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 2014.

Update on BPCA Prioritization

The BPCA requires that the NIH, in consultation with the Food and Drug Administration (FDA) and experts in pediatric research, develop and publish a priority list of needs in pediatric therapeutics. Part of fulfilling the NIH's authority and responsibility outlined in the BPCA legislation is to establish a program for pediatric drug testing and development and to publish a list of needs in pediatric therapeutics. The BPCA Priority List consists of key therapeutic needs in the medical treatment of children and adolescents; it is organized by therapeutic area, which can be a group of conditions, or a setting of care, or a subgroup of the population. The implementation of the BPCA prioritization process includes the following: initial outreach to solicit input from experts in pediatric medicine to gather information on drugs that need further study; data gathering through literature reviews and the development of therapeutic area working groups; and the enhancement of knowledge and resources through NIH and interagency collaborations.

Below is an update of the priority list developments to date:

- Annually, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) revisits the current list of needs in pediatric therapeutics. Based on the review, three therapeutic areas of interest are prioritized for the calendar year.
- All nominations received by the NICHD are 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.
- Minutes of all previous working group meetings conducted under the BPCA can be found on the BPCA Web site (http://bpca.nichd.nih.gov).

Below is an updated list of therapeutic areas that have been prioritized for study since the inception of the BPCA and a summary of the NICHD's plans and progress in all of these areas to date.

Priority List of Needs in Pediatric Therapeutics 2014

In accordance with the BPCA legislation, the following list outlines priority needs in pediatric therapeutics for the therapeutic areas listed below.

Table 1. Infectious Disease Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Methicillin-resistant *Staphylococcus aureus* (MRSA) infections	Clindamycin	Optimal therapy and management of community-acquired skin and soft tissue infections	Pharmacokinetics (PK), safety, and efficacy clinical studies	Pediatric opportunistic study by the Pediatric Trials Network (PTN) ongoing
	Trimethoprim-sulfamethoxazole	Biomarkers of disease	PK and efficacy (comparison) studies	Pediatric opportunistic study by the PTN ongoing
Infections	Acyclovir	Dosing, efficacy, and safety in neonates and infants with herpetic infections	PK, safety, and efficacy clinical studies	Pediatric PK study performed by the PTN and submitted to the FDA for review Additional data pending
	Doxycycline	PK, safety in children younger than 8 years	PK, safety, and efficacy clinical studies	Pediatric opportunistic study by the PTN ongoing
Tinea capitis	Griseofulvin	Safety and efficacy of higher doses in children < 20 kg with tinea capitis	PK, efficacy, and safety of higher doses in young children	Written Request (WR) received from the FDA Pediatric opportunistic study by the PTN ongoing
Antituberculous drugs	No specific drug	Safety and efficacy; formulations	New efficacy studies for global health, formulations	NIH-FDA Formulations Platform Initiative 2010–2012 Additional data pending
Antiparasitic drugs	Albendazole	PK, safety, and efficacy for Toxocara infections	New efficacy studies for global health, formulations	NIH-FDA Formulations Platform Initiative 2010–2012 Additional data pending
Influenza	Oseltamivir	Pharmaco-epidemiology data	Impact on clinical outcomes in hospitalized children with influenza	NICHD grant HD048689 funded and completed. http://bpca.nichd.nih.gov/clinical/studies/Pages/index.aspx

Drug and indications **in bold** have been identified by the NICHD as a new priority and have been added to the BPCA list.

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Table 2. Cardiovascular Disease Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Hypertension	*Hydrochlorothiazide	PK, safety, and efficacy in obese adolescents	Comparison studies, PK studies	Pediatric opportunistic study by the PTN ongoing
	*Beta blockers	PK, safety, and efficacy in obese adolescents	Comparison studies, PK studies	Under consideration
	Lisinopril	PK in children with kidney transplant	PK, safety, and efficacy clinical studies; formulations	Pediatric PK and safety study completed by the PTN Clinical study Report (CSR) under development for submission to the FDA
	Amlodipine	PK in children with kidney transplantation, formulations	PK, safety, and efficacy clinical studies	Pediatric study under consideration by the PTN
	Sodium nitroprusside	PK, safety, and efficacy	PK, short- and long-term safety and efficacy trials for controlled hypotension	WR received from the FDA; both clinical trials and data analyses completed; CSR to the FDA August 2012 Redacted data submitted to the FDA docket April and September 2013 **Label change in effect as of December 26, 2013**
Hypotension	Dopamine	Outcome measures in neonates and children treated for hypotension	Defining outcome measures	Collaboration with existing NICHD network (Neonatal Research Network) Clinical Trial #NCT00874393 Study closed
	Epinephrine	Dosage in resuscitation in children with elevated body mass index	PK studies	Pediatric opportunistic study by the PTN ongoing
Dyslipidemia	Statins	Risk/benefit profile of long-term use in children	Novel study designs, use of surrogate markers for determining the value of long-term statin use in children	Under consideration

Drug and indications **in bold** have been identified by the NICHD as a priority and are newly added to the BPCA list.
*Drugs listed twice for different indications or populations.

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Table 3. Respiratory Disease Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Asthma	Asthma therapeutics in young children	Objective measures of lung function and responses to therapy in children younger than 4 years	Standardization of outcome measures in research Identification of barriers to implementation of guidelines for asthma treatment	Trans-NIH and trans-U.S. Department of Health and Human Services (HHS) collaborations Meeting on Asthma Outcome Measures held March 2010; publication in the Supplement to *The Journal of Allergy and Clinical Immunology,* Volume 129, No. 3. March 2012 Co-funding with the Health Resources and Services Administration (HRSA) grant # UA6MC15585 to determine frequency of medication use via electronic health records (EHR) with the Pediatric Research in the Office Setting (PROS) Network
	Drug delivery systems	Effectiveness of drug delivery systems used in children	Improved technology for pulmonary function tests and drug delivery in young children	Under consideration
	Albuterol	Dose response, safety, and efficacy	Safety, efficacy, and appropriate mode of delivery in children in acute care settings	NICHD Collaborative Pediatric Critical Care Network data collection completed. Data analysis and publication ongoing.
Pulmonary hypertension	**Sildenafil**	Treatment strategies in children with pulmonary hypertension of differing etiologies	PK and pharmacodynamics studies in neonates receiving the drug Epidemiology of differing etiologies and age appropriate outcome measures in children	Pediatric observational and PK study by the PTN ongoing

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Table 4. Intensive Care Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Anesthesia/sedation	Ketamine	Safety	Preclinical and clinical studies of short- and long-term effects	Preclinical studies completed with the FDA/ National Center for Toxicological Research (NCTR) via Inter-Agency Agreement http://bpca.nichd.nih.gov/clinical/studies/Pages/index.aspx Pediatric opportunistic study by the PTN ongoing
	Inhaled anesthetics/isoflurane	Toxicity of inhaled anesthetics in developing brains	Identification of markers of apoptosis	Preclinical studies completed with the FDA/ National Center for Toxicological Research (NCTR) via Inter-Agency Agreement http://bpca.nichd.nih.gov/clinical/studies/Pages/index.aspx
	*Lorazepam	Dosing, safety	PK, safety, and efficacy trial comparing lorazepam with midazolam for sedation	WR received by the FDA Clinical trial completed; CSR under review

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Table 5. Biodefense Research Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Nerve agent exposure	Drug delivery systems	Need for pediatric auto-injectors		Trans-HHS collaborations
	Midazolam	Dosing studies for treatment of seizures and in obese children	PK studies	Trans-NIH collaborations PTN study in development
Cyanide toxicity	Hydroxyco-balamin	Dosing and effectiveness in inhalation injuries suffered during fires	Safety and efficacy	Pediatric opportunistic study by the PTN; real-time cyanide assay developed in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) http://bpca.nichd.nih.gov/resources/publications/Pages/index.aspx
Organophosphate poisoning	Pralidoxime	Dosing and safety		**Label changed September 2010**

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Table 6. Pediatric Cancer Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Neuroblastoma	13-cis-retinoic acid	New indication for neuroblastoma, pediatric formulation	PK studies, new formulation	Proposed Pediatric Study Request negotiated with the FDA; WR issued and declined by manufacturer and received from the FDA Collaboration with National Cancer Institute (NCI)/Children's Oncology Group (COG) Study complete and findings under review
Leukemias and solid tumors	*Methotrexate	Safety studies	Neurocognitive outcomes in young children with high-risk acute lymphoblastic leukemia	WR received from the FDA Collaborations with NCI/COG; clinical trial ongoing
	Vincristine	PK and safety studies	PK modeling and safety studies to evaluate for neurotoxicity	WR received from the FDA Collaborations with NCI/COG; clinical trial completed; data analysis ongoing Clinical and Translational Science Awards (CTSA) administrative supplement awarded to evaluate methods of determining neurotoxicity
	Daunomycin	PK studies	PK studies in children with elevated body mass index	WR received from the FDA Collaborations with NCI/COG; study completed; CSR under development
	Actinomycin-D	PK and safety studies	PK modeling and simulation, data mining for safety (hepatotoxicity)	WR received from the FDA Collaborations with NCI/COG; clinical trial completed; data analysis ongoing

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Table 7. Psychiatric Disorder Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Attention deficit and hyperactivity disorder (ADHD)	Methylphenidate	Safety and toxicity		Preclinical and clinical studies with NCTR and the National Institute of Environmental Health Sciences being finalized
Bipolar disease	Lithium	PK, safety, and efficacy	Dosing and tolerance, short- and long-term safety	WR received from the FDA PK data submitted to the FDA January 2010; safety and efficacy clinical trial completed April 2013 CSR in development for submission to the FDA
Psychosis, aggression	Atypical antipsychotics	Long-term safety—metabolic derangements Pharmacoepidemiology studies	Comparative long-term safety, epidemiology research on frequency of use	Translational research; co-funding with HRSA grant # UA6MC15585 to determine frequency of use via electronic health records (EHR) with the (PROS) Network PTN opportunistic study ongoing

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Table 8. Neurological Disease Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Cerebral palsy	Baclofen (oral)	PK, safety, and efficacy	PK and efficacy, pediatric formulation	WR received from the FDA Clinical trial completed; CSR submitted to the FDA December 2013
Migraines	No specific drug	Efficacy in prophylaxis	Efficacy in migraine prevention	NICHD co-funding of migraine clinical trial with NINDS grant number U01NS-076788
	Amitriptyline	Efficacy in prophylaxis	Efficacy in migraine prevention	Under consideration
Seizures	*Lorazepam	PK, safety, and efficacy	PK, safety, and efficacy in treating status epilepticus	WR received from the FDA PK trial data submitted to the FDA February 2009; safety and efficacy clinical trial completed CSR to the FDA third quarter 2014
	Fosphenytoin	PK, safety	PK, safety in treating seizures in young children	Under consideration

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Table 9. Neonatal Research Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Neonatal bronchopulmonary dysplasia (BPD)/lung development	Betamethasone	Dosing, efficacy	Determination of dosing and effectiveness	Reviewing existing data; NICHD grant funded and completed
	Azithromycin (IV)	Dosing, efficacy	PK, efficacy in treating ureaplasma infections to prevent BPD	WR received from the FDA; NICHD grant # HD056424 funding complete; HD067126 ongoing http://bpca.nichd.nih.gov/clinical/studies/Pages/index.aspx
	*Hydrochlorothiazide	Dosing, safety, and efficacy	Determination of dosing and effectiveness	Collaborations with the National Heart, Lung, and Blood Institute Prematurity and Respiratory Outcomes Program (PROP) network data collection ongoing
	Furosemide	Dosing and safety	Determination of dosing and safety in preterm neonates	Opportunistic PTN study and data analyses currently ongoing
Neonatal pain	Morphine	Pain	Optimization of dosing and biomarkers of pain in neonates	WR received from the FDA Current NICHD grant #HD048689 funded and completed http://bpca.nichd.nih.gov/clinical/studies/Pages/index.aspx
Neonatal abstinence syndrome (NAS)	Methadone	PK, safety	Treatment strategies of NAS in opioid-exposed neonates	CTSA administrative supplement PTN PK study ongoing
Infections in neonates	Metronidazole	PK and efficacy in neonates with abdominal infections	PK study	Pediatric PK study completed by the PTN; CSR submitted to the FDA
	Ampicillin	PK and safety in very low birth weight neonates	PK, safety clinical studies	WR received from the FDA Analysis of existing and new pediatric data under way by the PTN; CSR submitted to the FDA for review
	Fluconazole	Dosing and safety in very low birth weight neonates	PK, safety clinical studies	Pediatric PK and safety study completed by the PTN CSR submitted to the FDA for review
Neonatal necrotizing enterocolitis (NEC)	Meropenem	PK, safety in neonates		WR received from the FDA Clinical PK and safety trial completed; CSR to the FDA August 2011; redacted IND

				submission to the FDA (FDA docket number FDA-2011-N-0918)
Neonatal Seizures	No specific drug	Safety outcomes in medication exposure	Safety outcomes in mothers treated for seizure disorders	Co-fund with NINDS for Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic drugs (MONEAD) trial 2012-2014. https://web.emmes.com/study/monead/index.htm

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Table 10. Adolescent Research Priorities

Current or Proposed Listed Therapeutic Area	**Current or Proposed Listed Drug**	**Gaps in Knowledge/ Labeling**	**Type of BPCA Study and/or Scientific Needs**	**Plans and Progress**
Over-the-counter drug use	No specific drug	Health literacy		December 2007 symposium http://bpca.nichd.nih.gov/collaborativeefforts/index.cfm#07
Adolescent pharmacology	No specific drug	Effects of puberty on PK/ pharmacodynamics, adherence, and formulations research	Translational research, need to include adolescents in clinical trials	Pediatric Clinical Pharmacology Training grants thru NICHD and NIGMS co-funding http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/Pages/index.aspx

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Table 11. Hematologic Disease Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Sickle cell anemia	Hydroxyurea	Safety and efficacy in young children	PK, safety, and efficacy Oral formulation for children	WR received from the FDA BABY HUG trial completed in children 9–17 months of age, CSR in preparation PK and bioavailability study completed in December 2013 Long-term safety follow-up study under way CSR for PK study submitted to the FDA February 2014
Thrombosis and thromboprophylaxis	Anticoagulants, aspirin and antiplatelet agents	Data on incidence of venous thromboembolism in children to inform studies on anticoagulants	Pharmacoepidemiology, PK, and dosing studies in high-risk and unique populations Need for validated pediatric biomarkers/surrogate markers	Under consideration
	Low-molecular-weight heparin	Treatment and prevention of childhood strokes and venous thrombosis	Determine validated biomarkers/surrogate markers of anticoagulant drug including developmental hemostasis parameters and age-appropriate assays Adjunctive studies to evaluate toxicity	Under consideration

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Table 12. Endocrine Disease Priorities and Diseases with Limited Alternative Therapies

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Fragile X	MGluR5 antagonists	Outcome measures targets for intervention	Development of MGluR5 antagonists to treat Fragile X	Development of new therapeutics co-funded with NINDS grant #MH78260
Type 1 diabetes	No specific drug	Immunomodulatory therapies	Development of novel immunomodulatory therapies for children with type 1 diabetes	Collaborations with sponsored NIH networks, including TrialNET and DirectNET Funding completed

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Table 13. Dermatologic Diseases Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Atopic dermatitis	Hydrocortisone valerate	Effects on growth and hypothalamic-pituitary-adrenal axis suppression	Long-term safety data in children younger than 2 years	WR received from the FDA Under considerations
Severe inflammatory skin disease	*Methotrexate	Dosing, efficacy, and safety	Safety and efficacy in treatment of severe inflammatory disease	Co-fund of R13 workshop with NIAMS-2013 and 2014.
Hemangiomas	***Timolol**	PK, safety, and efficacy	PK, safety	Concept under review

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Table 14. Gastrointestinal Diseases Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Gastroesophageal reflux	Prokinetic drugs	New drugs; dosing, safety, and efficacy of existing drugs in neonates and infants	Effectiveness and outcome measures in young children	Under consideration
	H2 blockers and proton pump inhibitors	Dosing and efficacy data	Safety and effectiveness in infants	Pediatric PK/PD/Pharmacogenomics study of pantoprazole in development
Cyclic vomiting and weight gain	Cyproheptadine	Dosing, efficacy, and safety		Under consideration
Cholestatic disease	Ursodeoxycholic acid	Safety and efficacy in young children		Under consideration
Inflammatory Bowel Disease	**No specific drug**	Safety and efficacy of treatments in children		Participation in Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT II) meeting
Constipation	**Propylene glycol (Miralax)**	Dosing and safety in children	PK, safety	Concept under review

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Table 15. Renal Diseases Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Anemia of chronic kidney disease	**Epogen**	Optimal dosing and safety Pharmacoepidemiology data	Appropriate dosing and outcome measures in children with chronic kidney disease Determination of appropriate target hemoglobin levels	Under consideration
Acute kidney injury	No specific drug	Drug dosing, drug interactions	Population PK studies of multiple drugs used in this patient population to prevent sub-therapeutic dosing	PTN opportunistic study ongoing

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Table 16. Rheumatologic Disease Priorities

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of BPCA Study and/or Scientific Needs	Plans and Progress
Connective tissue disorders	Hydroxychloroquine	PK and safety in children with juvenile idiopathic arthritis	PK, safety studies	Under consideration

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Table 17. Special Considerations

Area of Consideration	Identified Therapeutic Area	Gaps in Knowledge/Labeling	Type of Study and/or Scientific Needs
Therapeutics in children with intellectual and developmental disabilities	No specific drug or indication	Identification of differences in drug disposition and response, including safety and efficacy outcome measures	Need for inclusion in clinical trials
Pediatric formulations	Multiple drugs and indications: Infectious diseases: HIV: antiretrovirals Tuberculosis: isoniazid Trypanosomiasis: benznidazole nifurtimox Parasitic infections: albendazole Malaria: mefloquine, sulfadoxine-pyrimethamine chlorproguanil-dapsone Hematology: hydroxyurea Oncology: 6-mercaptopurine methotrexate prednisone isotretinoin Spasticity: baclofen Hypothyroidism: l-thyroxine	Taste-masking technologies Orally dissolvable dosage forms that do not require water Heat-stable and light-stable dosage forms Safety data for excipients	Improving the technology and designs of child-friendly/easy-to-swallow dosage forms of drugs to improve adherence and effectiveness NICHD-FDA Formulations Platform http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/Pages/index.aspx
Pediatric devices	General Issues	Need for validation of existing devices used in children	Validation of existing methodologies

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