Best Pharmaceuticals for Children Act (BPCA)
Antipsychotics Safety Therapeutics Working Group Conference Call
September 25, 2009
11:00 a.m.–11:45 a.m. ET

Participants

Jeffrey Blumer, M.D., Ph.D.
Judith Cope, M.D., M.P.H.
Julie Dopheide, Pharm.D.
Beth Durmowicz, M.D.
Bob Findling, M.D.
Ron Manderscheid, Ph.D.
Dianne Murphy, M.D.
Merrily Poth, M.D.
Adelaide Robb, M.D.
Perdita Taylor-Zapata, M.D.
Benedetto Vitiello, M.D.
Julie Zito, Ph.D.

Purpose

The purpose of the conference call was to discuss the group's recommendations and presentation for the 2009 BPCA annual scientific prioritization meeting on November 18 and 19, 2009.

Discussion

Recommendations. Dr. Manderscheid reviewed the bullet points from the minutes of the August 25 conference call:

- The working group agrees that the six priority areas are important.
- Funding is needed to implement the working group's recommendations.
- There is a deficit in data for pediatric antipsychotic therapeutics, particularly long-term data.
- The working group or group members would like to recommend drafting a review article.
- The working group, the National Institutes of Health (NIH), and the Food and Drug Administration (FDA) need to identify the variables to be included in electronic medical records.
- The working group needs to learn more about the FDA Adverse Event Reporting System (AERS). Dr. Manderscheid noted that the group had received a description of AERS since the last call.
- There needs to be a design for studies of risk factors/predictors of adverse events (AEs) and effects of long-term use of antipsychotic medications.
- The working group has an important purpose and would like to continue its activities.

Dr. Manderscheid said that the group should communicate these recommendations at the November meeting. He asked whether the group was still in general agreement on these points.

Dr. Murphy asked whether individuals from the FDA Division of Psychiatry Products (DPP) participated in the previous conference call. Sara Kistler from Circle said that all participants are listed in the conference call minutes. Dr. Durmowicz said that it had been difficult to ensure that DPP representatives are available for conference calls. Dr. Murphy said that the minutes should be sent to Dr. Thomas Laughren, director of DPP. Drs. Murphy and Cope will follow up with Dr. Laughren to make sure he is aware of the group's recommendations.

Dr. Murphy said that the FDA Pediatric Advisory Committee is meeting in winter 2009 to discuss antipsychotics. The advisory committee would like a report from the working group.

The group discussed whether Dr. Andrew Mosholder from the FDA Office of Surveillance and Epidemiology (OSE) should participate in the working group. Dr. Murphy said the OSE has a lot of experience with safety issues and conducts use and adverse event (AE) reviews. OSE has assigned individuals to work on the topic of antipsychotics safety, but not Dr. Mosholder. The group could ask Dr. Mosholder to participate, but his supervisors would have to assign him this work.

Ms. Kistler will send Dr. Murphy the complete list of working group members, and Dr. Murphy will contact individuals who need to review the recommendations and report back to the group. Ms. Kistler noted that Dr. Laughren receives the conference call minutes.

Presentation. Dr. Manderscheid said that during the last conference call, the group established action items for developing a 20–25-minute presentation, which is scheduled for November 19. Representatives from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and FDA will be present. Registration for the meeting will open on October 1.

The presentation will be structured as follows:

- Dr. Manderscheid will introduce the presentation and discuss the group's general recommendations.
- Dr. Zito will discuss long-term studies.
- Drs. Poth and Findling will discuss the use of FDA 6- and 12-month studies.
- The presentation will be followed by an open discussion.

Dr. Findling asked about the presentation on FDA 6- and 12-month studies. A lot of data are available. Dr. Poth said that she and Dr. Findling were charged with summarizing the depth and breadth of the published and unpublished data. It was noted that FDA data are more available for use and analysis than in the past. Dr. Manderscheid said that the presentation should discuss the available data and the requirements for accessing these data. Dr. Poth added that the data may show that there are some important questions that have not been asked.

Dr. Manderscheid said he would schedule a call with Drs. Zito, Poth, and Findling to discuss the presentation. He asked whether the participants had received the list of studies Dr. Cope sent, and Dr. Poth said that she had. Dr. Poth will contact Dr. Findling by October 2 to discuss their

portion of the presentation. Dr. Manderscheid said he would schedule the call during the week of October 5.

Dr. Findling said that he, Dr. Vitiello, and other researchers are in the final stages of developing a manuscript that describes a 12-month prospective safety study that compared molindone, risperidone, and olanzapine. He will check with the other investigators about summarizing this research at the November meeting. Dr. Manderscheid said the audience would be interested in ongoing research on antipsychotics in children.

Dr. Zito discussed the outline of her portion of the presentation, which was circulated to the group. She started from a simple clinical question: what is the safety profile for antipsychotic use in U.S. children and adolescents? She suggested that an example of a research question might be: what is the incidence of metabolic abnormalities in relation to the length of antipsychotic medication exposure? Studies should create cohorts that represent a range of comorbidities, concomitant psychotropic medication use, and health statuses.

Dr. Zito said she would discuss available data sources, which include meta-analyses of completed clinical trials. Clinical trial data have limitations for studying long-term use of antipsychotics because the trials are too short, have too few subjects, do not include sicker children, do not include very young children, and are limited to major diagnostic groups. Federal probability sampling surveys are not helpful for relatively low-use drugs like antipsychotics. AERS is a voluntary system with very low reporting. Dr. Zito said that severe AEs were reported in AERS at a rate of less than 1 percent, but it was noted that the AERS general reporting rate is less than 10 percent. Dr. Zito said that AERS can be helpful for detecting immediate reactions to new drugs, but it is not helpful for finding long-term AEs that are not easily recognizable, such as diabetes. Dr. Murphy will send Dr. Zito slides on the limitations of AERS. Dr. Zito said the slides would be helpful, but the presentation would need to be less than 5 minutes.

Dr. Zito said that administrative claims from nationally representative insurance programs are another source of data. Medicaid data have grown in importance because Medicaid covers almost 40 percent of children in the United States. Medicaid data also include variables, such as race and ethnicity, which are not available elsewhere. However, the data are not reliable to verify drug exposure or the extent of consumption of dispensed medication. It is important to verify consumption and improve the reliability of information on concomitant medication use, health status, and health history.

Dr. Zito said she would recommend collecting data from a large epidemiologic retrospective model and a prospective clinical analysis. Claims data could be used to detect signals, and data could be stratified by length of exposure. Patients exposed for up to 5 years provide an opportunity to define long-term risk. Regional academic research sites are in a position to respond with a protocol to enroll community children, but it would not be a randomized model.

Dr. Manderscheid asked whether the group would need to submit slides for the presentation before the November meeting. Ms. Kistler said that slides should be submitted to her in advance so that handouts can be distributed at the meeting. Dr. Manderscheid hoped that everyone in the

working group could attend the November meeting to participate in advocacy work to make the case that more resources are needed.

Dr. Murphy said that the Pediatric Advisory Committee is in a quandary as to what to recommend. The FDA will be presenting the committee another antipsychotic product and will update the committee on the activities of this working group. Dr. Cope has gathered AE data from the last year and will be providing the committee data on metabolic and weight gain effects in the pediatric population. The committee will either want to take action on labeling or want more data. The working group will have a critical role in helping the committee decide how to move forward.

Dr. Poth asked whether the group would have access to the AE data that will be presented to the committee. Dr. Murphy said the group would not have access before the committee meeting. She could not share the dates for the meeting, but if the group designates a presenter, she will contact him or her about meeting dates. Dr. Taylor-Zapata asked how long the presentation to the committee should be. Dr. Murphy said she would add half an hour to the agenda for a presentation by the working group. Dr. Taylor-Zapata should give a brief introduction, and then another member of the group can give a more detailed presentation.

Dr. Poth said that the AE data might be important to the working group. Dr. Murphy said the AE data were from AERS data and would include some striking individual cases. Dr. Cope said that a public announcement of the Pediatric Advisory Committee meeting would be posted in the *Federal Register* before the November BPCA meeting. Dr. Manderscheid suggested that the working group discuss the FDA Pediatric Advisory Committee meeting at the November BPCA meeting.

Dr. Taylor-Zapata said that the conference call was the last call supported by NICHD. Dr. Manderscheid said he would arrange the call for Drs. Zito, Poth, and Findling. He asked whether FDA could support future calls. Dr. Murphy said she would ask the project manager at FDA to arrange a conference call for the working group in late October. Dr. Murphy asked that the call not be scheduled the last week in October because she will be out of the country. Dr. Suzanne Malli will help organize the October call.

Ms. Kistler will send the slides on the limitations of AERS, the NICHD literature summary, and Dr. Cope's summary of trials to the group. Dr. Manderscheid thanked NICHD for organizing the working group's calls. Dr. Murphy said that the NICHD working group has been a critical step, and she appreciates that the group will be able to report back so quickly. Dr. Taylor-Zapata thanked the working group participants.

Action Items:

- Drs. Murphy and Cope will follow up with Dr. Laughren to make sure he is aware of the working group's recommendations.
- Ms. Kistler will send Dr. Murphy the complete list of working group members.
- Dr. Murphy will contact individuals who need to review the group's recommendations and report back to the group.

- Dr. Poth will contact Dr. Findling by October 2 to discuss their portion of the presentation.
- Dr. Manderscheid will schedule a call with Drs. Zito, Poth, and Findling the week of October 5 to discuss the presentation.
- Dr. Findling will check with other investigators about summarizing the results of a 12-month prospective study at the November meeting.
- Dr. Murphy will send Dr. Zito slides on the limitations of AERS.
- Dr. Murphy will ask the project manager at FDA to arrange a conference call for the working group in late October.
- Ms. Kistler will send the slides on the limitations of AERS, the NICHD literature summary, and Dr. Cope's summary of trials to the group.
- Circle will prepare and distribute draft minutes of the conference call.