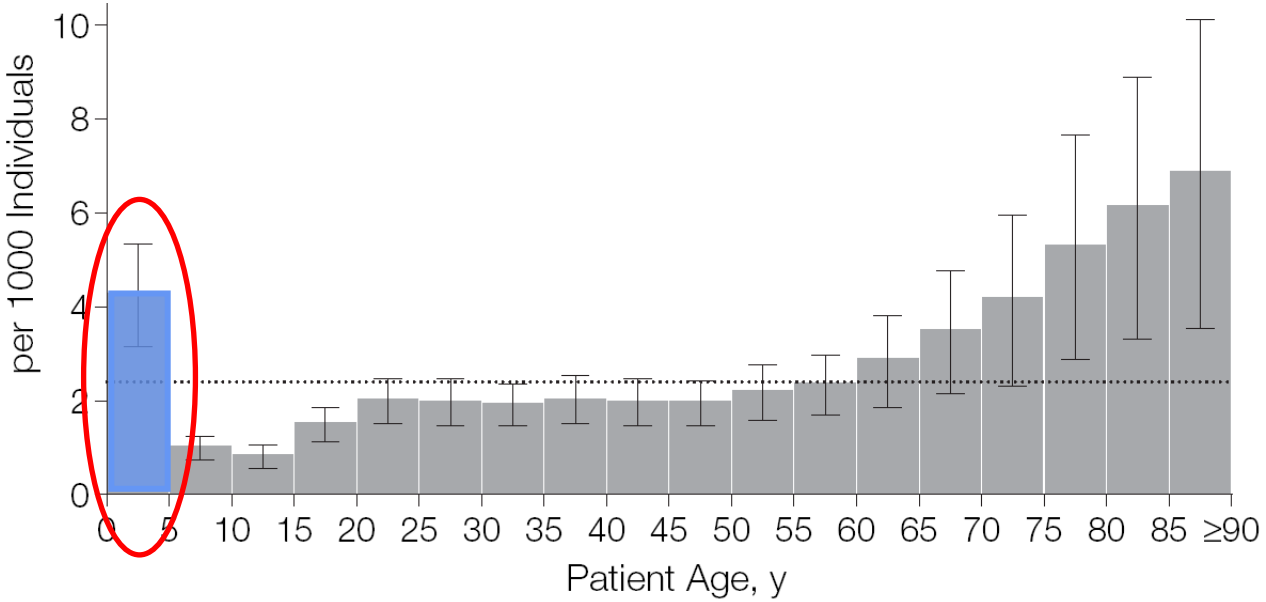
HOW Does ADE Surveillance Happen?

The “old-fashioned” way…. population-based sampling

- National Electronic Injury Surveillance Systems (NEISS)
  - Operated by the US Consumer Product Safety Commission
  - Cooperative (with CDC/FDA) Adverse Drug Event Surveillance (CADES)

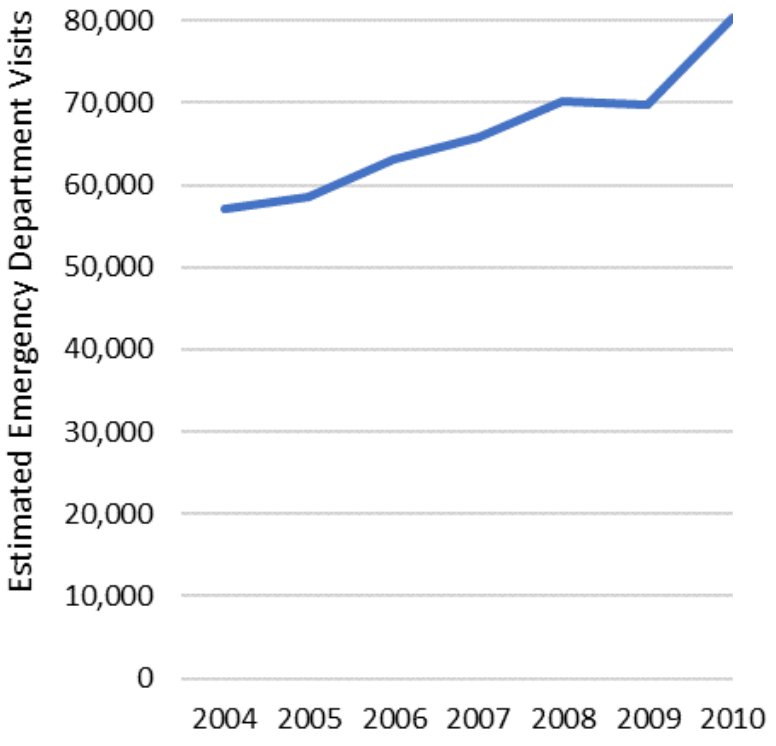
- National Probability Sample
  - ~80 hospital Emergency Departments (EDs)
  - Stratified by hospital size/ children’s hospitals
  - Cases weighted by inverse probability of selection

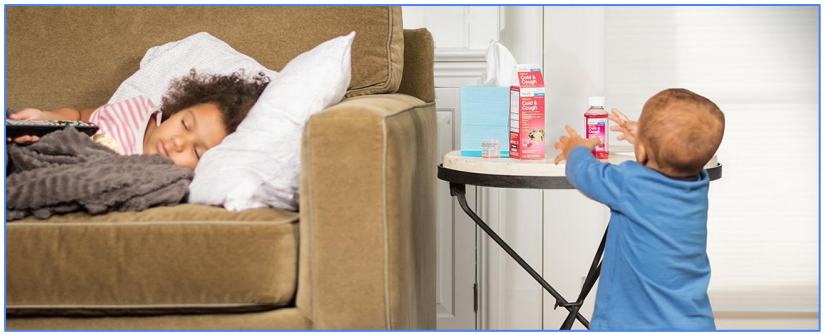
HOW many Outpatient ADEs occur?
WHICH patients experience ADEs?



Budnitz DS et al. *JAMA* 2006;296:1858-66

Increase in emergency visits for medication overdoses and exposures in children <6 years





NEISS-CADES, PROTECT Initiative Meeting 2021

PROTECT

Prevention of Overdoses and Treatment Errors in Children Taskforce

- 3-Pronged Approach
  1. **Improve Safety Packaging** to reduce unsupervised ingestions
  2. **Standardize Labeling** to reduce medication errors
  3. **Update educational messages** on safe use and storage

https://www.cdc.gov/medicationsafety/protect/protect_initiative.html

HOW to prevent ADEs among children (liquid meds)?

TYLENOL® For Healthcare Professionals

For Consumers | News & Events |

Home

For Pediatric HCPs

Order Resources

Patient Education Handouts

Guidelines & Studies

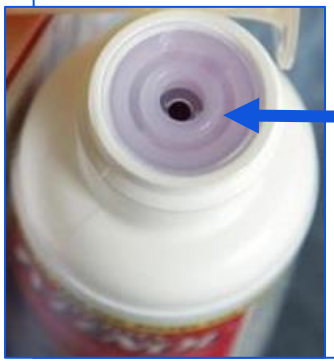
Pediatric Product Enhancements

NEW PRODUCT DOSING DEVICE ENHANCEMENTS FOR INFANTS' AND CHILDREN'S TYLENOL®

April 14, 2011

Dear Healthcare Professional:

I am pleased to inform you that McNeil Consumer Healthcare will be introducing dosing device enhancements on Infants' and Children's TYLENOL® products that will be available this upcoming cold and flu season. These enhancements are intended to help reduce the incidence and magnitude of accidental acetaminophen exposures in cases of unsupervised ingestions. McNeil has also shared these plans with other manufacturers of pediatric acetaminophen products.



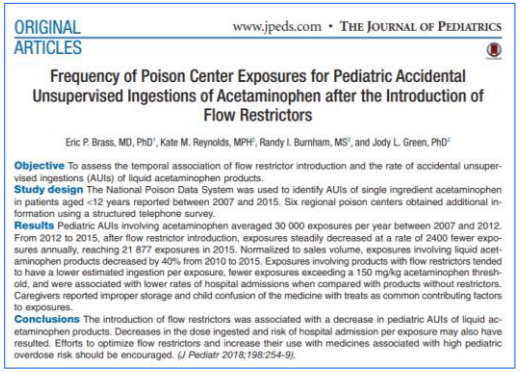
Infants' TYLENOL® will include a new, enhanced bottle with a protective flow restrictor opening and push-in syringe. We believe this innovation will:

- Increase dosing accuracy through use of the new, product-specific dosing syringe
- Provide caregivers with better control when dispensing the medication, reduce spillage and increase the ease of administration to infants
- Further reduce the risk of children being able to get to the medicine in the bottle

Children's TYLENOL® will feature a new, enhanced bottle with a protective flow restrictor opening designed to be used with a dosing cup.

www.tylenolprofessional.com/letter_pediatric-dosing-device-update.html

Flow restrictors…



ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

Frequency of Poison Center Exposures for Pediatric Accidental Unsupervised Ingestions of Acetaminophen after the Introduction of Flow Restrictors

Eric P. Brass, MD, PhD[1], Kate M. Reynolds, MPH[2], Randy I. Burnham, MS[2], and Jody L. Green, PhD[2]

Objective To assess the temporal association of flow restrictor introduction and the rate of accidental unsupervised ingestions (AUIs) of liquid acetaminophen products.

Study design The National Poison Data System was used to identify AUIs of single ingredient acetaminophen in patients aged <12 years reported between 2007 and 2015. Six regional poison centers obtained additional information using a structured telephone survey.

Results Pediatric AUIs involving acetaminophen averaged 30 000 exposures per year between 2007 and 2012. From 2012 to 2015, after flow restrictor introduction, exposures steadily decreased at a rate of 2400 fewer exposures annually, reaching 21 877 exposures in 2015. Normalized to sales volume, exposures involving liquid acetaminophen products decreased by 40% from 2010 to 2015. Exposures involving products with flow restrictors tended to have a lower estimated ingestion per exposure, fewer exposures exceeding a 150 mg/kg acetaminophen threshold, and were associated with lower rates of hospital admissions when compared with products without restrictors. Caregivers reported improper storage and child confusion of the medicine with treats as common contributing factors to exposures.

Conclusions The introduction of flow restrictors was associated with a decrease in pediatric AUIs of liquid acetaminophen products. Decreases in the dose ingested and risk of hospital admission per exposure may also have resulted. Efforts to optimize flow restrictors and increase their use with medicines associated with high pediatric overdose risk should be encouraged. *(J Pediatr 2018;198:254-9).*

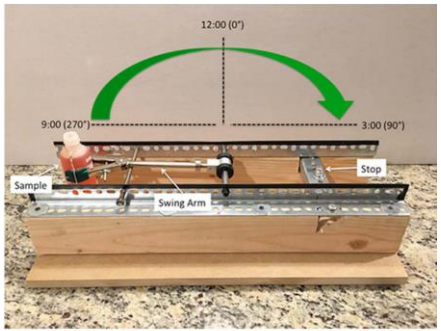


FIG. 1 Example Apparatus for Deceleration (Swing) Test

Restricted Delivery Systems: Flow Restrictors for Oral Liquid Drug Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Rhiannon Leutner (CDER) at 240-402-5998.

For questions about this document regarding CBER-regulated products, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products (OCP)

March 2020
Drug Safety

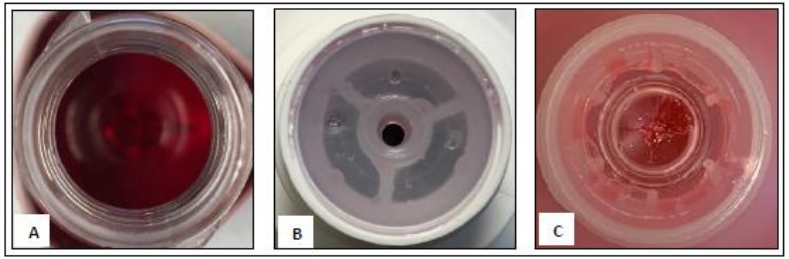
are efficacious

are effective

can be tested

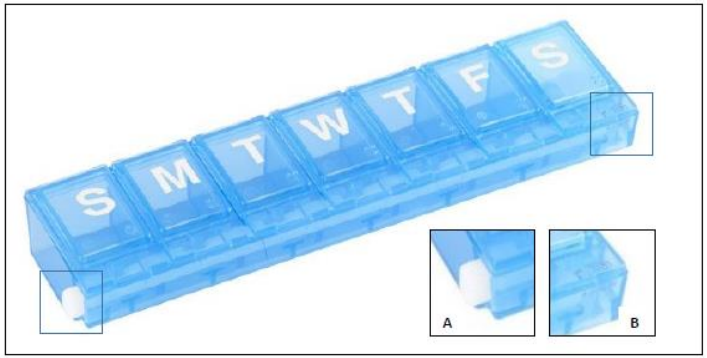
are recommended for broader use

https://pubmed.ncbi.nlm.nih.gov/23896185/
https://pubmed.ncbi.nlm.nih.gov/29622340/
https://www.astm.org/f3375-19.htm
https://www.fda.gov/media/136170/download



eFigure 1. Examples of the openings of liquid medication bottles. Bottle without a flow restrictor (A); Bottle with a small bore open orifice flow restrictor (B); Bottle with a valved flow restrictor (C). Medication is removed from bottles with flow restrictors using an oral syringe or by squeezing into a dosing cup.

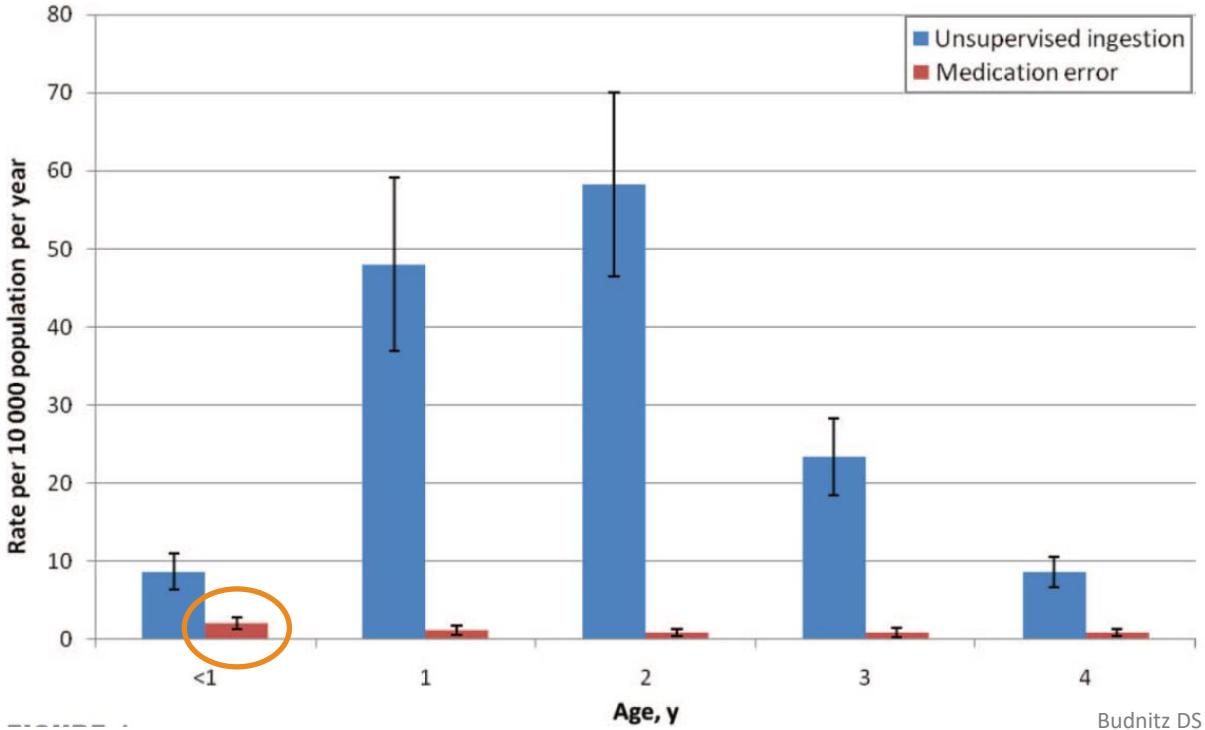
eFigure 3. Examples of existing packaging that can encourage adults to keep pills within the packaging and can be designed with child-resistant features. Blister packaging with perforations between doses, child-resistant or non-child-resistant designs available (A); Strip of unit dose pouches, currently typically non-child-resistant (B); Multi-dose blister card, currently typically non-child-resistant (C).



eFigure 4. Example of locking pill organizer. Push and hold button to release latch and open compartment lid (Inset A). Latch is spring loaded so automatically re-engages when lid is closed (Inset B).

ED Visits for ADEs Relatively Common in Children <5

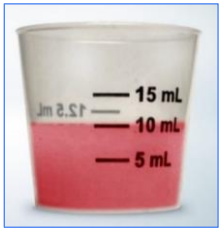
Medication Errors Most Common Among Youngest Children



Budnitz DS and Salis S. *Pediatrics* 2011;127:1597-9
Cohen AL, et al. *J Pediatr* 2008;152: 416-421
Schillie SF, et al. *Am J Prev Med* 2009;37:181-7

Administration mix-ups can lead to multi-fold medication overdoses (and underdosing errors)

Instruction	Mix-up	Outcome
Give 1 teaspoon	Gave 1 **Table**spoon	3-fold overdose
Give 1/2 teaspoon	Gave **2** teaspoons	4-fold overdose
Give 1 milliliter (mL)	Gave 1 **teaspoon**	5-fold overdose
Give .1 milliliter (mL)	Gave **1** mL	10-fold overdose
Give 1.0 milliliter	Gave **10** mL	10-fold overdose



Encouraged EDUCATION

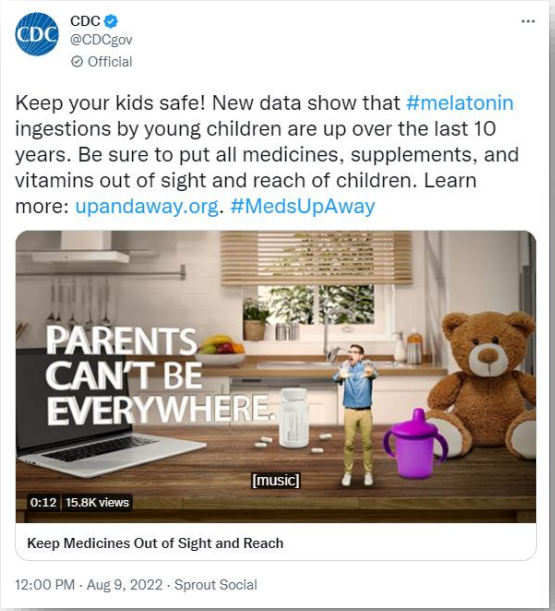
- For Prescribers

- For Parents/Caregivers

Encouraged ENGINEERING

- Encourage production of mL-only dosing devices

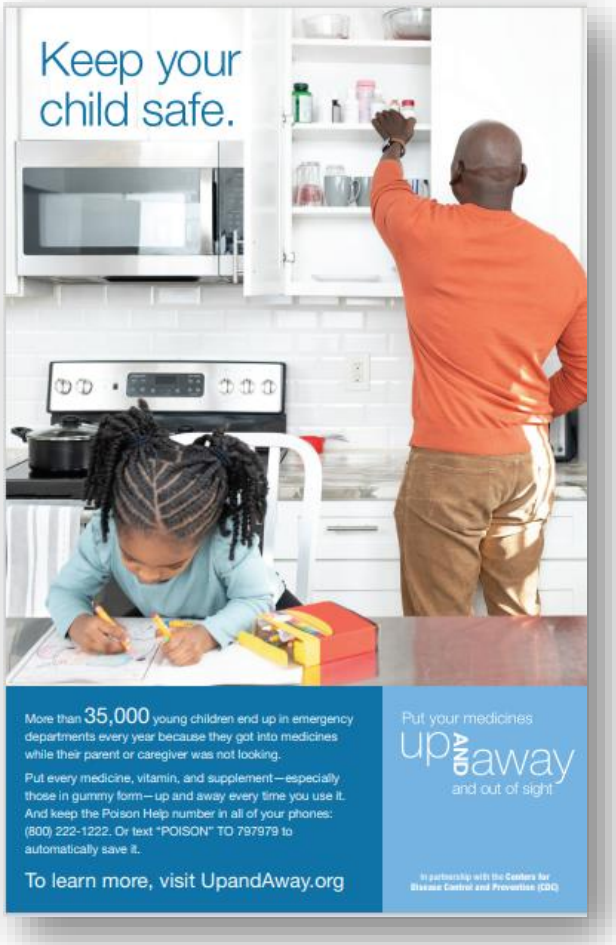
Up & Away Educational Campaign



www.UpAndAway.org

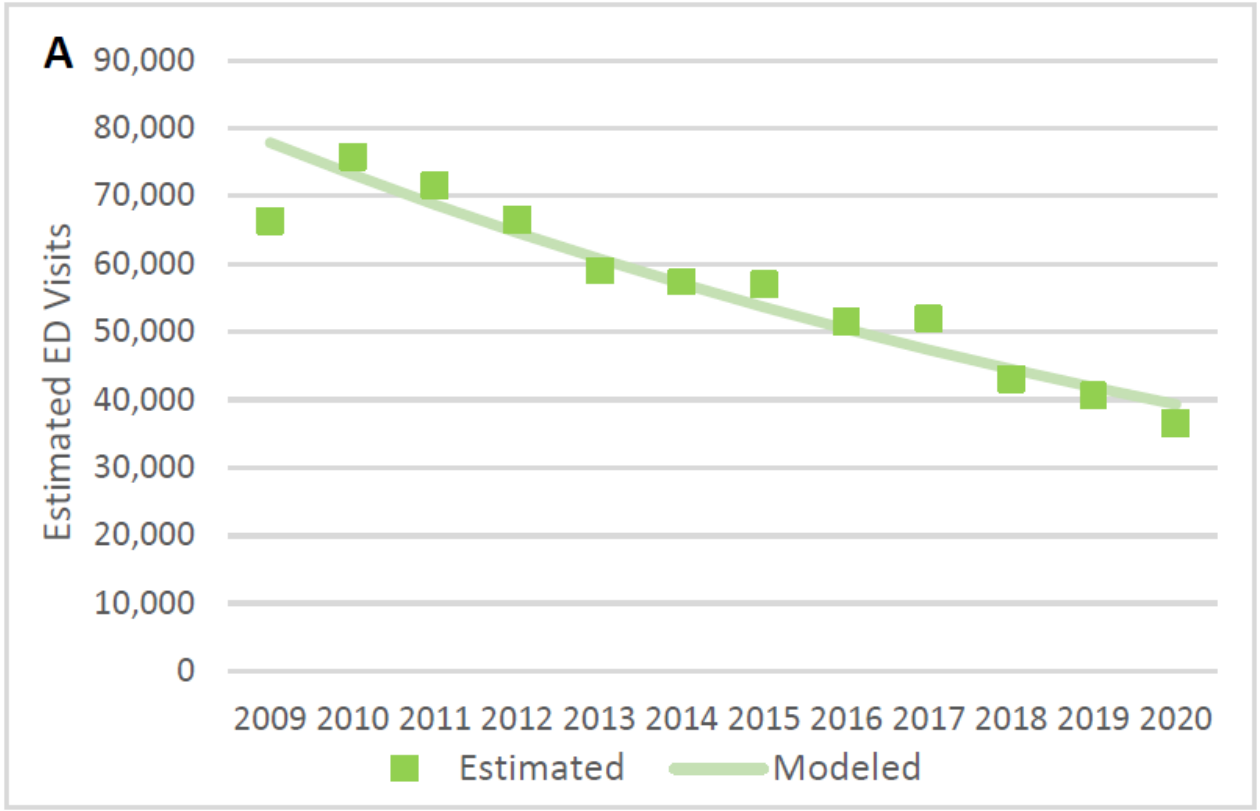
Up & Away Core Messages

1. Put medicines up and away and out of children's reach and sight.
2. Put medicines away every time.
3. Make sure safety caps are locked.
4. Teach your children about medicine safety.
5. Tell guests about medicine safety.
6. Be prepared in case of an emergency.



www.UpAndAway.org

Recent Declines in Estimates of ED Visits for Unsupervised Medication Exposures, Children Aged ≤5 Years



ED = Emergency Department

Lovegrove MC, et al. *Am J Prev Med* 2023;64:834-43

Declines in Unsupervised Exposure ED Visits Across Many Medications

Table 3. Medication Classes Implicated in Emergency Department Visits for Unsupervised Medication Exposures Among Children Aged ≤5 Years

Medication class and Dosage form combination	2009–2012 Annual national estimate			2017–2020 Annual national estimate			Difference in estimate 2009–2012 to 2017–2020	% Change 2009–2012 to 2017–2020		
	n	%	95% CI	*n*	%	95% CI		%	95% CI	
Solid dosage form prescription medications										
Antidepressants	3,801	5.4	(4.6, 6.2)	2,446	5.7	(4.6, 6.7)	−1,354	−35.6	(−51.7, −19.6)	↓
Prescription opioids	4,845	6.9	(5.8, 8.0)	2,249	5.2	(4.1, 6.3)	−2,596	−53.6	(−67.1, −40.1)	↓
Amphetamine-related stimulants	2,031	2.9	(2.2, 3.6)	1,582	3.7	(2.6, 4.8)	−449	−22.1	(−52.1, 7.9)	
Anticonvulsants	1,763	2.5	(2.0, 3.1)	1,568	3.6	(2.6, 4.7)	−195	−11.1	(−47.0, 24.9)	
Benzodiazepines	4,165	5.9	(4.9, 7.0)	1,529	3.5	(2.5, 4.6)	−2,636	−63.3	(−79.3, −47.3)	↓
Centrally acting antiadrenergics	1,652	2.4	(1.8, 2.9)	1,501	3.5	(2.3, 4.6)	−151	−9.1	(−38.1, 19.8)	
β-blockers	2,265	3.2	(2.6, 3.8)	1,490	3.5	(2.7, 4.2)	−775	−34.2	(−58.5, −9.9)	↓
Angiotensin-converting enzyme inhibitors	1,353	1.9	(1.5, 2.4)	1,179	2.7	(1.8, 3.6)	−174	−12.9	(−52.6, 26.8)	
Calcium channel blockers	1,290	1.8	(1.2, 2.5)	1,121	2.6	(1.8, 3.4)	−169	−13.1	(−47.1, 20.8)	
Atypical antipsychotics	1,603	2.3	(1.7, 2.8)	1,058	2.5	(1.6, 3.4)	−546	−34.0	(−64.4, −3.7)	↓
Oral hypoglycemic agents	1,525	2.2	(1.5, 2.9)	925	2.1	(1.4, 2.9)	−600	−39.4	(−71.8, −6.9)	↓
Thyroid hormones	879	1.3	(0.8, 1.7)	583	1.4	(0.9, 1.8)	−296	−33.7	(−61.4, −6.0)	↓
Non-steroidal anti-inflammatory drugs	902	1.3	(0.9, 1.7)	469	1.1	(0.5, 1.6)	−433	−48.0	(−79.8, −16.1)	↓
Skeletal muscle relaxants	1,536	2.2	(1.8, 2.6)	430	1.0	(0.5, 1.4)	−1,106	−72.0	(−88.4, −55.6)	↓
Angiotensin receptor blockers	349	0.5	(0.2, 0.8)	423	1.0	(0.6, 1.4)	74	21.2	(−67.5, 109.9)	
Antilipemic agents	686	1.0	(0.6, 1.4)	365	0.8	(0.4, 1.3)	−321	−46.9	(−79.8, −13.9)	↓
Diuretics	792	1.1	(0.8, 1.5)	356	0.8	(0.4, 1.2)	−437	−55.1	(−80.8, −29.4)	↓
Nonbenzodiazepine sedative/hypnotic agents	766	1.1	(0.6, 1.6)	326[a]	0.8	(0.3, 1.2)	−440[a]	−57.5[a]	(−91.9, −23.0)[a]	↓
Solid dosage form OTC medications										
Herbal/alternative remedies	1,566	2.2	(1.8, 2.7)	2,594	6.0	(4.6, 7.5)	1,028	65.6	(9.5, 121.7)	↑
Acetaminophen	3,028	4.3	(3.4, 5.3)	2,533	5.9	(4.3, 7.5)	−495	−16.3	(−52.8, 20.2)	
Vitamins/minerals	2,862	4.1	(3.3, 4.9)	1,824	4.2	(3.1, 5.3)	−1,038	−36.3	(−60.8, −11.7)	↓
Ibuprofen	1,758	2.5	(1.9, 3.2)	1,737	4.0	(2.8, 5.2)	−21	−1.2	(−39.1, 36.8)	
Diphenhydramine	718	1.0	(0.6, 1.4)	1,136	2.6	(1.8, 3.5)	419	58.3	(−25.8, 142.4)	
Selective antihistamines	970	1.4	(1.0, 1.8)	776	1.8	(1.1, 2.5)	−194	−20.0	(−66.4, 26.4)	
Aspirin	1,011	1.4	(0.8, 2.1)	558	1.3	(0.8, 1.8)	−453	−44.8	(−83.2, −6.4)	↓
Acetaminophen- or aspirin-containing analgesic combinations	1,234	1.8	(1.4, 2.2)	507	1.2	(0.8, 1.6)	−726	−58.9	(−75.3, −42.5)	↓
Cough and cold medications	935	1.3	(0.9, 1.8)	–	–	–	–	–	–	

ED = Emergency Department

Lovegrove MC, et al. *Am J Prev Med* 2023;64:834-43

Significant Increase in ED Visits for Melatonin Exposures

Table 3. Medication Classes Implicated in Emergency Department Visits for Unsupervised Medication Exposures Among Children Aged ≤5 Years

Medication class and Dosage form combination	2009–2012 Annual national estimate			2017–2020 Annual national estimate			Difference in estimate 2009–2012 to 2017–2020	% Change 2009–2012 to 2017–2020		
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421.1% increase (95% CI=68.3%, 774.0%) in ED visits for melatonin exposures

ED = Emergency Department

Lovegrove MC, et al. *Am J Prev Med* 2023;64:834-43

Characteristics of ED Visits for Unsupervised Medication Exposures, Children Aged ≤5 Years, 2019-21

Characteristic	National Estimates 2019-2021			
	Melatonin Products		Other Medications	
	No.	%	No.	%
Age				
<1 – 2 Years	3,471	46.5	76,091	74.1
3 – 5 Years	3,989	53.5	26,529	25.9
Sex				
Female	3,443	46.2	47,361	46.2
Male	4,017	53.9	55,259	53.9
Disposition				
Hospitalized	--	--	19,678	19.2
Not Hospitalized	7,019	94.1	82,942	80.8
No. Implicated Medications				
1	6,496	87.1	88,936	86.7
>1	--	--	13,684	13.3

PRELIMINARY FINDINGS, NEISS-CADES

-- Denotes unstable estimate

ED Visits for Pediatric Melatonin Exposures Involved Older (Young) Children Than Other Medication Exposures

Characteristic	National Estimates 2019-2021			
	Melatonin Products		Other Medications	
	No.	%	No.	%
Age				
<1 – 2 Years	3,471	46.5	76,091	74.1
3 – 5 Years	3,989	53.5	26,529	25.9
Sex				
Female	3,443	46.2	47,361	46.2
Male	4,017	53.9	55,259	53.9
Disposition				
Hospitalized	--	--	19,678	19.2
Not Hospitalized	7,019	94.1	82,942	80.8
No. Implicated Medications				
1	6,496	87.1	88,936	86.7
>1	--	--	13,684	13.3

PRELIMINARY FINDINGS, NEISS-CADES
-- Denotes unstable estimate

Nearly All ED Visits for Pediatric Melatonin Exposures by Young Children Involved Solid Dose Formulations, 2019-2022

Characteristic	No. of cases	National estimates of emergency department visits	
		No.	% (95% CI)
Total	**295**	**10,930**	**100**
Route[§]			
Oral ingestion	291	10,782	98.6 (96.3–100.0)
Dosage form[¶]			
Solid	278	10,465	95.7 (92.3–99.2)
Gummy	140	4,953	47.3 (35.5–59.2)
Chewable tablet	19	—[†]	—[†]
Unspecified solid dosage form	119	5,146	49.2 (37.1–61.3)
No. of units accessed**			
1–9	81	3,211	30.7 (21.9–39.5)
10–19	35	1,423	13.6 (8.3–18.9)
≥20	59	2,320	22.2 (14.1–30.2)
Unspecified	103	3,510	33.5 (23.2–43.9)
Intended age group of formulation[††]			
Family or adult	128	5,210	47.7 (39.6–55.8)
Pediatric	21	—[†]	—[†]
Unspecified	146	4,919	45.0 (36.7–53.3)

https://www.cdc.gov/mmwr/volumes/73/wr/mm7309a5.htm

-- Denotes unstable estimate

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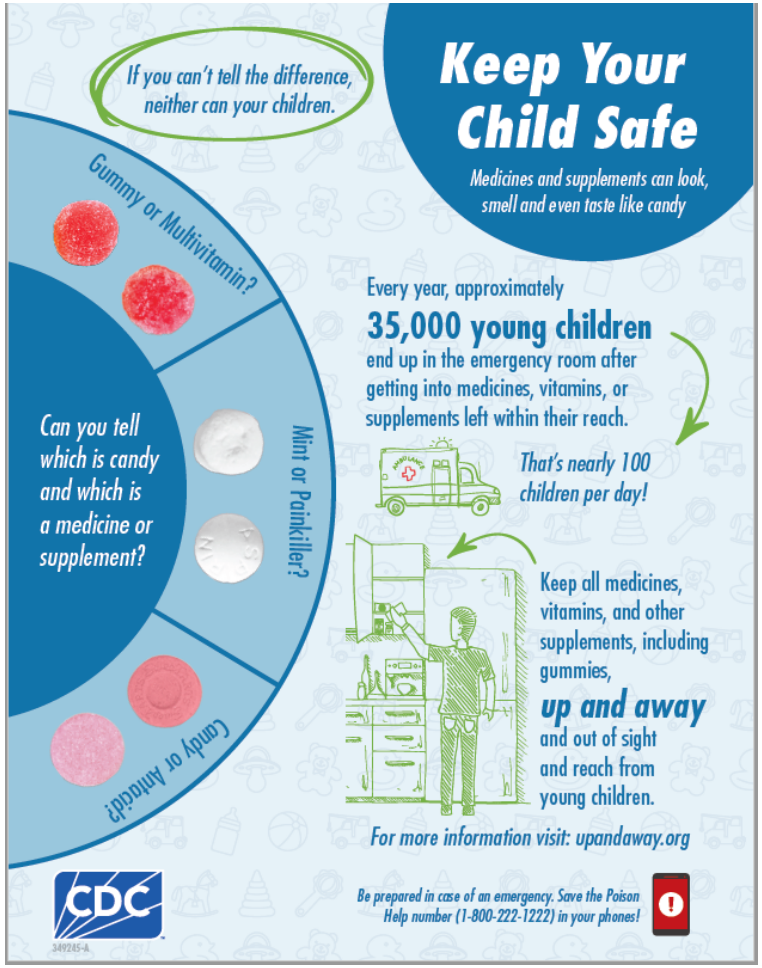

www.UpAndAway.org

Updated Safe Storage Messaging to Include “Gummies”

CDC
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Whether at home or on the go, it’s important to store medicine safely. Keep medicines, vitamins, and other supplements — including gummies — in a safe place young kids can’t see or reach. Learn more: bit.ly/3mQn3BD #MedsUpAway

You Can't Be Everywhere

Thank You!

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For more information, contact CDC
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