Partnering with Clinical Pharmacologists to Improve Medication Use in Children

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American children receive on average 3.5 prescriptions annually, with 62%-85% used off-label.[1,2] Lack of formulations suitable for children is a major reason for off-label and unlicensed use of medications.[3] Although this practice does not imply improper, illegal, contraindicated, or investigational use, it often lacks substantial evidence of effectiveness and/or safety from adequate and well-controlled studies. The passage of legislation (Best Pharmaceuticals for Children Act in 2002, the Pediatric Research Equity Act in 2003, the Food and Drug Administration Safety and Innovation Act in 2012; and the Food and Drug Administration Reauthorization Act in 2017) has helped to change >500 labels to include pediatric indications, yet 59% of drug labels still do not contain pediatric information.[2] Furthermore, clinical data for preterm and full-term neonates, infants, children <2 years of age, in addition to children with chronic or rare diseases, are lacking.[2,4]

The lack of pediatric clinical data can lead to subtherapeutic effects owing to underdosing or toxicity related to overexposure. Furthermore, children are also inherently predisposed to adverse drug events owing to developmental pharmacology, the age-dependent changes that affect response to and elimination of drugs.[1,2,4-6] It is also unethical to deny children the benefit of medications that are otherwise approved for adults just because they are a vulnerable population and the conduct of pediatric trials is difficult. Thus, it is necessary to conduct pediatric drug trials under conditions that optimize protection for children as participants in research.[2]

What Is Pediatric Clinical Pharmacology?

Pediatric clinical pharmacology aims for the safe and effective use of medications in children. Although the first pediatric clinical pharmacologists were physicians, the field has broadened to include individuals with advanced fellowship training from different backgrounds, medical subspecialties and doctoral training, including MD, DO, PharmD, and PhD. Although some duties (eg, drug dosing and medication safety) are managed by pharmacists, pediatric clinical pharmacologists enhance evidence-based bedside care by conducting basic science, translational, and clinical research; providing model-informed therapeutic drug management, pharmacogenetic assessments, and pharmacovigilance; and teaching pediatric clinical pharmacology principles to healthcare providers.[4] Most important, pediatric clinical pharmacologists are experts in how growth and development impact drug disposition and response in children. They have expertise in the design and conduct of pediatric studies in an ethical and scientifically rigorous manner to address critical knowledge deficits regarding the safe and effective use of medications in this population; these professionals complement pharmacists, who focus on medication management. Pediatric clinical pharmacology seeks to solve problems related to variability in drug disposition and response in preterm infants through adolescents. The discipline is collaborative and has global relevance to all disease areas in pediatric medicine; examples of current integration include neonatal and pediatric critical care, oncology, infectious diseases, and gastroenterology.

There is a global shortage of qualified, trained pediatric clinical pharmacologists; the number is estimated to be 1 pediatric clinical pharmacologist per 4 million children.[4] This ratio is more concerning considering the number of medicines used in children without formal research. As of 2017, there are 16 clinical pharmacology fellowship programs in the United States accredited by the American Board of Clinical Pharmacology (ABCP) (**Table**). Recognizing the need for specialized training to address the knowledge gaps in drug therapy for children, the Best Pharmaceuticals for Children Act has afforded fellowship programs dedicated to training pediatric clinical pharmacologists in the United States. There are 11 current sites with T32 pediatric clinical pharmacology fellowships funded by the National Institute of Child Health and Development and/or the National Institute of General Medical Sciences (**Table**). These fellowships include formal education and research training. Together, a combination of didactic and experiential learning is incorporated into the curriculum with the goal of training independent clinician-scientists. Upon

ABCP	American Board of Clinical Pharmacology
DRP	Drug-related problem

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Table. Clinical pharmacology training programs accredited or registered with the ABCP and training programs with T32 pediatric clinical pharmacology fellowship funded by the NICHD and/or the NIGMS

ABCP accredited or registered training programs	NICHD or NICHD-NIGMS T32 pediatric fellowship programs
Baylor College of Medicine	***NICHD funded***
Children's Mercy Hospitals and Clinics	Children's Mercy Hospitals and Clinics
Children's National Health System	Children's National Health System
Cincinnati Children's Hospital Medical Center	Cincinnati Children's Hospital Medical Center
Dartmouth-Hitchcock Medical Center	Indiana University School of Medicine
Indiana University School of Medicine	University of California, San Diego
Mayo Clinic College of Medicine	
The Ohio State University Medical Center	***NICHD-NIGMS funded***
The Johns Hopkins University	Mayo Clinic College of Medicine
Thomas Jefferson University and the Children Hospital of Philadelphia	Thomas Jefferson University and the Children Hospital of Philadelphia
University of California, San Francisco	University of California, San Francisco
University of Chicago	University of Chicago
University of North Carolina Eshelman School of Pharmacy/Duke Clinical Research Unit	University of North Carolina Eshelman School of Pharmacy/Duke Clinical Research Unit
University of Utah	Vanderbilt University Medical Center
Uniformed Services University of the Health Sciences and Walter Reed Army Institute of Research	
Vanderbilt University Medical Center	

NICHD, National Institute of Child Health and Development; *NIGMS*, National Institute of General Medical Sciences.

completion of 2 years of postdoctoral training in clinical pharmacology, graduates may take the ABCP examination to be certified in clinical pharmacology (physicians) or accredited in applied pharmacology (nonphysicians, nonlicensed physicians) and become diplomates of the ABCP.

Practical Ways the Pediatric Clinical Pharmacologist Can Help in Improving Pediatric Therapy Outcomes

The pediatric clinical pharmacologist can improve drug use by identifying knowledge gaps and needs, conducting and supporting research, and disseminating knowledge.

Knowledge Gaps

Dosing of medications in children must balance therapeutic effect while avoiding toxicity. Although standard pediatric regimens can be found in drug references, these doses are often for the average child and do not take into account patient specific factors (eg, chronic disease or concomitant drugs). This problem is further compounded by the fact that pediatric care is becoming increasingly complex as children with chronic conditions, life-threatening diseases, and congenital abnormalities are now thriving into adolescence and adulthood.[7] This leads to polypharmacy and opportunities for drug-related problems (DRPs), including drug-drug and drug-disease interactions, as well as overdosing and underdosing.[6] Pediatric clinical pharmacologists can identify current gaps in knowledge and decrease the risk for DRPs in children, particularly medically complex patients, through their understanding of how age and development affect medication dose and response. Some programs have integrated clinical pharmacologists into clinical practice by providing consultative services to evaluate DRPs, such as drug-induced diseases, adverse drug reactions, or drug-drug interactions.

Research

Extrapolation from adult studies without the understanding of pediatric clinical pharmacology and the relationship between the pathophysiology in adults and children may be suboptimal and even dangerous. Thus, it is important to understand these developmental changes when conducting research to close current knowledge gaps. Pediatric clinical pharmacologists are well-equipped to study and apply developmental pharmacokinetics-pharmacodynamics, the study of age-related maturation on the drug concentration-response of children to pharmacotherapy, and can provide invaluable data to neonatologists and pediatricians who care for this vulnerable population. A pediatric clinical pharmacologist adds value to the research team by way of understanding the limitations in pediatric clinical research and applying innovative technologies, such as pharmacometric approaches, to answer the research question as highlighted in the 21st Century Cures Act.[8] Critical areas of pediatric clinical pharmacology research include dose-exposure-response studies in pediatric psychopharmacology, analgesic and sedative optimization in critically ill children, cannabinoid use in children, and drug dose-finding and precision dosing in pediatric cancers.[9] To identify the research questions most urgent to address, clinical pharmacologists and clinicians must come together through regular meetings to share knowledge deficiencies in the area of pediatric therapeutics and the best approach to address these gaps.

Model-informed precision dosing of immunosuppressants, such as tacrolimus and sirolimus, are prime examples where clinical pharmacology has improved the use of drugs in pediatrics through research.[9-11] Model-informed precision dosing uses mathematical models extrapolated from clinical data to determine optimal drug dosing in patients. Tacrolimus is primarily used in solid organ transplant recipients to decrease the risk of organ rejection but has significant adverse effects, most notably nephrotoxicity.[9] Between-

individual variability for clearance and central volume of distribution has been reported to be as high as 110%.[12] Thus, the last decade has focused on optimizing and personalizing tacrolimus to achieve the lowest possible drug exposure to decrease adverse events and optimize quality of life, while preventing graft loss. Research has shown that using a population pharmacokinetics-based Bayesian model (a statistical pharmacology model using large volumes of clinical data) with sparse sampling improves target achievement over traditional therapeutic drug monitoring in adults, and has been applied to pediatrics clinically.[13,14] The incorporation of pharmacogenetics factors, such as *CYP3A5*3* and *CYP3A4*22* genotypes, has further reduced variability and improves prediction of drug exposure.[9] A randomized clinical trial in pediatrics showed that *CYP3A5* genotype-guided dosing based on age resulted in earlier attainment of target concentrations.[15]

There are little to no data in the dosing of sirolimus, an immunosuppressant frequently prescribed off-label in the pediatric population, for infants and newborns. In the last 5 years, clinical pharmacology research has led to the development of population pharmacokinetic models in this young population, and model-informed precision dosing has been used to achieve therapeutic response in children with vascular anomalies.[10,11]

With advances in genetic sequencing, clinical pharmacologists have also been vital in incorporating pharmacogenetics data into the dosing of drugs in pediatrics. Mercaptopurine can be safely decreased in patients with acute lymphoblastic leukemia who have a thiopurine methyltransferase heterozygote genotype (ie, lower enzyme activity compared with wild-type) without increasing the risk of relapse.[16] Voriconazole, an antifungal often used as antifungal prophylaxis in pediatric patients who have received hematopoietic stem cell transplantation, has wide interpatient and intrapatient variability, partially explained by *CYP2C19* polymorphisms. Using genotype-guided dosing algorithms have reduced time to attain target concentrations by weeks.[17]

Dissemination of Knowledge

Together with identifying knowledge gaps and conducting rigorous pediatric clinical studies, it is important to disseminate the information to improve drug use. At the bedside, healthcare providers trained in pediatric clinical pharmacology perform activities such as therapeutic drug management, model-informed drug dosage individualization, and advising the healthcare team in any pediatric field on optimal drug use. Programs generally provide these services through formal consultation of clinical pharmacologists. Moreover, pediatric clinical pharmacologists participate in institutional review boards and therapeutics committees, offering insights into research ethics or hospital formulary decision making. Last, pediatric clinical pharmacologists are resources for those seeking further learning in our discipline, teaching fundamental pediatric principles to students in various clinical fields. For example, clinical pharmacologists can educate pediatricians on the ontogeny of drug-metabolizing enzymes or transporters on drug pharmacokinetics and pharmacodynamics, and the necessity to account for the maturation of renal and hepatic function and drug-metabolizing enzymes effects on drug disposition. This information becomes especially important when dosing new drugs with little or no neonatal data, because many of these drug-metabolizing enzymes and transporters may not be fully developed.[18]

Research dissemination to the greater medical community is also critical. To achieve this goal, pediatric clinical pharmacologists are involved in organizations such as the American Society for Clinical Pharmacology and Therapeutics and the American College of Clinical Pharmacology, which are dedicated to the advancement of clinical pharmacology and therapeutics to improve medicines for patients. Other organizational members include scientists from academia, regulatory agencies, and the pharmaceutical industry. Altogether, pediatric clinical pharmacologists disseminate information through publication, influencing policy and decision making, contributing to research ethics and design, and optimizing clinical care through rational drug use.

Conclusions

Although US federal legislation requires new drugs to be assessed for safety and efficacy in children, a large number of drugs still lack pediatric data leading to actionable regulatory label changes. Inherent challenges in bringing forward quality and systematic research in pediatric therapeutics represent an opportunity for the pediatric clinical pharmacologist. As the number of patients with chronic conditions and medical complexity increase, polypharmacy and DRPs will become more of a pressing issue. With our increasing number of trained fellows, it allows for greater opportunity to collaborate across therapeutic areas to improve the evidence for drug therapy in children. We encourage other disciplines and healthcare providers to partner with pediatric clinical pharmacologists to define safe and effective use of medicines in children. ■

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