

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Hypertension Treatment Working Group Conference Call
May 30, 2007
11:00 a.m.–11:58 a.m. ET**

Participants

Donald Batsky, M.D.
Felicia Collins, M.D., M.P.H.
Mehul Desai, M.D.
Bonita Falkner, M.D.
Joseph Flynn, M.D.
Howard Higley, Ph.D.
Julie Rich Ingelfinger, M.D.
Rae-Ellen Kavey, M.D., M.P.H.
James Korelitz, Ph.D.
Mae Kuo, Ph.D., M.P.H.
Jan Leahey
Jennifer Li, M.D.
Ronald Portman, M.D.
Mark Schreiner, M.D.
Victor Shi, M.D.
Alan Sinaiko, M.D.
Perdita Taylor-Zapata, M.D.
Tom Wells, M.D.
Rick Williams, Ph.D.
Anne Zajicek, M.D., Pharm.D.

Dr. Taylor-Zapata presented an overview of the status of BPCA activities. The current BPCA legislation sunsets at the end of this fiscal year, but reauthorization of the Act by Congress is expected. The National Institutes of Health's (NIH) initial goal for BPCA in 2002 was to change labels, and although this remains an important goal for BPCA, several key areas need to be investigated before labels can be changed, including conducting clinical trials and designing trials in special populations. The BPCA project has shifted to a condition-based approach to prioritizing drugs and now involves identifying conditions that need pediatric study, such as pediatric hypertension, and drugs to treat those conditions.

The long-range goal of BPCA is to improve pediatric therapeutics by implementing:

- Scientific advancements
 - Identifying gaps in knowledge through literature and database searches
 - Convening expert panels (working groups)
- Labeling changes
 - Identifying labeling gaps through work with Food and Drug Administration (FDA) review and pediatric divisions
 - Working toward a common goal of the overall impact of labeling

- Developing clinical trial designs
- Changes in physician practice
 - Conducting symposia and workshops and developing publications
 - Developing a master formulary.

The role of the Pediatric Hypertension Treatment Working Group is to help implement BPCA by determining scientific areas that need investigation, identifying gaps in knowledge, and identifying opportunities to advance scientific understanding and treatment of pediatric hypertension. The Working Group can help NIH examine new paradigms and approaches to understanding treatment of pediatric hypertension and can address issues such as the developmental effects of treatment, novel approaches to clinical trial designs, and improving treatment modalities. Possible outcomes include publications or study proposals to FDA.

Dr. Taylor-Zapata described the Pediatric Hypertension Workshops held in June 2005 and April 2006. Members of the Working Group participated as experts in these two workshops. Some of the topics discussed were how to marry diagnosis and mechanism of disease with therapeutics, the risk of cardiovascular disease in children, and the association of obesity with pediatric hypertension. Dr. Taylor-Zapata mentioned an article that Dr. Kavey sent (Chiolero et al. Has Blood Pressure Increased in Children in Response to the Obesity Epidemic? *Pediatrics* 2007;119;544–553). Dr. Kavey said the article is a systematic review of all studies related to hypertension in childhood from 1986 to the present. The review could not demonstrate an increase in hypertension diagnoses since the beginning of obesity epidemic.

It was noted that one of the problems with the review was that it was difficult to discern exactly how the blood pressure measurements were determined in the studies reviewed. More recent studies show a far higher prevalence of pediatric hypertension. Dr. Kavey commented that she thinks a connection between pediatric hypertension and obesity will be difficult to demonstrate. She believes there is significant underdetection of hypertension in children.

Dr. Zajicek asked whether blood pressure readings in children are the same today as they were 20 years ago. Dr. Falkner answered that the answer is no; tables for blood pressure norms in children have been gradually increasing the number of blood pressure readings on which they are based. A problem is that all the blood pressures determining normal are mostly single measurements in a screening setting and do not represent what would be considered a baseline blood pressure.

Dr. Falkner was asked to comment about whether a comparison of tables of normative values would indicate very little difference between the two reports. Dr. Falkner said this was correct—there is very little difference between the most recent data and the earlier data. The reason is likely that measurement techniques have become more standardized and rigorous. The data originally were pooled from several sources with variations in how blood pressure was measured in the different studies. Some blood pressures were measured in schools and others in other sites. The oldest data are the least rigorous and uniform in terms of methodology. The newer data are more standardized. When looking at the data, the numbers are about the same, so it made sense

to merge the older and newer data. Dr. Falkner said she did not see how one could say for certain that blood pressures are not increasing with this shift in methodology.

Dr. Sinaiko said that this was a difficult question to answer. One change is the use of automated monitors, which find higher systolic pressures. Systolic hypertension accounts for most of the prevalence of hypertension; most scientists attribute systolic hypertension to an association with obesity. The history of hypertension is that a systolic elevation occurs first, followed by a diastolic elevation later. Most children with hypertension have small elevations, often associated with overweight or obesity. He identified a major issue as lack of knowledge about what happens to these children as they grow older.

A group member suggested that the focus on blood pressure normative data should be to identify children who are at risk for hypertension-related damage. Multiple studies have found a prevalence of at least 30 percent or higher of left ventricular hypertrophy (LVH) in hypertensive children. What this means to those children over the long term is a key question that has not been addressed. When treated, their LVH resolves, which is thought to be a good outcome. Many of the children had mild hypertension, as seen in a recent paper co-authored by Stephen Daniels, M.D., Ph.D. There is a definite correlation between higher grade or stages of hypertension and LVH. LVH is mostly seen in teenagers. Obesity is associated with LVH, although controlling for body size shows that hypertension causes LVH.

Some group members believe that a possible issue for the Working Group to consider is whether the approach to pediatric hypertension is different in different age groups. The incidence and prevalence of hypertension increase as children get into their teens.

Dr. Taylor-Zapata said that these are some points that BPCA may be able to begin to answer, such as follow-up on Dr. Daniels' data about what LV mass is in children. She suggested that there may be pilot studies that could be done to look at LV mass in children and effective treatment for LVH. A recommendation from the previous meetings of this group was to have a trial in children similar to the ALLHAT study, but that was a major international study of 42,000 subjects. Dr. Taylor-Zapata questioned whether there are preliminary or pilot studies that could be set up in preparation for doing some sort of ALLHAT trial.

Participants discussed the possibility of following up with participants of longitudinal childhood studies, such as the Bogalusa and Muscatine studies. It was noted that a paper about the Fels longitudinal study, with Shumei Sun, Ph.D., as lead author and co-authored by Dr. Daniels, was published recently. (Sun et al. Systolic Blood Pressure in Childhood Predicts Hypertension and Metabolic Syndrome Later in Life. *Pediatrics* 2007;119;237–246) The researchers found that certain blood pressure threshold values in childhood predict hypertension and metabolic syndrome in adulthood.

Dr. Sinaiko expressed concern about treating too many children for small blood pressure elevations and the lack of knowledge about the natural history of pediatric hypertension. He clarified that he was not referring to children who have LVH.

It was noted that because the long-term effects of drugs on growth and development are unknown, clinicians must weigh an unknown risk of untreated mild hypertension with the unknown risk of long-term treatment with drugs. FDA has been seeking long-term studies to follow up on growth and development. Some drugs may have a negative impact on final height, school performance, and bone mineralization, for example. The current normative data for echocardiograms in children are based on only a few hundred patients. A larger effort to gather several thousand normal echocardiograms on children of different ages and stages of development would be a tremendous service to help understand pediatric hypertension.

Dr. Taylor-Zapata asked whether obese patients need different doses than nonobese patients. Group members noted that a few trials have addressed that question, and the amlodipine trial did not find a difference. Dr. Portman commented that the data have not been analyzed. The numbers are probably too small.

Participants discussed reducing obesity rather than using drug therapy to treat hypertension. A study in New Orleans found that in the short term, no more than half of study participants lost weight, and when the aggressive intervention ended, the children gained the weight back. Participants agreed that although weight loss works to lower blood pressure and reduce other cardiovascular risks, it is very difficult to help children lose weight and to maintain weight loss.

Dr. Taylor-Zapata said that Dr. Kavey had mentioned a DASH-type dietary approach study in children. Dr. Sinaiko described an intensive study done years ago in New Orleans to reduce salt and increase potassium using supplements. The study had high compliance, but changes seen at 6 months were gone by a year. There were 70 children in each group who were seen once a week for a few months at first, then every other week, then twice a month, then once a month. Achieving dietary change in children is challenging. Dr. Kavey emphasized the difficulty of changing diets and sustaining weight loss in children. A DASH trial is important to try rather than drug treatment, but a pilot study will not be useful because it is not a real-world situation.

Dr. Taylor-Zapata asked what types of studies should receive highest priority. Dr. Kavey said she thought that a trial of hydrochlorothiazide would be useful. It is the easiest, lowest level of treatment, but how well it works is still unknown. She asked what happened to the planned hydrochlorothiazide trial. Dr. Taylor-Zapata replied that the Written Request has been evaluated at FDA, but she does not know the timeframe for the trial.

A participant asked how many children are enrolling in trials. Dr. Portman said that enrolling children for trials is not too difficult, and most trials enroll about 300 patients. He expressed doubts about conducting a hydrochlorothiazide trial. As a clinician, he never uses hydrochlorothiazide to treat hypertension as a first-line drug, but not because of lack of data. He seldom uses diuretics in active children unless they have renal disease. Other drugs are more suitable for treating active children, especially athletes, including ACE inhibitors or calcium channel blockers. In his view, because there are so many important issues and few dollars to spend on this kind of research, research on hydrochlorothiazide is not of particular interest. Another participant noted, however, that treating overweight, inactive children is a more common situation.

A participant asked how many children are being treated with any hypertensive drug. Dr. Taylor-Zapata referred to the NICHD draft monograph on hypertension. She explained that the monograph was prepared by three subcontractors: Westat looked at frequency of drug use in children; RTI looked at mortality, morbidity, and hospitalization rates in children; and CCS Associates did a literature search. She asked Dr. Korelitz to give some background information on the data prepared by Westat.

Dr. Korelitz explained that his group examined data from both Medicaid claims and commercial insurance claims. The methodology was to identify children who submitted a claim with a diagnosis of hypertension (both primary and secondary hypertension), and within those, to determine the percentage of children prescribed antihypertensive medication within 90 days after diagnosis. Approximately 20 percent to 30 percent of children with a diagnosis of hypertension are prescribed a hypertension-related medication within 90 days. The proportion of children receiving a diuretic is about 4 percent to 7 percent of children. Children are given hydrochlorothiazide alone or in combination with another drug. Dr. Portman commented that combination drugs are often expensive, so he uses lisinopril and hydrochlorothiazide as two separate prescriptions, which is a common practice.

Group members noted that the population of children with hypertension being treated with antihypertensive drugs is small and that, because not treating children with hypertension is acceptable, objections to a placebo-controlled trial should be minimal.

Dr. Portman said that hydrochlorothiazide is more often used in combination than as a primary drug, so doing a study of the drug as a primary medication would not be useful. A participant referred to a combination drug study that was rejected because there were no data on the individual drug components. The first step is to determine whether a drug is safe and effective for short-term therapy. If it is not safe and effective when used alone, the next step is to determine whether it is safe and effective when combined with other drugs. Both steps are necessary. Dr. Kavey agreed.

Another question is the time of drug trials. Long-term use of drugs raises growth and development issues. Dr. Schreiner commented that some drugs have had negative studies, for example, the ramipril study. Although there may have been a problem with the withdrawal design for the study, the magnitude of effect was relatively small. It is not unusual for antihypertensive drug trials to be negative. He believes trial A design should be used and doses should be spread over a fairly wide range. The study should be informed by pharmacokinetics (PK) to start with.

Dr. Portman said that several changes occurred that had an impact on the study, including imminent patent expiration of the drug. The natural progression is to do PK and pharmacodynamics first, then an efficacy trial. He believes that FDA agrees that the trial A design (using a simple parallel group with placebo and without use of withdrawal) obtains better efficacy data. Dr. Schreiner said that the idea that most children had secondary hypertension and the lack of a recommendation about when it is safe not to treat pediatric hypertension were what

drove withdrawal designs and made people wary of the placebo study design. Those factors are not obstacles any more.

Dr. Taylor-Zapata asked whether the FDA representatives had comments. Dr. Desai said that he generally agreed with the statements that had been made and planned to share his notes from the conference call with others at FDA. Dr. Li commented that one reason why some trials have been negative is that they did not dose per kilo of body weight. If data are analyzed to look at dose per kilo, a dose response is seen.

Dr. Taylor-Zapata asked for comments on the monograph. Several participants indicated that they would e-mail comments to her. A participant asked whether the monograph is being prepared for a specific publication. Dr. Taylor-Zapata said there were no specific plans for publication at this time, although the goal is to publish an article in a peer-reviewed journal and publish it on the BPCA Web site as well.

Other comments regarding the monograph included the need for more precision in the introduction and improving the discussion of metabolic syndrome. Dr. Kavey suggested a more thorough and exact review of the literature and a focus on the new drug data. It was also suggested that getting unpublished data from pharmaceutical companies would be helpful.

Regarding the proposed three-phase study for hydrochlorothiazide as described on page 27 of the monograph, a participant thought that it might be useful to add in another drug or randomize patients to receive effective doses of drugs such as enalapril, due to the interest in combination drugs. It was noted that a number of drug combinations are available commercially. FDA could offer pharmaceutical companies exclusivity for combination drugs if the companies conduct studies of each component as well as in combination.

Dr. Taylor-Zapata said that the monograph will be revised based on all of the comments. For the future, NICHD would like to keep the Working Group active by meeting more often than it has in the past. She mentioned the possibility of having an in-person meeting once a year to discuss issues related to pediatric hypertension.

Action Items:

- Dr. Kavey will send the group the recent article by Dr. Sun et al.
- Working Group members will send their comments about the draft monograph to Dr. Taylor-Zapata.
- Dr. Taylor-Zapata will coordinate making revisions to the monograph based on comments and suggestions from Working Group members.
- Circle Solutions will prepare and distribute the conference call summary.