

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Asthma Working Group Conference Call
June 19, 2007
11:30 a.m.–12:30 p.m. ET**

Participants

Joe Carcillo, M.D.
Christopher Carroll, M.D.
Denise Dougherty, Ph.D.
Peyton Eggleston, M.D.
Matthew Fenton, Ph.D.
Erwin Gelfand, M.D.
Theresa Guilbert, M.D.
Jan Leahey
Donald Mattison, M.D.
Christopher Newth, M.D.
Hari Sachs, M.D.
David Skoner, M.D.
Peter Starke, M.D.
Stanley Szeffler, M.D.
Virginia Taggart, M.P.H.
Amy Taylor, M.D., M.P.H.
Perdita Taylor-Zapata, M.D.
Alkis Togias, M.D.
Anne Zajicek, M.D.
Darryl Zeldin, M.D.

Purpose

The purpose of the conference call was to discuss the following:

- Background Information on BPCA
- Charge to BPCA Working Groups
- Overall gaps in scientific knowledge in diagnosis and treatment of asthma
- Key treatment gaps
- Priority drugs that need study and clinical trial design
- Future directions for research.

Background

Dr. Taylor-Zapata explained that BPCA, enacted in 2002, charges the National Institute of Child Health and Human Development (NICHD) to produce a priority list of drugs that need further study in children. Over the first 3–4 years, NICHD learned about the need for background studies in children and pediatric drug development. NICHD produced an initial list of drugs—organized by drug and by indication—derived from a Food and Drug Administration master list

of on- and off-patent drugs needing further study. Clinical trials are currently under way for some of the drugs identified on this initial list. NICHD also developed subcontracts to study the frequency of drug use and frequency of conditions in children.

In 2005, with the input of outside experts, NICHD switched to an approach focusing on therapeutic classes, enabling researchers to better compare on- and off-patent drugs within a particular therapeutic class. This approach allows NICHD to gather expertise in specific therapeutic areas and insights into gaps in scientific knowledge and appropriate study designs for those areas. In 2006, NICHD began examining drugs used to treat children for a variety of conditions, including attention deficit hyperactivity disorder, influenza, hypertension, parasitic diseases, and sickle cell anemia. In December 2006, an expert panel was convened to prioritize additional drugs and conditions for the coming year. The panelists determined that infectious diseases (specifically methicillin-resistant *Staphylococcus aureus*), pediatric cancer, neonatal conditions (including pain, bronchopulmonary dysplasia, and seizures), and asthma were important conditions to study in children.

The purpose of the Pediatric Asthma Working Group is to identify gaps in current scientific knowledge about the diagnosis and treatment of pediatric asthma, help NICHD identify areas that need further study, discuss clinical trial designs for these studies, and consider new paradigms and approaches to pediatric asthma treatment. Dr. Taylor-Zapata asked the participants to consider joining the Working Group and participating in two or three conference calls and one in-person meeting each year. She asked whether the participants had any questions about BPCA or the Working Group.

Dr. Fenton asked whether the Working Group would focus exclusively on pharmaceutical treatments, rather than nonpharmaceutical treatments such as bronchial thermoplasty. Dr. Taylor-Zapata confirmed that the group would focus only on pharmaceutical treatments. Dr. Szefler asked whether the group would prioritize or monitor drug trials. Dr. Taylor-Zapata answered that the purpose of the group is to discuss the types of drug trials that should be done, identify drugs that need further study in children, and discuss clinical trial designs for those drugs. Dr. Szefler asked whether the group had a specific mandate or budget. Dr. Taylor-Zapata replied that the initial focus of the group is exploring ideas. In the future, the group can discuss specific trials or funding.

Dr. Gelfand noted that there are research networks, funded through the National Institutes of Health, already studying asthma in children and conducting drug trials. The group should work with these existing networks. Dr. Taylor-Zapata agreed. She said that there is an Asthma Clinical Research Network sponsored by the National Heart, Lung, and Blood Institute's Division of Lung Diseases that conducts monitoring studies and drug trials in children. It was noted that the Childhood Asthma Research and Education Network and the Inner City Asthma Consortium (ICAC) sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) are also currently studying asthma in children. Dr. Taylor-Zapata said NICHD would like to partner with these networks.

Dr. Starke asked whether the primary focus of BPCA was off-patent drugs. Dr. Taylor-Zapata replied that off-patent drugs are one focus of BPCA. Dr. Mattison added that under BPCA, NICHD has the opportunity to study drugs that are on patent as well. The process for studying on-patent drugs involves notifying the sponsor or manufacturer of the drug. NICHD's authorizing legislation does not prevent the Institute from studying an on-patent drug, even if the manufacturer accepts a Written Request to study the drug. Dr. Mattison emphasized the importance of looking broadly at all drugs currently available to treat a condition.

Ms. Taggart asked Dr. Taylor-Zapata to elaborate on how NICHD would partner with research networks: by adding funds to existing studies, leveraging funding to make sure studies are conducted, or directing the kinds of trials research networks undertake. Dr. Taylor-Zapata replied that there are multiple ways NICHD can partner with research networks, but the group's first goal is to find out what research is already under way and whether there are gaps in that research. Once the gaps are identified, the group can discuss ways to partner with research networks to address these gaps. Possibilities include adding funding and expertise to existing research networks. Ms. Taggart asked how the BPCA efforts related to the Pediatric Pharmacology Research Unit (PPRU), which is also studying pediatric drugs. Dr. Mattison answered that PPRU is available for certain types of studies, particularly those focused on pharmacokinetics; other settings are more appropriate for studies of dosing, safety, and efficacy.

Dr. Skoner asked how pharmaceutical companies would be involved. Dr. Taylor-Zapata replied that pharmaceutical company participation would be considered; pharmaceutical companies participated in other BPCA initiatives, such as the Pediatric Formulation Initiative.

Dr. Szeffler asked whether the purpose of the group was to identify gaps not being addressed by other asthma research networks, and Dr. Taylor-Zapata agreed it was.

Dr. Taylor-Zapata explained that the Working Group includes several members who participated in a 2006 roundtable discussion on maximizing the management of asthma, chaired by Dr. Fenton and George Giacoia, M.D. The Working Group also includes individuals involved in the care of pediatric asthma patients in NICHD's clinical care network.

Discussion

Dr. Taylor-Zapata asked participants to identify gaps in the treatment of pediatric asthma and to prioritize particular drugs, drug categories, or devices that need to be studied in children.

Dr. Skoner said that long-acting beta-agonists (LABAs) need more study in children; the data available for children do not agree with data collected in adults, and safety issues with LABAs have recently emerged. Dr. Guilbert added that LABAs particularly need to be studied in children 0–4 years old.

Dr. Gelfand said available asthma drugs affect symptomatology but have little impact on the progression of the disease, which indicates that the available drugs are not sufficient. Studies of

early intervention are needed, although it is difficult to conduct adequate studies in subjects at the age of inception of the disease, which is younger than 2 years old.

Dr. Szeffler said the group should also examine chronic treatment versus acute treatment. At the December 2006 BPCA meeting, he outlined some of the age limitations of asthma medications. Because LABAs are increasingly popular for combination therapy and treatment of acute exacerbations, it is important to study safety, black box warnings, and delivery devices for LABAs in young children. He noted that pharmaceutical companies have been fairly responsible in studying and labeling the asthma drugs montelukast and nebulized budesonide for use in children. Few other asthma drugs are labeled for young children. He suggested dividing asthma drugs into chronic treatments, acute treatments, and early interventions to alter the progression of the disease, such as immunomodulators. Dr. Eggleston noted that immunological therapies (such as allergen immunotherapy and anti-immunoglobulin E) tested and approved for adults have high age limits for use. ICAC has begun to study these therapies, but has found it difficult to study asthma treatment in children younger than 6–8 years old.

Dr. Guilbert said more information is needed about the treatment of nonatopic asthmatics or wheezers, who make up the majority of asthmatic phenotypes and about 20–30 percent of the pediatric population. Dr. Gelfand suggested studying children whose asthma disappears in their late teens and reappears later in life. Studies of the differences between those who relapse and those who do not could provide a wealth of information about natural history and pathophysiology. Dr. Skoner added that many children who have asthma at the age of 6 go into remission by age 20, and approximately one-third relapse. Recent studies of 20-year-olds in remission show that their airways are remodeled and inflamed.

Dr. Guilbert said more information is needed about how well hydrofluoroalkane (HFA) formulation enters the airways of young children without the use of spacers. Many HFA studies were conducted without spacers, but those studies may not be applicable to young children. Dr. Taylor-Zapata noted there were gaps in scientific knowledge about two age groups: very young children and children in the transitional period between the teen and adult years.

It was noted that one gap not related to age is the lack of knowledge about the management of acute asthma. Dr. Skoner said pediatricians evaluate children with acute asthma symptoms during office visits in the same way they would in an emergency department. Studies should examine how to treat acute asthma symptoms during office visits and how to send those patients home. Dr. Newth said little is known about the group of pediatric patients who end up in intensive care units (ICUs) for acute asthma symptoms, how they are treated, and the long-term effects of their treatments. Management of these patients varies throughout the country. Dr. Gelfand suggested that the group develop practical asthma management guidelines for pediatricians and primary care physicians to help them assess whether a patient's asthma is controlled and determine how to respond to lack of control.

Dr. Taylor-Zapata asked what types of clinical trial designs should be used to study pediatric asthma.

Dr. Dougherty said head-to-head trials of different approaches to the emergency management of children with asthma should be conducted using cluster randomized trials, rather than using the individual patient as the unit of analysis. The most useful types of trials would take advantage of registries, if they exist, to study comparative effectiveness. She said studies do not need to randomize patients to treatments, as long as the studies are rigorous. It was noted that an important issue in pediatric trial design is that it is unethical and illegal to conduct pediatric trials that involve more than a minimal risk to the child without an immediate benefit. Dr. Carcillo suggested conducting phase IV trials of drug toxicity in ICUs to examine the efficacy of therapies and associated risks.

Dr. Taylor-Zapata asked the group for key areas for future research.

Dr. Fenton said NIAID's ICAC is working to establish biomarkers for asthma, with the goal of examining phenotypes in populations early in the progression of the disease. NIAID is supporting these studies in inner cities, but the studies have not been broadly applied through a network. For various types of immunotherapy, researchers can examine the responsiveness of the biomarkers in order to categorize treatments as preventive or therapeutic. Dr. Newth commented that this research could provide more information about patients who end up in ICUs with near-fatal asthma; currently little is known about this group of patients.

Dr. Szeffler said bronchiolitis—a wheezing-like illness, not always defined as asthma—has not been thoroughly studied. Treatments and studies of the value of treatments for bronchiolitis are needed. Studies are also needed to resolve two important issues: (1) the cost and safety of use of levalbuterol stereoisomer versus racemic isomer and (2) the use of inhaled steroids in young children, particularly with metered-dose inhalers and HFA formulations. There is confusion about the use of spacers.

Dr. Newth said more information is needed about ICU patients. The primary treatments for these patients are intravenous and inhaled beta-agonists, and it is not known whether the correct formulations are used. However, rather than using long-acting drugs, it might be more appropriate to use short-acting drugs, because they tend to be safer and produce a faster response in the ICU. For example, epinephrine and isoproterenol have not been evaluated against intravenous terbutaline or intravenous albuterol (which is not available in United States). The dosing, pharmacokinetics, and pharmacodynamics of intravenous terbutaline and intravenous albuterol have not been studied in children. He added that more information is needed on the use of inhaled anesthetic compounds in children who start to fail when put on intravenous beta-agonists.

Dr. Skoner noted that parents are often reluctant to place their children in clinical trials. He suggested that the group develop a teaching tool to help clinicians enroll children in trials.

Dr. Taylor-Zapata said she would follow up with Ms. Taggart, Dr. Fenton, and others about how NICHD might work with existing networks studying pediatric asthma. She said NICHD is developing a literature review of the current treatments for asthma, and NICHD subcontractors are examining the frequency of the use of various drugs to treat asthma in children. She will e-

mail this information to the group for review in the next month, and participants can e-mail their comments and suggestions, which will be discussed during the September conference call. In the long term, NICHD plans to develop a formulary of information on drugs used to treat children for various conditions.

Action Items:

- Dr. Taylor-Zapata will follow up with Ms. Taggart, Dr. Fenton, and others to discuss how NICHD might partner with existing research networks studying pediatric asthma.
- In the next month, Dr. Taylor-Zapata will e-mail participants NICHD's literature review of the current treatments for asthma and information about the frequency of the use of various drugs to treat pediatric asthma. This information will be discussed during the group's second conference call.
- NICHD will schedule a second conference call for the Pediatric Asthma Working Group in September.
- Circle Solutions staff will draft and distribute the conference call summary.