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Over-the-Counter Cough and Cold Preparations in Pediatric Patients

by Krystal Fike, Pharm.D.

Introduction: The use of over-the-counter (OTC) cough and cold products in children is a widespread and problematic issue surrounded by serious safety implications. These products are in a period of transition as regulatory recommendations continue to be released, prompting the availability and labeling of many of these medications to change. Healthcare professionals can assist with these transitions and mitigate negative consequences by remaining cognizant of the scope of this problem as well as of strategies to educate patients and caregivers.

Published Data: The results of a 7 year long survey published in the August 2008 issue of *Pediatrics*, indicated that approximately 7 million American children are exposed to cough and cold medications in any given week, and that 94.6% of children under the age of 2 years received liquid formulations of cough and cold products from 1999 to 2006. Moreover, a study by the Centers for Disease Control and Prevention (CDC) published in the April 2008 issue of *Pediatrics* reported more than 7,000 emergency department visits occurring each year as a result of the improper use of cough and cold medications in children less than 12 years old. More specifically, the report found that almost two-thirds of all adverse drug events in children ages 2 to 5 years were related to cough and cold products. Documented side effects of OTC cough and cold medications in children include seizures, altered consciousness, tachycardia, respiratory depression, and even death.

Public Advisory: A Food and Drug Administration (FDA) public health advisory warning about the potential dangers of administering OTC cough and cold medications to children was announced in August 2007. Subsequently, the Consumer Healthcare Products Association (CHPA), a major trade association in the OTC medication industry, advised that these products should not be used in infants. This provoked manufacturers to voluntarily withdraw from the market their OTC cough and cold medications marketed for children under the age of 2 years, an action that was staunchly supported by the FDA. However, it is important to note that no drug products were formally recalled. By January 2008, the FDA had completed a comprehensive review of available data, and declared that OTC cough and cold products are not recommended in children under the age of 2 years due to a lack of efficacy and the potential for life-threatening adverse events. Consequently, CHPA manufacturers voluntarily revised the labeling of their pediatric OTC cough and cold medications remaining on the market to state "do not use in children under 2 years of age."

Table 1: Select Products Not Recommended for Use in Children Under 4 Years

Manufacturer	Product Name	Active Ingredients (per 5 mL unless otherwise indicated)
McNeil Consumer Healthcare	Children's Tylenol Plus Multi-Symptom Cold	160 mg acetaminophen 1 mg chlorpheniramine 5 mg dextromethorphan 2.5 mg phenylephrine
	Children's Tylenol Plus Cough and Runny Nose	160 mg acetaminophen 1 mg chlorpheniramine 5 mg dextromethorphan
	Children's Tylenol Plus Flu	160 mg acetaminophen 1 mg chlorpheniramine 5 mg dextromethorphan 2.5 mg phenylephrine
	Children's Tylenol Plus Cold and Allergy	160 mg acetaminophen 12.5 mg diphenhydramine 2.5 mg phenylephrine
	Pediacare Long-Acting Cough	7.5 mg dextromethorphan
	Pediacare Decongestant	2.5 mg phenylephrine
	Children's Sudafed PE Cold and Cough	5 mg dextromethorphan 2.5 mg phenylephrine
Novartis Consumer Health, Inc.	Triaminic Chest and Nasal Congestion Liquid	50 mg guaifenesin 2.5 mg phenylephrine
	Triaminic Cold and Allergy Liquid	1 mg chlorpheniramine 2.5 mg phenylephrine
	Triaminic Cough and Sore Throat Softchews	160 mg acetaminophen per tablet 5 mg dextromethorphan per tablet
	Triaminic Flu, Cough, and Fever Liquid	160 mg acetaminophen 1 mg chlorpheniramine 7.5 mg dextromethorphan
	Triaminic Thin Strips Cold with Stuffy Nose	2.5 mg phenylephrine per strip
	Triaminic Thin Strips Daytime Cold and Cough	5 mg dextromethorphan per strip 2.5 mg phenylephrine per strip
	Triaminic-D Syrup Multi Symptom Cold	1 mg chlorpheniramine 7.5 mg dextromethorphan 15 mg pseudoephedrine
The Proctor and Gamble Company	Children's NyQuil	2 mg chlorpheniramine per 15 mL 15 mg dextromethorphan per 15 mL
	Vicks Pediatric Formula 44e	10 mg dextromethorphan per 15 mL 100 mg guaifenesin per 15 mL
	Vicks Pediatric Formula 44m	2 mg chlorpheniramine per 15 mL 15 mg dextromethorphan per 15 mL
Reckitt Benckiser Inc.	Delsym Cough Suppressant	30 mg dextromethorphan per 15 mL
	Children's Mucinex Mini-Melts	100 mg guaifenesin per packet
	Children's Mucinex Cough	100 mg guaifenesin 5 mg dextromethorphan
Wyeth Consumer Healthcare	Children's Dimetapp Cold and Allergy Elixir	1 mg brompheniramine 2.5 mg phenylephrine
	Children's Dimetapp Cough and Cold Long Acting Syrup	1 mg chlorpheniramine 7.5 mg dextromethorphan
	Robitussin Pediatric Cough Long Acting	7.5 mg dextromethorphan

Further Review: The FDA proceeded to evaluate the safety and efficacy of OTC cough and cold medications in children ages 2 through 11 years in order to provide additional recommendations. The FDA held a meeting to assess collected information as well as input from healthcare professionals. The outcome was the establishment of two key conclusions: 1) accidental ingestion and dosing errors are the most common causes of adverse events related to OTC cough and cold medications, and 2) a decisive separation exists between children under the age of 4 years and over the age of 4 years as related to these adverse events. Accordingly, leading CHPA manufacturers, including Wyeth and Novartis, began to voluntarily make another labeling alteration on their OTC pediatric cough and cold products to indicate that their use is inappropriate in children less than 4 years old. Although the labeling change was supported by the FDA, the agency will not mandate the removal of products with the former labeling from store shelves.

Active Ingredients: The active ingredients targeted by these recommendations and labeling changes are decongestants, antitussives, expectorants, and antihistamines. Many OTC cough and cold products contain more than one of these ingredients, and similar brand names may contain varying numbers and types of active ingredients. Likewise, products with different brand names may contain the same ingredients. See Table 1 for select products that are not recommended for use in children under the age of 4 years.

Patient Education: The education of consumers is a critical objective to ensure the safe use of OTC cough and cold medications in children. The labeling of some OTC cough and cold preparations may be inconsistent with regard to appropriate use in children, potentially causing consumer confusion. Therefore, healthcare professionals can play a valuable role in assisting parents and caregivers during the current transition period in which manufacturers are amending their product information. It is important to emphasize that these products are not recommended for children under 4 years despite the exact wording on outdated product labels and to provide further education on the appropriate use of these products in children over 4 years of age. For instance, parents and caregivers may need assistance with appropriate product selection and with calculating safe and effective doses for children of varying age and weight. Important advice to parents and other caregivers include following all dosing and administration directions on product packaging and utilizing only measuring devices that are purchased with a medication rather than household items such as kitchen spoons. In addition, parents and caregivers should understand that OTC cough and cold preparations are intended to relieve symptoms rather than to cure the illness or to sedate the child.

Conclusion: Due to lack of efficacy and potential serious adverse events, CHPA member manufacturers of OTC cough and cold preparations are in the process of modifying their product labels to state "do not use in children under 4 years of age." The FDA supports these actions based on an evaluation of safety data. Healthcare professionals should be aware of this change in order to better assist patients and caregivers with the safe use of properly selected products.

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Note: At the time of writing this article, Krystal Fike was a Pharm.D. Candidate from Ohio Northern University.

Did You Know. . .

Opioid Shortage

by Amy Balata, Pharm.D.

On March 30, 2009, the Food and Drug Administration (FDA) issued nine warning letters to manufacturers of unapproved opioid narcotics as part of a recently implemented policy to curtail the marketing of unapproved drugs. This safety initiative began in 2006 with focus on three major prescription drug categories: cough and cold products containing unapproved antihistamines, codeine and oxycodone as single-ingredient products, as well as sedatives such as phenobarbital and chloral hydrate.[1,2] The actions of the FDA were primarily seen in the removal of over-the-counter cough and cold products mislabeled for use in children younger than 4 years of age and products containing guaifenesin. The unapproved narcotics include immediate-release (IR) morphine sulfate, hydromorphone, and oxycodone tablets as well as oral morphine sulfate concentrated solutions are shown in Table 1.[3]

Affected manufacturers are required to discontinue the production of unapproved opioids within 60 days (by May 30, 2009) of receiving a warning letter from the FDA. Distributors, including the Cleveland Clinic's (CC) wholesaler Cardinal, are permitted to ship unapproved narcotics for a period of 90 days (though June 30, 2009) following the receipt of warning letters. Pharmacies that still have unapproved narcotics in stock are permitted to dispense these drugs for an unspecified period of time.[3]

Despite efforts to avoid shortages, many patients, caregivers, and pain management physicians are unable to obtain these medications. Several approved narcotic preparations are still available on the market and are listed on the FDA's website.[3] However, many of these approved medications are temporarily out of stock due to high demand. In response to convincing data from the palliative care community, the FDA rescinded the removal of oral morphine sulfate concentrated solution (20 mg/mL) on April 9, 2009.[4,5] Deemed a medically necessary drug, the FDA will permit the production of concentrated morphine sulfate until a manufacturer submits an abbreviated new drug application (ANDA) and it is accepted.[4]

This recent action by the FDA is not a drug recall and is separate from earlier communications from Ethex Corporation when formulations of extended-release morphine sulfate (June 2008) and immediate-release oxycodone (December 2008) tablets were removed from the market. The Ethex recalls were due to discrepancies in manufacturing that have resulted in the production of potentially double-strength tablets.[6]

The widespread narcotic shortage likely requires therapy adjustments and interchanges to meet patient pain management needs. When finding alternative medications, remember to use the appropriate formulation. Extended-release oxycodone (OxyContin®) should not be used in place of immediate-release oxycodone (Roxicodone® and others) for the management of acute, breakthrough pain.[6] There are potential potency disparities between different formulations of the same drug, such as tablet versus capsule. While it is acceptable to change to another formulation, especially during this shortage, the clinician should be aware of the possibility for non-therapeutic dose-responses. It is imperative to implement equianalgesic dosing principles when switching between narcotics to account for differing potencies. Equianalgesic charts are available through the CC Intranet from Lexi-Comp and Micromedex databases. The CC Drug Information Center Staff can be contacted to provide assistance with equianalgesic dosing (216-444-6456, option #1).

Table 1: Unapproved Opioid Products

Manufacturer	Products
Mallinckrodt Inc	Morphine sulfate oral concentrate (20 mg/mL)
Boehringer Ingelheim Roxane Inc.	Roxanol® oral solution (20 mg/mL)—morphine sulfate Roxicodone® tablets (5 mg)—oxycodone IR
Roxane Laboratories	Hydromorphone (Dilaudid®) tablets (2 mg and 4 mg)
Glenmark Generics	Morphine sulfate tablets (15 mg and 30 mg) Morphine sulfate IR concentrate (20 mg/mL) Morphine sulfate IR oral solution (20 mg/5mL)
Lannett Company	Morphine sulfate solution IR (20 mg/mL) Hydromorphone tablets (2 mg and 4 mg)
Lehigh Valley Technologies	Morphine sulfate tablets (15 mg and 30 mg) Morphine sulfate concentrate (20 mg/mL)
Physicians Total Care	Morphine sulfate tablets (30 mg) Hydromorphone tablets (2 mg) Hydromorphone tablets (2 and 4 mg)
Xanodyne Pharmaceuticals	Roxanol® oral solution (20 mg/mL) Roxicodone® tablets (5 mg)
Cody Laboratories	Morphine sulfate IR solution (20 mg/mL)

IR: Immediate-release

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Note: At the time of writing this article, Amy Balata was a Pharm.D. Candidate from the University of Toledo.

Formulary Update

The Pharmacy and Therapeutics Committee met on Tuesday, January 13, 2009, and the following decisions were made:

Additions:

1. **Zanamivir (Relenza®):** It is an *inhaled* neuraminidase inhibitor for the treatment and prevention of influenza A and B. Preliminary data from the Centers for Disease Control and Prevention (CDC) show high rates of resistance (>95%) to oseltamivir (Tamiflu®), the current formulary agent, among influenza A (H1N1) strains. The CDC has released interim recommendations for ***zanamivir or a combination of oseltamivir + rimantadine*** for the antiviral treatment and chemoprophylaxis of influenza A (H1N1) for the 2008-09 influenza season.
2. **Fomepizole (Antizol®):** It is used for the management of methanol and ethylene glycol poisonings. Additionally, it is no longer recommended to use IV ethanol for the management of these poisonings. An Adult IV Guideline is posted online and contains information about the dosing of fomepizole.
3. **Romiplostim (Nplate®):** It is an agent for thrombocytopenia and chronic immune thrombocytopenic purpura (ITP) in patients who have had insufficient response to corticosteroids, immunoglobulins, or splenectomy. Romiplostim is administered subcutaneously weekly. The prescriber and patient must be registered with the Nplate NEXUS program prior to receiving the medication. Several of the CC Hematology/Oncology Staff are registered prescribers. Its use is ***restricted*** to the Department of Hematology/Oncology.
4. **Fosaprepitant (Emend® IV):** It is used for the prevention of nausea and vomiting associated with highly- and moderately-emetogenic chemotherapy. The FDA-approved dosing is a one-time dose of 115 mg IV on Day 1 of the chemotherapy regimen, followed by 80 mg of oral aprepitant on Days 2 and 3. Its use is ***restricted*** to the Department of Hematology/Oncology in adult patients for the prevention of chemotherapy-induced nausea and vomiting (CINV) from highly- and moderately-emetogenic chemotherapy. Note: Fosaprepitant is an inhibitor of the cytochrome P450 3A4 enzyme; therefore, there are associated drug interactions (e.g., dose reductions of dexamethasone and methylprednisolone and there some are medications that are contraindicated). An Adult IV Guideline is posted online and contains additional information.
5. **Aprepitant (Emend®):** It is used for the prevention of nausea and vomiting associated with highly- and moderately-emetogenic chemotherapy. The FDA-approved dosing is 125 mg orally 1 hour prior to chemotherapy on Day 1 and 80 mg orally once daily in the morning on Days 2 and 3. Its use is ***restricted*** to the Department of Hematology/ Oncology in adult and pediatric patients for the prevention of chemotherapy-induced nausea and vomiting (CINV) from highly- and moderately-emetogenic chemotherapy. Note: Aprepitant is an inhibitor of the cytochrome P450 3A4 enzyme; therefore, there are associated drug interactions (e.g., dose reductions of dexamethasone and methylprednisolone and there some are medications that are contraindicated).

Changes in Formulary Restrictions:

Intravenous nicardipine (Cardene® IV): Formulary restriction now includes use by the Emergency Department for blood pressure control in acute ischemic or hemorrhagic stroke.

The Pharmacy and Therapeutics Committee met on Tuesday, April 28, 2009, and the following decisions were made:

Additions

1. **Tigecycline (Tygacil®):** It is a glycylcycline antimicrobial, and it is ***restricted*** to the Department of Infectious Diseases for treatment of infections due to multi-drug resistant Gram-negative organisms (i.e., crAB, KPC). Of note, tigecycline is not active against *Pseudomonas aeruginosa*. This formulary decision will be effective: June 1, 2009.
2. **Posaconazole (Noxafil®):** It is an oral azole antifungal active against mould and yeast, and it has enhanced activity against Zygomyces compared to other azole antifungals. Posaconazole is also active against *Aspergillus* sp., *Fusarium* sp., and *Scedosporium* sp. It is ***restricted*** to Infectious Diseases and the Bone Marrow Transplant service. This formulary decision will be effective: June 1, 2009.
3. **Japanese encephalitis vaccine (Ixiaro®)**: It is a newly approved vaccine for Japanese encephalitis. The former vaccine (JE-VAX®) was removed from the market. Ixiaro® is manufactured using cell culture technology which improves the manufacturing process and allows for mass production without compromising vaccine integrity. Ixiaro® also has fewer side effects than JE-VAX®. The vaccine will be used solely in the outpatient travel clinic. This formulary decision will be effective: June 1, 2009.
4. **Levetiracetam extended-release 500 mg tablets (Keppra® XR):** It is an extended-release formulation of levetiracetam. For partial onset seizures, the recommended initial dose in adults is 1000 mg once daily (may increase every 2 weeks by 1000 mg/day to a maximum of 3000 mg once daily). Keppra® XR will be used mainly for continuation of home therapy.

5. **Lacosamide tablets (Vimpat®):** It is FDA-approved for adjunctive therapy of partial onset seizures. It works by a different mechanism of action compared to other antiepileptic medications. For adults, the initial recommended dose is 50 mg twice daily and may be increased at weekly intervals by 100 mg/day. For adults, the maintenance dose is 200-400 mg/day. For patients with severe renal impairment (CrCl≤30 mL/minute), the maximum dose is 300 mg/day. For pediatric patients, guidelines for use will be developed. In addition, the intravenous formulation of lacosamide is ***restricted*** to pediatric patients.
6. **Rufinamide tablets (Banzel®):** It is FDA-approved for adjunctive therapy in the treatment of generalized seizures of Lennox-Gastaut syndrome. For pediatric patients with Lennox-Gastaut (adjunctive), the dosing recommendations are for children ≥4 years, the initial dose is 10 mg/kg/day in two equally divided doses and increase dose by ~10 mg/kg/day every other day to a target dose of 45 mg/kg/day or 3200 mg/day (whichever is lower) in two equally divided doses. For initiation of therapy in pediatric patients, rufinamide is ***restricted*** to Pediatric Neurology (however, it is not restricted if patient's are receiving rufinamide at home and it is continuation of therapy). Rufinamide use in adults will be reviewed at the May NeuroSciences Specialty Panel Meeting.
7. **Plerixafor (Mozobil®):** It is FDA-approved for mobilization of hematopoietic stem cells (HSC) for collection and subsequent autologous transplantation (in combination with G-CSF) in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). The adult dose for HSC mobilization is 0.24 mg/kg subcutaneously once daily ~11 hours prior to apheresis for up to 4 consecutive days. The maximum dose is 40 mg/day and there is a dose adjustment needed in patient with a CrCl ≤50 mL/minute (0.16 mg/kg; maximum dose: 27 mg/day). It is ***restricted*** to the Department of Hematology/Oncology for autologous bone marrow transplant.

Deletions:

1. **Darvocet® and Darvon®:** A recent FDA *Advisory Committee* voted in favor of removing propoxyphene products from the market due to marginal efficacy and some safety concerns. In January 2005, the United Kingdom removed propoxyphene from the market because of its limited efficacy and frequent use in suicides. Even though the FDA has not made a final decision, CC is removing propoxyphene products from the Formulary. Keep in mind that propoxyphene products are still be available from retail pharmacies until the FDA makes a final decision.
2. **Topical Papain Products (Accuzyme® and Panafil®):** The FDA has ordered companies to stop marketing unapproved drug products that contain papain in a topical dosage form. Manufacturers ceased shipping these products in late January 2009. Therefore, since these products are no longer commercially available, CC has removed them from the Formulary. Topical papain products are used for the removal of dead or contaminated tissue in acute and chronic lesions such as diabetic ulcers, pressure ulcers, varicose ulcers, and traumatic infected wounds. The CC Skin Care Team will be using Santyl® for the debridement of chronic dermal ulcers.

Changes to Formulary Restrictions:

1. **Rituximab (Rituxan®):** The formulary restriction now includes the use of rituximab by the Mellen Infusion Center and Neurology Staff for the management of multiple sclerosis (outpatient use).
2. **Bortezomib (Velcade®):** The formulary restriction now includes the use of bortezomib to treat antibody mediated rejection (AMR) in kidney transplant recipients.
3. **Injectable leucovorin:** Due to the shortage of injectable leucovorin, there are restrictions on the use (please contact Taussig Cancer Center for specific restrictions).
4. **Albumin:** There will be a 24-hour stop on all albumin orders due to the shortage.