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 2012.

Update on BPCA Prioritization

The BPCA requires that the NIH in consultation with the Food and Drug Administration 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 drugs/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, a subgroup of the population, or a setting of care. 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:

- The 2010 prioritization process resulted in a tiered list of nominations considered for prioritization. Tier One included the highest scoring nominations that were added to the priority list for 2011. Tier Two included the average scoring nominations of future interest to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). These nominations are revisited on an annual basis by NICHD. Tier Three included the lowest scoring nominations. These nominations are of least interest to the NICHD and are not being considered for prioritization at this time.
- At the beginning of every year, the NICHD revisits the current list of needs in pediatric therapeutics and reviews the recommendations from the prior annual meeting. Based on the review, three therapeutic areas of interest are prioritized for the calendar year.
- The prioritized therapeutic working groups consist of experts in that field along with representatives from the corresponding FDA divisions. In 2011, three working groups were formed: Hematology, Renal, and Pulmonary. In 2012, the current working groups include Pediatric Rheumatology, Dermatology and Oncology.
- All nominations from the working group members were reviewed by NICHD 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.
- Minutes of all 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 and drugs that have been prioritized for study since the inception of the BPCA, which includes new areas of prioritization from the 2010 outreach, recommendations from the 2011 working groups, and a summary of the NICHD's plans and progress in all of these areas.

Priority List of Needs in Pediatric Therapeutics 2012

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)
	Trimethoprim-sulfamethoxazole	Biomarkers of disease	PK and efficacy (comparison) studies	Pediatric opportunistic study by the PTN
Infections	Acyclovir	Dosing, efficacy, and safety in neonates and infants with herpetic infections	PK, safety, and efficacy clinical studies	Pediatric pharmacokinetic (PK) study by the PTN
	Doxycycline	PK, safety in children younger than 8 years	PK, safety, and efficacy clinical studies	Pediatric opportunistic study by the PTN
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	WR received from FDA. Pediatric opportunistic study by the PTN
Antituberculous (TB) drugs	No specific drug	Safety and efficacy; formulations	New efficacy studies for global health, formulations	NIH-FDA Formulations Platform Initiative 2010–2012
Antiparasitic drugs	Albendazole	PK, safety, and efficacy for Toxocara infections	New efficacy studies for global health, formulations	NIH-FDA Formulations Platform Initiative 2010–2012
Influenza	Oseltamivir	Pharmacoepidemiology data	Impact on clinical outcomes in hospitalized children with influenza	Current NICHD grant funding

Drug and indications **in bold** have been identified by NICHD as a priority and are newly 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	WR received from FDA. Pediatric study under consideration by the PTN
	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 study planned for 2012 by the PTN
	Amlodipine	PK in children with kidney transplantation, formulations	PK, safety, and efficacy clinical studies	Pediatric study under consideration by the PTN
Hypotension	Sodium nitroprusside	PK, safety, and efficacy	PK, short- and long-term safety and efficacy trials for controlled hypotension	Written Request received from FDA; both clinical trials and data analyses completed; clinical study report (CSR) to FDA August 2012.
	Dopamine	Outcome measures in neonates and children treated for hypotension	Defining outcome measures	Collaborating with existing NICHD network (Neonatal Research Network)
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	Pediatric study in development by the PTN

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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 collaborations Meeting on Asthma Outcome Measures held March 2010
	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
Pulmonary hypertension	**No specific drug**	**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**	**Under consideration**

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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 FDA/ National Center for Toxicological Research (NCTR). Pediatric opportunistic study by the PTN
	Inhaled anesthetics/isoflurane	Toxicity of inhaled anesthetics in developing brains	Identification of markers of apoptosis	Preclinical models, *in vitro* studies
	*Lorazepam	Dosing, safety	PK, safety, and efficacy trial comparing lorazepam with midazolam for sedation	WR received by FDA. Clinical trial completed; CSR for submission to 1st quarter 2013.

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*Drugs listed twice for different indications or populations

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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		Under consideration
	Midazolam	Dosing studies for treatment of seizures related to exposure and in obese children	PK studies	Trans-NIH collaborations
Cyanide toxicity	Hydroxycobalamin	Dosing and effectiveness in inhalation injuries suffered during fires	Safety and efficacy	Pediatric opportunistic study by the PTN; real-time cyanide assay under development with the National Institute of Neurological Disorders and Stroke (NINDS)
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 FDA; Written request issued and declined by manufacturer and received from FDA. Collaboration with National Cancer Institute (NCI)/Children's Oncology Group (COG)
Leukemias and solid tumors	Methotrexate	Safety studies	Neurocognitive outcomes in young children with high-risk acute lymphoblastic leukemia	WR received from 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 FDA. Collaborations with NCI/ COG; clinical trial completed; data analysis ongoing; Clinical and Translational Science Awards (CTSA) administrative supplement
	Daunomycin	PK studies	PK studies in children with elevated body mass index	WR received from FDA. Collaborations with NCI/ COG; study completed, CSR to FDA 2nd quarter 2012
	Actinomycin-D	PK and safety studies	PK modeling and simulation, data mining for safety (hepatotoxicity)	WR received from FDA. Collaborations with NCI/ COG; clinical trial completed; data analysis ongoing
	6-mercaptopurine	Formulations		NIH-FDA Formulations Platform

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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 near completion
Bipolar disease	Lithium	PK, safety, and efficacy	Dosing and tolerance, short- and long-term safety	WR received from FDA. PK data submitted to FDA January 2010; safety and efficacy clinical trial ongoing
Psychosis, aggression	Atypical antipsychotics	Long-term safety—metabolic derangements. **Pharmacoepidemiology studies**	Comparative long-term safety, epidemiology research on frequency of use	Translational research; outpatient epidemiology research effort under development

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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 FDA. Clinical trial completed; CSR to FDA 1st quarter 2013
Migraines	Propranolol	Efficacy in prophylaxis	Efficacy in migraine prevention	Under consideration
	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 FDA. PK trial data submitted to FDA February 2009; safety and efficacy clinical trial completed. CSR to FDA 2nd quarter 2013.
	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; current NICHD grant funding
	Azithromycin (IV)	Dosing, efficacy	PK, efficacy in treating ureaplasma infections to prevent BPD	WR received from FDA; current NICHD grant funding
	*Hydrochlorothiazide	Dosing, safety, and efficacy	Determination of dosing and effectiveness	WR received from FDA. Collaborations with the National Heart, Lung, and Blood Institute network data collection
Neonatal pain	Morphine	Pain	Optimization of dosing and biomarkers of pain in neonates	WR received from FDA. Current NICHD grant funding
Neonatal abstinence syndrome (NAS)	Methadone	PK, safety	Treatment strategies of NAS in opioid-exposed neonates	WR received from FDA. CTSA administrative supplement
Infections in neonates	Metronidazole	PK and efficacy in neonates with abdominal infections	PK study	WR received from FDA. Pediatric PK study completed by the PTN; CSR expected to be submitted to FDA 4th quarter 2012
	Ampicillin	PK and safety in very low birth weight neonates	PK, safety clinical studies	WR received from FDA. Analysis of existing pediatric data under way by the PTN
Neonatal necrotizing enterocolitis (NEC)	Meropenem	PK, safety in neonates		WR received from FDA. Clinical PK and safety trial completed; CSR to FDA August 2011; Redacted IND submission to FDA docket 2/17/12, docket number FDA-2011-N-0918.

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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 symposia 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	Under consideration

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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 FDA; BABY HUG trial completed in children 9–17 months of age, CSR in preparation; long-term safety follow-up study under way; PK and bioavailability study recruiting patients
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 pediatric therapeutic ranges**	**Collaborations with existing networks**
	Low-molecular weight Heparin	**Treatment and prevention of childhood strokes and venous thrombosis**	**Define therapeutic ranges of anticoagulant drug including developmental hemostasis and age appropriate assays** **Adjunctive studies to evaluate toxicity**	**Collaborations with existing networks**

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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 cofunded with NINDS; clinical research under way
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 through fiscal year 2010

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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 FDA. 2012 working group in progress
Severe inflammatory skin disease	Methotrexate	Dosing, efficacy, and safety	Safety and efficacy in treatment of severe inflammatory disease	**2012 working group in progress**

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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	Dosing and efficacy data	Safety and effectiveness in infants	Under consideration
Cyclic vomiting and weight gain	Cyproheptadine	Dosing, efficacy, and safety		Under consideration
Cholestatic disease	Ursodeoxycholic acid	Safety and efficacy in young children		Under consideration

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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
Chronic kidney failure	Devices used in dialysis	Drug distribution, elimination, and accumulation in continuous renal replacement therapy	Device validation studies in children on chronic renal replacement therapy	Under consideration
Anemia of chronic kidney disease	Agents to stimulate erythropoiesis	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**	Under consideration

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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	**2012 working group in progress**

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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 routine 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
Pediatric devices	General Issues Neonatal hypoxic ischemic encephalopathy (HIE) Increased intracranial pressure Sleep disordered breathing	Need for validation of existing devices used in children Brain cooling in conjunction with neuroprotective drugs to prevent HIE Cerebrospinal fluid (CSF) shunts Continuous positive airway pressure (CPAP) and nasal devices	Current focus is on pediatric pulmonary devices and the validation of existing methodologies Comparison study of the effectiveness of brain-cooling devices with drugs in collaboration with Neonatal Research Network Improved designs for CSF shunts for hydrocephalus Development of home-based nasal devices and CPAP machines for positive pressure ventilation in toddlers and infants

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