Best Pharmaceuticals for Children Act

Best Pharmaceuticals for Children Act (BPCA) Priority List of Needs in Pediatric Therapeutics 2023-2024

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Best Pharmaceuticals for Children Act (BPCA)

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Best Pharmaceuticals for Children Act (BPCA) Priority List of Needs in Pediatric Therapeutics

The National Institutes of Health (NIH) hereby announces the BPCA Priority List of Needs in Pediatric Therapeutics for 2023-2024. In accordance with the BPCA legislation, the following list outlines priority needs in pediatric therapeutics for the areas listed below. This list serves as a resource for all stakeholders who participate in pediatric drug development and therapeutics research, and clinical care. All relevant areas are reviewed by the NIH and the U.S. Food and Drug Administration (FDA) for the purpose of future studies that need to be considered by all relevant stakeholders.

BPCA Priority List Background

The BPCA legislation requires that the NIH, in consultation with the FDA and experts in pediatric research, develop and publish a priority list of needs in pediatric therapeutics; establish a program for pediatric drug development studies of primarily off-patent medications; and submit clinical trial findings to the FDA for drug label change consideration. The establishment and update of the BPCA Priority List is under the authority and responsibility of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and consists of key therapeutic needs in the medical treatment of children and adolescents. Historically, the list has been organized by therapeutic area, which can be a group of conditions, or a setting of care, or a subgroup of the population. Since 2003, the NICHD has published 10 Priority Lists that have included over 150 drugs included in the BPCA Clinical program through various clinical trial designs. From these lists, the NIH has funded 51 clinical trials and submitted 27 Clinical Study Reports (CSR) to the FDA for label change considerations for drugs that have gaps in pediatric labeling. The submitted data from the clinical trials have resulted in 20 drug label updates to date with dosing, safety, and/or effectiveness data to improve the knowledge of how medications are used in children. Updates on all BPCA activities can be found on the BPCA website. The success of the program has resulted in updates to drug labels for special populations such as pre-term neonates and in the very near future will include updates on drug disposition in other clinically relevant therapeutic areas such as dosing exposure in breastmilk. More information on the current studies conducted under the BPCA Program can be found on the Pediatric Trials Network (PTN) Studies Page.

Update on BPCA Prioritization

Since the last Priority List update in 2020, the BPCA Clinical Program has expanded and evolved to address the needs of therapeutics more readily in the space of pediatric drug development. A once in a 100-year pandemic, and many other relevant factors in health care and delivery have been important to the re-discovery of where the BPCA Clinical Program can and should have a broader reach and impact. Throughout 2020 and 2021, the BPCA Program, in collaboration with experts in pediatric therapeutics, conducted a review of existing resources for those who conduct and/or sponsor pediatric drug development research. The BPCA Framework to Enable Pediatric Drug Development is a list of relevant resources such as articles and guidelines for stakeholders who perform pediatric drug development studies and has been published on the BPCA website. Also in May of 2021, the PTN reviewed the role of diversity and inclusion in enrollment in the BPCA pediatric clinical trials program. A published article, Racial and Ethnic Diversity in Studies Funded Under the Best Pharmaceuticals for Children Act, *Pediatrics,* 2021, documents their review findings. In late 2022, the BPCA program staff solicited nominations utilizing a Request for Information for new therapeutics to be considered for prioritization. In addition, we held our annual BPCA stakeholders meeting where a 2 half-day discussion on the current and future status of pediatric drug development was

held. At that meeting, several recommendations indicated the need for precision medicine approaches in pediatrics, training the next generation of experts in clinical trials and therapeutics, drug studies in orphan diseases and in neonates, electronic health record reform for regulatory ready real-world evidence, minimizing the burden of clinical trials, and maximizing the inclusion of children in the design and implementation of clinical trials. Meeting minutes can be found on the BPCA Stakeholders Meetings page.

Below is an update of the Priority List developments to date.

As part of the original BPCA mandate, the NICHD engages and reaches out to experts in pediatrics to identify needs in pediatric therapeutics annually or biannually. Our most recent outreach for nominations occurred in 2022 and we appreciate those who submitted recommendations. Those recommendations have been reviewed, scored, and incorporated as appropriate into this current version of the Priority List.

All nominations received by the NICHD are reviewed, considered, and evaluated according to six key criteria:

- Relevance to BPCA mission and goals
- No disqualifying ethical concerns
- Level of evidence available and current gaps
- Potential impact on children, society, and delivery of care
- Consideration of the different populations that may benefit from the research
- Feasibility and availability of the resources needed to conduct the study

Throughout 2023, NICHD program staff reviewed the history and current status of the BPCA Priority List and have revised the list to better align with the new focus of the entire BPCA program. The development of new Priority Lists will continue to include vital input from our BPCA stakeholders through the established nomination program described in more detail below. The BPCA program will regularly update the Priority List as mandated in the BPCA legislation and will expand the existing program to focus on specific populations where therapeutic needs are still unmet and to further identify pragmatic approaches to therapeutics research. This revised paradigm will also include two new data sources as part of the prioritization program. The first new data source is a bi-annual literature search prepared by an Information Specialist at the NIH Library. The second new data source will utilize novel tools such as artificial intelligence (AI) informed searches to develop information streams in collaboration with the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub Knowledge and Resource Center (MPRINT Hub: Indiana University) who will assist the NICHD in performing deeper dives into existing drug literature and label gaps.

Introduction

Below is the BPCA Priority List of Needs in Pediatric Therapeutics for 2023-2024 that is organized by therapeutic relevance in the following categories: Therapeutic Area Priorities, Population Based Priorities, Pragmatic Design, and Approach Priorities and Label Changes to Date. Throughout the document, both historical and current priorities are reviewed and addressed. A summary of the NICHD's current plans and progress in all of areas prioritized to date is also provided.

Details on the studies that resulted in pediatric drug label updates can be found on the BPCA Accomplishments page. The Accomplishments page includes study details links to NICHD Data and Specimen Hub (DASH), a centralized resource that allows researchers to share and access de-identified data from studies funded by NICHD. Where possible, studies are identified by ClinicalTrials.gov ID numbers.

Therapeutic Area Priorities

Infectious Disease Priorities

Even though many antibiotics have been around for decades, there remains a need for optimizing therapy and management in the treatment of pediatric infections and a need for improving dosing and safety data for rare diseases, treatment resistant diseases, as well as for special populations such as pre-term and low birth weight neonates and patients with obesity. The BPCA program and the PTN have been instrumental in improving knowledge of medications used in pediatric infectious diseases through label change updates to drugs such as meropenem, acyclovir, Clindamycin, doxycycline, Bactrim, rifampin, ampicillin, and most our most recent label change, fluconazole. Details on these label changes are available in the Label Changes to Date section.

Historical:

Metronidazole (Infections in Neonates)

There is a gap in knowledge of the pharmacokinetics (PK) and efficacy in neonates with abdominal infections.

A pediatric PK study (NCT01222585) has been completed by the PTN and initial CSR submitted to the FDA in October 2012. A follow-up study (NCT01994993) has been completed and the CSR submitted to FDA in October 2022. Currently awaiting final FDA review for potential label change.

Piperacillin-Tazobactam (Infections in Neonates)

There is a need for dosing and safety research in pre-term very low birth weight neonates for the treatment of resistant bacterial diseases.

A pediatric PK and safety study (NCT01994993) has been conducted by the PTN. A CSR is in development to be submitted to the FDA in 2024.

Current Priorities:

Valganciclovir (Infections in Neonates)

There is a need for dosing safety and efficacy research in the treatment of cytomegalovirus (CMV) infections in term, pre-term, and very low birth weight neonates.

A platform clinical trial of valganciclovir and ganciclovir is under consideration as a collaborative effort with other networks supported by the NICHD.

Cardiovascular Disease Priorities

The National Heart, Lung, and Blood Institute (NHLBI) has led many efforts to develop cardiovascular health guidelines in the pediatric population [Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Full Report | NHLBI, NIH], as well as disease areas such as high blood pressure, childhood obesity, and sleep and lipid disorders. The NICHD and the BPCA program have collaborated with our sister institutes to continue to address remaining needs and gaps in these relevant therapeutic spaces. The BPCA program has been instrumental in improving knowledge of medications used in pediatric cardiovascular health through label change updates to drugs such as sodium nitroprusside for the control of

blood pressure during surgery and continues to identify and sponsor related cardiovascular therapeutic needs. Details on these label changes are available in the Label Changes to Date section.

Historical:

Collaborations

Co-Funding with the Health Resources and Services Administration (HRSA) to determine frequency of medication use via electronic health records (EHR) with the Pediatric Research in the Office Setting (PROS) Network. Those findings were published in the article, Diagnosis and Medication Treatment of Pediatric Hypertension: A Retrospective Cohort Study. *Pediatrics*, 2016.

A Pediatric Hypertension Workshop was held in September 2017 that consisted of a collaboration between NICHD, FDA, and NHLBI. Meeting minutes from the workshop are available on the Historical Initiatives page on the BPCA website and a subsequent article on the research gaps in primary pediatric hypertension was published, Research Gaps in Primary Pediatric Hypertension, *Pediatrics*, 2019.

Statins (Dyslipidemia)

Gaps remain in the risk/benefit profile of long-term use in children related to novel study designs and the use of surrogate markers for determining the value of long-term statin use in children are needed.

A pediatric opportunistic PK study by the PTN of pantoprazole was completed. A submission to FDA has been completed. No label change is anticipated. The relevant article, A Population-Based Pharmacokinetic Model Approach to Pantoprazole Dosing for Obese Children and Adolescents, *Paediatr Drugs,* 2018 was published.

Dopamine (Hypotension)

There remain limited outcome measures in neonates and children treated for hypotension. A study is needed to identify biomarkers of disease progression. Long-term follow up studies are needed as well.

There was a co-funding collaboration between the BPCA Clinical Program and the NICHD Neonatal Research Network to study anti-hypotensives in preterm neonates. A clinical trial (NCT00874393) was completed and findings have been posted.

Current Priorities:

Digoxin (Heart Failure)

There is a gap in knowledge in PK and safety in infants born with congenital heart disease and require treatment.

A clinical trial (NCT03877965) has been completed by the PTN. Recruitment was completed in 2022. A final CSR is in development and the BPCA program anticipates submission to the FDA in the Spring of 2024.

Bumex

There is a gap in knowledge for the PK, safety, and efficacy of medications used in the treatment of edema in pediatric patients. A PTN clinical trial is in development.

Hydrocortisone (Shock)

PK and comparative effectiveness studies are needed.

There is a co-funding collaboration between the BPCA Clinical Program and the NICHD Collaborative Pediatric Critical Care Network (NCT03401398) underway to study the use of medications in the treatment of shock in critically ill children.

Respiratory Disease Priorities

The NICHD and the BPCA program once again partner with our sister institutes in disease-focused areas where an Institute takes the lead. The NHLBI has led efforts in the diagnosis, management, and treatment of asthma [2020 Focused Updates to the Asthma Management Guidelines | NHLBI, NIH] and other related respiratory diseases that affect children. The NICHD has led efforts in areas specific to special populations in children, such as the diagnosis and treatment of bronchopulmonary dysplasia in pre-term neonates and has collaborated with NHLBI in the Prematurity and Respiratory Outcomes Program (PROP). The BPCA program and the PTN have been instrumental in improving knowledge of medications used in respiratory diseases in neonates through label change updates to drugs such as caffeine for the treatment of neonatal apnea. Details on these label changes are available in the Label Changes to Date section.

Historical:

Asthma Therapeutics in Young Children

There remain limitations in the objective measures of lung function and responses to therapy in children younger than 4 years.

There was a trans-NIH and trans-U.S. Department of Health and Human Services (HHS) collaboration called the Asthma Outcome Measures meeting held in March 2010. A paper, Asthma Outcomes: Biomarkers, *J Allergy Clin Immunol*, 2012 was published as a result.

A co-funding collaboration with the NICHD Collaborative Pediatric Critical Care Network data collection on fatal and near-fatal asthma admissions in the pediatric intensive care units has been completed. Fatal and Near-fatal Asthma in Children: the Critical Care Perspective, *J Pediatr*, 2012 was published as a result.

Current Priorities:

Terbutaline (Asthma)

There is a lack of knowledge of dose response, safety, and efficacy. A study is needed to identify alternative treatment options for the treatment of severe asthma.

Because of limitations in older data available on the use of terbutaline in adults, an adult PK study (NCT04973345) was recommended by the FDA and is currently underway. This study will then inform the extrapolation of PK data down into the pediatric population so that a pediatric dosing, safety, and efficacy study can be performed. The pediatric study is planned for launch in 2025.

Sildenafil (Pulmonary Hypertension)

There is a lack of treatment strategies and outcome measures in children with pulmonary hypertension of differing etiologies.

PK and PD studies are needed in neonates receiving the drug. Epidemiology of differing etiologies and age-appropriate outcome measures in children are also needed.

A pediatric PK study, safety, and dose escalation study (NCT01670136) of three cohorts of preterm and term neonates is currently underway by the PTN.

Analgesia and Anesthesia

The BPCA Clinical Program, in partnership with experts in critical care, anesthesia, and pain has identified the need for improving the knowledge of dosing, safety, effectiveness, and long-term impact of analgesia and anesthesia in the pediatric population. In 2021, BPCA Program staff participated in a workshop to identify current needs in pediatric anesthesia and analgesia. The PTN is currently studying the dosing and safety of anesthetics and analgesics in pediatric patients in the hospital setting.

Historical:

Inhaled Anesthetics (Anesthesia/Sedation)

There was a gap in knowledge regarding toxicity of inhaled anesthetics in developing brains identified along with the need to identify markers of apoptosis.

Preclinical studies were completed with the FDA/National Center for Toxicological Research (NCTR) via an Inter-Agency Agreement. Application of MicroPET Imaging Approaches in the Study of Pediatric Anesthetic-induced Neuronal Toxicity, *J Appl Toxicol,* 2013 was published as a result.

Lorazepam (Sedation)

The BPCA Program supported a large PK, safety, and efficacy study (NCT00109395) of the use of lorazepam for sedation. The study included evaluating many various outcome measures and excipients. Unfortunately, the study did not reach its original primary objective of superiority trial, however, it provided valuable information of non-inferiority and on PK modeling and safety assessments in the critical care population.

Current Priorities

There remain limitations in the PK, PD, and pharmacogenomic data on the use of anesthetics and analgesic in pediatric patients in acute and chronic care and settings. The PTN is currently conducting a study with the goal of optimizing dosing and identifying biomarkers for the treatment of pain and anesthesia in pediatric patients in the hospital setting. The following drugs are under study (NCT03427736) in a master protocol design:

Ketamine (Anesthesia)
Toradol (Analgesia)
Methadone (Analgesia)
Ketorolac (Analgesia)
Hydromorphone (Analgesia)

Dexmedetomidine (Anesthesia)

This is a new recommendation from the 2022 prioritization. There has been a need identified to conduct prospective and comparative clinical trials in children from neonates to adolescents who are critically ill and/or are mechanically ventilated.

Psychiatric Disorder Priorities

The NICHD and the BPCA program once again partner with our sister institutes in disease-focused areas where another Institute takes the lead. The National Institute of Mental Health (NIMH) has led efforts in the diagnosis, management, and treatment of mental health disorders that affect children. The NICHD has led

efforts in addressing specific treatment gaps in special populations, such as the diagnosis and treatment of bipolar disease in children. The BPCA program was instrumental in improving knowledge of the medication lithium and funded two studies that provided important information on the long-term treatment and tolerability of this medication in children between the ages of 10-17 years. Details on these label changes are available in the Label Changes to Date section.

Historical:

Methylphenidate (ADHD)

NICHD collaborated with the National Center for Toxicological Research and the National Institute of Environmental Health Sciences (NIEHS) to investigate a previously identified preclinical gene toxicity activity to determine if such toxicities were potentially expressed clinically. The NICHD co-funded additional research in these areas with our collaborators and found no evidence of clinical expression of gene toxicities. Information on the meeting held can be found on the Other Conferences & Symposia page of the BPCA website.

Current Priorities:

Atypical Antipsychotics: Risperidone, Aripiprazole (Psychosis, Aggression)

There is a gap in knowledge for long-term safety—specifically metabolic derangements and weight gain related to this class of medications. The PTN has conducted a prospective follow-up study (NCT03522168) of patients exposed to atypical antipsychotics. The study is complete and data are being collated to submit to the FDA for review and potential label updates.

Neurological Disease Priorities

The National Institute of Neurological (NINDS) has led many efforts to identify pathophysiological changes related to neurological diseases that span maternal health and pediatrics including the diagnosis and treatment of diseases such as seizures and migraines. The NICHD and the BPCA program have collaborated with our sister Institutes to continue to address the remaining needs and gaps in this therapeutic space. The BPCA program has been instrumental in improving knowledge of medications used in pediatric neurological health including funding studies that have led to label changes for drugs used to treat status epilepticus such as lorazepam and diazepam and has provided label information for the use of levetiracetam in obese patients. Details on these label changes are available in the Label Changes to Date section.

Historical:

Baclofen - Oral (Cerebral Palsy)

A Written Request (WR) was received from the FDA in 2003. A clinical trial was completed, and the CSR was submitted to the FDA in December 2013. No label change anticipated. The paper, Pharmacogenomic Variability of Oral Baclofen Clearance and Clinical Response in Children With Cerebral Palsy, *PM R,* 2018, was published that summarizes the results.

No Specific Drug (Migraines)

NICHD co-funded a migraine clinical trial (NCT01581281) of amitriptyline and topiramate with NINDS that was terminated in 2015.

Current Priorities:

The PTN has completed a dose finding study (NCT02993861) of anti-epileptic medications (AED) to determine if dosing changes are needed based on body mass index (BMI) in obese patients. The study collection is complete and study data are being evaluated by the FDA. Drugs under study include:

- Valproic Acid
- Topiramate
- Oxcarbazepime

Gabapentin (Neuropathic Pain)

This is a new recommendation from the 2022 prioritization process. There has been a need identified to conduct a prospective randomized trial for the treatment of neuropathic pain in pediatric patients older than neonates.

Hematologic Disease Priorities

The NHLBI has been in the forefront in pioneering new research in blood related disorders, including sickle cell disease. The NICHD and the BPCA program collaborated with NHLBI to address remaining needs and gaps in this therapeutic space as described below.

Historical:

Hydroxyurea (Sickle Cell Anemia)

A lack of knowledge in safety and efficacy in young children as well as PK, safety, and efficacy was identified as well as the need for an oral formulation.

A WR was received from the FDA in 2004. The BABY HUG trial (NCT00006400) was funded by NHLBI and portions were also co-funded by NICHD. The clinical study was completed in children 9–17 months of age. A PK and bioavailability study (NCT01506544) was conducted and completed by the PTN. Data was submitted to FDA in February 2014. The final BABY HUG study CSR was submitted to FDA in November 2019. Data from the studies were not included in the drug label because of the need for additional data, however many relevant articles from the original study can be found in the above BABY HUG trial link.

Current Priorities:

Low-molecular- weight Heparin (Thrombosis and Thromboprophylaxis)

There is a gap of knowledge in the treatment and prevention of childhood strokes and venous thrombosis. Research is needed to determine validated biomarkers/surrogate markers, including developmental hemostasis parameters and age-appropriate assays. Adjunctive studies to evaluate toxicity are also needed. The PTN is gathering pharmaco-epidemiology data on the use of medications in this therapeutic category.

Dermatologic and Rheumatologic Diseases Priorities

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has led many efforts to identify pathophysiological changes and treatments of various diseases that impact special populations. The NICHD and the BPCA program have collaborated with our sister institute to continue to address remaining needs and gaps in these related therapeutic spaces.

Historical:

Timolol (Hemangiomas)

There is a gap of knowledge in PK, safety, and efficacy.

A PK, safety and efficacy study (NCT02913612) of the use of timolol to treat infantile hemangioma has been completed. A CSR in development and planned for submission to the FDA in 2024.

Current Priorities:

Methotrexate (Juvenile Rheumatoid Arthritis)

A new research trial to evaluate the safety and effectiveness in collaboration with the Childhood Arthritis and Rheumatology Research Alliance (CARRA) network is under development.

Gastrointestinal Diseases Priorities

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has led many efforts to identify pathophysiological changes and treatment related to the relevant therapeutic areas overseen by the Institute. The NICHD and the BPCA program have had a long-standing collaboration with our sister Institute to continue to address remaining needs and gaps in the diagnosis and treatment of chronic kidney diseases in children.

Historical:

Pantoprazole (Gastroesophageal Reflux)

The is a lack of dosing and efficacy data.

Research in the safety and effectiveness of infants is needed.

A pediatric PK/PD/pharmacogenomics study (NCT02186652) has been completed. A CSR has been submitted to FDA in Spring 2017. There is no label change anticipated.

BPCA program participated in Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT II & III) which sought to engage researchers, clinicians and regulators in developing drug development paradigms for diseases that impacted relevant patient populations. Meeting slides for the GREAT VI Meeting are also publicly available.

Ondansetron (Nausea and Vomiting)

There is a need for more knowledge regarding dosing.

A pediatric opportunistic study (NCT01431326) was completed by the PTN. The CSR was submitted to FDA in March 2019. There is no pathway to label change.

Current Priorities:

Ondansetron in Breastmilk

See details below in the Exposure of Medications in Breastmilk Research Priorities section.

Renal Diseases Priorities

NIDDK has led many efforts to identify pathophysiological changes and treatment related to the relevant therapeutic areas in diabetes, digestive diseases, and kidney diseases. The NICHD and the BPCA program have a long-standing collaboration with the NIDDK to diagnose, treat, and identify neurodevelopmental outcome assessments in children with chronic kidney disease in children. NICHD has co-funded a long-standing clinical program with the NIDDK called the Chronic Kidney Disease in Children Prospective Cohort Study (CKiD) (NCT00327860). The BPCA Program also been instrumental in improving knowledge in the dosing of lisinopril in patients with kidney transplants. Details on these label changes are available in the Label Changes to Date section.

Population-based Priorities

Neonatal Research Priorities

Since its inception, the NICHD has been one of a few NIH Institutes that is not specifically disease-focused, but aims to improve research also in specific populations, such as neonates, young children, adolescents, as well as women's health. The BPCA Program, operating under its mandate to improve drug labels in pediatric populations, has made valiant efforts to improve the knowledge of medications in many special populations, specifically in neonates. As previously noted, there are many BPCA studies and have been several label changes that include updates in dosing, safety, and effectiveness of medications used in this population. Label changes include but are not limited to caffeine for the treatment of apnea of prematurity and various anti-infectives. Details on these label changes are available in the Label Changes to Date section.

Current Priorities:

Furosemide (Neonatal Bronchopulmonary Dysplasia (BPD)/ Lung Development)

There is a lack of knowledge in dosing and safety.

A study to determine dosing and safety in preterm neonates was identified as a need. An opportunistic PTN study (NCT01431326) and retrospective analysis of diuretics in children was conducted. In addition, a PK and safety study (NCT02527798) of preterm neonates is complete. The CSR was submitted to FDA in 2023 and an FDA review is underway.

Morphine (Neonatal Pain)

The need to optimize dosing and biomarkers of pain in neonates has been identified as a need. A WR was received from the FDA in 2004. Originally, a trial (NCT00494429) was funded and completed. No additional label changes anticipated.

Methadone (Neonatal Abstinence Syndrome (NAS))

There are gaps in PK and safety knowledge.

Research is needed to identify treatment strategies of neonatal opioid withdrawal syndrome in opioid-exposed neonates.

The Clinical and Translational Science Award (CTSA) administrative supplement has been completed. A PTN PK study (NCT01945736) has been completed. The CSR development has been completed. An initial

FDA submission was made in 2016 and a revised CSR was resubmitted in August 2018. An adult PK study (NCT05425420) is underway and additional pediatric studies in 2025 are anticipated.

No Specific Drug (Neonatal Seizures)

There are gaps in knowledge for safety outcomes in medication exposure and optimal dosing.

A study is needed to identify safety outcomes in neonates of mothers treated for seizure disorders. A platform trial design for dosing and safety evaluations is also needed.

There was co-funding with NINDS for Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) trial 2012-2015 and 2017-2021.

Exposure of Medications in Breastmilk Research Priorities

There is a significant gap in determining if maternal use of medications have an impact on lactation and if there is any medication exposure to the neonate. The BPCA Program has identified this as a priority and the PTN has designed an opportunistic PK sampling study of medications in mother-infant pairs to determine the presence and relative concentrations of medications in breastmilk. Medications included in the master protocol design include (but are not limited to):

Azithromycin
Clindamycin
Metformin
Ondansetron
Nifedipine
Oxycodone
Labetalol
Tranexamic acid
Escitalopram
Sertraline

A PTN study was developed in collaboration with FDA (NCT03511118). The first patient enrollment started in October 2018. The CSRs for oxycodone and ondansetron were submitted to FDA for review in 2022 and 2023, respectively. Updates to the oxycodone label have been approved by the FDA and posting of the label changes are pending to date.

In addition, the PTN also developed a collaboration with the NIH Office of AIDS Research to conduct a study (NCT04862975) of anti-retrovirals in breastmilk. The study is ongoing.

Pragmatic Design and Approach Priorities

Biodefense Research Priorities

Midazolam (Nerve Agent Exposure)

A PTN PK study has been completed. The BPCA Program formed a collaboration with the NINDS CounterACT Program to advocate for the inclusion of pediatric patients in biodefense research.

Hydroxycobalamin (Cyanide Toxicity)

A pediatric opportunistic study by the PTN has been completed. Real-time cyanide assay was developed in collaboration with NINDS. Comparison of a new cobinamide-based method to a standard laboratory method for measuring cyanide in human blood, *J Anal Toxicol*, 2013 was published with findings.

Personal Protective Equipment (PPE)

A prospective study was conducted and Impact of Personal Protective Equipment on the Performance of Emergency Pediatric Tasks, *Pediatr Emerg Care*, 2021 was published to summarize results.

Clinical Trial Designs

The PTN has built an infrastructure of expertise in complex clinical trial designs in pediatric drug development. In addition to the scientific questions, the program has also worked to identify how the research impacts patient and clinical site engagement and collaboration. Several articles have been published that highlight the importance of inclusion of patients in research designs.

Leveraging School Infection Data to Address Community COVID-19 Data Gaps, *J Pediatric Infect Dis Soc*, 2023

Developing Lay Summaries and Thank You Notes in Paediatric Pragmatic Clinical Trials, *Health Expect,* 2022

Racial and Ethnic Diversity in Studies Funded Under the Best Pharmaceuticals for Children Act, *Pediatrics*, 2021

Pediatric Pharmacology Opportunistic Study of Commonly Used Medications in Children Study (POPS)

The PTN has developed a novel trial design to collect dosing, PK, and PD data from patients previously prescribed drugs for various indications. Data from this study (NCT01431326) (NCT04278404) may be used to develop full clinical studies and/or inform PK data for drug labels. For more information on additional drugs listed under the opportunistic clinical study, please see the PTN website.

Special Considerations

Guanfacine (Therapeutics in Children with Intellectual and Developmental Disabilities)

There is limited understanding of the differences in drug disposition and response, including safety and efficacy outcome measures in patients with intellectual and developmental disabilities. PTN collaboration with the NIH-wide INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Project will conduct clinical trials of medication use in children with Down Syndrome.

Clinical studies are in development and anticipated for enrollment in 2024 for therapeutics in children with intellectual and developmental disabilities.

Pediatric Formulations

The NICHD has developed a long-standing relationship with the FDA in continuing to identify and address various needs in pediatric formulations. Topics of interest include but are not limited to:

- Gaps in knowledge/labeling: Taste-masking technologies
- Orally dissolvable dosage forms that do not require water

- Heat-stable and light-stable dosage forms
- Safety data for excipients
- New technology needed to improve water solubility of intravenous formulations, reducing the need for solvents
- Improving the technology and designs of child-friendly/easy-to-swallow dosage forms of drugs to improve adherence and effectiveness

Pediatric Formulations Platform

In 2010 and 2011, the NICHD and BPCA Program worked with various stakeholders to conduct the Pediatric Formulations Initiative Workshop on the needs in pediatric formulations. There are two outcomes of this initiative: a manuscript of the workshop as well as the NICHD-FDA Formulations Platform for how formulations work could be conducted.

General Issues

Pediatric Medical Devices

There is a lack of validation of existing devices used in children. A study to determine validation of existing methodologies is needed. The PTN has validated academic developed devices for weight estimation in collaboration with Children's Mercy Hospital. More information can be found below in the label change section. Currently a PTN study to validate an adult device for the treatment of neurogenic bladder is currently in discussion with the FDA.

There is currently a Pediatric Medical Devices public-private partnership. This partnership brings together partners from both the public and private sectors.

Therapeutic Approaches for Sleep Disorders in Pediatric Patients

This is a new recommendation for the BPCA priority list. Currently NHLBI oversees research priorities in this area [Sleep Science and Sleep Disorders | NHLBI, NIH], however, the NICHD will continue to partner with our sister institute to improve knowledge gaps in the treatments in this therapeutic area.

Label Changes to Date

The BPCA Program has been responsible for submitting data to the FDA to successfully update 20 drug labels with improved dosing information for pediatrics. Below is a table summarizing these label changes. More information can be found on the BPCA Accomplishments page at https://www.nichd.nih.gov/research/supported/bpca/accomplishments.

Table 1

Product Name	Labeling Change	Link to Label
Acyclovir	Update Dosage and Administration, Clinical Pharmacology, and Adverse Reactions sections of the label with information that dosing for neonatal HSV should be based on postmenstrual age (PMA) at doses higher than those included in the acyclovir label at the time of the study	Final Label Approved 1/25/2019
Ampicillin	Revise pediatric dosing to include neonatal dosing for meningitis and septicemia based neonatal gestational age at birth and postnasal day of life. Add seizures to adverse reactions.	Final Label Approved 2/15/2018

Product Name	Labeling Change	Link to Label
Bactrim/ Trimethoprim-Sulfamethoxazole (TMP-SMX)	Add pediatric pharmacokinetic data to the Clinical Pharmacology section.	Final Labels Bactrim Tablets Approved 7/28/2020 Bactrim Pediatric Suspension Approved 7/28/2020
Caffeine Citrate	Include a broader gestational age range of premature infants and longer treatment durations	Final Label Approved 3/2/2020
Clindamycin	Add clinical pharmacology and dosage information for obese children (clindamycin should be dosed based on total body weight)	Final Labels Cleocin Injection 3/4/2020 Cleocin Capsules 3/9/2020
Clindamycin	Add clinical pharmacology and dosing information for pediatric patients less than one month of age with intra-abdominal infections	Final Labels Cleocin Phosphate 12/4/2021 Clindamycin Phosphate 9/1/2022
Diazepam	Update dosage and administration, clinical pharmacology data, and adverse reactions sections for patients ages 3 months to 18 years old.	Diazepam Injection 50mg/10mL, Multi-Dose Vial 11/12/21 Diazepam Injection 8/26/21 Diazepam Injection 5mg/mL 9/2/21 Diazepam Injection 5mg/mL and 10 mg/2 mL 11/12/21 Diazepam Injection 10mg/2mL 11/12/2021 Diazepam Injection 50mg/10 mL Multi-Dose Vial 8/10/2021 Diazepam Injection 5mg/mL 3/23/22 Diazepam Injection 10mg/2 mL 3/23/22 Diazepam Injection 10mg/2mL Single-Dose Prefilled Syringe 3/23/22 Diazepam Injection 5mg/mL 4/25/23
Doxycycline	Add pediatric data to Pharmacokinetics subsection of Clinical Pharmacology section	Final Labels Vibramycin 12/20/19 Acticlate 3/4/2020 Doryx 2/12/2020
Fluconazole	Relabeled to include PK dosing and safety data in preterm neonates.	February 2024 Docket FDA-2019-N-2698
Levetiracetam	Add dosing information in Pharmacokinetics section for obese pediatric patients	Final Labels Keppra 8/31/2023 Spirtam 8/31/2023

Product Name	Labeling Change	Link to Label
Lithium	Add Pediatric Use information to the Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, and Clinical Studies sections of the label, along with updates to the Medication Guide	Final Label Approved 10/4/2018
Lisinopril	Add lisinopril pharmacokinetic data in children with kidney transplant and found to be comparable to children and adults without a kidney transplant	DailyMed - LISINOPRIL tablet (nih.gov) Approved April 2016
Lorazepam	Add to the Pediatric Use section, Status Epilepticus subsection, information from a randomized, double-blind, superiority-design clinical trial of Ativan versus intravenous diazepam demonstrating a failure to establish the efficacy of Ativan in the treatment of status epilepticus in pediatric patients.	Final Label Approved 5/27/2016
Mercy TAPE (children)	Device study—to evaluate the predictive performance of 2D and 3D Mercy Tape method of weight estimation	Access Mercy TAPE study description and details.
Mercy BabyTAPE (infants)	Device study—developed to use head and chest circumference measures to predict infant weight.	Access Mercy BabyTAPE study description and details.
Meropenem for Injection	Update dosing recommendations for the use of meropenem in neonates and infants less than 91 days of age for complicated intra-abdominal infections	Final Label Approved 12/19/2014
Oxycodone	Update dosing and safety information in the breastfeeding sections of the labels to include data from the BPCA/PTN Cuddle Study	Label update posting pending.
Pralidoxime	Add existing data on pediatric patient exposure after BPCA prioritization	Final Label Approved September 2010
Propylthiouracil	NICHD sponsored workshop in October 2008 resulted in data that showed increased risk of liver toxicity.	FDA Drug Safety Communication: New Boxed Warning on severe liver injury with propylthiouracil | FDA
Rifampin	Update Clinical Pharmacology and Adverse Reactions sections of the label with information for infants	Rifadin capsules and Rifadin IV for injection 2/17/2023
Sodium Nitroprusside	Update dosing, pharmacokinetics, tolerability, and safety information in pediatric patients from birth to 18 years of age who receive SNP for controlled reduction of blood pressure	Final Label Approved 11/22/2013