

**Best Pharmaceuticals for Children Act (BPCA)
Antipsychotics Safety Therapeutics Working Group Conference Call
July 22, 2009
10:00 p.m.–11:00 p.m. ET**

Participants

Jeffrey Blumer, M.D., Ph.D.
Judith Cope, M.D., M.P.H.
Julie Dopheide, Pharm.D.
Elizabeth Durmowicz, M.D.
Bob Findling, M.D.
Ingrid Kohlstadt, M.D., M.P.H.
Ron Manderscheid, Ph.D.
Merle Paule, Ph.D.
Merrily Poth, M.D.
Adelaide Robb, M.D.
Daniel Safer, M.D.
Dave Siegel, M.D.
Perdita Taylor-Zapata, M.D.
Benedetto Vitiello, M.D.
Julie Zito, Ph.D.

Purpose

The purpose of the conference call was to:

- Review the results of the priority areas evaluation
- Review, update, and finalize the working group’s recommendations
- Determine next steps.

Discussion

Dr. Manderscheid explained the method for scoring and ranking the priority areas. He noted that the second item (“FDA [Food and Drug Administration] can collate safety data from 6- and 12-month drug trials of antipsychotics that have FDA filings.”) was ranked highest. He also noted that the rankings correlate with the amount of available data. Priority areas with currently existing data are ranked higher. Areas without existing data are ranked lower.

Dr. Zito commented on the first item on the priority areas list (“BPCA funds could be used to access databases to determine safety signals in the use of antipsychotics.”). She proposed a modification of the approach of using administrative data sets, which may have problems such as unreliable diagnoses and missing diagnoses. The modification would be a hybrid model using administrative claims from a nationally representative data set as a descriptive tool to understand the patterns of use (for example, to determine the number of children who are on an antipsychotic drug fairly continuously over a 2-year period and their corresponding demographic

data). This approach would yield a general community-based profile of the children who are getting medicated. The profile would provide a sampling frame. For example, an existing academically based regional study could be used to establish a cohort of children and prospectively interview and assess a sample of children in care to embellish and ascertain actual exposures to antipsychotic drugs. Dr. Manderscheid commented that this approach plays to the strengths of administrative databases and downplays their weaknesses.

Dr. Manderscheid asked whether the rankings reflect the group's opinion. It was noted that not all working group members were on the conference call and that there has not been an extensive dialogue about the priority areas. Dr. Taylor-Zapata explained that the evaluation and evaluation results were sent to all working group members. In addition, conference call minutes are sent to all working group members, who have an opportunity to provide feedback.

Dr. Findling identified two issues:

- Any of the working group's recommendations will require resources to implement; the budget for implementing recommendations is not known.
- Data that the FDA evaluates may belong to drug companies, and because the data may be proprietary, they may not be available for evaluation.

Dr. Kohlstadt explained that BPCA and the Pediatric Research Equity Act require drug companies to submit proprietary data after they receive marketing or patent exclusivity.

Dr. Manderscheid said it is important for the working group to emphasize the importance of the FDA having appropriate resources to conduct pediatric studies of antipsychotic drugs. According to Dr. Manderscheid, resources are not available to carry out any of the working group's priority areas. The working group must continue to advocate that the FDA acquire the resources to implement the recommendations. It is important to make an investment in children and the future. The FDA needs the working group's support to move the agenda forward.

Dr. Manderscheid said that although the working group ranked the six priority areas, they are all important and all should eventually be implemented. Work should begin in the priority areas that have existing data and then move on to areas that currently have no data. Mechanisms to collect data need to be established.

Dr. Poth commented on the FDA data disseminated to the working group. Within the data sets, there were subgroups of children that had severe side effects, but when these effects were included with the larger group, the average side effects were not that severe. When evaluating preexisting data sets, it is important to determine whether children with severe side effects have pre-morbid conditions. It would be beneficial to identify which children are at higher risk for side effects before taking antipsychotic medications.

Dr. Zito noted that the observational literature resides in one "silo," the clinical trial data reside in another silo, and data from clinical practice with small sample sizes reside in a third silo. She proposed writing a review article of the published data that would lead to some conclusions about the status of pediatric antipsychotic therapeutics. In addition, the article would describe the

gaps in knowledge. Dr. Manderscheid asked whether the working group should write, or be involved in writing, such a review article. Dr. Manderscheid proposed that the working group add to its list of priority areas a recommendation to write one or more review articles of pediatric antipsychotic therapeutics. The articles would provide analyses and outline next steps.

Dr. Zito asked whether proprietary data at the FDA could be accessed to help prepare the review article. Dr. Blumer said the Pediatric Pharmacology Research Units (PPRU) network set a precedent and established a mechanism for accessing this type of data. The Duke University PPRU site contracted with the FDA to access all proprietary data on pediatric hypertension trials. Analyses of these data resulted in a number of publications. The data sets are not “unreachable,” and the working group should further explore accessing proprietary antipsychotic drug data at the FDA. The working group recommended exploring access to this type of data. Dr. Paule noted that industry has shared proprietary information when there was a well-defined and important goal.

Dr. Robb said the FDA requires drug companies to monitor suicidality in clinical trials of antiepileptics and antidepressants. The FDA could require monitoring of similar short- and long-term outcomes in pediatric trials of antipsychotics. Dr. Manderscheid asked what type of information related to drug use would need to be included in new electronic medical records for pediatric studies of antipsychotics. In addition to anthropomorphic data such as height and weight, it is important to know baseline health status before a child begins medications.

Dr. Poth commented that in her review of the FDA data, there were good short-term data and case reports of longer term medication use, but there were few data on long-term follow-up of short-term studies. Dr. Zito noted that there can be up to a 50 percent dropout rate in the open phase following the double-blind phase in clinical trials. For the future of drug therapy to have any meaning, for community-based monitoring of safety, there needs to be a systematic assessment of adverse events in children. There also needs to be a lab assessment for risk. Dr. Manderscheid asked whether the FDA’s adverse event reporting system has the right variables or a complete set of variables to track adverse events in children. Dr. Zito said large sample sizes are necessary to detect rare events, but the critical variables need to be measured up front to make sense of the rare events.

According to Dr. Paule, toxicology studies can be conducted in appropriate adolescent or peri-adolescent animal models to look for the signals of rare events. Animal studies can help focus the effort in pediatric studies. However, it was noted that animal data have low credibility with some clinical researchers. Dr. Zito noted the challenge of determining causal relationships between drugs and rare events.

Dr. Findling noted two gaps in current knowledge that warrant further attention:

- Data on outcomes associated with concomitant medicines routinely prescribed in clinical practice
- Data on long-term drug use.

What is needed is a large cohort that is followed for more than 1 year to answer questions about key variables that may not be ascertained other than by conducting prospective, longitudinal evaluations. Dr. Findling said it was not clear whether the National Institutes of Health (NIH) or the FDA were currently empowered to play a major role in conducting such a study. Dr. Vitiello commented that the NIH funds research that addresses specific questions but generally does not analyze databases or set up long-term surveillance systems to look for signals in particular drug classes. Dr. Zito commented that the NIH has the PPRU network and Research Units on Pediatric Psychopharmacology Autism Network, which are set up to handle small samples for very precise, limited measurements that relate to pharmacokinetics, dosing, safety, and efficacy. These networks have the infrastructure that could be extended to include longer term drug exposure studies.

Dr. Manderscheid summarized the discussion and recommendations as follows:

- 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 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. Robb commented that the paliperidone trial, which is a multinational registration trial for adolescents, has a 2-year, open-label extension. The extension was granted because the European regulatory agency wanted 2-year data. Dr. Robb proposed cooperation with international regulatory agencies that require 2-year safety data for pediatric trials. The working group recommended that U.S. studies of pediatric antipsychotics cooperate or collaborate with similar international studies.

Dr. Taylor-Zapata clarified that the working group was formed by the NICHD, and studies that result from the working group's recommendations would be funded by the NICHD in collaboration with the FDA. The working group's recommendations will go to both the NICHD and the FDA.

Action Items:

- Dr. Manderscheid or a panel will present the working group's recommendations at the 2009 BPCA annual scientific prioritization meeting in November.

- The working group will convene a fourth conference call to discuss, among other things, the presentation at the November meeting.
- Circle will prepare and distribute draft minutes of the conference call.