

**Best Pharmaceuticals for Children Act (BPCA)
Endocrine Therapeutics Working Group Conference Call and Webcast
April 28, 2010
2:00 p.m.–3:00 p.m. ET**

Participants

Elizabeth Durmowicz, M.D.
Oluchi Elekwachi, Pharm.D., M.P.H.
David Geller, M.D., Ph.D.
Mary Hediger, Ph.D.
Paul Kaplowitz, M.D., Ph.D.
Saul N. Malozowski, M.D., Ph.D., M.B.A.
Yeruk Mulugeta, Pharm.D.
Scott Rivkees, M.D.
Mary Roberts, M.D.
Perdita Taylor-Zapata, M.D.

Purpose

The purpose of this conference call and webcast was to:

- Give an introduction to BPCA
- Review the role of therapeutic area working groups
- Identify questions for experts in this area
- Provide an open forum for discussion.

Presentation

Dr. Taylor-Zapata gave a webcast slide presentation (also distributed to participants), reviewing the background of BPCA legislation and the work being carried out under BPCA. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is the lead agency responsible for establishing and conducting pediatric drug development activities, which are carried out by its Obstetric and Pediatric Pharmacology Branch. The drug development program involves a prioritization process to identify gaps in pediatric therapeutics that need further study and clinical trials of primarily off-patent drugs that have been prioritized.

Each year, the NICHD identifies three new areas for focus. For 2010, those areas are neurology, endocrinology, and gastroenterology. Working groups have been formed in these areas. The groups meet two or three times a year. Minutes of meetings are posted on the BPCA Web site and distributed to working group members. The Endocrine Therapeutics Working Group's recommendations will be presented at the annual BPCA prioritization meeting in November 2010 and could lead to publications, workshops, or studies. Everyone on the working group will be invited to participate in the annual meeting. Current BPCA interests in endocrinology include type 1 diabetes and the drug propylthiouracil (PTU). Dr. Rivkees and Dr. Donald Mattison, NICHD, organized a meeting in 2008 to address hepatic toxicity following treatment with PTU

for Graves' disease. As a result, in 2009 the Food and Drug Administration (FDA) issued an alert that PTU can induce liver failure and in April 2010 added a boxed warning to the label.

Dr. Rivkees presented at last year's BPCA prioritization meeting about endocrinology needs and outlined the following steps to address gaps in knowledge:

- Define the incidence and prevalence of endocrine disorders such as growth hormone deficiency, precocious puberty, and hypopituitarism
- Define treatment practices for these disorders
- Define off-label treatment practices, such as the use of aromatase inhibitors to increase height, recombinant IGF-1, and growth hormone
- Define complications of therapy
- Use postmarketing drug surveillance as a resource.

The questions posed to the experts on the working group were as follows:

- Has the NICHD captured key therapeutic gaps in the area of pediatric endocrinology?
- Are there other areas (drugs, therapeutic approaches) that the experts would like the NICHD to consider under the BPCA program?

Open Forum

Dr. Kaplowitz said that one of the major gaps in pediatric medications is a lack of convenient dosage forms for children, for example, for thyroid hormone and hydrocortisone. No drug company has taken on this probably because regulatory requirements are an obstacle.

Dr. Malozowski suggested changing the terminology from "orphan" diseases to diseases with limited therapeutic alternatives and noted that it is important to have good expectations about what different types of research studies can accomplish. There is a wealth of information that can be mined to gain insight about the safety of drugs.

Dr. Rivkees suggested two focus areas: (1) the issue of shortages of pediatric endocrine therapeutics (drugs such as diazoxide are sometimes in short supply) and (2) aggressive off-label marketing by some pharmaceutical companies. There is currently no forum for engaging federal agencies to help with this problem. Perhaps this working group can address this problem. Dr. Malozowski said this working group could be a forum to disseminate information to the scientific community about what is known and not known, what is approved, and so on.

Dr. Geller said that off-label marketing is a burgeoning problem that has gotten out of control the last few years. This is a problem for the pediatric endocrine society. It would be helpful for this issue to be addressed at the federal level. Dr. Rivkees noted that the BPCA and the FDA can provide a forum free of potential pharmaceutical industry influence. Dr. Taylor-Zapata said she could follow up with FDA colleagues.

Regarding specific drugs, Dr. Rivkees mentioned aromatase inhibitors, which are not approved to augment the height of a child, yet there is widespread off-label use for that purpose. Even though very few children have growth hormone resistance, a pharmaceutical company has

developed an aggressive marketing campaign and has essentially defined a new condition to be treated with recombinant IFG-1. Dr. Malozowski noted that with off-label use of the drug, adverse effects may occur that are not reported. Dr. Geller said the pediatric endocrine society's Drugs and Therapeutics Committee put out an article about the use of aromatase inhibitors and made it clear that the drugs cannot be endorsed to increase height. But in spite of this, the practice is clearly widespread. In addition, a combined growth hormone and IGF-1 product is on the horizon that many people will feel compelled to use right away.

Dr. Rivkees suggested that the working group could begin by identifying the major diagnoses. A contractor could be engaged to interrogate databases with ICD-9 codes to define the incidence of endocrine disorders, identify the medications being used to treat children, and look at where the safety signals are in the FDA's AERS database. He noted that it may be necessary to start with a broader code and then drill down to find the desired data. In addition, the working group could pursue some specific examples at the same time based on the group's discussion during this call.

Dr. Taylor-Zapata thanked the group members for their feedback. The call summary will be sent to everyone. She will follow up by e-mail over the next few weeks to get recommendations on the key diagnoses and drugs to consider. A follow-up call will be scheduled in about 6–8 weeks. In addition, she will try to engage some epidemiology experts.

Next Steps:

- Dr. Taylor-Zapata will follow up with working group members by e-mail regarding key diagnoses and drugs for further study.
- A second working group call will be scheduled in about 6–8 weeks.