



THE ANNUAL REVIEW

A MESSAGE FROM PTN LEADERSHIP



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The COVID-19 pandemic has continued to challenge us in unparalleled ways and we are grateful for the commitment the Pediatric Trials Network (PTN) has exemplified in learning more about COVID as related to our youngest of patients.

PTN’s Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care (POP02) Study continues to make strides in supporting the treatment of younger COVID-19 patients and is currently evaluating several therapeutics to potentially treat COVID-19 pediatric patients younger than 21 years of age.

In fact, POP02 has been engaged in a multi-institution, multi-study collaboration with National Institutes of Health (NIH) called The Collaboration to Assess Risk and Identify LoNG-term outcomes for Children with COVID (CARING for Children with COVID). This collaboration has worked to make de-identified data (or data that cannot be linked to a person’s identity) from children with COVID publicly available, in order to accelerate research on this important topic. The POP02 team was the first study to reach the important milestone of submitting these data and having them become available, and it is a testament to their tremendous effort and dedication. Click [here](#) for more on this.

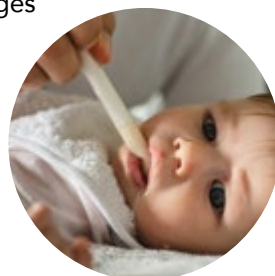
Additionally, this year PTN has released more than 20 publications and informed new label changes for clindamycin and diazepam.

The Annual Review is recognition of all our hard-earned accomplishments over the past year. We look forward to all that is to come and am grateful for your commitment to determining the safest and most effective use of medications and devices in children.



CLINDAMYCIN AND DIAZEPAM LABEL CHANGES

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



CHANGING LABELS

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)

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CHANGING LABELS (continued from page 1)

- **Caffeine** for non-antimicrobial medication given to intensive care unit newborns (label changed for efficacy, safety, and dosing)
- **Clindamycin** for treatment of infections in children (updated to include dosing guidelines for children with obesity)
- **Clindamycin** for treatment of infections in infants (updated to include dosing guidelines for premature and term infants)
- **Diazepam** for treatment of epilepsy (updated to include pharmacokinetic data for infants and children)
- **Doxycycline** for treatment of diseases such as Rocky Mountain Spotted Fever and methicillin resistant staph aureus in children under 8 years of age (label changes for safety and efficacy)
- **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)



HIGHLIGHTING PTN STUDIES AND ACCOMPLISHMENTS

Digoxin Study Reaches Enrollment Goal

In the summer of 2021, The Pharmacokinetics and Safety Profile of Digoxin in Infants with Single Ventricle Congenital Heart Disease study reached the targeted enrollment goal for its study population of infants with Congenital Heart Disease (CHD). Thanks to the hard work and diligence of the enrolling sites and the whole PTN team, the target enrollment goal was reached efficiently.

The Digoxin Study is collecting safety and efficacy data on infants with single ventricle CHD to determine the appropriate dosing and safety measures of the study drug, digoxin. Digoxin is approved by the U.S. Food and Drug Administration (FDA) to treat heart failure in patients with congenital heart disease. However, there has not been enough safety and efficacy data to determine proper dosing of this drug in pediatric patients with single ventricle CHD.

Fifty study participants have been recruited for this study, where the drug digoxin was given as part of standard of care to treat heart failure. Study participants are infants <6 months of age who have single ventricle CHD and who have received an initial surgery to correct it, and whose healthcare team is planning on providing digoxin treatment. Each year about 40,000 infants born in the U.S. are diagnosed with CHD, with single ventricle CHD being the most serious and complex form of the disease. [MORE](#)

Funding Received to Study Device Used to Treat Overactive Bladder

PTN received funding from the Best Pharmaceuticals for Children Act (BPCA) to study a device to treat Overactive Bladder (OAB) in pediatric patients. The project is planned as a collaboration with industry partner Laborie Medical Technologies Corp, who will provide devices for the study.

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HIGHLIGHTING PTN STUDIES AND ACCOMPLISHMENTS (continued from page 2)

Overactive bladder affects up to 47% of children and can be influenced by conditions such as recurrent urinary tract infection (UTI), psychiatric & developmental disorders, and obesity. This condition can negatively impact the quality of life of children and exacerbate or lead to other chronic health conditions. The most common medication therapies are oxybutynin (Ditropan) and solifenacin (Vesicare), and are approved by the Food and Drug Administration (FDA) in children and adults. However, there is concern that there can be long-term side effects of oxybutynin, which includes memory problems and possible development of dementia in late adulthood.

The device is a posterior tibial nerve stimulation (PTNS), called the Urgent PC System, and will be used to treat OAB. This device is approved to treat OAB in adults, however there is not enough safety and efficacy data yet to approve it as a treatment for children with the condition. To prescribe PTNS devices, such as the Urgent PC system, into future OAB therapies for children, the PTN will test the safety and efficacy of the device in children ages 5 to 21 years old. Safety events or side effects such as electrode site reaction, electrode site infection, and residual will be tested and data will be validated via the Vancouver Dysfunctional Elimination Syndrome (VDES) questionnaire.

Testing the Urgent PC system as a PTNS device therapy in children with OAB will further demonstrate the PTN's ability to study medical devices. Data from the study will be submitted to the FDA for consideration of adding pediatric data to the device label.

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LAPS Trial Meets Study and Sub-Study Milestones

The PTN Long-term Antipsychotic Pediatric Safety (LAPS) Trial, which aims to assess the long-term health of risperidone and aripiprazole in children, has enrolled more than 500 children in the main study. Risperidone and aripiprazole have been shown to be effective for the treatment of conditions such as schizophrenia and bipolar disorder in adults and

children. However, it is common for these drugs to be prescribed without FDA approval for conditions such as attention-deficit disorder, obsessive-compulsive disorder, and major depression. Regardless of indication, little is known about the long-term health risks and quality-of-life benefits for their use in children.

In addition to the main study, the team has established a sub-study registry that will continue to collect height and weights, from home, via the Pattern Health mobile app. This will allow for continued longitudinal assessment of pathologic weight change associated with these antipsychotics. In addition to the use of the app, parents of participants will also complete quality of life questionnaires, every six months, for their children participating in the sub-study. The team has enrolled more than 250 children in the sub-study portion of LAPS.

[MORE](#)

ANA Study Updates Protocol to Include New Medications

The PTN's Anesthesia and Analgesics in Children (ANA) study has updated its study protocol to include new medications to be studied in pediatric populations. These new medications being studied, known as drugs of interest (DOI), include morphine, oxycodone, and ketamine. Although often prescribed by providers for anesthetic and analgesic (or pain relief) reasons, the safety, efficacy, and dosing information of these medications have not been established in pediatric populations.

The PTN is thrilled to add these medications to the ANA study, which has enrolled participants aged 2 to 17 who currently receive anesthetic or analgesic drugs as part of their routine care. Once this study is completed and data are analyzed, the PTN will submit results to the Food and Drug Administration (FDA) to change the label of the medications studied and establish information and dosing guidelines for children. [MORE](#)





SHARING SCIENCE (2020-2021)

External Evaluation of Two Pediatric Population Pharmacokinetics Models of Oral Trimethoprim and Sulfamethoxazole. Wu YSS, Cohen-Wolkowicz M, Hornik CP, Gerhart JG, Autmizguine J, Cobbaert M, Gonzalez D. *Antimicrobial Agents and Chemotherapy*. June 2021.

Antibiotic Safety and Effectiveness in Premature Infants with Complicated Intra-Abdominal Infections. Smith MJ, Boutzoukas A, Autmizguine J, Hudak M, Zinkhan E, Bloom BT, Heresi G, Lavery A, Courtney S, Sokol GR, Cotton CM, Bliss J, Mendley S, Bendel C, Dammann C, Weitkamp JH, Saxonhouse MA, Mundakel GT, Debski J, Lewandowski A, Erinjeri J, Gao J, Benjamin DK, Hornik C, Smith PB, Cohen-Wolkowicz M, on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network. *Pediatric Infectious Disease*. June 2021.

Pediatric Trials Network: Stakeholder views on thanking families and providing study findings on pragmatic pediatric clinical research. Corneli A, Perry B, Benjamin DK Jr, Zimmerman KO. *Contemporary Clinical Trials Communications*. June 2021.

Prolonged Post-Discontinuation Antibiotic Exposure in Very Low Birthweight Neonates at Risk for Early-Onset Sepsis. Le J, Greenberg RG, Benjamin DK Jr, Yoo Y, Zimmerman KO, Cohen-Wolkowicz M, Wade KC; on behalf of the Administrative Core Committee of the Best Pharmaceuticals for Children Act – Pediatric Trials Network. *Pediatric Infectious Diseases Society*. May 2021.

Racial and Ethnic Diversity in Studies Funded Under the Best Pharmaceuticals for Children Act. Abdel-Rahman SM, Paul IM, Hornik C, Sullivan JE, Wade K, Delmore P, Sharma G, Benjamin DK, Zimmerman KO. *Pediatrics*. May 2021.

Estimation of Body Fat Percentage for Clinical Pharmacokinetic Studies in Children. Green TP, Binns HJ, Wu H, Ariza AJ, Perrin EM, Quadri M, Hornik CP, Cohen-Wolkowicz M. *Clinical Translational Science*. March 2021.

Pharmacokinetics of Hydrochlorothiazide in Children: A Potential Surrogate for Renal Secretion Maturation. Commander SJ, Wu H, Boakye-Agyeman F, Melloni C, Hornik CD, Zimmerman K, Al-Uzri A, Mendley SR, Harper B, Cohen-Wolkowicz M, Hornik CP. *Journal of Clinical Pharmacology*. March 2021.

Population Pharmacokinetics of Olanzapine in Children. Maharaj AR, Wu H, Zimmerman KO, Autmizguine J, Kalra R, Al-Uzri A, Sherwin CMT, Goldstein SL, Watt K, Cohen-Wolkowicz M, Hornik CP; on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee. *British Journal of Clinical Pharmacology*. February 2021.

Physiologically-Based Pharmacokinetic Modeling Characterizes the CYP3A-Mediated Drug-Drug Interaction Between Fluconazole and Sildenafil in Infants. Salerno SN, Edginton A, Gerhart JG, Laughon MM, Ambalavanan N, Sokol GM, Hornik CD, Stewart D, Mills M, Martz K, Gonzalez D; on behalf of the Best Pharmaceuticals for Children Act - Pediatric Trials Network Steering Committee. *Clinical Pharmacology Theory*. January 2021.

Early-Onset Sepsis in Term Infants Admitted to Neonatal Intensive Care Units (2011-2016). Bech Polcwiartek L, Smith PB, Benjamin DK, Zimmerman KO, Love A, Tiu L, Murray S, Kang P, Ebbesen F, Hagstrøm S, Clark RH, Greenberg RG. *Journal of Pediatrics*. January 2021.

Population Pharmacokinetics of Metoclopramide in Infants, Children, and Adolescents. Ge S, Mendley SR, Gerhart JG, Melloni C, Hornik CP, Sullivan JE, Atz A, Delmore P, Tremoulet A, Poindexter BB, Harper B, Payne E, Lin S, Erinjeri J, Cohen-Wolkowicz M, Gonzalez D. *British Journal of Clinical Pharmacology*. December 2020.

Simulated Assessment of Pharmacokinetically Guided Dosing for Investigational Treatments of Pediatric Patients With Coronavirus Disease 2019. Maharaj A, Wu H, Hornik CP, Balevic SJ, Hornik CD, Smith PB, Gonzalez D, Zimmerman KO, Benjamin DK Jr., Cohen-Wolkowicz M. *JAMA Pediatrics*. October 2020.

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Exchange Transfusion Safety and Outcomes in Neonatal Hyperbilirubinemia. Wolf MF, Childers J, Gray KD, Chivily C, Glenn M, Jones L, Kpa M, McMannen T, Reyes I, Zimmerman KO, Clark RH, Greenberg RG. *Journal of Perinatology*. October 2020.

Safety of Metronidazole in Late Preterm and Term Infants With Complicated Intraabdominal Infections. Commander SJ, Gao J, Zinkhan EK, Heresi G, Courtney SE, Lavery AP, Delmore P, Sokol GM, Moya F, Benjamin DK Jr, Bumpass TG, Debski J, Erinjeri J, Sharma G, Tracy ET, Cohen-Wolkowicz M, Hornik CP; on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee. *Pediatric Infectious Disease Journal*. September 2020.

Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia in Children: A Prospective Natural History Study. Ericson JE, McGuire J, Michaels MG, Schwarz A, Frenck R, Deville JG, Agarwal S, Bressler AM, Gao J, Spears T, Benjamin DK, Smith PB, Bradley, JS. *Clinical Infectious Disease*. August 2020.

Probiotic Use and Safety in the Neonatal Intensive Care Unit: A Matched Cohort Study. Gray KD, Messina JA, Cortina C, Owens T, Fowler M, Foster M, Gbadegesin S, Clark RH, Benjamin DK, Zimmerman KO, Greenberg RG. *Journal of Perinatology*. July 2020.

Authors' Response to Thrombocytopenia Following Exchange Transfusion in Neonates. Wolf MF, Childers J, Gray KD, Chivily C, Glenn M, Jones L, Kpa M, McMannen T, Reyes I, Zimmerman KO, Clark RH, Greenberg RG. *Journal of Perinatology*. July 2020.

Medications and In-hospital Outcomes in Infants Born at 22-24 Weeks Gestation. Puia-Dumitrescu M, Younge N, Benjamin DK, Lawson K, Hume C, Hill K, Mengistu J, Wilson A, Zimmerman ZO, Ahmad K, Greenberg RG; on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network. *JAMA Pediatrics*. May 2020.

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. *JAMA Pediatrics*. March 2020.

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 Pediatrics*. February 2020.

Validation and Human Factor Analysis of an Infant Weight Estimation Device. Abdel-Rahman SM, Paul IM, Delmore P, Chen JY, Mills M, Greenberg RG, on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network. *BMC Pediatrics*. January 2020.

Population Pharmacokinetics of Sildenafil in Premature Infants. Gonzalez D, Laughon MM, Smith PB, Ge S, Ambalavanan N, Atz A, Sokol GM, Hornik CD, Stewart D, Mundakel G, Poindexter BB, Gaedigk R, Mills M, Cohen-Wolkowicz M, Martz K, Hornik CP. *British Journal of Clinical Pharmacology*. December 2019.

Population Pharmacokinetics of Milrinone in Infants, Children, and Adolescents. Hornik CP, Yogev R, Mourani PM, Watt KM, Sullivan JE, Atz AM, Speicher D, Al-Uzri A, Adu-Darko M, Payne E, Gelber C, Lin S, Harper B, Melloni C, Cohen-Wolkowicz M, Gonzalez D. *Journal of Clinical Pharmacology*. December 2019.

Risk of Development of Treated Retinopathy of Prematurity in Very Low Birth Weight Infants. Gonski S, Hupp S, Cotton CM, Clark R, Laughon M, Watt K, Hornik CP, Smith PB, Greenberg RG. *Journal of Perinatology*. November 2019.

