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# Pediatric "Off-Label" Prescribing: What Every APN Should Know

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## Abstract

Surprisingly few medications routinely prescribed for children have actually been studied for pediatric use. Medications that are safe for adults may have detrimental effects on children. However, the trend of forgoing pediatric drug research continues. The lack of pediatric data leads to "off-label" prescribing by health care providers, although most advanced practice nurses follow specific prescription protocols. The history and scope of "off-label" prescribing and its effects on the general public are discussed. The need for pediatric clinical trials is addressed as well as the FDA's attempts to improve the safety of pediatric drug therapy.

## INTRODUCTION

Many advanced practice nurses (APNs) now have prescriptive authority. Nurse practitioners (NPs) gained significant advances in 1993 when the Drug Enforcement Administration (DEA) granted NPs their own DEA registration numbers.<sup>(1)</sup> There is a variance among states regarding prescriptive guidelines, <sup>(2)</sup> though most APN's follow set protocols.

This article examines the issues related to children being treated with medications that have not been approved by the FDA for pediatric use. The history of pediatric dosing, the obstacles to change and the risk to benefit assessment of unapproved use of medications are investigated. The current perspectives, professional responsibilities, effects on the health care industry, and recommendations for change are also discussed.

## HISTORY

In the United States, a dilemma currently exists whereby children are commonly treated with drugs that have not been approved for pediatric use by the FDA. In 1962, the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act were designed to ensure safety and effectiveness for human drug use. However, infants and children were excluded from the protections that these amendments were to provide. Once a drug is approved for use by the FDA further studies to determine safety and efficacy in infants and children are rarely conducted.<sup>(3)</sup>

The issue of the lack of pediatric drug data is important because effective treatment may be withheld or children may be treated with medications without a full understanding of the risks, benefits, and implications. How many parents realize that their child is treated with medications whose safety has not been established?

Unsuccessful proposals for pediatric drug research were introduced in 1979 and 1992.<sup>(4)</sup> Progress was not made because it was difficult to gain the support of the government, the drug manufacturers, the practitioners, and the general public. In a December 1994 initiative, the FDA hoped to increase the number of drugs studied and labeled for children by requiring manufacturers to include a package insert disclaimer stating that safety and efficacy in children had not yet been proven.<sup>(5)</sup> Although these statements are included in package inserts, the FDA has found that health care providers continue to treat infants and children with drugs that have not been approved for pediatric use. These FDA guidelines do not prevent the widespread use of many of the medications, nor does it give the practitioner the information needed to adequately treat the patient. The FDA relies on drug manufacturers to advise as to whether there is a pediatric indication for certain drugs and does not independently assess for pediatric use.<sup>(6)</sup> As recently as August, 1997, the FDA has acknowledged the need for stricter regulation of pediatric drug therapy.<sup>(5)</sup>

## **OBSTACLES TO CHANGE**

Several obstacles to the voluntary inclusion of pediatric populations in clinical trials exist. Once a pharmaceutical company's drug is approved by the FDA there is little incentive for pediatric drug testing when pediatric use is a small portion of the total market.<sup>(7)</sup> Therefore, a drug company may simply insert the pediatric use disclaimer with their product and be in compliance with the 1994 FDA guideline. Inserting a product disclaimer does not increase drug safety for children because it does not give any information to the patient other than the fact that risks and side effects in children are unknown. Another obstacle to pediatric drug research is that government and funding foundations frequently support original over applied research, thus decreasing the chance of monies being spent on a drug already approved. Some government officials feel it is the responsibility of pharmaceutical companies to fund pediatric drug testing. Drug manufacturers may view pediatric drug testing as a governmental responsibility since a governmental agency is regulating the approval. Still others are opposed to pediatric drug testing secondary to ethical issues. However, ethical issues related to clinical trials are now overseen by Institutional Review Boards (IRBs), thus diminishing this argument. There is concern over the legal liability and side effects involved when using drugs that have not been studied in pediatric clients.<sup>(7)</sup>

## **DANGERS OF UNAPPROVED DRUG USE**

The latest FDA guideline (1994) does little to protect the nation's children. The continued "off-label" use of medications by practitioners for pediatric clients can lead to dangerous outcomes. Examples of poor outcomes due to the absence of pediatric data include tetracycline-induced dental dysplasia and neonatal deaths due to chloramphenicol-induced "gray baby" syndrome.<sup>(6)</sup> Other instances of pediatric side effects have included colonic strictures in pediatric cystic fibrosis patients receiving high-dose pancreatic enzymes and kernicterus from sulfa drugs.<sup>(5)</sup> It is estimated that approximately 80% of drugs approved by the FDA contain a labeling disclaimer for children. Some examples are: adenosine, albuterol, Demerol, dopamine, dobutamine, fentanyl, Prozac, Versed, and Brethine.<sup>(3)</sup> The drug cisapride has been found to cause prolonged QT intervals and bradycardia in some infants. Adenosine is now being used as the drug of choice for pediatric supraventricular tachycardia without any controlled pediatric studies.<sup>(6)</sup> The FDA itself admits, "the percentage of new products entering the marketplace that contain adequate

pediatric safety and effectiveness information has not shown consistent improvement in the last decade".<sup>(5)</sup>

Current perspectives of "off-label" use of drugs and pediatric drug testing differ among those who are effected. Legislation is currently pending in Congress that may extend the patent life of drugs supported with pediatric research, thus providing a financial incentive for drug manufacturers.<sup>(4)</sup> On the other hand, the government seems to support off-label use by practitioners as evidenced by the case of *US vs Evers*, 643F2d1043 (5th Circuit 1981). In this case a physician's right to prescribe a drug for unapproved use was upheld. The court decided that a physician could prescribe a drug for a different dose if it was not contraindicated.<sup>(8)</sup> In unapproved pediatric use the drugs are not contraindicated in children because they contain the FDA disclaimer in the package insert that efficacy and safety has not been proven. The *Ever's* court case may protect practitioners when prescribing drugs which have not been effectively studied.

Gaining public support for pediatric drug research can be difficult as people oftentimes feel "used" for academic research when communication is not clear between subjects and researchers.<sup>(4)</sup> One survey showed parents did not realize the drug studies involving their children were to assess not only for efficacy, but for safety. Only one-third of the parents knew they could withdraw their child from the study at anytime. Others responded that the informed consent was unnecessary because they would do whatever the doctor recommended.<sup>(6)</sup> To have the support of the general population for pediatric drug testing the consumer must be better informed of the process. Most institutional review boards for pediatric research require assent and consent forms. Researchers also face the question of determining the age that a child is old enough to choose to dropout or continue participation in drug studies. Researchers may conclude that there are simply not enough clients to participate in pediatric research. Multi-site studies could be encouraged to ensure sufficient pediatric participation. APN's must always keep the client's safety and well being as a top priority. This is especially true in a child whose decision to either participate in drug studies or perhaps unknowingly take drugs unapproved for their age group can produce serious consequences.

## **PROFESSIONAL RESPONSIBILITY**

APNs must strive to familiarize themselves with the common "off-label" use of drugs and must decide what is safest for the patient depending on community standards and

practices. The Scope and Standards of Advanced Practice Registered Nursing states in the prescriptive authority guidelines that "Appropriate information about intended effects and potential adverse effects of the proposed prescription...is provided to the client". (10) FDA disclaimers in package inserts do not fulfill this ANA requirement. APNs can work through their local and national associations to help ensure that drugs they prescribe are safe for their client population. The National Association of Pediatric Nurse Associates and Practitioners does support participation in research protocols.(1) Physicians and APN's oftentimes do not have much of a choice with such a small percentage of drugs having pediatric information and guidelines. Therefore, the provider frequently makes decisions regarding prescribing based on past clinical experiences and general practices among the professional community. Again, it must be clear that APN's most frequently follow set protocols for prescribing medications. Off label use is rarely included in protocols. Therefore, APNs need to refer appropriately or ensure that the collaborating physician prescribes and documents such.

Implications of improper drug use can affect other members of the health care team including physicians, dentists, and pharmacists. Pharmacists are now required to counsel patients about adverse effects and precautions under the Omnibus Reconciliation Act.(11) How does a pharmacist accurately discuss pediatric implications with a family when the drug has not been researched in controlled pediatric studies? For a physician it is a duty to act in good faith towards the patient. According to Torres, (8) "If a physician undertakes to prescribe a drug for an unapproved use, that physician, after a good-faith effort to become aware of all facts, must be convinced that the benefit outweighs the possible risk and be ever vigilant to any change in the risk/benefit".

Many pharmacology associations including the American Society for Pharmacology and Experimental Therapeutics (ASPET), the American Society for Clinical Pharmacology and Therapeutics (ASCPT), the American College of Clinical Pharmacology (ACCP) and the Association for Medical School Pharmacy (AMSP) are working to institute improved pediatric testing and labeling.(7) Such groups are discussing ways to integrate all pertinent disciplines into the process. The health care industry as a whole is working to achieve approval for pediatric dosing. In 1995, a conference was cosponsored by the FDA and National Institute of Mental Health to discuss pediatric drug testing. The FDA

currently allows drug companies to use data from adult studies and extrapolate that data to children to determine safety and effectiveness.(5) The group included over one hundred researchers, family and patient advocates, and representatives of mental health professional associations.(4) The group concluded that adult data frequently cannot be extrapolated to children. The Department of Health and Human Services has also recently stated that proper pediatric dosing cannot be extrapolated from adult data.(5) Conference participants agreed that to facilitate further research, support of all stakeholders including families and patients must be obtained.

Another piece to consider in today's changing health care environment is managed care. In some cases, managed care companies may not cover payment for "off-label" use. Most third-party payers will reimburse for "accepted standards of practice" or "labeled uses" of drugs. However, payment for "unlabelled" drug uses varies among organizations.(8)

### **RECOMMENDATIONS FOR CHANGE**

The need for controlled studies for medications commonly used in children is important because infant and children's body systems may vary from adults, thus altering drug efficacy and safety. Examples of poor outcomes related to some medications support the need for pediatric studies. Support, of course, must be gained from all parties involved, including the government, the consumer, and researchers. The FDA and the Institutional Review Boards need to develop strict guidelines to ensure that pediatric drug studies are safe and ethical. Many drugs are already so commonly used in pediatrics that a large multi-site study population could be achieved without great difficulty. Parents must be given the most accurate information on medications and fully understand the consent for treatment and participation in clinical drug trials. (5)

The FDA is proposing a guideline in which certain medications would actually require pediatric drug trials instead of disclaimers. New drugs which would be expected to provide a therapeutic benefit to children or those medications that are indicated for very serious or life-threatening illnesses would be required to undergo pediatric clinical trials.(4) However, this guideline does not address drugs that are already on the market and commonly used in pediatric patients.

Drugs with a high percentage of pediatric use must be scientifically proven to be not only effective, but also safe. Incentives must be provided for the drug manufacturers to

ensure pediatric safety and efficacy. Financial support is needed to make this hope a success. As one physician stated, "Pediatric Clinical Pharmacologists will seize the emerging opportunities with a deafening voice, one which does not allow denial of resources embarrassingly withheld during the 20th century". (7) Perhaps if more groups hold fast to this conviction the nation's children can be protected.

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