Best Pharmaceuticals for Children Act (BPCA)
Adolescent Therapeutics Working Group Conference Call
July 14, 2009
10:00 a.m.–10:30 p.m. ET

Participants

Felicia Collins, M.D., M.P.H.
Oluchi Elekwachi, Pharm.D., M.P.H.
Norma Gavin, Ph.D.
Jonathan Goldsmith, M.D.
Lynn Haverkos, M.D., M.P.H.
Rosemary Higgins, M.D.
Roberta Kahn, M.D.
Bill Kapogiannis, M.D.
James Keim, M.S.W., L.C.S.W.
Patricia Kokotailo, M.D., M.P.H.
Natella Rakhmanina, M.D.
Michael Spigarelli, M.D., Ph.D.
Perdita Taylor-Zapata, M.D.
Maria Trent, M.D., M.P.H.
Kathy Woodward, M.D.

Purpose

The purpose of the meeting was to review the evaluation results of recommendations for general therapeutic needs for adolescents and discuss the top priority areas to be presented at the BPCA 2009 annual scientific prioritization meeting.

Introduction

Dr. Taylor-Zapata welcomed the call participants and thanked them for their participation in the previous two conference calls.

Evaluation Results and Comments

In two previous conference calls, the working group identified current therapeutic needs for adolescents. The needs were compiled and distributed to the working group. An evaluation was implemented to attempt to prioritize the identified needs. Ten responses were recorded—ranking the choices first, second, or third—and comments were solicited. Based on those results, a preliminary prioritization was obtained.

The rank-ordered evaluation results are as follows:

1. Effects of puberty on pharmacokinetics (PK), pharmacodynamics (PD), pharmacogenetics (PG); effect of tanner stage and body weight on drug distribution and metabolism; PG

changes in the expression of enzymes in adolescents; and extent of weight gain seen in older children taking antipsychotics and Depo-Provera

2. Recommendation to the Food and Drug Administration (FDA): develop a protocol across review divisions to evaluate the endocrine impact of psychiatric and other drugs used in adolescents
3. Where to draw the line between pediatric and adult dosing guidelines for all drugs (e.g., when administering HIV drugs for a 12-year-old who is at adult weight)
4. Effects of nutrition (overweight and underweight) on therapeutics in adolescents
5. Increase of "adult diseases" and their treatment in young patient populations—the need for more short-term efficacy and long-term safety studies (e.g., type 2 diabetes, hypercholesterolemia, and hypertension)
6. Treatments for drug abuse and drug withdrawal should adolescents be included in clinical trials
7. Adherence, confidentiality, and consent/assent concerns
8. Impact of adolescent pregnancy on the PK and PD of medicines—specifically HIV drugs and antidepressants
9. Health literacy—improving written and oral communication between health care providers and patients/parents
10. The impact of drug interactions on PK and PD in adolescents (includes over-the-counter, prescription, and concomitant medications).

Evaluation responders' comments were as follows:

- Currently, medications that are proposed or in trials for drug abuse treatment include only ages 18 years and older. Younger age groups need to be addressed directly. PK and PD issues related to age and body weight have an impact for a large variety of medications.
- The general issues regarding adherence (i.e., how the medications are really being used) and literacy communication (i.e., adolescent understanding of how to use medications) are of primary importance. Effectiveness as a concept has simply been ignored in this population. Starting with reality and contrasting the pharmacology with how the drugs are really being used should be the starting point.
- Effect of nutrition—The epidemic of obesity and the adult morbidities associated with obesity make this area a significant issue affecting practice guidelines and practitioner comfort in the short-term efficacy of "adult treatment regimens" versus the long-term safety of statins, metformin, and blood pressure medications for the next 60 years of life. Without the medication data, many teenagers will be limited to "lifestyle changes" instead of effective pharmacology.
- Drug interactions—This area may have the biggest impact across reviews of drugs in many different divisions to produce protocols that look at the endocrine and developmental impact of medications used in adolescence.
- Pediatric and adult dosing guidelines—This area asks the basic question: Is it age (as a marker of biologic and endocrine development) that influences the appropriate dose or is achieving adult weight (>40–45 kilograms) the more correct dosing schedule regardless of biology and endocrine development. Is this correct dosing based on short-term efficacy and is it safe in the long term?

- Research should focus on basic developmental physiologic issues with the most common clinical problems.
- "I chose my priorities on the overall impact and scope of the option, as well as its particular tie with adolescents, which underlies my support for my first and second choices—both (unique) short-term and potentially long-term consequences of drugs used for treatment of adult diseases. I think health literacy is a major issue, but not limited to this population, although advocating for an early investment in health literacy should also have long-term (adult) pay off."

The top priority areas (as modified by Dr. Spigarelli) are as follows:

- Understand the effects of pubertal development and body weight on PK, PD, and PG of pharmaceutical agents, with particular emphasis on understanding:
  - The effect of sexual maturity and body weight on drug distribution and metabolism
  - PG changes in the expression of enzymes in adolescents
  - Extent and mechanism of weight gain seen in older children and adolescents taking antipsychotics, Depo-Provera, and other agents.
- Develop a protocol across review divisions within FDA to evaluate the endocrine impact of psychiatric and other drugs used in adolescents.
- Understand how and where to draw the line between pediatric and adult dosing guidelines for all drugs. Determine when weight-based and/or age-based dosing regimens are no longer applicable (e.g., when administering HIV drugs for a 12-year-old who is at/or above adult weight).

The following modifications were proposed:

- "Effects of psychosocial and pubertal development" should be used instead of "effects of pubertal development."
- "Injectable contraceptives" should be used instead of "Depo-Provera."
- "Psychotropic" drugs should be used instead of "psychiatric" drugs.
- "Endocrine and metabolic impact" should be used instead of "endocrine impact."
- "Distinguish between" should be used instead of "Understand how and where to draw the line between."

Discussion

Dr. Spigarelli asked whether the working group should develop a list of specific drugs versus a list of generic drugs or drug classes that should be identified as needing study in adolescents. Dr. Rakhmanina said a list of specific drugs would impose limits on adolescent pharmacology as new drugs come on the market. Such a list would require constant updating. Dr. Collins noted that within the FDA all drugs in the same class are reviewed by the same division and that the safety and efficacy of drugs in the same class are compared. The call participants agreed that a list of specific drugs is not needed.

With regard to effectiveness versus efficacy, Dr. Trent said that, although it is important to conduct biologic and pharmacologic studies in adolescents to understand how drugs ideally

work, many adolescents are responsible for managing conditions on their own and taking their own medications. Therefore, it is equally, if not more, important to understand adolescent behavior and adherence/compliance to medication regimens. Dr. Trent noted the significant impact of adherence to HIV drug regimens and the potential affect on HIV status and transmission. Dr. Spigarelli proposed adding "ability to adhere" to the first bulleted item of top priorities listed above. Dr. Kapogiannis proposed the phrase "adherence and adherence readiness." Dr. Trent proposed the phrase "strategies to assist adherence." She cited weight gain associated with Depo-Provera and Risperdal use as affecting adherence.

Dr. Spigarelli said his introduction to the working group's priority list will emphasize psychosocial and compliance/adherence issues related to adolescent therapies.

Next Steps

- Dr. Spigarelli will revise the priorities list and distribute the new version to the working group.
- Dr. Spigarelli will draft a consensus statement on the working group's recommendations.
- The working group will review and comment on Dr. Spigarelli's revised priorities list and draft consensus statement.
- The working group will present its recommendations at the BPCA 2009 annual scientific prioritization meeting on November 18 and 19.
- Circle Solutions will prepare and distribute a draft of the meeting minutes.