



Indian Health Service National Pharmacy and Therapeutics Committee Formulary Brief: Pediatric Medication Management



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Background:

It has been over 130 years since Dr. Abraham Jacobi, the father of American pediatrics, stated that “Pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but ... it has its own independent range and horizon.” Despite the obvious truth of this statement and the tragic history of ignoring its wisdom, the medical care of children has too often relied on what we know from adult medication dosing, safety, and efficacy. In fact, each stage of human development requires its own study if we are to avoid otherwise unknowable pitfalls. Each area of pharmacokinetics (e.g., absorption, distribution, protein binding, metabolism, elimination) undergoes dramatic changes from birth to adulthood¹. Failure to study these changes before developing dosing guidelines has caused both massive underdosing, as with the drug efavirenz for hundreds of thousands of HIV infected children², and the fatal overdosing of premature children receiving morphine³ and chloramphenicol⁴. In addition to the special biological and psychological qualities of pediatric patients, it is also important to remember that their parents are as much our patients as the child. Unless they are willing and able to successfully implement a treatment plan, the soundness and thoughtfulness of that plan will be meaningless.

Discussion:

Until roughly twenty years ago, there were no requirements for drug manufacturers to provide clinicians with data-driven recommendations on the safety or efficacy of their products. As a result, the American Academy of Pediatrics (AAP) described the predicament facing pediatricians as “an uncontrolled experimental situation virtually every time they prescribe for children”⁵. Even in 2009, over half of FDA approved drugs lacked any pediatric labeling⁶. To address this problem, the United States Congress passed the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) in 2002 and 2003 respectively. Together, these laws require pediatric safety and efficacy studies for new drugs, including dosing information for each pediatric subpopulation. The BPCA also led the National Institute of Health to create the Pediatric Trials Network, which has helped enroll more than 7000 children in 38 studies and submitted data to the FDA regarding 21 off-patent drugs⁷. These laws have resulted in nearly 800 pediatric labeling changes. An [updated summary](#) of each of these recommendations is available for review.

As monumental as these laws have been, they also have major limitations. Nearly half of new drugs are given exemptions under PREA, and extended deferrals are common (e.g., FDA approval given under the condition that pediatric studies will be forthcoming). Between 2004 and 2014, 117 new drugs were given such deferrals but after 6.8 years of follow-up, only 33.8% of mandated pediatric studies had been completed⁸. Another significant limitation of the current laws is that they do not require any ongoing study of how a drug affects pediatric growth and development. Between 2007 and 2014, of the 81 drugs FDA approved for chronic use in children, the median trial duration was 44 weeks and two-thirds of the trials lasted less than a year⁹. Therefore, it is important to counsel parents of patients with chronic diseases that FDA approval of their medication does not guarantee long-term safety.

According to a comprehensive review of pediatric outpatient visits in the United States (US) between 2006 and 2015, nearly one in five resulted in an off-label prescription, including 49% of infant visits¹⁰. Some of the most common off-label medications were antihistamines, antidepressants, and corticosteroids. In 2014, 53.9% of inpatients received at least one off-label medication according to a retrospective review from over 45 US Children’s Hospitals. The most common medications identified were albuterol, ketamine, morphine, and lorazepam¹¹. Although off-label prescribing is not ideal, it is important to recognize that it often represents a perfectly safe and effective treatment plan (e.g., fluoride varnish to prevent early childhood caries).

Findings:

When developing general recommendations for pediatric medication management, it is important not to lose sight of the most obvious facts first. If the parent cannot accurately draw up the correct dose, or if the child will not reliably swallow the medication (e.g., due to taste, volume, or preparation), then nothing else we do will matter. Parent dosing errors are very common. According to one randomized, controlled trial of

over 2000 parents, 84% made a medication dosing error of more than 20% (of the prescribed dosage), and 21% of parents made a medication error that doubled the prescribed dosage. Use of the dosage measurement unit “cups” was associated with more than four times as many errors when compared to oral syringes¹². In light of this, providing effective dosing education and “press in bottle” adaptors which facilitate easy dosing with a syringe are highly recommended for any liquid medication. Dosing cups should not be given to parents.

In order to increase the odds that a child will reliably swallow the medication, it is also highly recommended that only medications with an acceptable taste, in the smallest volume, and with the simplest dosing schedule be kept on formulary. Remember that strict medication administration times may worsen adherence (e.g., during school or parent’s work). Medications that fit this profile may be more costly but the return in improved compliance and better patient care is worth considering.

Other important factors when considering a pediatric medication for formulary addition include:

- Long-term drug safety is rarely addressed in clinical trials. Chronic diseases are becoming more prevalent among children, and this is particularly worrisome for drugs that are prescribed early in development or for drugs with neuro-psychiatric effects.
- If adding an off-label medication to a pediatric formulary, that medication should have a well-documented track record of safety in the age group for which it’s being added to the formulary. Ideally, its use would be supported by relevant guidelines.
- There is no comprehensive, evidence-based understanding of the effects of childhood obesity on drug pharmacokinetics. Studies have identified important but unpredictable differences in drug clearance and volume of distribution among obese patients¹³. Given the prevalence of childhood obesity, this lack of clarity is concerning.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

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