

**Best Pharmaceuticals for Children Act (BPCA)
Antipsychotics Safety Therapeutics Working Group Conference Call
August 25, 2009
11:00 a.m.–12:05 p.m. ET**

Participants

Judith Cope, M.D., M.P.H.
Alyson Karesh, M.D.
Ingrid Kohlstadt, M.D., M.P.H.
Ron Manderscheid, Ph.D.
Merle Paule, Ph.D.
Merrily Poth, 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 in November. Minutes from the previous call and slides were distributed to call participants.

Discussion

Dr. Taylor-Zapata described the agenda for the annual meeting to be held November 18 and 19, 2009. The first day will be dedicated to discussing global prioritization issues. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the European Medicines Agency, the World Health Organization, and other organizations participating will discuss how to prioritize clinical research in pediatrics. On the second day, BPCA-related groups will discuss three working areas and future areas under consideration for 2010. A representative for each working group will present the group's findings and recommendations. Each group's presentation will last about 20–25 minutes, followed by response from the BPCA expert panel. Panel members may be from different therapeutic areas. After the response, there will be time for comments and questions from the audience. In the afternoon, participants will go through the priorities from these groups and for the future.

Dr. Manderscheid suggested that the group review its findings from the previous call and look at the slides in that context. He reviewed the group's findings as summarized in the minutes of the July 22, 2009 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. Data on short-term effects cannot be used to predict long-term effects.

- The working group or group members would like to recommend drafting a review article, outlining what is currently known and drawing conclusions about current status and future direction. The review article could be very useful in moving the field forward.
- The working group, the NIH, and the Food and Drug Administration (FDA) need to identify the variables to be included in electronic medical records regarding antipsychotic therapeutics.
- The working group needs to learn more about the FDA adverse event reporting system (for example, a presentation on the system by the FDA) to determine whether the system will detect the important variables related to antipsychotic therapeutics.
- There needs to be a design for studies of (1) risk factors/predictors of adverse events and (2) effects of long-term use of antipsychotic medications.
- The working group has an important purpose and is committed to field of pediatric antipsychotic therapeutics. The group would like to continue its activities.

Dr. Manderscheid said the group was asked to identify the top three priority areas, but the group decided all six priority areas were important. He noted that the group had agreed to work together to create its presentation, and he thought a group presentation would be needed to show that there is broad-based support for the group's recommendations. The findings listed above included five action items.

Dr. Manderscheid discussed a slide titled "BPCA Antipsychotics Safety Therapeutics WG Evaluation Results." The group members were asked to rank the top three items, which produced rankings ranging from 6.3 to 1.3. Those rankings fit closely with the five action items that were identified. Dr. Manderscheid asked the group whether those five actions are what should be presented at the November meeting and whether it might be possible to begin to make progress on action items even before the November meeting.

Dr. Zito said that collecting information on longitudinal exposure to antipsychotics is critically important to pick up the kind of signals that researchers are looking for (if the signals exist) in adolescents who have been exposed for considerable periods of time. The data from follow-up studies of clinical trials could be mined. She suggested forming longitudinal cohorts from claims data using several sources, including commercially insured children and the Medicaid population, for the power to detect relatively weak signals. MAX files from the Center for Medicare & Medicaid Services (CMS) could be used to create large longitudinal cohorts of antipsychotic drug users who used the drugs for 6 months and longer periods up to 4 years. These large cohorts might have the power to detect readily measurable events that may be related to use of these drugs (such as development of diabetes).

Dr. Vitiello asked how researchers would deal with concomitant treatments. Dr. Zito said they would need to define concomitant treatment. They might want to have the ability to measure cumulative exposure to an antipsychotic drug (or drugs) and differentiate the atypical drugs from conventional drugs. They would identify whether there were one or two (or no) concomitant drugs within another class and the length of time of that exposure; there could be short exposures to concomitant drugs.

Dr. Vitiello said that taking multiple drugs is more the rule than the exception because patients change drugs during treatment. For instance, in the early treatment of psychosis, few patients are still on the same drugs they started on after 12 months. This finding was in a control study trying to keep patients on the same treatment. Out of 120 patients, only about 15 were still on the same medication after 12 months. There are several common reasons for failing to continue medications, and sometimes the reason is unknown.

In response to a question about the MAX files, Dr. Zito explained that CMS collects annually all the data the state Medicaid programs send to the government. There are data sets available from every state. Recently, people have begun to put together a data set that is representative of all the children in the country. These are large data sets, but they can be worked down to the patient level. There are many variables—the patient's state, region, demographics including race, and every prescription that was written during the year. These data sets can be purchased. The data must then be cleaned to put together a data set that includes the desired variables. The data come from three files: outpatient prescription claims data, outpatient physician visit data, and patient descriptions.

Dr. Manderscheid commented that he used to put these cohorts together, and it is possible to do that with Medicaid data. He asked the group members whether they agreed with what Dr. Zito said about the group presentation including a statement about the importance of long studies and how feasible it is to do them. The group members agreed. Dr. Paule said it is critical to know and stratify by the age when treatment started. Animal models have shown that as age increases, sensitivity changes dramatically from infant to adolescent.

Dr. Manderscheid asked what other topics in addition to longitudinal studies should be included in the presentation, such as electronic medical records (EMR) or what should be in FDA short-term (6- and 12-month) studies.

Dr. Zito said the main thing missing from EMR is the reason the medication was discontinued. Having the reason, such as an adverse event or lack of effectiveness of the drug, would be helpful. Dr. Poth added that there was a need for some codable growth data, such as body mass index.

Dr. Manderscheid asked about elaborating on the 6- and 12-month studies. Dr. Poth said data already available from the FDA should be used. The data would need to be analyzed. The drug companies are responsible for furnishing those data. The data may lack information about why medications were discontinued, and it is important to get that information. The data should be more broadly available for independent assessment.

Dr. Taylor-Zapata said although the data are not broadly available yet, there are mechanisms to make the data available. Dr. Manderscheid suggested that the group needed help identifying those mechanisms so it can say the mechanisms need to be made available.

Dr. Manderscheid said another topic relates to design of studies of risk factors, adverse events, and so on. He asked whether the group needed to say there needs to be work done in developing these designs and perhaps present an example of a design.

Dr. Zito commented that some areas that are particularly challenging relate to risk assessment from naturalistic data that involves confounding by indication and how to get around that. Some sort of hybrid approach is needed, starting with significant data, such as a twofold increase in glucose levels—that is, a good strong signal. But still there is not precise enough information to hold the drug totally accountable. The next step could be drilling down and asking EMR agencies to set up a prospective survey using length of exposure to the drug as the critical selection criterion.

Dr. Poth noted that people with a family history of diabetes and minorities are at higher risk for metabolic side effects. By getting vital signs, height, weight, and other measurements, one could see whether a patient was overweight to start with and then became obese.

Dr. Zito said that part of the research should be done prospectively. The only variable for weight is obesity, but obesity may not appear on the claim in many cases even though the children are obese. She recommended (1) determining that something is going on and mining the data, and (2) getting EMR people engaged in a prospective study based on this profile. Many risk factors require longer exposures than are typical in clinical trials.

Dr. Poth said that patients who are referred to her are those who rapidly become very obese and develop glucose intolerance very quickly. She does not see the patients who psychiatrists see. She would like to know what happens to all of them who are treated and wonders why the patients gain weight, that is, whether they are lethargic or hungry, or whether some other factors are involved. The basic mechanistic questions have not been addressed. In response to a question, Dr. Poth said she did not think there was relevant animal work on weight gain.

Dr. Manderscheid said he thought those pieces seemed to fit together well. The group's presentation should have two pieces. First, the group can recommend looking at long-term risk assessment, which includes use of large-scale data systems and how to use them to do longitudinal studies. The group can say that these studies are feasible and need to be done. Second, the group can recommend prospective research to pick up people before they develop symptoms and predict who would develop symptoms.

Dr. Manderscheid said that regarding the FDA 6- and 12-month studies, the group can make the case that it is essential that more be done with the data and that there is a need to learn more about the mechanisms that can be used to do these studies. The group could mention some designs that could be applied to look at those issues.

Dr. Poth suggested that Dr. Manderscheid present the group's findings. Dr. Manderscheid said he could weave the material together, but he thought other group members should talk about some of the content. He suggested that Dr. Zito talk about large-scale studies and prepare, at most, two or three slides. Dr. Zito agreed to do so. Regarding the prospective piece, Dr. Poth

agreed to speak to the effects that the study would look for over time. Dr. Taylor-Zapata suggested that Dr. Poth work with Dr. Bob Findling, who has data.

Dr. Zito raised the question of the setting for the research and who could speak to this issue. Dr. Taylor-Zapata said that she did not think there would be time to talk about the setting in the group's initial presentation, but this issue could be brought up during the afternoon discussion.

Dr. Manderscheid said that Dr. Findling might be the best person to speak about the 6- and 12-month studies, but he was not on the call. Dr. Zito noted that the group did not have key people on the call such as an industry person or FDA representative. Dr. Manderscheid suggested putting together a list of people who should be invited to the meeting, including industry people. Dr. Taylor-Zapata said that FDA representatives would be present, but not industry representatives. However, the group could reach out to them with the group's recommendations in the future. There is no rule that industry representatives cannot be at the meeting, but the invitations have gone out, and there are space and funding issues. Group members are free to mention names of people they would recommend be invited. Dr. Manderscheid said he would think more about the question of an industry representative.

Dr. Manderscheid summarized the content of the 20-minute presentation, which will contain two major pieces: one on long-term risk assessment and one on short-term studies. Dr. Zito will talk about long-term risk assessment and mention several specifics about how to get the large-scale data sets and work with them. Dr. Poth will work with Dr. Findling on the other piece about drilling down on the variables. The group will not take up the setting issue in its presentation but will allude to it and then discuss it in the afternoon session. Everyone agreed that Dr. Findling would be the best person to address the 6- and 12-month studies.

Dr. Manderscheid will introduce the presentation, give the context of the group's meetings and discussions, and explain that group members will be presenting what the group thinks are important recommendations. He thought the group might need another call or two to finalize the details. The group members need to do the homework to create two or three slides for each piece of the presentation. Ideally the group can share and critique the slides during the next call. Everyone agreed that was a reasonable plan.

Dr. Manderscheid suggested having a presentation about the new FDA Adverse Event Reporting System (FAERS) during the group's next call. It would be valuable to know more about this system and variables that will be reported.

Dr. Cope said FAERS is an evolving electronic system for receiving, processing, evaluating, and analyzing the MedWatch reports. The new FAERS database will encompass all the adverse events databases, including the Adverse Event Reporting System (AERS) and the Manufacturer and User Facility Device Experience databases. FAERS will streamline existing databases. It will include mandatory manufacturer reporting and voluntary reports. It will not necessarily include detailed information. The FDA receives adverse event reports, and then safety evaluators may call the manufacturers that submitted the reports and ask for more information, but sponsors may not have it. Some biases exist, and more than half the time, no specific age information is

given. A report may say “a teenager.” Thus, important information may be missing from the reports.

Dr. Manderscheid asked whether the group should say it would be good to get age information to improve the quality of the reporting. Dr. Cope said it would strengthen the information.

Dr. Zito said she thought there are forms now that ask for age. The reporting comes to the FDA, and the FDA reviewer may choose to talk to a knowledgeable person and get additional information to get a retrospective assessment of the problem. The fundamental problem with AERS is the denominator. Dr. Zito said it would be exciting to understand the FDA’s Sentinel Initiative, its goals, and how it could advance understanding of risk in children.

Dr. Taylor-Zapata said that BPCA would not be able to support a presentation by the FDA to this group. Only one more call can be supported by September 30 to finalize the group’s recommendations. However, group members could send questions for the FDA to her, and she can ask FDA representatives to respond to the questions at the November meeting. Dr. Manderscheid suggested that the group take that on as homework, and the group can finalize questions during the next call. The group will create slides for the presentations and think of questions about the FDA’s Sentinel System, including FAERS, to discuss during the next call.

The group discussed a time for the next conference call and tentatively chose Friday, September 25, at 11:00 a.m.

Action Items:

- Dr. Manderscheid, Dr. Zito, and Dr. Poth, who will work in collaboration with Dr. Findling, will present the working group’s recommendations at the 2009 BPCA annual scientific prioritization meeting in November.
- Dr. Manderscheid will introduce the presentation and provide context for the group’s recommendations.
- Dr. Zito will discuss long-term risk assessment using large-scale data systems.
- Dr. Poth will discuss the prospective piece and the kind of effects the study would look for.
- Dr. Findling will be asked to present about the FDA 6- and 12-month studies.
- Each presenter will prepare two or three slides for his or her portion of the presentation and share them with the group during the next call to obtain feedback.
- Group members will suggest questions for the FDA concerning the FAERS system and the Sentinel Initiative during the next call. Dr. Taylor-Zapata will forward them to the FDA for possible response during the annual meeting.
- The working group will tentatively have its final conference call on September 25 at 11:00 a.m.
- Circle will prepare and distribute draft minutes of the conference call.