Best Pharmaceuticals for Children Act (BPCA)
Antipsychotic Safety Therapeutic Working Group Conference Call
April 1, 2009
10:00 a.m.–11:00 a.m. ET

Participants

Jeffrey Blumer, M.D., Ph.D., Case Western Reserve University
Judith Cope, M.D., M.P.H., Office of Pediatric Therapeutics (OPT), Food and Drug Administration (FDA)
Elizabeth Durmowicz, M.D., Center for Drug Evaluation and Research, FDA
Robert Findling, M.D., Case Western Reserve University
Norma Gavin, Ph.D., RTI International
Ingrid Kohlstadt, M.D., M.P.H., OPT, FDA
James Korelitz, Ph.D., Westat
Michael Kronen, M.D., Inova Fairfax Hospital
Jan Leahey, NICHD, NIH
Laura Panko, M.D., University of Pittsburgh School of Medicine
Merrily Poth, M.D., Uniformed Services University of the Health Sciences
Marsha Rappley, M.D., Michigan State University
Adelaide Robb, M.D., Children's National Medical Center
Daniel Safer, M.D., Johns Hopkins Medical Institutions
Perdita Taylor-Zapata, M.D., NICHD, NIH
Anne Zajicek, M.D., NICHD, NIH
Julie Zito, Ph.D., University of Maryland, Baltimore

Purpose

The purpose of the meeting was to:
- Review BPCA activities (history, accomplishments, studies, therapeutic areas)
- Identify current needs regarding antipsychotic therapeutics for children.

Introduction

Dr. Taylor-Zapata welcomed the call participants and described the purpose of the call. She provided background information on the BPCA legislation and described NIH's roles, responsibilities, and accomplishments for BPCA. For example, as of the June 2008 annual priority meeting, 106 therapeutics have been discussed with experts and 76 drug/indication pairs have been identified and listed as priority drugs requiring further pediatric studies. Dr. Taylor-Zapata listed the overall lessons learned, current and pending studies, and currently prioritized therapeutic areas. She discussed the prioritization process, the stakeholders involved, and the working group's responsibility. She noted that when BPCA was reauthorized in 2007, its focus shifted from prioritizing drugs to identifying gaps in pediatric therapeutics, including drugs, indications, biologics, and devices that require further study in children. As of March 2009, NICHD has developed a list of needs in pediatric therapeutics:

- 18 therapeutic areas listed as priority, which include psychiatry and adolescent medicine
- 33 conditions listed as priority
- 15 new therapeutics (drugs and/or delivery systems) listed as priority.

In November 18, 2008, an FDA Pediatric Advisory Committee recommended that additional information be gathered on on- and off-label use of atypical antipsychotic drugs, with specific attention to age and indications for which the drugs are prescribed. The advisory committee cited two drugs that are frequently prescribed to children for different indications: olanzapine (Zyprexa) and risperidone (Risperdal). There are data on how many children are taking atypical antipsychotics, but there is limited information on the long-term use of this class of drugs and the extent of the associated diagnoses for which these drugs are being prescribed. NIH has gathered some information from Medicaid and commercial databases, and FDA has also gathered some data with their current access to their prescription databases.

Dr. Taylor-Zapata posed the following questions:
- What is the frequency of off-label use and the associated diagnoses for this class of drugs?
- What databases are appropriate to gather this information?
- What are the frequency and extent of metabolic and extrapyramidal side effects?
- In addition to literature reviews, what other sources of information are available?
- What additional research is needed? (e.g., pharmacogenomics, receptor differences)
- Besides the work of the Research Unit in Pediatric Psychopharmacology, what other studies are being conducted on the long-term effects of atypical antipsychotics?
- What are the needs for prospective studies? (e.g., registry trials, epidemiological studies)
- What are the needs for studies on polypharmacy in patients with chronic and/or refractory disease (for example in adolescents)?

Discussion

Dr. Findling explained that one of the key problems in determining drug use and associated diagnoses is that practitioners use diagnostic codes for which they will be reimbursed. In addition, comorbid conditions that may also be targets for pharmacotherapy are oftentimes not coded. As a result, a child psychiatrist may prescribe a drug for one disorder but use a diagnostic code for a different disorder that is also present (e.g., attention deficit/hyperactivity disorder [ADHD]) in order to get reimbursed. Dr. Zito commented that ADHD and other disruptive behavior disorders are common diagnoses in Medicaid and other data sets. Dr. Findling noted that comorbid disorders such as disruptive behaviors are often not reimbursable in Ohio. But because ADHD is reimbursable and accurately conveys an existing condition that is also a focus for the outpatient visit, it is a frequently used diagnostic code. Dr. Zito said comorbidities can be examined in the Medicaid databases.

Dr. Rappley said that, although the limitations of data sets are well recognized, they still provide essential information. One of the working group's tasks is to identify multiple, complementary data sets and determine the best ways to use the data sets to advance knowledge on use and diagnosis. For example, Medicaid-based data sets can show the increasing use of medications, but electronic data sets such as the Kaiser system can provide details about the symptoms and

problems that are prompting the use of particular drugs. Dr. Kohlstadt said that FDA is developing two continuing medical education (CME) modules around the atypical antipsychotics and sending them to several thousand practitioners across the country through Audio Digest, Medscape, and a professional society. This activity will gather pretest data through the CME to assess practitioners' knowledge of label information and management of side effects.

Dr. Robb commented that initial diagnosis codes may not change as patients get older and diagnoses change. A child may be diagnosed with ADHD at 5 years of age, but by age 7 or 8, the diagnosis may change to bipolar disorder. Yet, the diagnosis code will remain ADHD in a database because the databases do not change.

Dr. Taylor-Zapata stated that NICHD has conducted a literature review and clinical trials database review to determine the frequency and extent of metabolic and extrapyramidal side effects of atypical antipsychotics. Results from these reviews will be available soon and will be distributed to the working group. Dr. Poth said it is important to gather premorbid data and information on early indications of side effects. There should be early and ongoing monitoring of side effects when atypical antipsychotics are prescribed. Based on her experience with registration trials for most of the atypical antipsychotics, Dr. Robb said that the side effects vary by drug. For example, risperidone is known to increase prolactin levels, whereas aripiprazole (Abilify) is known to decrease prolactin levels. These drugs are known to cause weight gain, but each drug causes different amounts of weight gain. Extrapyramidal side effects are known to vary by gender and race. Therefore, lumping the "atypicals" into a single drug class may be problematic.

Not all atypical antipsychotics are equal, and not all children are equal. Dr. Robb noted that there is an HLA subtype with an increased risk of Stevens-Johnson syndrome from carbamazepine (Tegretol) use. People who are at risk can be tested before taking the drug. This sort of testing for the potential of other side effects for other atypicals cannot be done at this time. Dr. Poth commented that knowing a patient's family history may help to predict which patients would be most susceptible to side effects (e.g., dysmetabolic syndrome, diabetes, obesity). Dr. Findling noted that what often gets lost in considerations of potential risks and side effects are the potential benefits of these drugs for some children. It would be advantageous to be able to identify which children are more susceptible and which are less susceptible to concerning side effects. Dr. Findling said that most practitioners who prescribe atypicals are actually trying to help children with psychiatric disorders.

Dr. Cope explained that little is known about the off-label use of the atypicals, particularly in very young children. As a result, the FDA Pediatric Advisory Committee in November 2008 recommended that safety issues be investigated by age group. Dr. Kohlstadt said that advisory committee member Leon Dure, M.D., was concerned about the extrapyramidal effects of these drugs, particularly risperidone. One of this drug's new indications is treating autism-related irritability in children 5 years of age and older. Dr. Dure noted that it is difficult to distinguish tardive dyskinesia and dystonia associated with autism from the side effects of risperidone. Dr. Dure believes that the dystonia associated with risperidone is underrecognized. Dr. Cope further explained that the underlying psychiatric disorder being treated may actually worsen or

complicate the understanding of side effects. For example, risperidone causes weight gain and somnolence in some children. The weight gain is associated with sleep apnea. Therefore, one of the possible metabolic side effects is overlooked because the disease itself also causes somnolence. In such situations, it is more difficult to identify side effects. Dr. Poth said this is one of the reasons why it is important to gather good pre-use data.

Dr. Cope said some of the large databases may be of value in investigating both use and safety issues. Age groups can be stratified readily in commercial insurance (e.g., the Kaiser system) and Medicaid databases. There is a high probability that there are cohorts of children within the Medicaid system that, because of the severity of their needs, will be in the system over many years. These cohorts could be used to measure prior exposure and other variables, which would help understand underlying illnesses, comorbidities, and postexposure changes with different drugs. Dr. Poth noted that the Department of Defense (DOD) has a database for its health care system, which is the largest in the world. This powerful database could offer another means to investigate the use and side effects of the atypical antipsychotics. A few investigators (e.g., Peter S. Jensen, M.D.) have analyzed the DOD database.

In addition to research on the associations of gender, age group, and race/ethnic group differences with side effect profiles, other potential research areas include comorbidities, concomitant drug use (i.e., using more than one atypical antipsychotic or other psychiatric drug—anticonvulsants, antidepressants, anxiolytics), and polypharmacy (i.e., drugs for nonpsychiatric conditions—diabetes, cardiovascular disease, hypertension). There are additional risks with polypharmacy, and the potential for drug interactions with polypharmacy has not been investigated in children and adolescents.

Dr. Rappley said it is important to study cumulative risk over time. Databases that capture treatments of children over many years allow analysis of cumulative risk. Another aspect to investigate is inconsistency of use among the medications. Many of these drugs appear to be prescribed using an “as needed” approach over many years of a child’s development. Understanding the patterns of drug use would be helpful. Some rare outcomes will not be seen unless a database allows investigators to follow children over many years, which also allows consideration of developmental aspects. There may be differences in cumulative risk for a child who begins a drug at age 5 compared with a child who begins the same drug at age 10.

With regard to investigating long-term cumulative effects over time, prospective studies may be more informative than database analyses. Dr. Findling commented that a large registry trial would be good for studying the atypical antipsychotics. Such a trial would address key fundamental questions that existing databases alone cannot answer. It was acknowledged that large registry trials or epidemiological studies would require substantial resources. A registry trial or study would give simple descriptions of which children are receiving which drugs. Dr. Poth proposed that any registry be independent of the companies that manufacture the drugs.

Dr. Rappley commented on a potential study that would take advantage of electronic medical record systems. The study (Dr. Rappley described it as her “dream study”) would enroll several hundred thousand children. Electronic medical records for these children would have a limited

number of add-on questions for each day's encounter record. A written protocol would be distributed to all the pediatricians and psychiatrists in the system. Practitioners would provide information on children with specific diagnoses for specific periods (months, years).

Dr. Rappley agreed that a registry is the best way to proceed, but investigators will need to pull "signals" from all existing data sets to justify undertaking the registry. Implementing a registry for atypical antipsychotics would need to compete with resources for other compelling conditions such as asthma, cardiac conditions, diabetes, and obesity. Investigators cannot stop using the less-than-perfect databases as they work toward a much preferred registry. Dr. Robb noted that, because one of the atypicals' side effects is obesity, resources could be shared with other, related projects. A registry will require careful planning and development to determine the ideal set of data to be collected. Dr. Robb cited the General Practice Research Database (GPRD) in the United Kingdom as a model for an atypical antipsychotic registry.

Dr. Cope said there have been recent publications and FDA warnings regarding cardiovascular disease and increased mortality associated with use of atypical antipsychotic in elderly patients. The association of cardiovascular disease with use of atypical in children should be assessed.

Next Steps

- Dr. Taylor-Zapata will distribute the link for the minutes of the November 18, 2008, FDA Pediatric Advisory Committee Meeting. DONE
- Dr. Taylor-Zapata will distribute the results of the literature review for comments and suggestions.
- The Obstetric and Pediatric Pharmacology Branch will investigate relevant databases (e.g., the GPRD).
- Circle will prepare and distribute a draft of the meeting minutes.
- The working group will review and comment on the draft minutes.
- The next conference call will be on May 27 from 10:00 a.m. to 11:30 a.m.