Best Pharmaceuticals for Children Act (BPCA)
Adolescent Therapeutics Working Group Conference Call
March 24, 2009
11:00 a.m.–12:15 p.m. ET

Participants

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Rosemary Higgins, M.D., Center for Developmental Biology and Perinatal Medicine, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH)
Roberta Kahn, M.D., Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse, NIH
Alyson Karesh, M.D., CDER, FDA
James Keim, M.S.W., L.C.S.W., Bay Area Oppositional and Conduct Clinic
Pamela Murray, M.D., M.P.H., Division of Adolescent Medicine, Children's Hospital of Pittsburgh
Natella Rakhmanina, M.D., Special Immunology Program, Children's National Medical Center
Michael Spigarelli, M.D., Ph.D., Pediatrics and Internal Medicine Division of Adolescent Medicine, Cincinnati Children's Hospital
Perdita Taylor-Zapata, M.D., Center for Research for Mothers and Children, NICHD, NIH
Maria Trent, M.D., M.P.H., Department of Pediatrics, Johns Hopkins University
Sue West, Ph.D., Research Triangle Institute
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Purpose

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

Introduction

Dr. Taylor-Zapata welcomed the call participants and described the purpose of the call. The call participants introduced themselves, stating their affiliations and areas of scientific interest.

Dr. Taylor-Zapata provided background information on BPCA legislation. She described NIH's roles, responsibilities, and accomplishments for BPCA. She listed the overall lessons learned, current and pending studies, and currently prioritized therapeutic areas. Dr. Taylor-Zapata 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.

She posed the following general questions to the call participants:

- Does the field of adolescent pharmacology exist? If not, should it exist?
  - Observed differences in drug responses in adolescents (side effects, effectiveness, toxicity)
    - Reference article—*Clinical Pharmacology and Therapeutics*, December 2008
- What are other important factors in adolescent clinical care and research?
  - Drug interactions
  - Drug use/abuse
  - Psychiatric comorbidities
  - Nutrition (obesity, anorexia)
  - Pregnancy in adolescence and therapeutics
- What are some of the research issues in adolescent therapeutics?
  - Adherence
  - Parental consent
  - Trial design issues
  - Transition into adulthood diseases.

Discussion

Dr. Spigarelli explained that the field of adolescent pharmacology *does* exist, although it is a relatively new and developing field. There are drug-response differences in adolescents. Side effects in adolescents are not well characterized but are well known. Interactions with the atypical antipsychotics is one area in which adolescent pharmacology exists, and this research area is generating preliminary data. Weight gain associated with atypical antipsychotics is well known. What is missed is when this weight gain coincides with the pubertal growth spurt. Adolescents who begin therapy with these drugs at the time of pubertal growth gain weight much more rapidly and to a much greater extent than do younger or older adolescents who are taking these drugs. Similar weight gain is seen in girls who begin the injected contraceptive Depo-Provera during the pubertal growth spurt. Certain drugs interfere with development during adolescence. There have been concerns about the use of steroids in adolescents for asthma and other conditions with respect to their effect on growth. Another area of concern is nutrition. Little is known about the effects of underweight and overweight on therapeutics in adolescents. One area of emerging concern is "super-obesity." Teenagers with morbid obesity often present with pulmonary hypertension, which can affect drug therapies and dosing regimens.

Dr. Rakhmanina said the field of adolescent pharmacology *should* exist. There is a great need for knowledge in this area. For example, there is a lack of knowledge on the clinical use of antiretroviral drug therapy in adolescents. Practitioners need to understand where to draw the line between pediatric and adult dosing guidelines. For example, the guidelines consider Tanner stages 1 and 2 as pediatric and Tanner stage 5 as adult, but the guidelines are not clear about Tanner stages 3 and 4. Adherence issues are important during adolescence, and simplification of the therapeutic regimen can be crucial to adherence. Yet the effects of Tanner stage on the distribution of antiretroviral drugs are not known. Two other issues are drug interactions and developmental pharmacogenetics. The pharmacogenetic changes in the expression of multiple enzymes and cytochrome P450 in early postnatal children are well studied, but little is known of

pharmacogenetic changes that occur in adolescents. Little is known about the relationship of these changes and the pubertal growth spurt. With regard to drug interactions, the use of contraceptives, alcohol, illicit substances, and smoking should be considered.

Dr. Trent noted that there are insufficient data on the effects of drugs on teenagers as they go through developmental stages. For example, a Tanner-stage-5, 17-year-old girl is very different from a 12-year-old girl who is the early stages of puberty. How medications affect adolescents at different developmental stages may vary. Body weight and Tanner stage should be considered in adolescent therapeutics. Pregnancy may affect the use of drugs. Adolescent pharmacology *should* exist, and the developmental process must be considered. Two big issues are polypharmacy and adherence. Adolescents must often manage their own care, and adhering to treatment regimens can be challenging. There are data on adolescents' adherence to HIV and diabetes treatment regimens, but there are few data on adherence to other therapies.

Dr. Murray commented that adolescent obesity is an emerging issue. For example, pediatric doses are determined by body weight, but by a certain age (generally around puberty), adolescents are given adult doses. Children in early adolescence who are given adult doses may not be functioning physiologically as adults. The effects of behaviors such as smoking and alcohol consumption on adolescent pharmacology are not known.

Dr. Murray noted that health literacy may play a role in adolescent clinical care. Dr. Spigarelli commented that provider education can be a factor in clinical care. For example, a primary care physician who prescribes an antibiotic for an adolescent girl may instruct her to stop taking birth control pills. Dr. Spigarelli said there is a deficit of knowledge among practitioners who treat adolescents. He cited an example in which a 200-kg, 15-year-old adolescent dosed by body weight may receive a dose that exceeds the adult dose. Dr. Rakhmanina cited another example in which a physician providing acute care may not ask about medications for chronic conditions. Medications from other sources must be considered when prescribing for acute conditions in adolescents. The potential of significant drug interactions must be considered when initiating new therapeutics.

Dr. Taylor-Zapata asked the call participants whether there is a need to study the use of antipsychotic medications, or any psychiatric medication, in adolescents. Particular areas of need would be safety, puberty changes, endocrine impact, and neurological impact. Dr. Spigarelli mentioned the meta-analysis of suicidality among adolescents taking antidepressants. Those studies were not powered to determine that endpoint. The immediate impact of the meta-analysis was many teenagers being taken off antidepressants, which probably led to worsening outcomes. It is currently believed that antipsychotics are overused and understudied. These medications are commonly prescribed for many indications. Dr. Trent noted that many children and adolescents who are treated with multiple psychiatric drugs—particularly those who are institutionalized or who have severe disabilities—may also have other health problems (e.g., overweight, hypertension). Other medications are used to treat these other health problems. There is the potential of interactions among psychiatric and nonpsychiatric medications.

Dr. Spigarelli said that current rates of hypertension and type 2 diabetes (both linked to the obesity epidemic) among children and adolescents are higher than ever seen before. With these increasing rates of hypertension there is also an increase in hypercholesterolemia and hypertriglyceridemia, for which treatment in adults is considered lifelong. Few type 2 diabetes medications have been studied in children or adolescents. There have been no short-term efficacy studies of drugs to treat these ever more prevalent diseases in children and adolescents.

Dr. Kahn said another issue is treatment of drug abuse. These medications have been studied in adults but not in children. Bupropion is being studied for the treatment of methamphetamine abuse. Modafinil is being studied for the treatment of methamphetamine and cocaine abuse. There is some potential for these drugs in treating adolescents, but there is also some potential for abuse of these medications. Dr. Kahn recommended that studies of adolescents focus on drugs with fewer public health concerns and less potential for abuse, as well as drugs with potential for safety concerns, particularly those that are used chronically. Intramuscular (IM) naltrexone (Vivitrol), which is an effective treatment for alcohol abuse, is now being studied for treatment of opioid and cocaine abuse. Adolescent studies of naltrexone should be a high priority. Studies would focus on pharmacokinetics, efficacy, and safety. Another drug that is being studied for treating narcotic abuse is lofexidine. This drug is safe and has no potential for abuse. There are no data on the safety of many drugs for treating adolescents. Three neurologic medications that could be studied are topiramate, baclofen, and vigabatrin. There is a significant risk associated with vigabatrin to treat seizures, but the benefits outweigh the risks. Vaccines are another group of drugs that could possibly be studied.

Dr. Spigarelli commented that one of the problems with studying drugs to treat substance abuse is trial design. Dr. Kahn noted that all of the labeling of the aforementioned drugs states that they are not approved for pediatric age groups. Dr. Higgins said one of the overriding issues for clinical trials of adolescent therapies—particularly for treatment of substance abuse and oral contraceptives—is assent and consent. In most states, parents must consent for children younger than 18 years. Confidentiality is another issue. Dr. Rakhmanina said confidentiality is a tricky issue in the study of HIV. A parent may not have disclosed to a child, or a child may not have disclosed to a parent. Human subjects research in adolescents is a underdeveloped field. There are no formal training programs. Dr. Murray commented that institutional review boards are more conservative in their willingness to look at adolescent consenting for participation in trials. Dr. Higgins said state laws often dictate the terms for consent of minors, in particular, adolescent mothers. Thus, the age of entry for most studies in maternal–fetal medicine is 18 years. Adherence in clinical trials can be problem for high-risk adolescents who consent for themselves. Dr. Trent explained that one issue in adolescent trials is efficacy versus effectiveness. Medications may be efficacious, but teenagers without adequate support system may not be able to adhere to a trial on their own. Thus, the treatment is not effective. Another approach is having adolescents consent to their parents' involvement, particularly in studies of sexually transmitted diseases.

Dr. Higgins described a maternal lifestyle study. This is an observational study that tracks children who were exposed to cocaine *in utero*. Study subjects are mainly from a lower socioeconomic class. The mothers are mostly single. Incentives for the mother and children have

helped with retention. Many of these children want to participate in the research and take the initiative to ensure attendance at yearly study visits. Clinical trials in adolescents should be tailored to the study population. Confidentiality remains a major barrier to getting children into trials.

One of the gaps in adolescent therapeutics is pregnancy in teenagers. There is a critical need for studies of HIV medications and antidepressants in this population.

Next Steps

- Circle will prepare and distribute a draft of the meeting minutes.
- The call participants will review and comment on the draft minutes.
- The next conference call will be May 15, 1:00 p.m.–2:30 p.m.

Addendum: Comments from Mr. Keim

- The majority of referrals of adolescents for psychiatric consultation have to do with impulsive aggression, impulse problems, and conduct problems. However, current psychiatric medication and drug development guidelines call for medication per *Diagnostic and Statistical Manual* diagnosis rather than by symptom (with the exception of agitation related to autism). An important step forward would be to allow for impulsive aggression in adolescents to be defined as a reasonable target for psychiatric drug development.
- Beta blockers are sometimes used off-label for impulsivity and aggression in adolescents, but further investigation through commercial sponsors is unlikely because most are off-patent. Further investigation of this class of drugs is worthy of federal support, especially because they are probably safer than many of the alternatives.
- The FDA approval process for psychiatric medications for adolescents does not specify much in the way of investigation of endocrine disruption. The guidelines fall into the old emphasis on neurotoxicity with faint attention paid to endocrine disruption. Development of psychiatric drugs for adolescents would be facilitated by clearer guidelines on the investigation of endocrine disruption given that this population is especially vulnerable.