PEDIATRIC TRIALS NETWORK

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

2019–2020

THE ANNUAL REVIEW

A MESSAGE FROM PTN LEADERSHIP

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This year has been unprecedented for our society and for clinical research at large. The COVID-19 pandemic has challenged us all in ways we could have never anticipated. However, the PTN has responded with tremendous strength and has remained focused on improving care for our youngest patients.

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 caffeine, doxycycline, and clindamycin, bringing the total list of PTN-informed label changes to 14. We have released 17 publications outlined below, met a number of key study milestones, and remained at the forefront of researching COVID-19 in children.

PTN's Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care (POP02) Study continues to evolve in an effort to support 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.

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.

CAFFEINE, DOXYCYCLINE, AND CLINDAMYCIN LABEL CHANGES

Under the Best Pharmaceuticals for Children Act (BPCA), the PTN worked to provide the FDA with information to inform label changes for caffeine, doxycycline, and clindamycin 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)
- **Caffeine** for non-antimicrobial medication given to intensive care unit newborns (label changed for efficacy, safety, and dosing)
- **Clindamycin** for treatment of infections (updated to include dosing guidelines for children with obesity)
- **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** (relabeled for use in organophosphate poisoning)
- **Sodium nitroprusside** for hypertension (label changed for efficacy, safety, and dosing)

HELPING UNDERSTAND COVID-19 IN YOUNGER PATIENTS

Chi Hornik, MD

The PTN, NICHD Funded, Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care (POP02) Study continues to evolve in an effort to support the treatment of younger COVID-19 patients. POP02 is now evaluating several therapeutics to potentially treat COVID-19 patients age 0 – <21 years old.

"With the increase in the number of COVID-19 cases, we are in dire need of more timely data on the use of therapeutics for children affected by COVID-19. The POP02 Study is evaluating several therapeutics," said Dr. Chi Hornik, POP02 Study Principal Investigator.

The drugs of interest currently being studied are: Anakinra, Aspirin, Azithromycin, Colchicine, Canakinumab, Interferon alpha & beta, Lopinavir/Ritonavir, Remdesivir, Ribavirin, Ruxolitinib, Sarilumab, and Tocilizumab.

More

"With the increase in the number of COVID-19 cases, we are in dire need of more timely data on the use of therapeutics for children affected by COVID-19. "

In addition to PTN's POP02 work, PTN received additional funding, in September 2020, to **study multi-system inflammatory syndrome (MIS-C) in children** and is **actively supporting The ABC Science Collaborative**, which works to pair scientists and physicians with public school and community leaders to help understand the most current information about COVID-19.

SUPPORTING NIH INCLUDE INITIATIVE

The Pediatric Trials Network (PTN) has enrolled the first child participant with Down syndrome into the Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care (POP02) study.

This marks an exciting and significant milestone for the network. As part of the INCLUDE initiative, a directive from the National Institute of Health (NIH), PTN is committed to supporting clinical trials on conditions and diseases that affect people with Down syndrome, both to accelerate the development of new therapies for individuals with Down syndrome and to include them in ongoing clinical trials.

More

MEETING MILESTONES

CUDDLE Completes Study Enrollment

In March of 2020, PTN's study (NICHD-2017-BMS01) of Pharmacokinetics and Safety of Commonly Used Drugs in Lactating Women and Breastfed Infants (CUDDLE,) completed study enrollment for nine off-patent drugs; marking a substantial milestone in determining the safety of drugs passed through breastmilk. **Learn more**

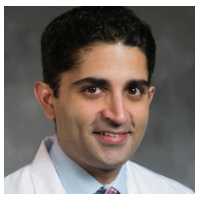
Database Locked for Levetiracetum

Susan Arnold, MD

In April of 2020, the database was locked for Levetiracetam, one drug included in the Pharmacokinetics (PK) of Anti-epileptic Drugs in Obese Children (AED) study.

"With this study, the PTN and its sites have addressed the important, but under recognized problem of how obesity impacts drug pharmacokinetics in children. It can be hoped that the results will lead to improved anti-seizure medication use in overweight children, and subsequent reductions in seizure frequency," said Susan Arnold, PTN site investigator and Director of the UT Southwestern Medical School Comprehensive Epilepsy Center. **Learn more**

Digoxin Achieved More Than 20% of Participant Goals



Karan Kumar, MD

In May of 2020, the PTN digoxin study achieved more than 20% of participant enrollment goals and activated all sites.

The study, which enrolled the first participant in the summer of 2019, will determine the pharmacokinetics (PK) and safety of digoxin prescribed to infants with single ventricle congenital heart disease (CHD).

"Unfortunately, there are no drugs currently proven to reduce death during this period. However, digoxin represents a promising drug to reduce mortality and is routinely used in this population," said Dr. Karan Kumar, a PTN faculty member contributing to the digoxin study. **More**

LAPS Trial Passes Halfway Mark of Enrollment

Linmarie Sikich, MD

In June of 2020, The PTN Long-term Antipsychotic Pediatric Safety (LAPS) Trial passed the halfway mark of enrollment, marking a substantial study milestone.

The two-year LAPS study will follow children aged 3 to 17 who are already taking an antipsychotic (risperidone or aripiprazole) to treat disorders such as schizophrenia, bipolar disorder, and irritability associated with autism. The study will assess both the long-term health risks and quality-of-life benefits of these two drugs, which have been shown to be effective and may even prevent mental illness in adulthood.

"Antipsychotic treatment of children and adolescents has greatly increased over the past 20 years," said Dr. Linmarie Sikich, principal investigator for the study and associate professor in the Department of Psychiatry and Behavioral Sciences at the Duke University School of Medicine. **More**

Sildenafil Study Opens Second Cohort

Matthew Laughon, MD

In July, PTN opened the second cohort, or group of study participants, in the Safety of Sildenafil in Premature Infants study. The study aims to assess the safety of sildenafil in premature infants at risk of bronchopulmonary dysplasia (BPD) and determine preliminary effectiveness and pharmacokinetics.

"BPD is a serious, potentially life-long lung problem for premature infants that often leads to prolonged hospitalization, and even death. While 17,500 U.S. infants develop BPD each year, it is an important public health goal to find a drug that can help," said Dr. Matthew Laughon, the study's Principal Investigator. **More**

SHARING SCIENCE (2019-2020)

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-Wolkowiez 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 and Systems Pharmacology*. July 2019.

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Drug Labeling in Adults and Children with Obesity. Zimmerman K, Benjamin D, Taylor-Zapata P, Anand R, Hornik CP. *Pharmaceutical Regulatory Affairs*. October 2019.

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Dosing of Continuous Fentanyl Infusions in Obese Children: A Population Pharmacokinetics Analysis. Maharaj AR, Wu H, Zimmerman KO, Speicher D, Sullivan JE, Watt K, Al-Uzri A, Payne E, Erinjeri J, Lin S, Harper B, Melloni C, Hornik CP; on behalf of the Best Pharmaceuticals for Children Act-Pediatric Trials Network Steering Committee. *Journal of Clinical Pharmacology*. December 2019. (ePublication ahead of print)

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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*. February 2020.

Systemic Timolol Exposure Following Topical Application to Infantile Hemangiomas. Drolet BA, Boakye-Agyeman F, Harper B, Holland K, Lewandowski A, Stefanko N, Melloni C. *Journal of the American Academy of Dermatology*. March 2020.

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-Wolkowiez M, Gonzalez D. *Clinical and Translational Science*. April 2020. (ePublication ahead of print)

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