Rigorous scientific investigation is the foundation for many of the remarkable advances in medical care that have occurred over the course of the last century. Patients with cardiovascular diseases, in particular, have received considerable benefit from such research, especially that which pertains to drugs and medical devices. Infants and children, however, have not benefited proportionally from this great increase in knowledge, due to several factors: the economic return on investment is often insufficient for industry to justify the commitment of substantial resources to meet the opportunity cost of a relatively small patient population; the research capacity for pediatrics has been limited; and child patients have been considered ethnically unsuitable subjects for study. As a result, drug therapy of many sorts in pediatric patients has been guided too often by theory or extrapolation from practice with adults and by expert experience and good intentions rather than by evidence obtained through clinical trials. To this day, most pediatric pharmacotherapy is based on the off-label use of drugs.1 This must change.

Off-label drug use was defined as prescribing a drug for a patient who was younger than the age specified on the drug label approved by the US Food and Drug Administration. Where weight-based drug ranges were specified, the 75th percentile for age was used in calculations. Data regarding patient demographics, drug charges, payer status, and limited outcome variables were also collected. A value of \( P<0.05 \) was considered to be statistically significant.

The authors’ results underscore the concern. A total of 31,432 patients were studied, with a median age of 10.4 months. Those with congenital heart disease constituted 67% of the study population; within this group, approximately half were managed medically alone, whereas the remainder required a surgical or catheter-based intervention. Sixty-five different cardiovascular medications were prescribed. For this group of drugs, 60% were used off-label 100% of the time, whereas 69% were used off-label >50% of the time. Two of the 5 most frequently used drugs (furosemide and epinephrine) are approved for pediatric use, and each was prescribed in accordance with the approved label; the other 3 (dopamine, lidocaine, and milrinone) were used in 26.6%, 22.7%, and 19.1% of the patients, respectively, yet they have not been approved for pediatric use. Another group of drugs (enalapril, sotalol, lisinopril, amiodipine, losartan, and fenoldopam) has been approved for pediatric use, but although given to 19.9% of the study population, were prescribed at an off-label dose 62.1% of the time. Cardiac transplant patients and surgical congenital heart disease patients received the largest number of drugs off-label, a median of 6 for the former and 3 for the latter. Multivariate analysis identified neonates, patients who received the greatest number of cardiovascular medications, and patients who died in the hospital as those most likely to receive off-label pharmacotherapy. Race/ethnicity, payer status, and hospital volume of care had no effect on prescribing patterns.

The authors are to be commended for this work. Their article captures a large pediatric experience. The broad diagnostic categories—congenital heart disease, other cardiovascular diseases (rheumatic fever, endocarditis, pulmonary hypertension, myocarditis, and cardiomyopathy), heart transplant, and rhythm and conduction disturbances—represent the full spectrum of diseases likely to be encountered by the physicians providing care to these children: pediatric cardiologists; cardiovascular surgeons and anesthesiologists; intensivists; and emergency medicine physicians. The knowledgeable practitioner can infer, from the median ages, distribution of diagnoses and procedures, length of stay, and inpatient disposition reported, that this study population, although critically ill, is clearly representative of practice challenges routinely posed to these providers in the “real
world.” Similarly, the list of drugs is comprehensive, and their frequency of use is consistent with current practice.

The article has some limitations. For example, patients with Kawasaki disease are not clearly identified, although they could be subsumed within other categories (eg, rhythm and conduction disturbances or myocarditis). Similarly, it is not clear whether pulmonary hypertension is related to other cardiac diseases, such as structural or functional heart disease; this is an important distinction when evaluating clinical outcomes in this population. The authors’ academic affiliations, if characteristic of the Pediatric Health Information System database as a whole, raise the consideration of whether therapeutic enthusiasm may skew the results through a practice pattern that emphasizes off-label therapy with new agents based on single-center experiences. This is not necessarily harmful. Of greater concern is the narrow definition of off-label use, which should consider indication for treatment and dose as well as age; to their credit, the authors themselves have identified this concern. In addition, adverse outcomes secondary to off-label drug use are not identified; both mortality and length of stay analyses suggest that these outcomes might not have a great effect in this regard.

The reader should not conclude from this article that off-label pharmacotherapy is always detrimental to pediatric patients with cardiovascular diseases. As the authors note, there are many obstacles to conducting clinical trials in pediatric patients with cardiovascular diseases, including low disease frequency and high heterogeneity, which result in small numbers of subjects and lack of statistical power, an under-resourced pediatric research enterprise, and challenges in identifying meaningful yet realistic clinical end points for study. At this time, to restrict drug therapy in these patients to evidence-based practices alone would be, in many cases, a step backward. Neither patients nor practitioners would benefit. That does not mean, however, that we should be complacent with the status quo. As Pasquali et al and others note, the risks that follow from an incomplete evidence base are both substantial and unacceptable.3,4

There is a way forward, once we recognize that we cannot apply the same paradigm to research with children that we do with adults.

1. Pediatric cardiovascular providers must commit themselves to the research enterprise as a core part of their practice. That commitment requires that they work to engage their patients. That commitment should not be an unfunded mandate.

2. Pediatric cardiovascular providers must emulate their colleagues in oncology,5 organizing themselves into research networks to develop the evidence base. Entities that could be developed further include the Pediatric Health Information System, the Neonatal Research Network,6 the Pediatric Heart Network,7 the Pediatric Pharmacology Research Units Network,8 and several “natural history” studies,9 as well as individual institutional and organization-based registries.10,11

3. Research programs must be framed to use all of the resources available, with study design following from the questions asked. Innovative linkages (eg, those specified in the US Food and Drug Administration Critical Path Initiative)12 should be developed. Those programs must be realistically supported.

4. The beneficial impact of federal legislation and regulation13–16 on developing the pediatric evidence base has been considerable and should be disseminated in a broader and more compelling fashion. Incentives to industry have brought about an explosion of knowledge.17–19 Much work, however, remains to be done.20 Benefit should be carefully considered when granting incentives (eg, extended exclusivity) to industry; in particular, the impact on overall drug costs must be scrutinized closely. It is equally important, however, that we take into account the commitment we make to this vulnerable patient population. Cost savings, too, may be realized over time.

5. It is imperative that providers incorporate the results of that research into their routine practice; thus, an effective, provider-focused program of information dissemination and education must be developed and implemented. There is a clear role for government and professional organizations to collaborate in this process.

None of this will be easy. Financial pressures, in particular, argue against pursuing this course. If we do not, however, we will in effect deny the full benefits of research to infants and children with cardiovascular disease. That is simply unacceptable.

Disclosures

None.

References


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