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RESEARCH ARTICLE

Flow Restrictors and Reduction of Accidental Ingestions of Over-the-Counter Medications

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Introduction: Flow restrictors are child-resistant packaging innovations designed to limit the amount of liquid dispensed from a medication bottle. In 2011, flow restrictors were added to pediatric liquid single-ingredient acetaminophen formulations. The hypothesis of this study is that implementation would be associated with reduced volume and severity of pediatric acetaminophen exposures reported to the U.S. National Poison Data System.

Methods: This study describes accidental unsupervised ingestions of acetaminophen in children aged <6 years. Exposures were grouped into pre-implementation (pre-period; January 4, 2010−July 17, 2011); transition (July 18, 2011−July 15, 2012); and post-implementation (post-period; July 16, 2012−December 25, 2016) periods. Cumulative and annual rates of change per million units (i.e., bottles) sold were calculated for the pre- and post-periods for acetaminophen and pediatric liquid ibuprofen (comparator without flow restrictors). Pre- to post-period rate ratios were used to compare products and to estimate the potential effect on other over-the-counter medications. Analysis was conducted in 2017 and 2018.

Results: The pre- and post-period cumulative acetaminophen exposure rate was 507.2 (95% CI=481.1, 534.6) and 325.6 (95% CI=305.8, 346.7) per 1 million units sold, respectively. Declines in the pre- versus post-period rate ratios were seen for exposures with any effect (0.642, 95% CI=0.591, 0.696) and with clinically significant outcomes (0.728, 95% CI=0.581, 0.913). In the post-period, acetaminophen exposures decreased faster than ibuprofen with a rate of change ratio of 0.936 (95% CI=0.912, 0.960) for all exposures and 0.939 (95% CI=0.909, 0.970) for exposures with any effect.

Conclusions: The addition of flow restrictors to pediatric liquid acetaminophen was associated with a reduction in the number and severity of exposures. Application of flow restrictors to other liquid medications should be considered.

INTRODUCTION

Each year, approximately 1 million exposures involving children younger than 6 years are reported to U.S. poison centers.[1] Roughly 16% of these exposures involve commonly used over-the-counter (OTC) medications that are analgesics, antihistamines, or cough and cold medications (CCMs).[1] Unlike those in older age groups, most exposures in young children involve accidental unsupervised ingestions (AUIs), which result in approximately 60,000−70,000 visits per year to U.S. emergency rooms,[2] with AUIs being the most common exposure reason associated with pediatric fatalities reported to poison centers.[1]

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Some factors that contribute to AUIs of medications include increased curiosity and mobility of young children, as well as inadequate storage and packaging of medication. The Poison Prevention Packaging Act (PPPA) of 1970 was the first formal act to address packaging issues in the context of unintentional exposures to medications.[3] This act requires that some household substances be packaged in child-resistant packaging, which makes the package significantly more difficult for children younger than age 5 years to open, without creating additional difficulty for adults to access the medication. These regulations have resulted in a variety of packaging systems, including the commonly used bottle and closure systems that require specific actions to open and close the medication, as well as unit dose blister packaging. Though these PPPA packaging interventions have been effective,[3] AUIs continue to be common occurrences.[1]

In 2008, the Preventing Overdoses and Treatment Errors in Children Taskforce (PROTECT) Initiative[4,5] was launched as a collaborative effort between public health agencies, private sector companies, professional organizations, consumer/patient advocates, and academic experts to develop strategies to prevent unintentional medication overdoses. Although the large number of exposures to pediatric OTC medications that resulted in healthcare utilization, especially OTC CCMs, sparked the formation of PROTECT, whose mission has expanded over the past decade to more broadly reduce pediatric AUIs of both OTC and prescription medications. Partly as a result of PROTECT, efforts to continue to reduce AUIs have included the implementation of flow restrictors on liquid medications (Appendix Figure 1, available online). Flow restrictors represent a physical design change to the medication bottle that include adapters added to the necks of liquid medicine bottles to limit the amount of liquid that can come out of the bottle, even when turned upside down, shaken, or squeezed. This addition to the bottle is designed to reduce or prevent the release of medication and the amount ingested in the event that a child accesses a medication and defeats other parts of the child-resistant packaging. All manufacturers of pediatric liquid single-ingredient acetaminophen began implementing flow restrictors on all infant medications beginning in 2011, with all manufacturers also including flow restrictors on children's formulations shortly thereafter. In simulated settings, flow restrictors have been shown to be effective.[6] The goal of this study is to evaluate the real-world impact of flow restrictors on the volume and severity of exposures reported to U.S. poison centers involving pediatric liquid single-ingredient acetaminophen as well as those with clinically significant outcomes. The authors hypothesize that flow restrictors reduced the rate and severity of acetaminophen exposures during the period following implementation (post-period), when compared with the period prior to implementation (pre-period) and when compared with exposures involving a comparator product without flow restrictors. The secondary objective is to estimate how flow restrictors potentially reduce exposures to other common OTC liquid medications that do not currently have flow restrictors (ibuprofen, CCMs, diphenhydramine) if similarly implemented as part of their child-resistant packaging.

METHODS

This is an observational study of exposures reported to the National Poison Data System throughout the U.S. The National Poison Data System serves as a repository of exposure call information reported to regional poison centers for the purpose of medical management. Regional poison center staff collects key exposure information using standardized data collection tools. Data include demographics, products involved, reasons for exposure, and outcomes. Exposures are triaged and followed until no further information is needed or no further recommendations are required.[1] Cases are followed to a known medical outcome in ~47% of exposures, with the remaining 53% of exposures being unable to follow or determined not to require ongoing monitoring.[1]

Study Sample

For this analysis, four cohorts of exposure were identified by formulation (infants' or children's liquid formulations) and by active ingredient involved: acetaminophen (pediatric liquid single-ingredient acetaminophen); ibuprofen (pediatric liquid single-ingredient ibuprofen); CCMs (pediatric liquid CCMs); and diphenhydramine (pediatric liquid single-ingredient diphenhydramine). CCM exposures were identified by searching for product exposures containing at least one of the eight most common CCM ingredients (brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, phenylephrine, and pseudoephedrine). Pediatric liquid single-ingredient diphenhydramine exposures were a subset of the CCM exposures, as single-ingredient diphenhydramine is one of the most common products involved in pediatric exposures.[1] Only single-product exposures were included to focus on the relationship between product-specific factors and exposure outcomes and trends.[7] Exposures within the product cohorts were included if they involved an AUI in a child aged <6 years; involved only a single substance (no other substances); and occurred from 2010 through 2016.

Measures

Unit sales (i.e., bottles) via food, drug, and other major retailers were obtained from Information Resources, Inc., for the period 2010 through 2016 by 4-week intervals. Sales data were not available before 2010 because of limitations in vendor methodology. The sales data were used to generate cumulative and annual rates of exposure per million units sold.

Statistical Analysis

The demographic, exposure, and outcome characteristics in each of the product cohorts were examined using descriptive statistics. To evaluate the change in acetaminophen exposures after implementation of flow restrictors, exposures were grouped into the pre- (January 4, 2010–July 17, 2011), transition (July 18, 2011–July 15, 2012), and post- (July 16, 2012–December 25, 2016) periods. These periods were determined by review of the sales data, with the start of the transition period corresponding to the 4-week interval during which products with flow restrictors exceeded 5% of the market share, and the length of the period was selected to be 1 full year to account for seasonality of exposures. The end of the transition period corresponded to products with flow restrictors reaching >80% of their maximum market share. The end of the transition period also corresponded with <5% of sales of infant 80-mg/0.8-mL products without flow restrictors.

For acetaminophen exposures, cumulative rates of exposure per 1 million units sold were calculated by taking the sum of exposures divided by the sum of unit sales for the pre- and post-periods. Poisson regression was used to compare a cumulative rate ratio with a 95% CI and corresponding *p*-value. Seasonally adjusted annual rates of change for the pre- and post-periods were calculated using a temporal model and were compared with a rate ratio *p*-value and 95% CI to determine the change in trend between periods. An auto-regressive model of order one was selected to account for higher correlations of adjacent time points. For all models, residual diagnostics were performed to review the accuracy of model fit, and significance of seasonal model parameters were evaluated to determine if seasonality adjustment was appropriate. Visual review of the distribution of residuals was performed coupled with review of residual quantile plots.

Ibuprofen was selected as a comparator product as it is also an OTC analgesic used to treat pain and fever in children. Exposures to ibuprofen were also categorized into pre-, transition, and post-periods using the definitions applied to acetaminophen exposures, and analyses were performed using the same methods as for acetaminophen. Post-period annual rates of change for acetaminophen and ibuprofen were compared by calculating the rate ratio *p*-value and 95% CI.

Changes in the pre- and post-period rates of acetaminophen exposures were evaluated for all exposures (regardless of medical outcome or level of healthcare facility [HCF] treatment), as well as exposures with any documented clinical effect and with clinically significant outcomes. Any effect exposures were defined as those involving at least a minor medical outcome or involving treatment in an HCF.[1] Exposures with clinically significant outcomes were defined as those involving moderate effect, major effect, or death or were admitted to an HCF.[1] Using the estimated rate of change for acetaminophen, the predicted change in rates of exposure for ibuprofen, CCMs, and diphenhydramine were modeled for all exposures, any effect exposures, and exposures with clinically significant outcomes.

This study was determined not to be human subjects research by the Colorado Multiple IRB.

RESULTS

During the pre-period, 16,508 AUI exposures to acetaminophen were reported, with the majority occurring among children aged 2 to <4 years (Table 1). Nearly all exposures (97.8%) occurred in the child's home, and 19.2% involved the recommendation for or receipt of care at an HCF. Among the 3,166 seen at an HCF, 121 (3.8%) children were admitted. From the entire sample, only 188 children had exposures that resulted in minor or moderate effects, and no deaths were reported. During the post-period, other than an observed distributional shift in the age group of exposures (higher percentage of exposures involving children aged <2 years, $p<0.001$), there was a similar pattern of acetaminophen exposures between time periods in terms of other demographics, case characteristics, or exposure outcomes.

In the 18-month pre-period for acetaminophen products, the cumulative exposure rate was 507.2 (95% CI=481.1, 534.6) per 1 million units sold as shown in Table 2. The approximate 4.5-year post-period showed a significantly lower cumulative exposure rate of 325.6 (95% CI=305.8, 346.7) per 1 million units sold resulting in a pre- versus post-period rate ratio of 0.642 (95% CI=0.592, 0.697, $p<0.001$). Significant declines in the pre- versus post-period rate ratios were seen for exposures resulting in any effect (0.642, 95% CI=0.591, 0.696, $p<0.001$) and those with clinically significant outcomes (0.728, 95% CI=0.581, 0.913, $p=0.006$). For modeling purposes, the authors assumed that 100% of the decrease in exposures was due to the implementation of flow restrictors. With this assumption, an estimated total of 19,836 exposures were prevented in the post-period (annual average of 4,462), of which 115 would be expected to have had clinically significant outcomes. Although the cumulative exposure rate differed between the pre- and post-periods, the annual rate of change was similar during the two periods.

Compared with acetaminophen, ibuprofen also declined in cumulative exposure rates from the pre- to post-period, with cumulative rate ratios for all exposures of 0.591 (95% CI=0.555, 0.629, $p<0.001$); any effect of 0.642 (95% CI=0.594, 0.694, $p<0.001$); and clinically significant outcomes of 0.558 (95% CI=0.387, 0.805, $p=0.002$). However, when examining the post-period annual rate of change ratio for ibuprofen and acetaminophen, acetaminophen exposures decreased at a faster rate than ibuprofen with a rate of change ratio of 0.936 (95% CI=0.912, 0.960, $p<0.001$) when examining all exposures and 0.939 (95% CI=0.909, 0.970, $p<0.001$) when examining those with any effect (Figure 1). Significant differences were not detected for exposures with clinically significant outcomes.

To assess how flow restrictors could potentially reduce exposures to other common OTC pediatric liquid medications (ibuprofen, CCMs, diphenhydramine) if similarly

Table 1. Demographics, Exposure Characteristics, and Outcomes Following Accidental Unsupervised Ingestions

	Pre-period exposures, January 2010–July 2011		Post-period exposures, July 2012–December 2016			
Variable	**Acetaminophen exposures (*n*=16,508)**	**Ibuprofen exposures (*n*=26,190)**	**Acetaminophen exposures (*n*=35,580)**	**Ibuprofen exposures (*n*=45,738)**	**CCM exposures (*n*=36,066)**	**Diphenhydramine exposures (*n*=17,550)**
Age, years, *n* (%)						
<2	3,521 (21.3)	6,053 (23.1)	9,718 (27.3)	11,082 (24.2)	5,998 (16.6)	3,357 (19.1)
2 to <4	11,191 (67.8)	17,392 (66.4)	21,545 (60.6)	29,114 (63.7)	23,408 (64.9)	11,785 (67.2)
4 to <6	1,783 (10.8)	2,730 (10.4)	4,292 (12.1)	5,513 (12.1)	6,648 (18.4)	2,401 (13.7)
Precise age unknown (<6)	13 (0.1)	15 (0.1)	25 (0.1)	29 (0.1)	12 (<0.1)	7 (<0.1)
Male sex, *n* (%)	8,449 (51.2)	13,966 (53.3)	18,578 (52.2)	24,548 (53.7)	19,573 (54.3)	9,378 (53.4)
Exposure site, *n* (%)						
Own residence	16,145 (97.8)	25,680 (98.1)	34,792 (97.8)	44,935 (98.2)	35,197 (97.6)	17,131 (97.6)
Other residence	282 (1.7)	379 (1.4)	581 (1.6)	592 (1.3)	653 (1.8)	305 (1.7)
Healthcare facility	3 (<0.1)	7 (<0.1)	10 (<0.1)	7 (<0.1)	17 (<0.1)	12 (0.1)
Other/unknown	78 (0.5)	124 (0.5)	197 (0.6)	204 (0.4)	199 (0.6)	102 (0.6)
Any effect, *n* (%)	2,828 (17.1)	1,720 (6.6)	6,090 (17.1)	3,264 (7.1)	10,671 (29.6)	5,810 (33.1)
Clinically significant outcome, *n* (%)	126 (0.8)	40 (0.2)	308 (0.9)	66 (0.1)	1,353 (3.8)	607 (3.5)

CCM, cough and cold medication.

Table 2. Acetaminophen Exposure Rates per 1 Million Units Sold

Exposure group	Pre-period cumulative rate (95% CI)	Post-period cumulative rate (95% CI)	Cumulative rate ratio (95% CI)	Pre-period annual rate of change (95% CI)	Post-period annual rate of change (95% CI)	Annual rate of change ratio (95% CI)
All exposures	507.2 (481.1, 534.6)	325.6 (305.8, 346.7)	**0.642 (0.592, 0.697)***	0.840 (0.788, 0.895)	0.844 (0.830, 0.859)	1.005 (0.941, 1.073)
Any effect	86.9 (82.3, 91.7)	55.7 (52.4, 59.3)	**0.642 (0.591, 0.696)***	0.859 (0.811, 0.910)	0.856 (0.839, 0.874)	0.996 (0.937, 1.059)
Clinically significant outcome	3.9 (3.2, 4.6)	2.8 (2.5, 3.2)	**0.728 (0.581, 0.913)****	0.870 (0.576, 1.312)	0.798 (0.737, 0.864)	0.918 (0.604, 1.396)

Note: Boldface indicates statistical significance (*$p<0.001$; **$p<0.01$).

implemented, a model was created that assumed the reduction in acetaminophen exposures was entirely due to flow restrictors. With that assumption, the cumulative exposure rates were estimated for these products as well as the number of exposures that would be prevented during the post-period if these products also had flow restrictors as part of their packaging (Table 3). The estimated number of exposures that would have been prevented by the addition of flow restrictors during the post-period was 16,372 for ibuprofen and 12,910 for CCMs (including 6,282 for diphenhydramine alone). This is equivalent to average annual reduction of 6,587 exposures (3,683 exposures for ibuprofen and 2,904 for CCMs [including 1,413 for diphenhydramine alone]).

DISCUSSION

Child-resistant packaging has evolved over the past half century since passage of the PPPA. Although all pediatric exposures appear to be declining,[1] the annual frequency of AUI exposures suggests substantial work still needs to be done. Data presented in this study show that implementation of flow restrictors as part of pediatric liquid medication packaging for OTC medications could have a substantial impact on exposures for children younger than 6 years. Although acetaminophen exposures were already showing signs of annual decline,[8] the rate of decline continued following the addition of flow restrictors and declined more rapidly than a comparator drug, ibuprofen. These data further suggest that when applied to other commonly administered OTC medications, thousands of AUIs could be prevented each year. Although this model of potential impact of the implementation of flow restrictors on other products assumed the full maximum benefit, even assuming 50% of the reduction in acetaminophen exposures was due to flow restrictors would be substantial.

Although not addressed in this study, the implementation of flow restrictors may also be of value with prescription medications, particularly because pediatric AUIs of prescription medications can result in more severe outcomes. The impact of packaging measures has been demonstrated recently with a solid dose prescription opioid (buprenorphine) medication.[9,10] As the implementation of unit dose packaging with buprenorphine increased, pediatric AUIs dramatically decreased as measured by emergency department visits[9] and exposures reported to poison centers.[10] Although this demonstrates effectiveness with solid dose formulations, similar work is warranted for effectiveness of flow restrictors on liquid prescription medications to prevent AUIs.

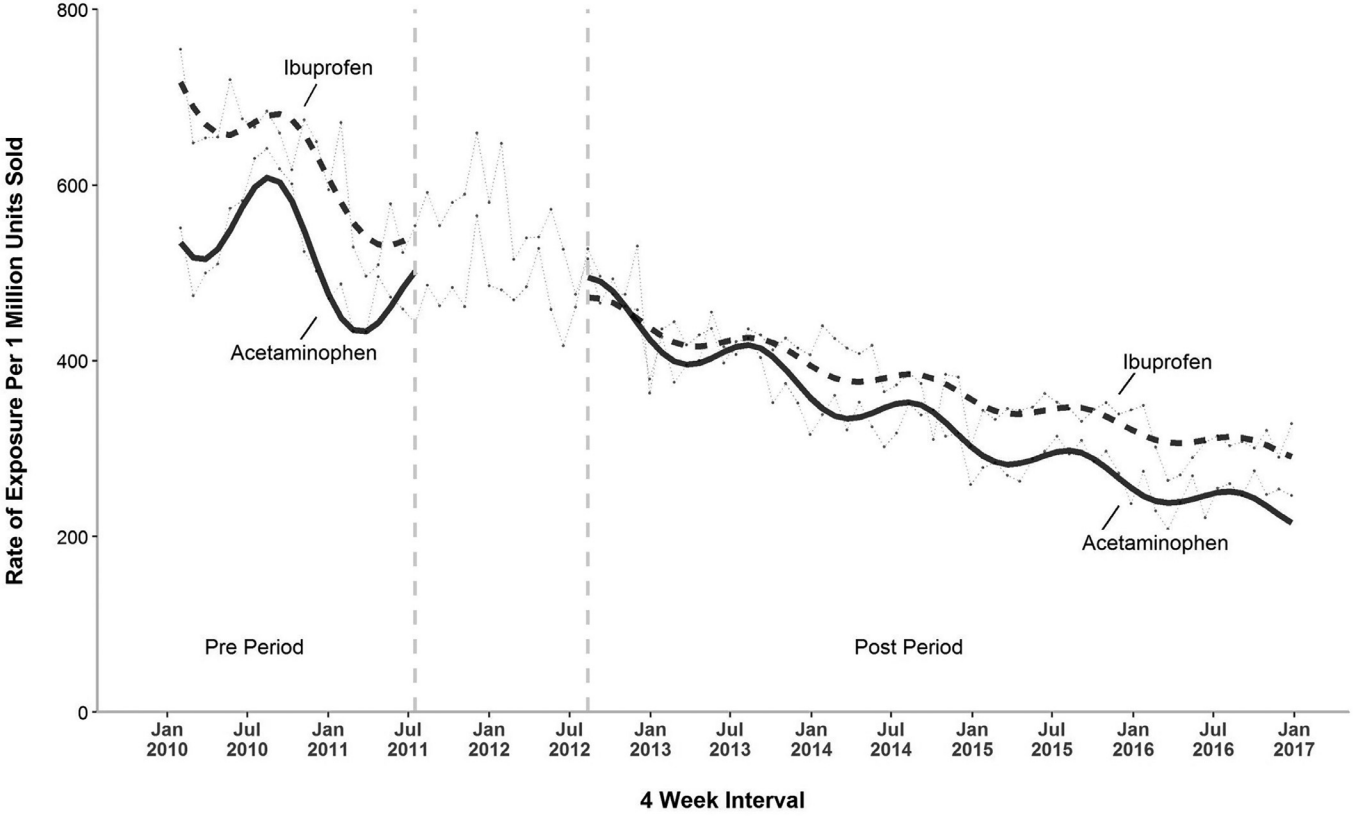

Figure 1. Observed versus predicted rates per 1 million unit sales over 4-week intervals for ibuprofen and acetaminophen.
Note: The light-gray line in the background indicates actual observed rates, overlaid with predicted rates using Poisson regression modeled for acetaminophen (solid line) and ibuprofen (dashed line) in the pre- and post-periods.

Table 3. Predicted Change in Rates of Exposure per 1 Million Units Sold for Ibuprofen, CCM, and Diphenhydramine[a]

Exposure group	Ibuprofen			CCM			Diphenhydramine		
	Post-period cumulative rate	Potential post-period estimated cumulative rate	Number of exposures potentially prevented	Post-period cumulative rate	Potential post-period estimated cumulative rate	Number of exposures potentially prevented	Post-period cumulative rate	Potential post-period estimated cumulative rate	Number of exposures potentially prevented
All exposures	368.4	236.6	16,372	124.8	80.1	12,910	373.6	239.9	6,282
Any effect	26.3	16.9	1,171	36.9	23.7	3,826	123.7	79.3	2,083
Clinically significant outcome	0.5	0.4	18	4.7	3.4	368	12.9	9.4	165

[a]For modeling purposes, it was assumed that 100% of change in acetaminophen exposures are due to flow restrictors, equivalent to a 35.8% reduction in all exposures and those with any affect as well as a 27.2% reduction in those with clinically significant outcomes.
CCM, cough and cold medication.

The data presented here extend those reported by Brass et al.,[11] who described a reduction in medication error exposures to pediatric liquid single-ingredient acetaminophen since 2011 following the change to a single pediatric concentration of acetaminophen that coincided with packaging innovation. Although medication errors and AUIs are two distinct and very different reasons for potentially dangerous pediatric exposures, the publication by Brass and colleagues[11] serves as a reminder that other changes to OTC medications have occurred in recent years that could also have contributed to the reduction in acetaminophen AUIs. Nonetheless, the volume and severity of exposures prevented suggest that even if a fraction of this reduction was due to flow restrictors, there is a substantial number of acetaminophen AUIs that have been prevented by flow restrictors, and other AUIs might be similarly prevented if flow restrictors are applied to other commonly administered OTC products.

The data here likely underestimate the number of exposures that flow restrictors can prevent considering the evaluation only accounts for exposures reported to U.S. poison centers. Events in which the child was unable to access any amount of the medication would not likely be reported to the National Poison Data System. Events in which a parent was more confident that the child was able to access only a small amount of the medication are also less likely to be reported than events where the child may have emptied the bottle, spilling some and ingesting an unknown amount. In most instances, an AUI involving single-ingredient acetaminophen results in minor, if any, clinical effects. However, the burden on the healthcare system can be significant. Additional studies are warranted to understand the cost savings associated with the demonstrated 30% reduction in the number of children evaluated and released from the emergency department as well as the cost savings associated with a decrease in approximately 4,462 exposures managed by poison centers annually. When expanded to other medications (OTC or prescription or both), these savings could increase dramatically while also decreasing severity. These savings would be particularly dramatic with medications like CCMs, including diphenhydramine, where rates of hospitalization and severe medical outcomes are two to three times higher than acetaminophen.

Limitations

These data illustrate the initial experience with new technology, but the flow restrictors used in these products varied by company and were not all created equal. According to a Consumer Reports evaluation, all products with a flow restrictor prevent a child from simply

pouring out the medicine, but the closed versions either greatly reduced or completely eliminated the amount of liquid that a young child could squeeze, shake, or suck out of a bottle.[12] The current study was unable to compare the different types of flow restrictors because of limitations of the data; however, as real-world experience is gathered it will be important to understand how to maximize the potential safety benefit of this technology. Considering the many technological advances and market changes since 1970, a review and update to the PPPA is warranted and could provide a more effective overall strategy for AUI prevention and reduction in AUI-related harm.

This study has other limitations as well. Not all exposures are reported to poison centers; thus, the rates are an underestimate of total exposures. Poison center records rely on self-report. Although measures are taken to ensure correct product identification, the information cannot always be confirmed. Furthermore, pediatric exposures reported to poison centers are decreasing. The comparison with ibuprofen suggests that acetaminophen exposures decreased more than ibuprofen exposures, and other research[8] shows that unintentional acetaminophen exposures are decreasing more quickly than unintentional exposures to other medications. However, the influence of overall poison center utilization trends is unknown. Furthermore, ibuprofen is not a perfect comparator for several reasons: (1) the associated outcomes with acetaminophen overdose are usually more severe; (2) infant concentrated formulations of acetaminophen were removed whereas infant concentrated formulations of ibuprofen remain available; (3) ibuprofen is not recommended for children younger than 6 months whereas the American Academy of Pediatrics suggests that acetaminophen can be administered to children as young as 3 months.[13] Nonetheless, ibuprofen is the only other pediatric liquid antipyretic/analgesic available OTC, and the drugs have relatively similar utilization. Though all infant formulations had flow restrictors put in place during the post-period, not all children's formulations had flow restrictors put on them simultaneously in 2011. Further, the authors are unable to account for the time when the medication was purchased, and it is likely that some older bottles of acetaminophen were involved in AUIs during the post-period. The study results illustrate a temporal relationship but cannot confirm a causal relationship.

CONCLUSIONS

The period following the addition of flow restrictors to pediatric liquid single-ingredient acetaminophen has been associated with a decrease in the rate of AUI exposures reported to U.S. poison centers compared with the period prior to implementation of this preventive measure. These findings also apply to acetaminophen exposures that resulted in clinically significant outcomes. Future application of flow restrictors to other liquid medications that are commonly administered to children, accessed by children, or associated with significant pediatric morbidity should be considered.

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The American Association of Poison Control Centers (AAPCC; www.aapcc.org) maintains the national database of information logged by the country's regional poison centers serving all 50 United States, Puerto Rico, and the District of Columbia. Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, inhalation, or topical exposure), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to poison centers, and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

The information contained herein is based in part on data from Information Resources, Inc., as solely interpreted by Denver Health and Hospital Authority and not by Information Resources, Inc.

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Author contributions were as follows: conceptualized the study (IMP, KMR, JLG), drafted the initial manuscript (IMP), managed the data management steps (HD-C), performed data management and analysis (RIB), supervised the data management and analysis (IMP, KMR, JLG), interpreted data analysis (IMP, KMR, HD-C, RIB, JLG), supervised the data analysis (HD-C), revised the manuscript (IMP, KMR, HD-C, RIB, JLG), reviewed the manuscript (KMR, HD-C, RIB, JLG), and approved the manuscript as submitted (IMP, KMR, HD-C, RIB, JLG).

SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2018.12.015.

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