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Impact of Pediatric Labeling Changes on Cough and Cold Products

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On October 18 and 19, 2007, an advisory panel of the Food and Drug Association (FDA) met to discuss the safety and efficacy of over-the-counter (OTC) cough and cold medications in young children.[1] This meeting was prompted by a small but significant number of reports of serious adverse effects, including respiratory depression, seizures, arrhythmias, as well as fatalities associated with their use.[2] While the panel failed to reach consensus on measures to limit pediatric use at that time, they identified the need for further study and discussion. Later that month, based on the preliminary findings of the advisory panel, the Consumer Healthcare Products Association (CHPA), a group representing OTC medication manufacturers, announced a voluntarily withdrawal of cough and cold products designed for use in infants.[3,4]

After completing their review of the available data, on January 17, 2008 the FDA issued a public health advisory stating that OTC cough and cold products should not be used in children less than 2 years of age.[4] This recommendation was based on both a lack of data supporting their efficacy in this age group and the reports of toxicity associated with medication errors and unintentional ingestions. In September 2008, CHPA announced the decision by its members to voluntarily modify the labeling of OTC cough and cold medicines to restrict their use to children over 4 years of age and provide more detailed dosing instructions. The following month, the FDA issued a statement in support of the CHPA decision.[5] Additional changes came in 2011 when the FDA removed a number of prescription cough and cold products from the market that lacked adequate documentation of safety and efficacy.[6] Similar restrictions on cough and cold products have been instituted in many other countries.[3]

Impact on Use by Families

Nonprescription cough and cold products are widely used by the US population, generating approximately $8 billion dollars in revenue per year. The market for these products is currently growing at a rate of 1.3% annually. While the FDA public advisory and OTC product labeling changes have been in place for several years, many parents remain unaware of the potential risks to young children with these commonly used medications. In an on-line survey of 330 parents of children less than 6 years of age conducted within 45 days of the original FDA announcement, 82.5% stated they had given one or more OTC cough and cold products to their child.[7] When asked about efficacy of treatment, 40% of parents considered these products somewhat effective, with 18.4% rating them as slightly effective, and 2.4% as not effective. Approximately a third of parents (28.9%) were unable to identify the active ingredients in the products they used from a list of options. Of the parents who were already aware of the new FDA recommendations to avoid use in children less than 2 years of age, 32% intended to continue to give their children OTC products. Another 30% rated themselves as unsure of what to do when managing their children's cold symptoms.

A more recent national survey was conducted in January 2013 by the C.S. Mott Children's Hospital which showed little change in parental OTC medication use patterns over time.[8] Of the 498 parents of children 0-3 years of age surveyed, 44% reported giving their children multi-symptom cough and cold products. Forty-two percent reported giving their children cough medicine and 25% gave their children decongestants. The authors found no relationship between medication use and parent gender, race, ethnicity, or household income.

In 2013, Lazarus and colleagues conducted a cross-sectional observational study of families of 65 children less than 6 years of age being seen in an urban pediatric emergency department.[9] Fifty-two caregivers (80%) had completed 12 or more years of education. Caregivers were shown six common OTC cough and cold products and asked about how they would use these medications in their children. Fifty-three caregivers (85%) stated they would give these products to their children for a cold. Eighteen (34%) stated they would treat their child's symptoms with more than one product. Thirteen caregivers (20%) reported having received recommendations to give one or more of the products by healthcare providers, including ten physicians (6 pediatricians, 4 other), two pharmacists, and a nurse.

The authors identified a clear need for medication education. Only 46% of caregivers were aware of the warnings on the label about use in young children. Seventy percent were unaware of the potential for adverse effects with these products, and 72% were unaware of the risk for interactions with other drugs. When asked to demonstrate how they would prepare a dose for their child, 38 caregivers (72%) made errors in either determining the correct dose or in measurement of the dose. The prevalence of dose preparation errors in this study reflects a continued need to improve the labeling on pediatric OTC products.

The FDA provided specific recommendations for manufacturers regarding the content and format of labeling and the types of measuring devices to be included for oral liquids in 2011, echoing earlier guidance provided by CHPA to its members.[10] The recommendations were categorized as top tier (having the potential to prevent three-fold or greater dosing errors) or low tier. Examples of top tier recommendations are listed below:

- including a measuring device with clear markings for all liquids
- avoiding doses on measuring devices that are more than the largest recommended dose
- using standard units, such as mL, rather than nonstandard language such as dropperfuls
- using small fractions (½) instead of 1/2
- using leading zeros in front of all decimals
- avoiding trailing zeros after decimals
- avoiding use of both teaspoon and tablespoon in the labeling of a single product.

In the February 2014 issue of *Pediatrics*, Budnitz and colleagues at the Centers for Disease Control and Prevention evaluated the labeling of common OTC medications for children to assess their adherence to FDA and CHPA guidelines.[11] Sixty-eight products were evaluated, including analgesics/antipyretics, cough and cold, and allergy products. The authors found that 91% of the dosing directions and 62% of enclosed dosing devices (droppers, oral syringes, or dosing spoons) complied with all of the top tier recommendations. Adherence with the low tier recommendations ranged from 26% to 91%. The discordance between these results and the rate of medication preparation errors in the Lazarus study highlights the difficulty in creating consumer labeling that is easily understood.

Impact on Recommendations from Providers

Within the past five years, several groups have evaluated the effect of the FDA restrictions on recommendations made by health care providers and prescriptions written for cough and cold products. In 2013, Mazer-Amirshahi and colleagues assessed the impact of the restrictions and labeling changes on use of OTC and prescription cough and cold products in young children using data from the National Hospital and Ambulatory Medical Care Surveys.[12] The authors compared data in children 12 years of age and younger before the restrictions (2005-2006) and after (2009-2010). The authors found no change in the use of OTC cough and cold products in the Emergency Department (ED), although there was a significant decrease in the use of prescription products (6.7% versus 2.9%, $p = 0.001$). In ambulatory care clinics, OTC product use increased overall (6.3% versus 11.1%, $p = 0.001$). In children less than 2 years of age, OTC product use remained unchanged but prescription product use declined.

Sen and colleagues published a similar assessment of prescription cough and cold product use in 99,176 children less than 2 years of age in Italy and the Netherlands.[13] Data from 2005 and 2008 were assessed to represent use before and after the change in labeling. Prescriptions for cough and cold products decreased from 83/1,000 children to 77/1,000 in Italy ($p = 0.05$), but increased in the Netherlands from 72/1,000 to 92/1,000. Prescriptions for both nasal sympathomimetics and opium alkaloids for cough increased in the Netherlands ($p < 0.01$), but there were significant reductions in the use of opium alkaloids and other cough suppressants as well as nasal sympathomimetic combination products in Italy. The authors noted that international safety warnings appear to have failed to reduce prescribing and may demonstrate a lack of prescriber recognition of the risk to benefit profile for these agents in young children.

Impact on Adverse Effects and Ingestions

While initial studies have failed to demonstrate a clear decline in cough and cold product use in young children, there have been several reports of a reduction in the frequency of adverse effects and unintentional ingestions caused by these products. In 2012, Forrester evaluated toxic cough and cold product ingestions reported in Texas poison centers.[14] The study included all cases documented in children up to 5 years of age between October 1998 and September 2009. Prior to September 2007, the number of ingestions had been increasing by 2.5% each year. Between October 2007 and September 2008, the number declined by 16%. From October 2008 to September 2009, the rate of decline slowed to 9.3%. The largest decline was seen in children 0 to 1 year of age (26.5%), compared to 13.5% in children 2 to 3 years of age, and 5.4% in children 4 to 5 years of age. The majority of incidents (23.4%) were related to dosing errors or adverse drug effects.

In 2013, Hampton and colleagues evaluated the effects of the labeling changes by assessing Emergency Department (ED) visits related to cough and cold products contained in the National Electronic Injury Surveillance System between 2004 and 2011.[15] For children under 2 years of age, the percentage of ED visits that were associated with cough and cold product use declined by 41%, from 4.1% of all ED visits to 2.4% (difference -1.7%, 95% CI -2.7%, -0.6%). The number of visits related to adverse effects decreased from 3.3% to 1.5% (difference -1.8%, 95% CI -2.9%, -0.6%), while the number of visits resulting from unintentional ingestions did not change.

In children 2 to 3 years, there was a 32% decline in ED visits associated with cough and cold products, with a drop from 9.5% of all ED visits to 6.5% (difference -3.0%, 95% CI -5.4% to 0.6%). As in the younger children, ED visits related to adverse effects from treatment showed a significant decline from 5.4% to 2.5% (difference -2.9%, 95% CI -5.4%, -0.5%). Visits related to unintentional ingestions declined by 88.8% (95% CI 83.8%, 93.8%), suggesting a potential benefit from the improvements made in in safety packing and recommendations for product storage. The authors also evaluated the impact of the OTC cough and cold product labeling changes on the ED visits associated with other drugs used for these conditions. They theorized that decreased use of traditional OTC products might have an unintentional effect on increasing adverse effects from drugs substituted in this setting. In their analysis, however, there was no increase in ED visits associated with antihistamine or analgesics in children under 12 years of age.

Mazer-Amirshahi and colleagues examined this relationship using ingestions reported to US poison centers between 2000 and 2010.[16] Data from the National Poison Data System was divided into two periods: pre- and post-labeling changes. Unintentional ingestions were 33.4% lower after the labeling changes and therapeutic errors were 46% lower. Referral to a healthcare facility for management of toxic cough and cold product ingestions decreased by 28.9% in children less than 2 years of age and 19.9% in children 2-5 years of age (both $p < 0.0001$). While the relationship between the decline in toxic ingestions and serious adverse effects and the OTC cough and cold product labeling changes has not been clearly established, the authors suggest that labeling changes may have led to fewer families keeping a supply of OTC cough and cold products in their households, reducing the potential risk.

In a study designed to evaluate the changing nature of toxic ingestions in children throughout the United States, Spiller and colleagues reviewed 2,577,036 toxic exposures reported to five poison centers which involved children less than 6 years of age.[17] The five centers, located in Kentucky, Louisiana, North Carolina, Ohio, and Texas, used the same electronic medical record to document their calls. There was a 33% increase in poisonings involving medications from 2000 to 2010. The only category of medications that demonstrated a decrease in the number of ingestions over the study period was cough and cold products. While there was an 11% increase in toxic ingestions of these products from 2000 to 2007, there was a 35% decline in reports from 2008 to 2010.

In a follow-up article, the authors evaluated medication errors occurring outside the hospital in children less than 6 years of age which were documented in the National Poison Database System between 2002 and 2012.[18] A total of 696, 937 incidents were included, for an annual rate of 26.42 errors per 10,000 children. Analgesics were the most common medications involved (accounting for 25.2% of reports), followed by cough and cold products (24.6%), antihistamines (15%), and antimicrobials (11.8%). As in other studies, the number of errors with cough and cold products decreased significantly over the study period while the overall rate of medication errors continued to rise.

Summary

The 2007-2008 FDA recommendations and voluntary actions taken by pharmaceutical manufacturers to prevent the use of OTC cough and cold products in children less than 4 years of age have produced only a modest effect. Parents continue to use these products in their young children, and the frequency of recommendations for these products by healthcare providers appears not to have changed substantially since the restrictions. It is promising, however, to see that the numbers of emergency department visits for adverse effects or unintentional ingestions of these agents appears to have declined significantly. Additional education for both parents and healthcare providers is needed to provide decision makers with the tools they need to make an informed decision about the use of these products in young children.

References

1. United States Food and Drug Administration. Joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee. October 18-19, 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-323m1-Final.pdf (accessed 11/11/14).

2. Anon. Infant deaths associated with cough and cold medications – two states, 2005. MMWR Morb Mortal Wkly Rep 2007;56(1):1-4.

3. Fan Y, Ji P, Leonard-Segal A, et al. An overview of the pediatric medications for the symptomatic treatment of allergic rhinitis, cough, and cold. J Pharm Sci 2013;102:4213-29.

4. United States Food and Drug Administration. FDA releases recommendations regarding use of over-the-counter cough and cold products: products should not be used in children under 2 years of age. January 17, 2008. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm (accessed 11/8/14).

5. United States Food and Drug Administration. FDA statement following CHPA's announcement on nonprescription over-the-counter cough and cold medicines in children. October 8, 2008. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm (accessed 11/8/14).

6. Food and Drug Administration. Drugs for human use: unapproved and misbranded oral drugs labeled for prescription use and offered for relief of symptoms of cold, cough, or allergy; enforcement action dates. Federal Register 2011;76(42):11794-8. Available at: http://www.gpo.gov/fdsys/pkg/FR-2011-03-03/pdf/2011-4703.pdf (accessed 11/8/14).

7. Hanoch Y, Gummerum M, Miron-Shatz T, et al. Parents' decision following the Food and Drug Administration recommendation: the case of over-the-counter cough and cold medication. Child Care Health Dev 2010;36:795-804.

8. Anon. Parents ignore warning labels, give cough and cold meds to young kids. C.S. Mott Children's Hospital National Poll on Children's Health 2013;18(2):1-2. Available at: http://mottnpch.org/reports-surveys/parents-ignore-warning-labels-give-cough-cold-meds-young-kids (accessed 11/8/14).

9. Lazarus SG, Lanski SL, Smith AS, et al. Cold preparation use in young children after FDA warnings: do concerns still exist? Clin Pediatr 2013;52:534-9.

10. Food and Drug Administration. Guidance for industry: dosage delivery devices for orally ingested OTC liquid drug products. May 2011. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM188992.pdf (accessed 11/12/14).

11. Budnitz DS, Lovegrove MC, Rose KO. Adherence to label and device recommendations for over-the-counter pediatric liquid medications. Pediatrics 2014;133:e283-e290.

12. Mazer-Amirshahi M, Rasooly I, Brooks G, et al. The impact of pediatric labeling changes on prescribing patterns of cough and cold medications. J Pediatr 2014; Epub ahead of print. doi: 10.1016/j.jpeds.2014.07.047.

13. Sen EF, Verhamme KM, Felisi M, et al. Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age. Br J Clin Pharmacol 2011;71:943-50.

14. Forrester MB. Effect of cough and cold medication withdrawal and warning on ingestions by young children reported to Texas poison centers. Pediatr Emerg Care 2012;28:510-3.

15. Hampton LM, Nguyen DB, Edwards JR, et al. Cough and cold medication adverse events after market withdrawal and labeling revision. Pediatrics 2013;132:1047-54.

16 Mazer-Amirshahi M, Reid N, van den Anker J, et al. Effect of cough and cold medication restriction and label changes on pediatric ingestions reported to United States poison centers. J Pediatr 2013;163:1372-6.

17. Spiller HA, Beuhler MC, Ryan ML, et al. Evaluation of changes in poisoning in young children: 2000 to 2010. Pediatr Emer Care 2013;29:635-40.

18. Smith MD, Spiller HA, Casavant MJ, et al. Out-of-hospital mediation errors among young children in the United States, 2002-2012. Pediatrics 2014;134:867-76.

Formulary Update

The following actions by the Pharmacy and Therapeutics Committee in October:

1. Stomatitis cocktails #3 and 5 were deleted; cocktails #1, 2, and 4 were retained.
2. Benzylpenicilloyl polylysine injection (Pre-Pen®), positive control–histamine glycerinated, and buffered saline were added for beta-lactam allergy skin testing in the inpatient setting.
3. Abacavir/dolutegravir/lamivudine (Triumeq®) was added with restriction to Category A approval by Infectious Diseases.
4. The restriction requiring approval by ID for use for hepatitis B treatment in the absence of HIV was removed.
5. Escitalopram 20 mg tablets were removed; 10 mg tablets were retained.
6. Gabapentin 600 mg tablets were removed.
7. Ethosuximide oral solution was added for management of absence seizures.
8. Citalopram oral solution was added.

Pediatric Pharmacotherapy is available on the University of Virginia School of Medicine website at http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharm-news/home.html. For comments or suggestions for future issues, please contact us at mlb3u@virginia.edu.