

Inside the Medicine Cabinet: Making Children's Medicines a Grown-Up Issue

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ABSTRACT: Children need medicines that are properly designed and formulated specifically for pediatric use. However, the majority of medicines prescribed for children have insufficient clinical data to support pediatric use or to determine how children will react to such medicines. In particular, children living with HIV/AIDS have limited access to pediatric-specific antiretroviral drugs used to fight the disease. Recent improvements to U.S. and European pediatric drug testing laws may help generate more drugs tested and approved for children, but more must be done to ensure that children do not lag behind in access to lifesaving AIDS medicines, particularly in resource-poor countries. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 97:5074–5079, 2008

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INTRODUCTION

“There should be an uproar of children shouting, ‘What about me?’ But they often can’t speak, and so their plight goes unnoticed until an outraged parent decides to speak out.”

Elizabeth Glaser

As adults, we have certain expectations about the medicines we take: that they will treat our ailments, improve our health, and make us feel better, while doing no harm. In that expectation,

we rely on a system of researchers, scientists, medical experts, and regulators who have carefully tested and reviewed data on the medicine, secure that they will protect us, and look out for our general health. In the case of medicine for adults, the availability of extensive clinical data usually ensures that safe and effective medicines reach the marketplace. But the same assumption cannot be made about medicines prescribed for children.

The reason: the majority of medicines prescribed for children do not have sufficient clinical data to support pediatric use,¹ and as a result, we have insufficient hard data on how children will react to the majority of medications they take. We often have very little clinical data on optimal dosages, frequency of dosing, or efficacy and safety in children when new drugs reach the market. Through clinical experience, practice, and careful observation, pediatricians are fairly experienced

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at estimating safe doses for children. But ultimately, there is very little evidence-based information, in the form of scientific clinical trials, about the risks and benefits of pediatric drugs to allow doctors and parents to be certain that they are safe and effective for children. In some tragic cases, children may suffer from adverse effects or even die after taking medicines proven safe in adults.

For example, in January 2008, the Food and Drug Administration (FDA) issued a public health advisory warning parents and doctors against the use of over-the-counter cough and cold medicines for infants and young children under the age of 2. FDA cited "serious and potentially life-threatening side effects" from use of the drugs and is now examining whether the drugs are safe in older children.² Many of these medications had not been carefully evaluated in well-controlled clinical trials.

The absence of pediatric data may also be denying medications that would improve treatment of diseases or conditions specific to children. Studies have shown, for example, that the active ingredient in a certain erectile dysfunction drug could be useful in preventing pulmonary hypertension in infants suffering from a type of respiratory failure.³ The drug reduces the time infants need to spend on a ventilator and, as a result leads to shorter duration of their stays in intensive care. The use of an adult drug for a serious pediatric disorder is only one of many potential novel applications of approved drugs that can substantially benefit children. However, that benefit will only be recognized if efforts are made to test the drugs in children.

The plain lesson here is that the development of pediatric drugs should proceed more expeditiously, in concert with adult drug development, and formulating pediatric medicines demands more than just cutting an adult-sized pill in half. Children are not just smaller and lighter adults. The unique physiology, metabolism, and growth and development of young children demand a careful and systematic drug development process to produce the safest and most effective pediatric drugs. Children react differently to some medicines and sometimes experience different side effects. Some of those side effects can be dangerous, particularly if medicines are prescribed incorrectly. Often children are under- or overdosed, because doctors lack the evidence-based assessments they need to make an informed decision about the optimum drug dose for a child.

A MOTHER'S COMMITMENT

Unfortunately, developing pediatric medicines, particularly prescription medications, to serve children's special needs can be a great challenge. Elizabeth Glaser, wife of Hollywood actor and star of *Starsky and Hutch*, Paul Michael Glaser, experienced this challenge first-hand when trying to find AIDS medicines suitable for her own children.

In 1981, Elizabeth contracted HIV through a blood transfusion while giving birth, and unknowingly passed the virus to her daughter, Ariel, through breastmilk, and later to her son, Jake, during pregnancy. Although great progress has been made in developed countries in significantly reducing mother-to-child transmission of HIV since the 1980s, the vast majority of children in resource-poor settings acquire HIV from their mothers. Today, sadly, one in six new HIV infections is in children.⁴

After discovering that the same drugs available to treat her HIV were not available to her daughter because they had not yet been tested for children, Elizabeth became one of the first to champion the needs of children with HIV/AIDS through demanding access to lifesaving antiretroviral (ARV) medications. Her efforts resulted in a \$10 million appropriation in 1989 for basic pediatric HIV/AIDS research at the National Institutes of Health (NIH), the first time federal tax dollars were specifically targeted toward research for children with AIDS.

But research alone would not be enough to ensure that lifesaving drugs developed for adults were also manufactured for children. In 1988, Elizabeth and her two best friends, Susie Zeegan and Susan DeLaurentis, created the Pediatric AIDS Foundation. Although Elizabeth succumbed to AIDS in 1994, the Foundation she started took on her name—the Elizabeth Glaser Pediatric AIDS Foundation—and continued to carry out her vision and passion for children's health, advocating for pediatric-specific AIDS medications and working with Congress to create laws to improve children's access to safe and effective drugs across the United States.

As a result of hard work by the Foundation, the American Academy of Pediatrics, and other organizations and individuals, Congress subsequently adopted legislation creating incentives for drug companies to conduct pediatric studies for their products. Because pediatric populations are relatively small, the market offers insufficient financial

incentive for drug manufacturers to develop drugs for children, given the cost of conducting expensive and complex pediatric clinical trials. But the 1997 *Better Pharmaceuticals for Children Act* marked the first legislation targeting the problem. As an inducement to conduct such testing, the law provided drug manufacturers 6 months of market exclusivity for the tested drug. Testing is voluntary, but the incentive has significantly increased the number of products tested for safety and efficacy in children. In 2002, an expanded version of this legislation, the *Best Pharmaceuticals for Children Act* (BPCA), was enacted.

At about the same time, the FDA issued what came to be known as the "Pediatric Rule," requiring that certain new products be tested for pediatric use. In 2001, the Rule was successfully challenged in court and in 2003 Congress essentially wrote the Rule into law in the *Pediatric Research Equity Act* (PREA). Together, PREA and BPCA are a "carrot and stick," ensuring that more drugs are tested for pediatric use. Both laws were strengthened and renewed in September 2007 as part of the *Food and Drug Administration Amendments Act (FDAAA) of 2007*. FDAAA also included provisions to spur development and safety testing of medical devices for children, aiming to do for pediatric medical devices, what BPCA and PREA did for pediatric drugs.

"CARROT AND STICK" APPROACH WORKS

To date, BPCA and PREA have been very successful, resulting in more than 147 regulatory approvals or revised drug labeling for pediatric use of drugs under BPCA and 64 under PREA.^{5,6} These new or revised drug labels provide important pediatric information on dosing, formulations, and safety and efficacy. As a result, doctors are able to make more informed decisions about whether to prescribe or recommend certain medications for children, and in what dosages.

Pediatric studies resulting from BPCA and PREA regulations often produce striking results. For example, clinical trials conducted on a chemotherapy drug revealed that, although effective in treating adults with cancer, the product was ineffective in children with recurrent, malignant tumors. Given the medication's often severe side effects, pediatric studies were critical in ensuring that children were not exposed to an

extremely powerful drug without the promise of clinical benefit.

In other instances, studies have shown that children are often over- or under-dosed. Pediatric studies of lamivudine, a drug used to treat patients with AIDS, revealed that the amount of drug effective in treating older children differed from the effective dose for younger children.⁷

Pediatric studies also help us better understand how drugs interact in children's bodies, given differences in rates of food absorption, as with the case of the anti-AIDS drug, nelfinavir. Adult data showed that certain foods increased or decreased nelfinavir exposure, so additional pediatric pharmacokinetic and pharmacologic studies were necessary to determine how the drug would react in children, given their eating habits, how often they eat, whether they eat pureed foods or are formula-fed, etc.⁷ In another example, pediatric studies of a particular epilepsy drug showed that children under 5 were being under-medicated, because earlier dosing scales did not take into consideration children's faster metabolisms.

HIV/AIDS DRUGS FOR CHILDREN

Although these examples demonstrate the success of pediatric drug testing laws in generating important pediatric information for drugs, many additional medicines still need to be studied for children's use, including those used to fight HIV/AIDS.

Currently, children represent 17% of all new HIV infections, but constitute only 7% of all people worldwide on ARV medicines.⁸ With treatment, HIV-positive children can live much longer, healthier lives. But only a fraction of children in need of AIDS drugs receive them. Without treatment, approximately one-third of HIV-infected infants will die within their first year of life, and half will die before their second birthday.⁹

Very few ARV drugs are formulated specifically for use in children. In many resource-poor countries, providers and parents are left with little choice but to crush or break adult AIDS tablets in order to try to get the correct dose for pediatric patients. Such imprecise dosing can put children at serious risk. Too much of an ARV may be toxic to children, and too little may prove ineffective against the AIDS virus, potentially facilitating the emergence of drug resistant virus strains over time.

Table 1. List of Available Pediatric ARV Drugs That Are FDA Approved, Tentatively Approved, or WHO Prequalified*

Drug	FDA Approved	FDA Tentatively Approved	WHO Prequalified	Studied Under BPCA or PREA (and Year of Resulting Label Change)
Abacavir	X	X	X	BPCA, 1998
Amprenavir	X		X	
Didanosine	X	X	X	BPCA, 2002
Efavirenz	X	X	X	
Emtricitabine	X			BPCA, 2005, 2006 ^b
Enfuvirtide	X			BPCA, 2006
Fosamprenavir	X			PREA, 2007
Lamivudine	X	X	X	BPCA, 2002
Lamivudine/Stavudine ^a		X		
Lamivudine/Stavudine/Nevirapine ^a		X	X	
Nelfinavir	X		X	BPCA, 2004
Nevirapine	X	X	X	
Ritonavir	X		X	BPCA, 2005
Ritonavir/Lopinavir ^a	X		X	
Stavudine	X	X	X	BPCA, 2002
Tipranavir	X			
Zidovudine	X	X	X	

*A product that has met the rigorous regulatory standards set forth by the FDA is considered FDA approved and can be sold legally in the US. A product that is FDA tentatively approved has met all of FDA's requirements but is only available abroad and cannot be distributed in the US because of existing patents or market exclusivity. A WHO prequalified product has met WHO regulatory standards of safety and efficacy. Some drugs have multiple formulations available for pediatric use that may fall into different approval categories.

^aPediatric fixed-dose combination.

^bTwo changes were made to the label for emtricitabine.

While 32 ARV drugs, including fixed-dose combinations, are currently available to adults, only 17 are available for children, and only 10 are for children under 2 years of age.¹⁰⁻¹³ Of the available pediatric ARV drugs, nine have been studied under BPCA or PREA (Tab. 1), but more are desperately needed. Even when pediatric ARV drugs are available, they are often not formulated to treat all pediatric populations of differing ages and weights—in chewable and liquid forms, for example. As children grow in size and weight, the appropriate drug dosages also change. It is vital that precise ARV formulations be developed by drug companies to accommodate proper dosing for all pediatric age groups—from infancy to adolescence.

In August 2007, the FDA tentatively approved and the World Health Organization (WHO) prequalified the first generic pediatric fixed-dose, three- in-one combination ARV drug for children. Fixed-dose combination drugs, or FDCs, are critical because they reduce the number of

individual tablets a patient must take each day, making it easier for patients to comply with their drug regimens. The development of a pediatric fixed-dose combination marks an important milestone for children living with HIV/AIDS, but more combination tablets must become available in pediatric formulations and at drastically reduced costs.

Children also need better access to second-line AIDS treatments. Currently, most ARV drugs available for children are intended for use in first-line treatment regimens. Long-term therapy of HIV often requires treatment switches to second-, third-, or fourth-line regimens when the drugs fail to completely suppress viral replication, drug side effects occur, or the virus becomes resistant to ARV drugs over time. Second-line and subsequent regimens are therefore necessary. Unfortunately, very few second-line ARV drugs have been developed for pediatric use.

In 2008, the WHO Pediatric ARV Working Group released a draft report highlighting the

urgent need for the formulation of HIV/AIDS drugs for children, particularly FDCs.¹⁹ The pediatric formulations and dosing guidelines in the report provide an important platform to improve future pediatric HIV/AIDS drug development worldwide.

MOVING FORWARD

The recent reauthorization of BPCA and PREA holds great promise for generating more drugs that are tested and approved for children's use. The new law will enable BPCA and PREA to work more cohesively together under a more streamlined review process—improving the amount and quality of pediatric information generated, while also increasing transparency and accountability by making the results of pediatric studies more accessible to the public. Building on the success generated from BPCA and PREA, the European Medicines Agency (EMA) has also taken important steps to improve pediatric drug development, including the number of HIV/AIDS drugs tested for children. Signed into law in January 2008, Europe's Pediatric Rule expands on the US pediatric drug testing laws, offering 6-month patent exclusivity to drug companies and requiring companies that apply through the EMA process to conduct pediatric studies and submit a pediatric investigation plan prior to approval.

However, despite recent improvements in the US and Europe, children still remain an afterthought when it comes to access to lifesaving medicines for HIV/AIDS, particularly in resource-poor countries. As drug manufacturers develop more products for diseases like HIV/AIDS that reach patients both in the US and abroad, regulatory processes are becoming increasingly important in ensuring that pediatric studies are generated and important safety and efficacy information is available for children. Moving forward, the global health community must continue to advocate for increased availability of pediatric-specific drugs. The reward for the effort will be a healthier generation of children around the world.

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