Unsupervised Ingestions by Young Children: Monitoring Emergency Department Visits for Opioid Overdoses

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Disclosures

- No financial disclosures to report

- The findings and conclusions in this presentation are those of the author and do not necessarily represent official position of the Centers for Disease Control and Prevention.
Outline

- Brief Background
- Packaging for Prevention
- Post-Market Data
- Lessons from Post-Market Monitoring
Preventing Opioid Overdoses and Opioid-Related Harms

- Conduct surveillance and research
- Empower consumers to make safe choices
- Build state, local, and tribal capacity
- Support providers, health systems, and payers
- Partner with public safety
NEISS-CADES: Population Representative Surveillance

- National Electronic Injury Surveillance System (NEISS)
  - Operated by the U.S. Consumer Product Safety Commission (CPSC)
  - Cooperative (with CDC/FDA) Adverse Drug Event Surveillance (CADES)

- National Probability Sample
  - ~60 hospital Emergency Departments (EDs)
  - Stratified by hospital size & children’s hospitals
  - Cases weighted by inverse probability of selection

- “Injury” from the use of a drug
  - ED visit

- Injury “from the use of” a drug
  - Treating physician explicitly attributes to drug effects
  - Pathognomonic drug-symptom sequence
  - Therapeutic intent

- Injury from the use of “a drug” (up to 2 implicated)
  - Prescription product
  - Over-the-counter product
  - Supplement (vitamin, herb, homeopathic)
  - Vaccine

- Allergic Reactions
- Side Effects
- Supra-therapeutic Effects (Therapeutic Overdoses)
- Errors
- Misuse/Abuse
- Self Harm
- Unknown Intent
NEISS-CADES: Case Definition (2016-)

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- Misuse/Abuse
- Self Harm
- Unknown Intent
Rate of Emergency Visits for Adverse Drug Events (ADEs) in Children <5 Years Similar to 70-75 Year-olds

Budnitz DS et al. JAMA 2006;296:1858-66
Most Emergency Visits for ADEs in Children <5 years Due to Unintentional Medication Exposures or Overdoses

How do Medication Exposures & Overdoses Happen?
Mostly by **Unsupervised Ingestions**

~1 out of every 150 2 year-olds brought to ED

Budnitz DS and Salis S. *Pediatrics* 2011;127:1597-9
Which **Solid Dosage Form Classes Cause ED Visits for Overdoses in Children ≤5 years?**

<table>
<thead>
<tr>
<th>Most Commonly Implicated Medications</th>
<th>ED Visits: Annual National Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Oral prescription solid medications</td>
<td></td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>4661</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>4293</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>3594</td>
</tr>
<tr>
<td>β-blockers</td>
<td>2080</td>
</tr>
<tr>
<td>Amphetamine-related stimulants</td>
<td>1965</td>
</tr>
<tr>
<td>Centrally acting antiadrenergics</td>
<td>1847</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>1715</td>
</tr>
<tr>
<td>Oral hypoglycemics</td>
<td>1454</td>
</tr>
<tr>
<td>Skeletal muscle relaxants</td>
<td>1437</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1377</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>1318</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>1239</td>
</tr>
</tbody>
</table>

Lovegrove M et al. *Pediatrics* 2014:134;e1009-16
Which **Solid Dosage Form Ingredients** Cause Hospitalizations in Children ≤5 years

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Annual National Estimate of Hospitalizations</th>
<th>Proportion of ED Visits Resulting in Hospitalization, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>734</td>
<td>7.7</td>
</tr>
<tr>
<td>Clonidine</td>
<td>701</td>
<td>7.4</td>
</tr>
<tr>
<td>Glipizide</td>
<td>386&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>368</td>
<td>3.9</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>314</td>
<td>3.3</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>309</td>
<td>3.3</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>298</td>
<td>3.1</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>295</td>
<td>3.1</td>
</tr>
<tr>
<td>Bupropion</td>
<td>265</td>
<td>2.8</td>
</tr>
<tr>
<td>Glyburide</td>
<td>257&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.7</td>
</tr>
<tr>
<td>Hydrocodone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>252&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.7</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>249</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Lovegrove M et al. *Pediatrics* 2014:134;e1009-16
For every 500 Adults Treated with Buprenorphine, 1 Child Hospitalized, 2007-2011

Lovegrove M et al. *Pediatrics* 2014;134:e1009-16
Hypothesis: Would Passive Exposure-Limiting Features Reduce Child Ingestions and Overdoses?

Re-engagement Required → **Automatic Protection**

Seatbelts → Air Bags

Unit-Dose Packaging

zubsolv.com
Hypothesis: How Would Passive “Exposure-Limiting” Features Reduce Child Ingestions?

1. Additional passive protection
   – Unit-dose packaging remains in place for remaining doses after one dose is used

2. A little is less harmful than a lot (dose-limiting)
   – incorporates child resistance around every dose
Data: After Unit-Dose Packaging & Re-formulation, ED Visits for Child Ingestions ↓65%
Data: After Flow Restrictors Added, Amount Ingested Declines Based on Calls to Poison Centers

- 6 participating Poison Centers (August 2013 – January 2014)
- 289 cases of pediatric acetaminophen ingestions
- Primary Finding:
  - 2.5 higher odds of ingesting >150 mg/kg dose of acetaminophen in “old” packaging vs. “new” packaging with flow restrictors
- Conclusion:
  - More extensive use would likely reduce morbidity and mortality
  - Further implementation packaging should be encouraged

Geller RJ et al. 2015 Annual Meeting of the North American Congress of Clinical Toxicology (NACCT) *Clinical Toxicology*, 53:7, 641-2
93. The impact of repackaging from bottle to blister on paediatric intoxications with the levothyroxine brand Thyrax®

Antoinette J. H. P. van Riel, Tessa E. van Riemsdijk, Claudine C. Hunault and Irma de Vries
University Medical Center Utrecht (UMCU), Utrecht, The Netherlands

Objective: In December 2013, the packaging of levothyroxine with the brand name Thyrax® was changed by the manufacturer from a bottle to a blister pack in order to improve protection against various environmental factors such as light, air, and humidity. We hypothesized that this change also increased child safety, and analysed the telephone inquiries to our Poisons Information Center (PIC) to investigate the influence of this repackaging on intoxications in young children.

Methods: Cases of exposure and acute overdose with Thyrax® in children under 7 years were included from January 2010 to December 2015. A bottle of Thyrax® contained 90 tablets, so it is likely that between January and March 2014 patients were still using the remaining tablets from their bottle. Cases from January to March 2014 were therefore considered not representative for evaluating the effect of repackaging. Trends in the number of cases per month before and after repackaging were compared using Interrupted Time Series analyses. An unknown dose or an ingested dose of more than 0.05 mg/kg of levothyroxine was defined as a toxic dose. The proportional decreases in the number of cases exposed to a toxic versus a non-toxic dose, before and after repackaging were compared using a z-test.

Results: After repackaging, the number of enquiries per month concerning exposures to Thyrax® decreased from a mean of 12.1/month in 2010–2013 to 5.8/month in 2014–2015 ($p = .03$). Furthermore, the decrease in the number of children exposed to a toxic dose of Thyrax® was proportionally larger ($–65\%$) compared to children exposed to a non-toxic dose ($–38\%$; $p = .002$).

Remarkably, even two years after repackaging, part of the Thyrax® tablets were still packed in a bottle. It is unclear whether the tablets were still delivered in a bottle. In five cases the parents indicated that they transferred the tablets from a blister to a bottle themselves. In 2015, 50% of the cases with a toxic dose of levothyroxine still came from bottled tablets.

Conclusion: Changing the packaging of Thyrax® from bottle to blister has led to a significant decline in the total number of accidental exposures to Thyrax®. The proportion of decrease was even larger for the number of toxic doses. Clearly, blister packaging of tablets is more child safe than bottle packaging. Users, especially those with small children in their household, should be instructed not to repackage tablets from blisters to bottles.
Post-Market Data Considerations: Numerator

- Definition of harm
  - Exposures, Visits, Toxicity?

- Attribution of harm
  - Are symptoms due to the drug?
  - Are multiple substances involved?

- Intention of administration
  - Documentation limitations?

- Categorization of the product
  - By active ingredient, brand, formulation, packaging, source?
Post-Market Data Considerations: Denominator

- Units of exposure
  - Prescriptions written, prescriptions dispensed, days supply, dose supplied, patient-days, patients?
- Time period
  - Shelf-life, washout?
- Intention of administration
  - Documentation limitations?
- Categorization of the product
  - By active ingredient, brand, formulation, packaging
Post-Market Data Considerations: Time Trends

- Correlation is not causation
  - Assessing secular effects?
- Maturation of monitoring systems
  - Both numerator and denominator drift?
- Timing requirements
  - Availability of baseline?
  - Market penetration of packaging?
- Statistical testing
- Unknowns over time