

**Best Pharmaceuticals for Children Act (BPCA)
Adolescent Therapeutics Working Group Conference Call and Webcast
April 16, 2010
10:00 a.m.–10:45 p.m. ET**

Participants

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George Ricaurte, M.D., Ph.D.
William Rodriguez, M.D., Ph.D.
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Amy Taylor, M.D., M.H.S., FAAP
Perdita Taylor-Zapata, M.D.
Maria Trent, M.D., M.P.H.

Purpose

The purpose of this conference call and webcast was to review the following:

- 2009 BPCA annual scientific meeting recommendations and comments
- Current ideas/plans for recommendations
- Current plans for 2010 prioritization and meeting.

An open forum for questions and discussion concluded the call.

Presentation

Dr. Taylor-Zapata reviewed the 2002 BPCA and the 2007 BPCA and described the role of the National Institutes of Health (NIH) in the BPCA program. The focus of 2007 BPCA activities shifted from prioritizing drugs to identifying the needs of pediatric therapeutics. The NICHD has primary responsibility for implementing the BPCA program, including organization and development of the prioritization process, awarding and monitoring clinical trials, investigational new drug development, collection of data for potential label modification, and drafting and submitting label modifications for specific ages and indications. The NIH develops—in collaboration with the Food and Drug Administration (FDA), Institutes, experts, parents, and others—an updated priority list of needs in pediatric therapeutics, identifying primarily off-patent therapies that “most urgently” require study in pediatric populations. The main goal of the BPCA program is to advance the science of pediatric pharmaceuticals and improve pediatric labeling. Dr. Taylor-Zapata described the guiding principles of the revised BPCA prioritization framework, the prioritization process, and the steps for therapeutic area and pediatric need

nominations. In the near future, a request for information will be posted asking for research nominations concerning pediatric needs and gaps in therapeutic areas. A preliminary list of nominations will be published in the *Federal Register* in July or August 2010. The list will be finalized in late 2010 or early 2011.

2009 BPCA Annual Scientific Meeting Recommendations and Comments

The Adolescent Therapeutics Working Group's findings are summarized as follows:

- Adolescent therapeutics can be defined by
 - Age (typically somewhere around 12–24 years of age)
 - Behavior (risk and prevention)
 - Specific diseases and developmental stages.
- Adolescent therapeutics is an area in which every medication seems to have a black box warning or in which medication use is typically off-label.
- Diseases are impacted by development, and development is impacted by disease. Disease–development interactions include changes in
 - Hormonal influence
 - Body composition
 - Disease processes
 - Adherence
 - Metabolism.
- Pharmacokinetics (PK), pharmacodynamics (PD), and safety and efficacy of drugs are affected by development.
- Development can affect a drug's mechanism of action and/or metabolic side effects.

The Adolescent Therapeutics Working Group made the following recommendations:

- Understand the effects of pubertal development and body weight on PK, PD, and pharmacogenetics (PG) of pharmaceutical agents in children and adolescents, with special emphasis on
 - The effect of both stage of sexual maturity and body weight on drug distribution and metabolism
 - PG changes in the expression of drug-metabolizing enzymes in adolescents related to age, family history, and pubertal maturation
 - Extent and mechanism, risk factors, and consequences of weight gain seen in older children and adolescents treated with antipsychotics, parenteral contraceptives, and other agents associated with weight gain
 - Impact of adherence on the pharmacotherapy and therapeutic outcome in adolescents because adolescents frequently are responsible for managing their own medications and treatments.
- Develop a protocol across review divisions within the FDA to evaluate the endocrine and metabolic, psychological, and reproductive impact of pharmacotherapy in adolescents, with particular emphasis on psychotropic and other drugs frequently used in adolescents.
- Develop understanding of how and where to distinguish between pediatric (preadolescent) and adult dosing guidelines for all drugs used in adolescents, including

- Determining when weight- and/or age-based dosing regimens are no longer applicable (for example, when administering HIV drugs for a 12-year-old who is at or above adult weight or in a young adult who is significantly below adult weight)
- Determining whether development of specific adolescent dosing guidelines needs to be considered for the therapeutic agents most commonly used within adolescents and young adults.

Current Ideas/Plans for Recommendations

- With regard to the effects of puberty on PK, PD, and PG, the NICHD is considering funding opportunities (R01, R03) for 2011 or 2012. Research areas include mechanisms of adverse effects of drugs and developmental pharmacology, with special emphasis on puberty. The Obstetric and Pediatric Pharmacology Branch already has a developmental pharmacology funding announcement (<http://grants.nih.gov/grants/guide/pa-files/PAR-07-416.html>) and is considering expanding it to include an emphasis on puberty.
- The NICHD and FDA Pediatric Divisions met in January 2010 to discuss options for developing FDA protocols for endocrine effects of drugs across divisions. Because the divisions tend to function independently, there are challenges to conducting protocols across all of the divisions. In addition, the protocols are often drug-specific.
- With regard to developing pediatric and adult dosing guidelines:
 - The NICHD and the National Cancer Institute are co-sponsoring an investigation of PK/PD changes based on body mass index for a cancer drug, including the effects of age and development stage on dosing.
 - For an emerging initiative with the Federal Liaison Group for Asthma Education and Research, Dr. Taylor-Zapata will introduce issues about PK/PD for asthma drug dosing guidelines in pediatric populations versus adults.
 - Plans for addressing HIV drugs dosing guidelines are pending.

Current Plans for 2010 Prioritization and Meeting

The 2010 BPCA annual scientific meeting is tentatively scheduled for November. Adolescent Therapeutics Working Group members will be invited. BPCA program activities in 2010 will focus on four therapeutic areas: endocrine, gastrointestinal, devices, and neurology. New working groups will be formed to address these areas. Working group members are invited to participate in 2010 teleconferences and to become stakeholders who evaluate new therapeutic areas under consideration for BPCA funding. Dr. Taylor-Zapata proposed that the working group draft a paper that describes its work over the past year and provides an update on the current state of adolescent pharmacology.

Open Forum

Dr. Rodriguez noted that one therapeutic area that has been overlooked is adolescent migraines. All but one drug used to treat adolescent migraines has been ineffective. Research could help develop new ways of identifying which adolescents would benefit from migraine medications. Dr. Rodriguez also noted that there is a new Office of Adolescent Health in the U.S. Department

of Health and Human Services (www.hhs.gov/ophs/oah). Dr. Rodriguez proposed contacting the Office to inquire about possible collaboration with the BPCA program. Dr. Haverkos said one of the Office's areas of interest is reproduction, including oral contraceptives and other forms of birth control, adolescent parenting, and pregnancy prevention.

Dr. Haverkos noted that the National Institute of Neurological Diseases and Stroke (NINDS) will be holding a meeting on long-term planning for headache research. It will be held at the Bethesda North Conference Center on May 16–17, 2010. Dr. Haverkos agreed to provide additional information about the meeting. Dr. Taylor-Zapata said the new Neurology Working Group will be working with the NINDS to identify the needs of pediatric neurology. One of the areas of interest is migraines.

Drs. Kapogiannis and Kokotailo volunteered to help write the article on the working group's activities and the current state of adolescent pharmacology.

Dr. Ricaurte commented that the working group should consider which particular drugs classes provide adequate models for clinical and preclinical investigations of age effects on PK and PD. Psychomotor stimulant drugs offer one clear opportunity for these types of investigations. Dr. Rodriguez said drug to treat diabetes offers another opportunity.

Dr. Taylor-Zapata agreed to contact Roberta Kahn, M.D., from the National Institute on Drug Abuse (NIDA) to inquire about possible collaboration in the area of adolescent substance abuse and addiction.

Dr. Trent volunteered to participate in the new Endocrine Working Group. She noted that the use of weight-loss drugs is another possible area of interest for the Adolescent Therapeutics Working Group.

Next Steps

- Dr. Taylor-Zapata will keep working group members abreast of developments in the area of adolescent pharmacology.
- Dr. Haverkos will send to Dr. Taylor-Zapata information about the NINDS headache research meeting in May 2010. Dr. Taylor Zapata will distribute the information to the working group.
- Dr. Taylor-Zapata will contact Roberta Kahn, M.D., from the NIDA to inquire about possible collaboration in the area of adolescent substance abuse and addiction.
- Dr. Taylor-Zapata will provide information on the article by Dr. Kapogiannis and Dr. Donald Mattison titled "Adolescents in Clinical Trials" (www.ncbi.nlm.nih.gov/pubmed/19008903).