



## PEDIATRIC TRIALS NETWORK

Making drugs safer & more effective for use in the youngest patients

November 2019

# THE ANNUAL REVIEW

## A MESSAGE FROM THE LEAD PRINCIPAL INVESTIGATOR



The PTN Annual Review provides an opportunity to take a step back and appreciate the recent accomplishments of the network. Over the last year, the PTN has provided research to the U.S. Food and Drug Administration (FDA) that has resulted in label changes for lithium and acyclovir, bringing the total list of PTN-informed label changes to eleven. We have released 16 publications outlined below, met a number of key study milestones, and the work of PTN has been highlighted within the greater pediatric community.

We have made significant accomplishments this year; but our work is far from finished. We have much to do to determine the safest and most effective use of medications and devices in children. This Annual Review should serve as recognition and celebration of what we have accomplished, while providing motivation for our voyage ahead. Thank you for your continuing support and commitment to improving care for our youngest patients.

**Danny Benjamin, MD, PhD, MPH**



## LITHIUM AND ACYCLOVIR LABEL CHANGES

Under the Best Pharmaceuticals for Children Act (BPCA), the PTN worked to provide the FDA with information to inform label changes for **lithium** and **acyclovir** over the last year. Both label changes provide doctors with the necessary information to prescribe the most appropriate doses of the medications to children.



## LABEL CHANGES

**As a result of research conducted through the Best Pharmaceuticals for Children Act (BPCA) program, led by the PTN, the following label changes have been made:**

- **Acyclovir** for treatment of neonatal HSV infection/encephalitis (label changed for dosing and safety)
- **Ampicillin** for treatment of sepsis and/or meningitis (label changed for safety)
- **Lisinopril** for hypertension (label changed for treatment of pediatric renal transplant patients)
- **Lithium** for treatment of bipolar disorder (label changed for efficacy, safety, and dosing - BPCA legacy)
- **Lorazepam** for seizures (label changed for efficacy, safety, and dosing)
- **Mercy babyTAPE** device to assess weight without electricity in infants from birth to 90 days of age
- **2D and 3D Mercy TAPE** devices to assess weight without electricity in children 2 months through 16 years of age
- **Meropenem** for complicated abdominal infections (label changed for safety and dosing; efficacy extrapolated)
- **Propylthiouracil** for hyperthyroidism (label changed for safety and dosing)
- **Pralidoxime** (re-labeled for use in organophosphate poisoning)
- **Sodium nitroprusside** for hypertension (label changed for efficacy, safety, and dosing)



**Population Pharmacokinetics of Intramuscular and Intravenous Ketamine in Children.** Hornik CP, Gonzalez D, van den Anker J, Atz A, Yogev R, Poindexter B, Chong K, Delmore P, Harper B, Melloni C, Lewandowski A, Gelber C, Cohen-Wolkowicz M, Hau Lee J, on behalf of the Pediatric Trial Network Steering Committee. *Journal of Clinical Pharmacology*. April 2018. (ePublication ahead of print)

**Innovative Study Designs Optimizing Clinical Pharmacology Research in Infants and Children.** Balevic SJ, Cohen-Wolkowicz M. *Journal of Clinical Pharmacology*. October 2018.

**A Population-Based Pharmacokinetic Model Approach to Pantoprazole Dosing for Obese Children and Adolescents.** Shakhnovich V, Smith PB, Guptill JT, James LP, Collier DN, Wu H, Livingston CE, Zhao J, Kearns GL, Cohen-Wolkowicz M. *Paediatric Drugs*. October 2018.

**Prolonged Furosemide Exposure and Risk of Abnormal Newborn Hearing Screen in Premature Infants.** Wang LA, Smith PB, Laughon M, Goldberg RN, Ku L, Zimmerman KO, Balevic S, Clark RH, Benjamin DK, Greenberg RG. *Early Human Development*. October 2018.

**Prevalence and Safety of Diazoxide in the Neonatal Intensive Care Unit.** Gray KD, Dudash K, Escobar C, Freel C, Harrison T, McMillan C, Puia-Dumitrescu M, Cotten CM, Benjamin R, Clark RH, Benjamin DK Jr, Greenberg RG. *Journal of Perinatology*. November 2018.

**Population Pharmacokinetics and Exploratory Exposure-Response Relationships of Diazepam in Children Treated for Status Epilepticus.** Ku LC, Hornik CP, Beechinor RJ, Chamberlain JM, Guptill JT, Harper B, Capparelli EV, Martz K, Anand R, Cohen-Wolkowicz M, Gonzalez D. *CPT: Pharmacometrics & Systems Pharmacology*. November 2018.

**National Survey of Neonatal Intensive Care Unit Medication Safety Practices.** Greenberg RG, Smith PB, Bose C, Clark RH, Cotton CM, DeRienzo C. *American Journal of Perinatology*. December 2018.

**Furosemide Exposure and Prevention of Bronchopulmonary Dysplasia in Premature Infants.** Greenberg RG, Gayam S, Savage D, Tong A, Gorham D, Sholomon A, Clark RH, Benjamin DK, Laughon M, Smith PB. *The Journal of Pediatrics*. December 2018. (ePublication ahead of print)

**Safety, Effectiveness, and Exposure-Response of Micafungin in Infants: Application of an Established Pharmacokinetics Model to Electronic Health Records.** Rivera-Chaparro ND, Ericson J, Wu H, Smith PB, Clark RH, Benjamin DK, Cohen-Wolkowicz M, Greenberg RG. *The Pediatric Infectious Disease Journal*. February 2019.

**Systemic Timolol Exposure Following Topical Application to Infantile Hemangiomas (research letter).** Drolet BA, Boakye-Agyeman F, Harper B, Holland K, Lewandowski A, Stefanko N, Melloni C. *Journal of the American Academy of Dermatology*. February 2019. (ePublication ahead of print)

**Pharmacokinetics of Ticarcillin-Clavulanate in Premature Infants.** Watt KM, Hornik CP, Balevic SJ, Mundakel G, Cotten CM, Harper B, Benjamin DK, Anand R, Laughon M, Smith PB, Cohen-Wolkowicz M; Best Pharmaceuticals for Children Act - Pediatric Trials Network Steering Committee. *British Journal of Clinical Pharmacology*. February 2019. (ePublication ahead of print)

**Rifampin Pharmacokinetics and Safety in Preterm and Term Infants.** Smith PB, Cotten CM, Hudak M, Sullivan J, Poindexter BB, Cohen-Wolkowicz M, Boakye-Agyeman F, Lewandowski A, Anand R, Benjamin DK, Jr, Laughon MM, on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee. *Antimicrobial Agents and Chemotherapy*. March 2019. (ePublication ahead of print)

**Impact of Gastrostomy Tube Placement on Short-Term Weight Gain in Hospitalized Premature Infants.** Puia-Dumitrescu M, Benjamin DK Sr, Smith PB, Greenberg RG, Abuzaid N, Andrews W, Chellani K, Gupta A, Price D, Williams C, Malcolm WF, Clark RH, Zimmerman KO. *Journal of Parenteral and Enteral Nutrition*. March 2019. (ePublication ahead of print)

**Dosing and Safety of Off-label Use of Caffeine Citrate in Premature Infants.** Dumitrescu MP, Smith PB, Zhao J, Soriano A, Payne EH, Harper B, Bendel-Stenzel E, Moya F, Chhabra R, Ku L, Laughon M, Wade KC. *The Journal of Pediatrics*. May 2019. (ePublication ahead of print)

**Physiologically-Based Pharmacokinetic Modeling of Fluconazole Using Plasma and Cerebrospinal Fluid Samples From Preterm and Term Infants.** Gerhart JG, Watt KM, Edginton A, Wade KC, Salerno SN, Benjamin DK, Smith PB, Hornik CP, Cohen-Wolkowicz M, Duara S, Ross A, Shattuck K, Stewart DL, Neu N, Gonzalez D, on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee. *CPT: Pharmacometrics & Systems Pharmacology*. May 2019. (ePublication ahead of print)



## PTN STUDY MILESTONES

### The Long-term Antipsychotic Pediatric Safety (LAPS) Trial enrolls more than 100 patients

The enrollment of more than 100 children helps achieve nearly 30 percent of the overall enrollment goal of the LAPS Trial and is a key accomplishment for the two-year observational study. [More](#)

### First participant enrolled in digoxin study

The digoxin study achieved a major study milestone by enrolling its first infant in August 2019. The study team will enroll up to 48 infants to determine the pharmacokinetics and safety of digoxin prescribed to infants with single ventricle congenital heart disease (CHD). [More](#)

### Finalized first cohort of sildenafil study

The study will assess the safety of sildenafil in premature infants at risk of bronchopulmonary dysplasia (BPD) and determine preliminary effectiveness and pharmacokinetics. The study will enroll a total of up to 120 children and has rounded out the first cohort that includes 40 children. [More](#)

### Database locked for SCAMP study

The study, which enrolled the first child in 2014, is designed to assess the safety, efficacy, and pharmacokinetics of three commonly prescribed antibiotic regimens for infants with intra-abdominal infections. The study database was locked in October 2018. [More](#)



## PTN RESEARCH INFORMS RED BOOK UPDATE

PTN research on fluconazole dosing helped to inform a recent update to the AAP Red Book. The changes were based on a study conducted from 2008 to 2011 in collaboration with PTN that analyzed safety data on the use of fluconazole to treat infections caused by the Candida yeast. Red Book, the leading resource on pediatric infectious disease, provides the most up-to-date information on a wide variety of diseases that doctors see in children. [More](#)

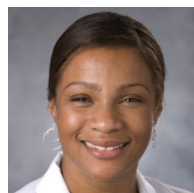


## THE AMERICAN ACADEMY OF PEDIATRICS (AAP) FEATURES PTN

The AAP featured the PTN's work in an article written by Dr. Perdita Taylor-Zapata of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and Dr. P. Brian Smith of the PTN and the Duke Department of Pediatrics. [More](#)



## DUKE STAR PROGRAM



Kanecia Zimmerman, MD, MPH

The Summer Training in Academic Research (STAR) Program trained 25 participants during the 2019 summer academic break. The program is designed to provide a high-quality research experience for undergraduate students, high school students, and middle and high school teachers.

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***"The purpose of the program is to make sure we're giving these students the opportunity to learn each day about various aspects of clinical research."***

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"The purpose of the program is to make sure we're giving these students the opportunity to learn each day about various aspects of clinical research," said Dr. Kanecia Zimmerman, leader of the program and associate professor of pediatrics at Duke University Medical Center. "The students may have never thought seriously about a career in medical research, and they come away thinking, 'This is actually something I can do.'"

[Learn more about the 2019 STAR Program.](#)



## PTN SYMPOSIUM AT PAS MEETING

In April, PTN hosted a symposium at the annual Pediatric Academic Societies (PAS) meeting in Baltimore, Md. The symposium began with a brief overview of the PTN and the Best Pharmaceuticals for Children Act (BPCA). Dr. Matthew Laughon of the University of North Carolina at Chapel Hill and Dr. Kelly Wade of the Children's Hospital of Philadelphia presented on [real-world applications of PTN's work and the impact of clinical research in practice](#), a panel of International Children's Advisory Network (iCAN) participants discussed [how researchers can better engage with participants and caregivers](#), and Dr. Janice Sullivan of the University of Louisville spotlighted [partnering opportunities and work being done within and across research networks](#).