NATIONAL INSTITUTES of HEALTH

NATIONAL INSTITUTE of CHILD HEALTH and HUMAN DEVELOPMENT

Best Pharmaceuticals for Children Act (BPCA)

List Prioritization Review Panel

+ + +

Monday, October 25, 2004

VOLUME I

+ + +

Bethesda Marriott
Bethesda, Maryland

PERFORMANCE REPORTING
Phone: 301.871.0010 Toll Free: 877.871.0010

PARTICIPANTS:

Experts

William E. Berquist, M.D.
Associate Professor of Pediatrics
Stanford University
Palo Alto, CA

Jeffrey Blumer, Ph.D., M.D.
Professor of Pediatrics and Pharmacology
School of Medicine, Case Western Reserve University
Cleveland, OH

Roselyn E. Epps, M.D.
Chief
Division of Dermatology
Children's National Medical Center
Washington, DC

Thomas P. Green, M.D.
Professor and Chairman
Department of Pediatrics
Feinberg School of Medicine, Northwestern University
Chicago, IL

Stanley E. Grogg, D.O.
Professor of Pediatrics
Center for Health Sciences
Oklahoma State University
Tulsa, OK

Stephen T. Lawless, M.D., M.B.A.
Chief Knowledge Officer
Nemours Foundation
duPont Hospital for Children
Wilmington, DE

Jay M. Meythaler, M.D., J.D.
Professor and Chairman
Department of Physical Medicine and Rehabilitation
School of Medicine, Wayne State University
Detroit, MI

Susan R. Orenstein, M.D.
Professor of Pediatrics
Pediatric Gastroenterology Division
School of Medicine, University of Pittsburgh
Pittsburgh, PA

PARTICIPANTS *(continued)*

Gary D. Overturf, M.D.
Professor, Pediatrics and Pathology
Department of Pediatrics
University of New Mexico
Albuquerque, NM

DeWayne M. Pursely, M.D., M.P.H.
Neonatologist-in-Chief
Neonatology Department, Beth Israel Deaconess
Medical Center
Boston, MA

Wayne R. Snodgrass, M.D., Ph.D.
Professor of Pediatrics and Pharmacology-Toxicology
Head, Clinical Pharmacology-Toxicology Unit
University of Texas Medical Branch
Galveston, TX

Alan D. Stiles, M.D.
Brewer Distinguished Professor and Chair
Department of Pediatrics, School of Medicine
University of North Carolina
Chapel Hill, NC

Robert M. Ward, M.D. ***(Panel Chair)***
Professor of Pediatrics
Director, Pediatric Pharmacology Program
Health Sciences Center, School of Medicine
University of Utah

Bernhard L. Wiedermann, M.D.
Attending Physician in Infectious Diseases
Associate Professor and Vice Chair for Education
Department of Pediatrics
Children's National Medical Center, School of Medicine
George Washington University
Washington, DC

Karen K. Winer, M.D.
Medical Officer
Endocrinology, Nutrition and Growth Branch
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Teri Moser Woo, R.N., M.S.
Certified Pediatric Nurse Practitioner
Kaiswer Permanente
University of Portland
Portland, OR

PARTICIPANTS *(continued)*

Charles R. Woods, M.D., M.S.
Associate Professor of Pediatrics
School of Medicine, Wake Forest University
Winston-Salem, NC

Theoklis E. Zaoutis, M.D.
Director, Antimicrobial Stewardship
Infectious Diseases Section
The Children's Hospital of Philadelphia
Philadelphia, PA

Julie Magno Zito, Ph.D.
Associate Professor of Pharmacy and Psychiatry
University of Maryland, Baltimore
Baltimore, MD

Working Group Members

Debbie Avant, R.Ph.
Pharmacist
U.S. Food and Drug Administration
Rockville, MD

Tamar Lasky, Ph.D. ***(Working Group Chair)***
Epidemiologist
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Jan Leahy
Program Coordinator
Obstetric and Pediatric Pharmacology Branch
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Lisa L. Mathis, M.D.
Acting Director
Division of Pediatric Drug Development
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Donald R. Mattison, M.D.
Acting Branch Chief
Obstetric and Pediatric Pharmacology Branch
Center for Research for Mothers and Children
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

PARTICIPANTS *(continued)*

William J. Rodrigues, M.D., Ph.D.
Pediatric Science Director
Office of Counter-Terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Hari Cheryl Sachs, M.D.
Pediatrician
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Anne Zajicek, M.D., Pharm.D.
Pediatric Medical Officer
Obstetric and Pediatric Pharmacology Branch
Center for Research for Mothers and Children
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Attendees

Duane F. Alexander, M.D.
Director
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

John Alexander, M.D., M.P.H.
Medical Team Leader
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Lynn Bosco, M.D., M.P.H.
Director, Pharmaceutical Studies
Agency for Healthcare Research and Quality
Department of Health and Human Services
Rockville, MD

Mary Beth Clarke
Associate Director, Regulatory Affairs
Genzyme Corporation
Cambridge, MA

PARTICIPANTS *(continued)*

Norma Gavin, Ph.D.
Senior Research Economist
RTI International
Research Triangle Park, NC

George Giacoia, M.D.
Program Scientist
Pediatric Pharmacology Research Unit Network
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Melvyn Greberman, M.D., M.S., M.P.H.
Director, Public Health Resources
Silver Spring, MD

Rosemary D. Higgins, M.D.
Program Scientist and Medical Officer
Pregnancy and Perinatology Branch
Center for Development Biology and Perinatal Medicine
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Howard Higley, Ph.D.
Senior Scientist, Regulatory Affairs
CCS Associates
Mountain View, CA

Mya N. Hlaing
Contracting Officer
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Tina Ipe, M.P.H.
Social Marketing Research Associate
Westat
Rockville, MD

James Korelitz, Ph.D.
Associate Director and Senior Epidemiologist
Westat
Rockville, MD

PARTICIPANTS *(continued)*

Carl N. Kraus, M.D.
Medical Officer
Division of Special Pathogen and Immunologic Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Lolita A. Lopez, M.D.
Medical Officer
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Glenn B. Mannheim, M.D.
Medical Officer
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Brian Mayhew
Global Regulatory Policy Analyst
Merck Research Laboratories, Inc.
Bethesda, MD

Mikhail Menis, Pharm.D., M.S.
Clinical Research Assistant
School of Pharmacy, University of Maryland
Baltimore, MD

Bindi Nikhar, M.D.
Medical Officer
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Andreas Pikis, M.D.
Division of Antiviral Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Tonse Raju, M.D., D.C.H.
Medical Officer and Program Scientist
Center for Development Biology and Perinatal Medicine
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

PARTICIPANTS *(continued)*

Matthew Reynolds, Ph.D.
Metaworks, Inc.
Elkton, MD

Daniel J. Safer, M.D.
Associate Professor
Division of Child Psychiatry
Johns Hopkins Medical Institutions
Baltimore, MD

Philip H. Sheridan, M.D.
Medical Reviewer
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Juliette Shih, M.P.H.
Manager, Compliance Operations
Genzyme Corporation
Cambridge, MA

Caroline C. Sigman, Ph.D.
President, CCS Associates
Mountain View, CA

Thomas Smith, M.D.
Medical Officer
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Perdita Taylor, M.D.
Pediatric Medical Officer
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Benedetto Vitiello, M.D.
Chief
Child and Adolescent Treatment and Preventive Intervention
Research Branch
National Institute of Mental Health
National Institutes of Health
Bethesda, MD

PARTICIPANTS *(continued)*

Anne Willoughby, M.D., M.P.H.
Director
Center for Research for Mothers and Children
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Celia Winchell, M.D.
Medical Team Leader, Addiction Drug Products
Division of Anesthetic, Critical Care, and Addiction
Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

Carolyn L. Yancey, M.D.
Medical Officer
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD

C O N T E N T S

CONTENTS *(continued)*

CONTENTS *(continued)*

CONTENTS *(continued)*

P R O C E E D I N G S

[8:05 a.m.]

Welcome/Opening Remarks

Dr. Donald R. Mattison, NICHD

DR. MATTISON: We have two fairly long days in front of us with a lot of discussion and action, so I would like to begin, if we could.

I would like to take this opportunity to welcome all of you from the NIH, and most especially NICHD. As all of you know, this is the third exercise in which we have looked at the drugs that are off-patent and tried to identify the most compelling reasons or indications for studying those drugs.

As we have had in the past, each of these listening meetings has two general goals. The first is to identify the indications and the drugs which you all will deem are our highest priority.

The second encompasses a learning process for the NIH and the FDA. Any thoughts that you might have that would help us sharpen and improve our processes -- [off mic].

I would like to begin by thanking, especially,

the experts we have here -- [off mic] and the materials collected to help us through the first -- [off mic].

I would also like to thank members of the NIH and FDA Steering Committee for their work on this, and also notice the FDA for helping us as we discuss the future of these drugs.

Finally, I would like to thank Tim for pulling together this process this year, for putting together a schedule and a set of activities, a more thoughtful process -- [off mic].

Now I would like to turn the microphone over to the FDA and Lisa Mathis, who is the acting director of the Food and Drug Administration.

U.S. Food and Drug Administration (FDA) Overview

Dr. Lisa L. Mathis, FDA

DR. MATHIS: Good morning. I'm Lisa Mathis, the acting director of FDA. First of all, I would like to thank the experts for giving us your time and your expertise, and also developing the list of priority drugs that you have studied -- [off mic].

We have now a process through which -- [off mic] that allows for the study of off-patent drugs. As you

know, today we will be making our priority list of off-patent drugs.

[PowerPoint presentation.]

DR. MATHIS: As you can see up here, what we are going to be doing today is making the priority list, but I wanted to give you some idea of what happens with this priority list once you guys are done with it.

The next step is that the FDA will issue a written request. Now, a written request is basically a written agreement where we list the minimum requirements that we want from the study in order to appropriately label drugs. We initially issue that written request to both AMDA and MPA [ph] holders of the drugs, so off-patent and on-patent manufacturers of the drugs.

They have 30 days to tell us whether or not they agree to do the study. If they agree to do the studies, then industry pays for those studies. However, if they decline, then we go ahead and refer those written requests to NIH.

Just some more detail about what happens is that, once you guys give us the list, we go through that list and select the drugs in order to go ahead and start

issuing the written request. We talk to different FDA review divisions, and we also get input from NIH and NICHD.

We put together a literature review, look at the labels, obtain safety data and news data, and then we go ahead and talk again with the review divisions and the appropriate institutes at NIH as well as NICHD, and then we write a draft written request.

Once that draft is put together, we go through a pretty extensive process with NIH as well as with the FDA. We go to a pre-PDX where we talk internally, and then we go to the PDX group, which is the pharmacologists group that look at both the PK and PD sections of the study. Then we go to PDX, which is actually cross-divisional. We have pharmacists, project managers, statisticians, and we all look at the written requests to make sure that it's both consistent and appropriate.

Then we go ahead and issue the written request to the holders, as I discussed before, and if they agree to do it, they do it. If not, we give it to NIH, and NIH goes through the process of putting it in their contract.

This is just the process that we go through, a

timeline for development of the written request. As you can see, once we have the list that you all will produce today, we go through a pretty extensive timeline in order to get those written requests issued. Then once they are issued, again, NIH has to go through an extensive process to issue the contract.

Now, what happens once the clinical studies are completed is still theoretical at this point. However, what we would like to do is that the final study reports are submitted to both the NIH and FDA and then submitted to public docket. We look at them and review them, remembering that all pediatric submissions in response to written requests have a six-month review clock.

Then we will go ahead and draft it into labeling and negotiate with the sponsors, as well as putting it into the public record, probably through the Federal Register.

Now, today, we are asking you to provide us with your judgment regarding the value of finding and conducting additional studies of the specific drugs that are on the somewhat final list, and then also to help us with scientific questions that need to be addressed

regarding the drugs and the indication in the pediatric population, as well as identifying gaps in the labeling. So that way, we do the right studies to get these drugs labeled for pediatrics.

We do have a website, if you want to contact the FDA in the future. This is our contact information, and also, that is where our link is. Then this is our contact information as well.

I would like to finish up by really thanking all the experts again for showing up to give us your common expertise. This means a great deal to FDA. I would also like to thank my colleagues at the NIH and FDA for showing up and really providing us with a lot of support and effort.

Now, we are going to start with Dr. Lasky talking about prioritizing the drugs.

Prioritization Overview

Dr. Tamar Lasky, NICHD

DR. LASKY: I wasn't going to thank anybody until the two days were over, but I was going to thank everybody for coming, and then after the two days, see.

[PowerPoint presentation.]

DR. LASKY: Don actually summarized what I was going to say, but he did it so well and he did it very briefly. Still, I would like to go over some of the details. I think everyone is familiar, but I think it is also useful to go over some of the details of what led to the process as it is now.

As you will all know, BPCA mandates that NICHD, in consultation with FDA, develop this list on an annual basis. He mentioned that this is our third year. These are the drugs that we have already listed.

We have learned a lot each year, and we expect to continue learning. This year, when we set out to plan the process, we set three goals: one, which was to improve the documentation and written record, because as this grows and becomes more recognized, we know that people will want to look into the process and understand the process.

One of our goals was to expand the range of expertise and input from the public, and the third major goal was to expand the knowledge base and adapt this process as we expand the knowledge base.

I see we also made another really big change,

and this kind of was less deliberate and less conscious, but in our work with FDA as we learned about the written request process, we learned that when FDA issues a written request, they generally link a drug to an indication. As we worked on the written requests and worked on developing the contracts, we saw it was useful to know what indication we were talking about when talking about the drugs.

So we are shifting over from previous years where we would talk about a drug in a general manner to trying to specify the indications that we are talking about. A person's opinion would be very different from one indication compared to another, and this really rests on our experience.

As I went over preparations for today's meeting, I realized it is a bigger shift than we probably realized at the time, but it is going to change a little bit the nature of our conversation and thinking.

Some of the process highlights. As you know, we have an annual List Development Working Group. I'm the chair of the working group. We have participants from NICHD and from FDA, and we have been meeting close to

monthly, or at least have monthly phone calls talking about when we can't meet that month.

We have incorporated input from FDA on a constant basis, as well as from the NIH institutes and Centers for Disease Control and Prevention, and from a wide range of professional organizations.

Another feature that we added this year was publication of a preliminary list in the summer. This year, it was in August 2004. There were 23 drugs, and it is available for public comment; we haven't caused much of a stir.

Another feature was the move to having the meeting in October instead of December and to have it be a two-day meeting and have it be expanded to scientific considerations of the kind of studies we would like to do. So prioritization and thinking about the kind of scientific questions.

In the process this year, we referred closely to the legislation, which lists these four points on how we prioritize drugs. They are not very specific. We haven't gone beyond it, but they do leave room for us to develop our thinking further.

Points A and B address the issue of availability of information. Point C talks about whether we think these studies are going to have an impact on health of the pediatric population. Neither of these are defined further.

The fourth one is whether reformulation is necessary. That is kind of a different criteria that we haven't incorporated as closely, either.

So in operationalizing availability of information, we began this year with a pilot study approach with the company Metaworks, and they did an assessment of the count of abstracts for each of 64 drugs and the type of study design, the topic, and the age groups.

What we wanted to do with this availability information is operationalize it in a way where we could have systematic assessments, systematic literature reviews, and eventually lead to meta-analysis.

In our pilot study, this is the type of output that we receive. I think this is the drug Quinidine. You can see if you go across the top, it was broken down by indication, and as we go down, you will see where the

studies took place. You can see what kinds of studies they are, the age groups studied, and the outcomes of focus in the study.

This will help us in evaluating the literature, because we could take an indication and look up or down and see whether that indication has been studied in a particular age group, and then come to some kind of quantitative assessment of whether we consider this adequate or not. It is not a rigid criteria, because you can have 10 lousy RCTs compared to two excellent RCTs, but just having these quantify what the literature is.

Our marker for availability in this kind of quick and dirty first cut was whether there were 10 or more randomized clinical trials in the literature since 1990. Again, it is not a rigid criteria.

We did come up with some interesting findings which we hope to get out into published literature as well for the 64 drugs. They were broken down by the number of studies, and you can see that most of the drugs had very few studies. Twenty-five only had one to five RCTs, but there are a few drugs that had an enormous amount of RCTs published in the literature since 1990, in particular,

Amoxicillin, Quinidine, Dexamethasone, Epinephrine, Methotrexate, and Prednisolone.

Our thinking was, there is such an abundance of literature, it may all be inferior quality, but it certainly needs to be looked at before we would say equivocally that the literature is inadequate. These drugs will be reviewed intensively by the contractors who are going to be working on systematic review, and they will go beyond looking at abstracts but do systematic literature reviews and, if possibly, meta-analyses.

The other criteria that we put a lot into was the issue of frequency of use, basically how many kids use the drugs. There are many more ways to quantify this issue. We can start thinking about dose and duration, but in the beginning we want to know just how many kids are we talking about.

We had a very nice relationship with Express Scripts Data. They did this for us on a voluntary basis, which is great. They did it quickly and promptly, and then said they had no time to continue it. So we got what we got. They are a pharmacy benefits management company with 30 million covered members in 50 states. This was

from 2002; 380,000 were continuously enrolled. They gave us data on 941 unique or combination products.

The way we conceptualized it is to think about the prevalence curve, 100 continuously eligible children. Again, for the future, we would want to know about children who are not necessarily continuously eligible, but as a first cut, these were the data we got.

What we found is, I think, again, very, very interesting. Unlike the adult population where we could say 45 percent of adults are on a daily medication, most children are not on medication. Very few children take medication. The highest frequency was for very few drugs, which was over 10 percent of the kids getting that drug in a particular year.

We ended up stratifying the frequencies on orders of magnitude, going over six orders of magnitude, and then grouping the top four orders of magnitude, which is a very big spread quantitatively, from greater than one in 10,000 all the way up to greater than one in 10. This was concerned high frequency, and we considered low frequency the lower two amounts, which are the less than one in 10,000 and greater than one in a million.

Then we have the zero category, where we either did not have data, or it is used on an inpatient basis, or it is not used at all.

We applied these numbers to a list of off-patent drugs. Sixty-four of them were high frequency. Remember that high frequency is over four orders of magnitude. Thirty-nine were low frequency, and 97 were without frequency of use information. We have a long way to go in getting more comprehensive data.

We conducted an outreach last January or February, and we gave people until the end of April to respond to this list of drugs and the frequency information. We sent the mailing to about 150 professional organizations, as well as to our NIH sister institutes and to FDA and to CDC.

We did not suggest an indication but asked respondents to specify the indications they felt were of concern.

I think the responses were from a little more than 90 organizations. There are binders on the table, about six, with copies of the responses. These are some of the organizations that responded.

We had a separate MPA input which recommended 56 new drugs for further study. We ranked the input from all these different sources, giving one point to each recommendation and five points to the FDA recommendations because, as you know, FDA has really worked on this and brings a special level of expertise to this issue.

This is the distribution of rankings for the approximately 200 drugs. For some reason, there were two drugs that people took the time to write in and say we should look at them, so we gave them negative one point. These would go in the zero category. Most drugs are in the zero or one category. That is, very few people thought they were of critical importance.

We used the cut-off of three or above, because that gave us a group of 70 drugs. This shows the low. We had 225 drugs in February. There was a lot of movement in and out of this group of drugs. Drugs go back on patent.

That is something we didn't know about. They are granted exclusivity or are discontinued. So we have to take them off the list for consideration in the off-patent process, then drugs rise to the surface.

An interested group will recess tomorrow. It is

a group of dermatological drugs which were added in April. They have always been off-patent, but they have been added in response to FDA hearings last fall about safety issues. So we will be discussing it tomorrow.

In the end, we had 70 drugs that were ranked three or higher. I just wanted to let you know that we did not follow the frequency of use information, blindly. We considered it, but we did not let it dictate whether a group was considered.

Nonetheless, we had 20 of the drugs with no information on frequency of use. Thirteen had a low level, less than one in 10,000 kids using it per year. Thirty-seven were drugs where frequency of use was greater than one in 10,000 per year, so it is kind of a nice distribution.

In moving from the 70 to 23, it was not as mathematical as, probably, we would all like to see it. We sat together and talked about it, and we realized that if we did it mathematically, we would have 19 dermatologic drugs in the final group. We didn't want that. We didn't think that would serve any of the purposes, and we tried to distribute the shortages in each of the groups that

were present.

We also tried to honor the input from, in particular, NIH institutes, Centers for Disease Control, as well as the other organizations that really voluntarily took the time to write in their comments. Some of them were quite lengthy and quite helpful.

NIH, for example. We received responses from the National Institute for Mental Health, and they suggested Citalopram and Clonidine. It turns out that Citalopram was either granted exclusivity or back on-patent. Something happened there.

NHLBI had nominated Azithromycin and Cefuroxime, both in children with sickle cell disease. Azithromycin is already on our list twice for different indications and, you know, there may be a time when we bring it on again for this particular indication, but we ended up just going with one of them.

So it is not a straight mathematical process. Here is a good example of how we used the frequency data as well as our other criteria. It only received a ranking of three, but it is a very high frequency drug. There were one in 100,000 kids using it in a given year. That

is not high frequency. I tried to remember -- no, it is still in our high frequency group.

It stayed off patent. It is off-patent and hasn't been granted exclusivity. It hasn't been discontinued.

The Metaworks review found 19 randomized clinical trials since 1990 for any indication, but it found zero in patients with sickle cell anemia. So while there is literature about this drug, there isn't a literature about this drug in this indication. We could comfortably say that we felt the literature was not adequate for this indication.

The charge for today and tomorrow, as has been said, is we are going to be looking at 23 off-patent drugs. We are also going to look at four on-patent drugs which go through a different process and get not fully developed. The drugs were referred by FDA, the foundation for NIH, and from the NICHD.

Our charge, which has been said already: whether we study this drug and indication and what are the scientific questions that need to be addressed.

The format, which is approximately the primary

review of a talk, summarizes pertinent comments for approximately 10 minutes. The secondary review will add some comments.

Our FDA colleagues are here, medical officers from all the divisions, and they will have an opportunity to speak for five minutes or so, and there will be about 10 minutes for discussion.

Dr. Bob Ward, professor of pediatrics at the University of Utah, has graciously agreed to be chair of this panel. He will let you know when you have around one minute.

I did want to say, when you see a green light, you have two minutes. When you see a yellow light, you have 30 seconds. When you see a red light, time is up.

Now, over to Bob.

Review 3: Off-Patent Drugs

Dr. Robert Ward, Moderator

DR. WARD: I think there is actually very little to add to what has been said. Our charge is to rank these drugs and evaluate them on behalf of children so that we can, at the end of the day, create a list of drugs that we feel will be of most benefit to children based on their

study.

As many of you in this room know -- I see Dr. Blumer over at the corner -- there is a limited amount of funds available for these studies, so our task is not a small one. We don't have limitless funds, and so they have to be spent wisely. I think we have to balance what we think is the most important for children and also what is feasible for children.

With that, we will go ahead and get started on the review process. Let me just mention, there are some representatives from industry here. What I would ask would be that if you are from industry, to speak with the individual person on the panel who is reviewing your particular medication. We are going to try to not make this an open-ended discussion that could occur around a specific proprietary product.

With that, let's start with Ethambutol.

Dr. Wiederman.

Review of Ethambutol

Dr. Bernhard Wiederman

DR. WIEDERMAN: Thanks. Good morning. Don't worry; I just have a short presentation. I did want to

put some of my thoughts down.

[PowerPoint presentation.]

DR. WIEDERMAN: What I was hoping I had there, I was thrilled to see that Metaworks had gone through and done all this summary in relation to all these drugs, and a few days later, I realized they hadn't done that process with Ethambutol.

But in the packet, a product of the FDA, was actually, I think, 39 studies dealing with Ethambutol, which was very helpful. I looked around for a few more. I just wanted to summarize a few things.

This is obviously a drug that has been around for a long time, since the 1960s. There are studies documenting increasing frequency of use of Ethambutol in pediatric tuberculosis. This is mostly driven by emerging drug resistance in TB, so Ethambutol is often the fourth drug added for a child with TB but suspicion or in an area of high drug resistance.

I think going through the studies -- I won't spend a lot of time on that -- there are a lot of data on efficacy of regimens using Ethambutol for treatment. It is very responsive to tuberculosis in children. It is

possible to pull out enough from those studies, if there is enough detail, to make an efficacy claim. An FDA-approved efficacy claim, I'm not sure. It takes some work to pull some of that out.

I did want to focus just briefly on the main sticking point of using Ethambutol in children, and that is the ocular side effects. The most serious side effect in patients who are given Ethambutol is primarily retrobulbar optic neuritis, which usually is related, usually irreversible, and, at least at lower doses, is most uncommon and perhaps rare. But because of the difficulty at a particular age in testing visual fields and color vision in young children, it has caused some concern for using this drug in children.

This is just one of the early studies that shows essentially a little bit of the dose-related effect of this. You can see very high doses are not used anymore for extended periods of time; there are only six patients. Two of them in this study of patients in Chicago developed visual side effects for what we would now call a higher range dose, about 5 percent of patients. At a little bit lower dose, nine out of 200. These are all

adult patients.

When you look through some of the studies of the treatment of TB and try to tease out children in those studies and how well or not so well they were followed for ocular problems, there are sort of three types of studies. This is from the Medical Research Council of the U.K. The study was done in Korea.

One is where there is more formal or active follow-up for visual problems. So we did a lot of tests on these kids who were included in there. It was unclear in this study, as it is in most studies, of what they do with the very young children in terms of some of the tests they were measuring or using here wouldn't have been possible in very young children because you need cooperation. They mentioned 27 children under five years of age who received Ethambutol -- [off mic] have any problems detected.

This is a more typical study in terms of ocular toxicity, where the authors were clearly aware of a potential problem, but they just commented that nobody complained about visual problems. There was apparently no formal surveillance for ocular problems. This kind of

passive surveillance is the majority of studies.

This may be the only study where a group of individuals in India measured visual-invoked responses in children three to 13 years of age, and 47 children, again, with -- [off mic] all had normal studies.

There is one nice literature review, apparently recently, that really combined all the studies -- [off mic] with the better, more active follow-up. There were, combining all six studies, it ends up being 343 children. There was one possible ocular toxicity case, although the study that mentioned this doesn't go into a lot of detail.

This author commented that at the usual dosage, which is equal to a dosage of 15 milligrams per kilogram per day, the effects are rare, and advocated for going ahead and using Ethambutol in young children. Obviously, just that one author's opinion.

In terms of filling out my score sheet, for the Task 1 score sheet, I came up with a score of four. Of the three drugs that I was assigned to be primary or secondary reviewer, this was the lowest score of my three drugs. This happens to be the drug I think would be most important of those three drugs to stay on the list.

I think the scoring system is actually quite good, but I think what is missing and why I think Ethambutol might have a little higher importance than the score would predict, is because of more of the epidemiology and type of problem that pediatric tuberculosis represents. I think emerging resistance means we are going to be pushed to do this more and more to get a lot of drugs available.

No. 2, unfortunately, young children with TB are similar to canaries in coal mines. So when you see a young child with active tuberculosis, it usually represents recent infection from somebody who is spreading it throughout the community, as opposed to reactivation disease that doesn't become a problem until the adolescent age group. So from that ideologic standpoint, pediatric tuberculosis is important.

As I indicated, I think there may be enough efficacy data out there. If someone could go through and piece out the results of these larger studies, although many of them are in other countries, not the U.S.

I think what would be important to focus on are the ocular toxicity problems, to include both better

follow-up studies, not necessarily randomized trials but just in everyday treatment settings, but also some studies perhaps using visual-invoked responses in younger children and infants who at least get some level of security. Still, this is a known side effect of the drug and it certainly will happen in children.

That's all I have.

DR. WARD: Thank you very much.

Dr. Overturf.

Secondary Review of Ethambutol

Dr. Gary D. Overturf

DR. OVERTURF: I just have a couple of points. I agree that the major issue is ophthalmic toxicity. To my knowledge, really, there has not really been a well confirmed single case of toxicity in children; that is, ophthalmic toxicity.

The problem is just as has been stated, that a lot of the studies have not really looked at this closely, or they have been conducted in developing countries where there has been virtually technology to do so.

The other thing is that this has become a more important drug in recent years because of the emerging

resistance. In 1990, the World Health Organization estimated there were about 1.3 million new cases of tuberculosis in children in that single year, and there are about 450,000 deaths in children.

That is exceeded only by one other really common infectious disease that we see in the non-developed world, and that is actually measles. Obviously, malaria has a major impact in those countries as well.

The other thing is that the annual incidence of tuberculosis in children increased from 40 percent from 1985 and to 1993, and especially is high in minority populations. So that, if you look at the non-childhood population, the increase in tuberculosis during that time was only about 13 percent. So the rates in children have tripled and increased, and much of that has been due to resistance, which has developed primarily in HIV-infected individuals.

Actually, Ethambutol is recommended not only as a single drug but often as a combination drug to replace one of the two primary drugs when there is resistance. So it has become a more important drug, again, to know exactly what its safety is for children, because it

becomes an important issue.

Now, it also has been affected by resistance, and resistance in most studies now of Ethambutol, it can be as high as 5 to 10 percent, so that along with its resistance.

So I agree with most of the comments. I think the major issues are safety with this drug. The PK and PD data are pretty well known with this drug.

There is one additional comment, and that is that it may have major importance in children because children suffer disproportionately from the complications of CNS disease in tuberculosis, and this has very good CNS pharmacology. It is one of the unique drugs. It is not as good as Rifampin and INH, but it has very uniquely good pharmacology. That has been well studied in the past, but not in children, again, not as to its pharmacology.

So my score was a little higher. I gave it a seven, and that was the highest score that I had given any drug. So I generally agreed with the comments.

Thank you.

DR. WARD: Thank you.

FDA Review Officers Krause and Meyer, any

comments?

FDA Review of Ethambutol

Dr. Carl N. Kraus

DR. KRAUS: Carl Kraus, FDA reviewer. My only comment might be more of a pragmatic one. Having reviewed some of the utilization data for Ethambutol in the United States, it seems as though there is little to any use of Ethambutol in children in the U.S. Of course, this was a cursory review.

I'm not sure if other folks around the table have more information on the number of pediatric cases seen in this country, but that being the case, it seems even if it were to be evaluated, it would be difficult at best to try and conduct a safe review of sufficiently large to be robust enough that it would provide evidence of safety in kids.

Secondly, there are alternates means of evaluating safety from data overseas. There are 505(b)(2) evaluations that have been conducted recently. There is one in which there has been 20 or 30 years of use internationally of a drug, which points to a probable, reasonable safety profile. Ethambutol, too, has been used

for more than three decades overseas.

I haven't had a chance to look at the literature overall, but my guess is there may be some ways of compiling all the data and seeing if these are ways to look at this.

Open Discussion

DR. WARD: It looks like we have a discrepancy between your data about use and our Infectious Disease colleague's experience here.

Gary.

DR. OVERTURF: I would agree that it is probably not used a lot in the United States, but this is one of those issues -- and I agree with the comments that were made -- that is primarily of worldwide use. It probably is used a great deal in other countries, because it is a less expensive drug, it can be given orally, and tuberculosis is obviously more common.

DR. ZAOUTIS: You know, the published literature, including that article by Leff and Leff [ph], which they had done a series of surveying public health clinics, did point to an increase and suggested, I believe, about a quarter of kids being treated for TB in

these settings were receiving a combination of contained Ethambutol. So I'm not sure if there are different databases or what exactly. I can only comment anecdotally that, certainly in my practice in D.C., it is very common to put children on Ethambutol.

DR. LASKY: I was going to make a comment on the frequency of use data that our Express Scripts data set did not have information about it, but this was a data set that looked at commercially insured children. My sense is that when we look at the Medicaid data and the uninsured data, we will find differences.

The other option we ought to look at is, at some point we will have data on prevalence or physician visits for tuberculosis, and we really need to know the underlying condition here rather than whether Ethambutol is used. I'm not sure that we have that yet.

DR. WARD: My experience has been that you are only as good as your database, and when it is a database almost of convenience, it really will depend on who their population is. If it is commercial, it is really not going to capture --

PARTICIPANT: I would suspect, even children

with insurance will get their TB drugs through the local health department, so an Express Scripts, I think, will not pick it up. But the information ought to be available.

DR. WARD: Other discussion?

Yes.

DR. GROGG: Yes, a couple comments. I would like to see it available in a suspension form, if that is possible, for pediatric patients. I know it can be mixed at the present time, but suspension form would be nice.

Understanding all the comments that have been made, we have seen a lot of resistance of tuberculosis coming to the United States with a lot of foreign travel coming into the United States. It would be nice to have this drug available for those resistant strains.

DR. WARD: Jeff.

DR. BLUMER: Just a word of caution. I think the point about safety is indeed the most important. Assessing safety in the context of other drugs, which is the only way that this is used, is truly a challenge, and I think we have to keep in mind, whether we would be able to effectively generate data that would be useful in

labeling in the context of varying regimens for anti-tuberculins therapy is difficult, although things that may be satisfactory for us as clinicians may not be satisfactory.

I would like to hear the FDA reviewers' response to that in terms of what the yard stick might be to get safety data people will label when you are using a drug like this in varied contexts.

DR. KRAUS: I completely agree. I think that the cleaner data sets probably are the older ones where there weren't four drug regimens available to patients. Again, I have not had a chance to look back and see what exactly is available in the literature, but I think in doing so there may be some reasonable amounts of data.

DR. WARD: Let me ask our Infectious Disease consultants before we go on, are there four drug regimens that could include Ethambutol and an alternate fourth drug without ocular side effects as a comparator?

DR. ZAOUTIS: Well, usually the choice we are up against is that fourth drug being either Ethambutol or an aminoglycoside, Streptomycin or Kanamycin. So that is where we are, and obviously, we would prefer Ethambutol,

but with a concern. But there are other possibilities.

DR. OVERTURF: I thought the question was specifically whether there were other drugs that were thought to have the same toxicity, and I don't think there are. This is a unique toxicity to this drug in all tuberculosis combinations that I know of.

DR. ZAOUTIS: I think the only problem would be if you included patients with TB meningitis, who get cortical blindness, optic atrophy, and all those. That would be a very difficult population to look at for this toxicity, but aside from CNS disease --

DR. KRAUS: Currently, the CDC recommends a four-drug regimen for everyone in the United States because of the more than 4 percent drug resistance rates in the United States. If that were the case, you don't get your census back for at least six weeks afterwards with your cultures. I'm not sure how you could conduct a reasonable study. I mean, it is difficult.

DR. ZITO: Non-Infectious Disease addressing. I'm wondering if it would be useful to know a little bit about what proportion of children's needs are not being met by the current options so that you get a sense of what

the size of the benefitted population might be. In other words, is every child who would come in become a candidate.

DR. ZAOUTIS: I don't think the kids' needs are being met. We are just plowing ahead and giving it regardless. I think the issue is, have we created some visual problems down the road that we are not hearing about. My sense is that it can't be very common or we would be hearing about it. It is sort of an unknown.

DR. WARD: It is the CD recommendation, though, at this point for drug therapy for children, or is that dependent upon identification of resistance?

DR. OVERTURF: Well, the organism is nearly always not acquired from a child. It is usually acquired from the contact. So there are really three situations. There is a situation in which the child is known to be exposed to an individual and they earn susceptibility from that individual.

There is the rare situation where we acquire the organism from a child, and actually, with modern microbiology, organisms are grown and sensitivities are available much earlier than they used to be, but they are

still somewhat lengthy.

Then there is the third situation, where we don't have an index case and we don't have an isolate from the child. In those situations where we know of resistance or we suspect resistance because of the potential origin of the infection, then Ethambutol is frequently used as one of the combinations.

Sometimes aminoglycosides are used as well, and a lot of times aminoglycosides are used in some jurisdictions because people are concerned about the current label, which does not allow the drug to be used in children less than 13 years old, or does not recommend its use.

DR. WARD: I was going to ask for a clarification. Okay.

DR. OVERTURF: So it is not recommended for use under 13 years.

DR. WARD: Okay. Yes.

DR. SNODGRASS: Just a brief comment. How would one specifically measure ocular toxicity in a one-year-old or two-year-old? I mean, I guess you would have to have some sort of an agreed-upon definition.

DR. WARD: I think it is the date at BER.

DR. SNODGRASS: You are going to be limited to that. In other words, will that pick up more subtle defects?

DR. OVERTURF: No, it doesn't, because the early problem is really color distortion and other kinds of problems, which really can't be picked up by those technologies, to my knowledge.

DR. WARD: So it would reach a point of established damage to be picked up by BER, okay.

Other comments, discussions?

[No response.]

DR. WARD: You have in front of you a blue sheet for which you need to put your score for the experts on the panel, and those will be collected at the end of the day.

Let's move on to Flecainide for arrhythmias.

Dr. Stiles.

Review of Flecainide

Dr. Alan D. Stiles

DR. STILES: Flecainide is an anti-arrhythmia. It is used primarily in treatment for -- [off mic].

Having reviewed the information that came with this, I actually scored this a five, and in general found several issues that I thought were of particular importance in considering in discussions.

One is that there are limited bits of information available about the oncology of this particular drug in very young children, that being the zero- to six-year-old group.

Secondly, most of the studies used it in conjunction with other drugs and after other drugs had been used, and it is very difficult to glean from the literature any information on whether there are actually interactions between those drugs and what those were.

Thirdly, this is used with existent arrhythmias, so your patient situation is very atypical. Although in the adult literature, where this drug is primarily steady, it is known that ventricular dysfunction is a major problem, some of the children, particularly the young ones, actually have significant amounts of ventricular dysfunction left over from either in utero events or a period of time where issues have led to the treatment of the dysfunction.

Having said that, in the literature there are no reports of pro-arrhythmic activity in children, which was of some interest and, I think, an issue that is important to consider following.

So to summarize what I think are the issues to put on the table, one is the interaction with other drugs, and the second is actually whether or not there is enough information to intelligently dose this drug using the dosing schedule and so on that we are aware of.

The one caveat is that -- [off mic] very small children will compare -- [off mic] of the drug orally, and that may make some difference to dosing that may lead to an unusual situation.

DR. WARD: Thank you.

Steve, do you want to speak from the podium or there?

Dr. Lawless.

Secondary Review of Flecainide

Dr. Stephen T. Lawless

DR. LAWLESS: I actually gave it a higher score, a seven, the high of four. What struck me was the utilization number of Flecainide. I was actually, to use

a technical term, blown away by the relative usage of it for the indication it was there for.

It should be for intractable arrhythmias. Utilization looked more like what I would have expected for something like Lidocaine or an oral drug or something for the same thing. So it tells me that the usage out there is being used a lot more commonly for kids who probably aren't really good candidates for it. So there is that side effect there.

The indication for it is to prevent ventricular arrhythmias and sudden death. The main side effect is sudden death, even though the side effect is rare. So that scared me. I think this is a relatively dangerous drug used for a selected indication, which is probably being over-used. So that is why I gave it the higher score.

DR. WARD: Would either of you comment, or maybe someone in the audience here, about its pathway of metabolism with respect to drug-drug interactions? I confess I'm not familiar with what its pathways of metabolism are. Or, do we know?

DR. STILES: I think as far as what is

available, at least in the papers that I looked through, there is some information about its excretion. Largely, it is in the kidney, a little bit of change in the liver. But beyond that you are getting beyond my level of expertise to comment.

DR. WARD: Let me ask the FDA review officers if they would like to make some comments. If not, that is fine. This is the opportunity.

FDA Review of Flecainide

Dr. Susan McCune

DR. McCUNE: I'm Susan McCune, and I'm in the Pediatrics Division. I'm also a neonatalogist, so I'm much more comfortable in the neonatal period.

Just a couple of comments about the label. While it is not labeled specifically as an indication for pediatric use and it does say that safety and efficacy in the fetus, infant, or child have not been established in double-blind randomized placebo control trials, there is a fair amount of information about the metabolism PK information, even in the newborn up through the adolescent.

There is dosage information provided in the

label as well. It specifically stated that it should be undertaken under the care of a pediatric cardiologist.

There was a question, I believe, about the safety information. There are some reports in the literature about the co-arrhythmic events. The question is how severe they are. There is a wide spectrum of severity associated with it.

Open Discussion

DR. LAWLESS: Yes. The one thing that struck me is that, even though you had the incidence of the outpatient prescriptions, is that my guess would be that the drug is primarily used in kids who have congenital heart disease who have been repaired and are on this because afterwards their heart is irritable and they are put on something. So that is where the outpatient prescriptions come in.

But if you look at the dosage PK and information, there is a lot of variability there. So the idea of the highest-risk kids, probably my guess would be if you looked at distribution, would be the lowest-ages kids and how long you stay on it. So that is also, I think, a high reason for it to be studied.

DR. McCUNE: That is correct. In addition, it is not the first-line drug that would be used, and obviously, with the concerns about safety, but in some kids, this is the only thing that is available.

DR. LAWLESS: Right. And they are on Digoxin, most of them. My guess would be for the period of time that the effect of Digoxin and Flecainide, there may be kind of an interaction or a combination effect. It is a little bit uncertain territory.

DR. WARD: Also, I think that there is significant use of this drug in patient lives that never reaches an outpatient environment. Probably, the children at greatest risk are the ones who have been given this drug on the inpatient side, not the outpatient side. We have no utilization information as far as I'm aware with that.

Do you use this for infant SVT?

DR. BLUMER: We have used it for infants with refractory SVT, and I think that the problem with this, as I see it -- and I agree with what Steven said, but I think that we will run into a problem in trying to assess this. I think that the information on the label, if you look at

least in the published literature that supports it, is a hodgepodge. People have done pharmacokinetic studies of convenience so that patients who happen to be exposed and some of them happen to get some levels, and the doses that are recommended are doses that have been used, not doses that have been studied, and that creates difficulty.

On the other hand, in the context of use, if it were to be studied in the context of its current use, we would be doing this with the next millennium by the time patients get to that point.

So I think if we are going to consider recommending it, if it is a viable tool, and it appears to be, you may have to do it, in some ways, the way antibiotics are studied, and that is, take children with SVT and actually use it as a first-line drug to get that critical data about pharmacokinetic safety, exposure, and efficacy, and then put it in its context. That creates a problem when you have this unknown pro-arrhythmic effect there.

So I just think in terms of identifying need, we have to identify the feasibility of potential cautions that have to be exercised in moving forward.

DR. WARD: That would be a tough consent form, wouldn't it.

DR. LASKY: I just want to ask FDA again, this was a drug suggested by FDA? So I just wanted to make sure you got all your points across about why we need this study.

DR. WARD: It is the old Tommy Smothers "Take it."

[Laughter.]

PARTICIPANT: I would definitely defer to Dr. Mattison.

[Laughter.]

DR. LAWLESS: I have a question, then, on the recommendation for study to the point that Dr. Blumer just said.

This drug is primarily -- my guess would be a lot of it would be started in hospital.

DR. WARD: Right.

DR. LAWLESS: Would the recommendation for study be something that has to be started in hospital and then proceed on? I mean, I would think if therapy were started in the outpatient.

DR. WARD: It would seem to me that in that type of a design and that clinical situation in which you have refractory SVT, one of the questions would be, is it just SVT, what does your electrophysiology actually show you. But you would start it with careful monitoring, but the pro-arrhythmic effect may be months down the road. At least in the adults, it has been relatively random, it seemed to me, when it occurred.

Any other comments?

DR. HIGGINS: I would like to add that the Cardio-Renal Division actually thought that it wasn't properly labeled according to the current usage, which would be starting as an inpatient and then going over to oral outpatient therapy. So, basically, the review division had looked at it and looked at the data in labeling and, you know, tried to assess whether or not that really reflected actual use.

DR. BLUMER: In terms of trying to answer your initial question, there are polymorphisms in its clearance. I don't remember what they are, but it is a drug that always appears on one of those lists. That does confound us, so there will be those complications as well.

DR. WARD: Any other discussion?

[No response.]

DR. WARD: Thank you.

We have been joined by Dr. Duane Alexander, director of NICHD, who wants to make some remarks about the whole process we are about today.

Comments

Dr. Duane F. Alexander, Director, NICHD

DR. D. ALEXANDER: Good morning, everyone, and thank you for fitting me in. I promise not to take much of your valuable time. You have many more important things to do today rather than just listen to me, but I did want to say a special thanks to all of you for joining and participating in this very important process.

When the Congress passed the Pharmaceuticals Procurement Legislation, it assigned to NICHD the responsibility for the very first step in that whole process, which is identifying and prioritizing the list of drugs for study.

This is extremely important because there are far more than can be studied. There are $25 million available each year for these studies. While that sounds

like a lot of money, when you get to actually funding costs of the studies that are involved, it doesn't go very far. So the prioritization process is extremely important.

We have been working together in partnership with the Food and Drug Administration on this process and have done it several different ways. The first year, we were in a hurry. There wasn't time to do very much.

So what we did was rely on wise people. We pulled together wise people. We gave them a list of all the off-patent drugs and said, "Which of these are the most important to study?" It is actually a little easier when you are picking the first ones. It gets a little harder each time you go, each round, but they did an excellent job of selecting off that list the most important ones just based on their general knowledge and information.

But that can't go on forever. We were lucky the first time. We did very well, a pretty good job, I think, of it, but as you go on with the second and then the third lists, the process needs to become more sophisticated.

Our staff during the course of the last year has

devoted a major effort to trying to make this process as scientifically based and as information-based as possible, so that rather than just top-of-the-head knowledge and experiential use as a guide, we now are making efforts to provide information to you and the future groups that will be engaged in this process of priority-setting with additional information to go on: what is the extended use; what is the information in the literature that is available about usage and metabolism of these drugs; what is the need perceived in the community by actual survey and query from practitioners and their perception of these for further information and actual labeling of drugs for their use.

So this process is getting more sophisticated. This is far and away the most sophisticated one that we have had, and we are committed to making this process even better each succeeding year as we go about it.

So you are quite an entity with an extremely important role, and working for your colleagues in practice on providing us with information about which are the most important drugs for us to study, given the limited resources that we have, to get information for

pediatric labeling that will help guide their practice and help protect children who are receiving these drugs.

So thank you for doing it. We are committed to making the best effort we can to provide information.

At the end of the day tomorrow, we would hope that you would give us your suggestions for what might make this process even better for you as participants, and for other participants in the next year, because there is going to be a next year and a next year. Any additional information that you would find useful before you came to this meeting to help you make a judgment and provide the guidance that we depend on so much.

So any thoughts that you have as you participate in this process about what else might be helpful to you in providing the information that we seek.

So thanks to all of you for participating. We appreciate and value it very much. We hope that you find this process useful and can also give us guidance in how we can make it even better. Thank you very much.

DR. WARD: Thank you, Duane.

I just want to emphasize exactly what is said. This has been a process in evolution, and input and

feedback will be terribly important in refining it for next year. This is far and away the best organized approach to this, providing a comprehensive review of literature on a CD to make it convenient for you to review. I think that has enhanced it.

So other aspects that can be improved would be useful to the process and useful to make it serve children better.

Dr. Tom Green was to talk about Chlorothiazide for hypertension.

Review of Chlorothiazide

Dr. Thomas P. Green

DR. GREEN: Chlorothiazide is a diuretic that has been used for a long time in children and in adults. It acts by blocking electrolyte reabsorption in the renal tubule, primarily in the distal renal tubule. For that reason, it has a whole lot of indications and use in disorders of fluid electrolyte imbalance, particularly those of edema.

The indication that we are asked to look at this for is in hypertension, and in fact, the mechanism of action in the treatment of hypertension is a little less

well defined. It probably is in part related to its actions in the renal tubule, but it may have other actions as well.

The formulation for Chlorothiazide that we have been asked to look at are the labeling for Chlorothiazide is for the intravenous administration, and we can talk about that. I think, given the order that we are in, we are going to talk about Hydrochlorothiazide next, and I think there is a balance of indications that we will see in Chlorothiazide and Hydrochlorothiazide.

Fortunately, it appears that the therapeutic index for Chlorothiazide is fairly wide. Therefore, the problems with its use tend to be related to the drug mechanism of action. In other words, imbalances of food and electrolytes.

For children, the use of Chlorothiazide is related to hypertension in its use, although I think Hydrochlorothiazide is much more widely used. It is used in the newborn period for hypocalcemia, where there are disorders of electrolyte imbalance and fluid disorders where loop diuretics and other more highly effective diuretics are used. Hypocalcemia tends to be a

complication of loop diuretics, like Furosemide. The Thiazides have the offsetting benefit of decreasing urinary calcium excretion and thereby reversing or preventing the calcium deposition, the nephrolithiasis and so forth, that is seen with loop diuretics.

For those indications, it is fairly widely used, although I don't have good data on how widely used that is. I think that might vary from center to center. However, there are not good alternatives for the Thiazides in that hypocalcemic indication.

The labeling of Chlorothiazide precludes or does not encourage the use in children. There are no specific data provided in order to guide the use in children on the label.

The currently available information is really quite sparse. The literature that was provided in the review here actually kind of indicates, I think, how poor the literature is on Chlorothiazide. In fact, most of the articles that were included were for Hydrochlorothiazide and not specifically for Chlorothiazide.

I think I only found six of the articles that dealt specifically with information relative to

Chlorothiazide in any indication, and those were by and large case reports and reports in combination with other agents. So really a dearth of literature that is currently available.

As I mentioned earlier, I think the drug is thought to have -- I hate to kind of extrapolate too far when I just said there is not much data about it, and then reassure you that the efficacy and the safety is good, but I think the impression is that the therapeutic index is wide. Nonetheless, it would be, I think, fair to say that the information available for children is sparse, and the quality of information is not great.

I think that that leads to kind of a paradox in trying to assess the value of getting further information. If the drug is not widely used, used for only a few indications, and thought to have a wide therapeutic index without significant toxicities that would directly relate it to what you know to be the mechanism of action, it is not clear to me that the benefit of prioritizing this particular drug for further study would be high.

DR. WARD: Steve?

Dr. Stephen T. Lawless

DR. LAWLESS: Echoing what Tom has said, I think the idea of the use of the drug, the two major side effects are the electrolyte problems, especially the sodium and potassium stuff, because these kids are usually on it for a long period of time. That is usually a bigger problem.

The other thing is the confusion a lot of times between Hydrochlorothiazide and Chlorothiazide, so people mistaking one versus the other.

DR. WARD: It is only a twenty-fold difference.

DR. LAWLESS: That's right.

[Laughter.]

DR. LAWLESS: The other thing, actually, is it is used more abundantly and used for hypertension in the acute setting. Its use in renal failure actually is a contraindication. It is not that well known or well appreciated that it can actually cause renal failure or worsen renal failure, as opposed to other diuretics, so a little caution that way. But, really, Tom, it generally has a wide therapeutic index. It is not a big deal.

The other thing, with the tendency now with the

guidelines for hypertension to be more strict, people are going to be looking for drugs which just have a mild effect, to get the systolic from like a 120 to a 118 type of a thing. So the use of this may go up only because you don't want to use a big gun just to drop a pressure just a little bit in a six-year-old.

So there may be that balance there, but it usually tends to be safer. I did rank it lower in terms of not a high priority because it is safer that way.

DR. WARD: Dr. Grylack?

FDA Review of Chlorothiazide

Dr. Laurence Grylack

DR. GRYLACK: Thank you. Larry Grylack, Division of Pediatric Drug Development.

I generally agree with the comments made. I would raise a general issue, though, and certainly this is something the Division of Pediatrics feels strongly about, namely that with any of the anti-hypertensives that are being studied, that adequate long-term follow-up studies be done specifically looking at growth and development.

As you all know, in the literature during the last year, there have been some useful studies recognizing

the fact that there are some neurodevelopmental sequelae from hypertension itself, so it will be important in studies of hypertensives to try to distinguish the effects of medication from the effects of the disease itself.

Secondly, I raise the question to the experts on the panel as to whether both Thiazides need to be studied at this time, whether they are both priorities. I know that Dr. Green had made some comments about distinguishing the indications and the priority for Chlorothiazide and Hydrochlorothiazide, so that would be another issue that I would want to mention.

Finally, of course, being a neonatalogist, I have to make some remarks about the newborn. Certainly, protein binding for these compounds is variable, and certainly that has to be taken into consideration in looking at issues such as jaundice in the newborn.

So those are my remarks.

DR. WARD: Dr. Pursley?

FDA Review of Chlorothiazide

Dr. DeWayne M. Pursley

DR. PURSLEY: For full disclosure, my name is DeWayne. I'm also a neonatalogist.

DR. WARD: And neonatology is well represented around the table here.

[Laughter.]

DR. PURSLEY: I would comment that I would hazard a guess that the use of Chlorothiazide is actually quite prevalent among neonatal intensive care units around the country and probably not for this indication. I don't recall that I have ever used a diuretic as an anti-hypertensive in an acute setting. However, it is used quite commonly for babies with bronchopulmonary dysplasia. In fact, it is probably one of the most common medications which we discharge infants with chronic lung disease.

I think that the experience in Boston, at least in this case, is similar to the experiences of other NICUs around the country. We are using it quite a bit in our NICUs.

DR. GRYLACK: I agree, and certainly in our discussions prior to this meeting, we were talking about its use in BPD, but alas, the indication is hypertension so we couldn't get our teeth into the BPD issue.

Open Discussion

DR. WARD: Jeff.

DR. BLUMER: I think that both Thiazides raise an interesting paradox here. First of all, I think despite the increase in utilization and really thoughtfulness about the use of Thiazides in adult patients with hypertension, I think I want to echo what was said. We virtually have no experience using Thiazides for hypertension in children. When we use Thiazides, it is as a diuretic.

So the whole issue of pharmacokinetics, pharmacodynamics, and whether these are effective as hypertensives for the kids that we see with hypertension remains open. I think that that underscores the potential importance here of looking at one or the other of these drugs.

I think the other issue is that with the questions that are raised by Thiazides and the large utilization of them in the neonatal intensive care unit and as an adjunct to loop diuretics, it probably does need to be considered.

So I think this is an area that I would suggest we don't just put aside, but I do think in terms of

siloing the indications we probably need to think about them and then look at them again.

DR. WARD: Tom, would you comment on the calcium-spearing action in the neonate? Do we really have data that demonstrate that?

DR. GREEN: I hate to make a comment with all the neonatologists in the room because I'm not one of them.

[Laughter.]

DR. GREEN: But my impression is -- please comment -- that it looks like there is adequate data on prevention or even resolution of calcinosis and calcium excretion when Thiazide is used either alone or in combination with loop diuretics.

So, please, any comments?

DR. LAWLESS: Yes. I mean, I did one year in a nephrology fellowship, so I'm half-representative of that.

[Laughter.]

DR. WARD: You are the collecting duct.

DR. LASKY: Just one kidney.

DR. LAWLESS: One kidney, that's right.

[Laughter.]

DR. LAWLESS: We actually never used Thiazides for the hypocalcemic effect -- I mean, the calcium-spearing effect in the kidneys. I forget the Thiazide that was used, but it was not Chlorothiazide per se. There was a third type of Thiazide, but I forget the name of it. It wasn't as strong of a calcium-spearing effect. So if you have somebody with hypocalcemia, Chlorothiazide actually wouldn't be the Thiazide you would go to.

DR. GREEN: Well, I could just ask the neonatologists here, especially when we are dealing with prioritizing drugs and only being able to choose some of the indications here, my impression -- again, this is doing a reality check here -- is that the value of Chlorothiazide as opposed to Hydrochlorothiazide is it has an intravenous formulation.

So, in the period when you are still using IVs and so forth you have Chlorothiazide, but when you are switching to an oral agent, are you using Hydrochlorothiazide exclusively, or is there a reason to choose another Thiazide other than Hydrochlorothiazide when going for the longer term oral outpatient use?

PARTICIPANT: We would virtually always switch

to Hydrochlorothiazide, but I couldn't agree more, we would never use this for its anti-hypertensive effect.

DR. WARD: How does that impact our task here today, in that it was labeled for hypertension?

PARTICIPANT: I was going to come around to that. I was going to transfer the response to that aspect to Dr. Mathis and Dr. Mattison here and let them discuss that.

DR. MATHIS: I think if you look back to our first list that came out, you will see a significant number of anti-diuretics for BPD. In response to this, NICHD and FDA really developed a working group spearheaded by Dr. Giacoia that looked at this indication.

One of the problems that we have is just the problem of studying BPD: how do we define it; how do we define improvement. So part of the problem with developing drugs for this indication is the lack of clarity in defining this indication and improvement in this indication. That is probably something that we are going to need to address prior to being able to develop drugs for that indication, but we would like to look at them ultimately because we do know that that is a primary

use.

DR. WARD: I think that Chlorothiazide has reached this list with this indication based on the extrapolation from adults almost purely.

DR. MATHIS: Let me just remind people, we have these booklets. These were sent out to people beforehand.

The American Heart Association suggested Hydrochlorothiazide occasionally used as a diuretic in CHF. They have about eight drugs. It is a one-page comment, so we don't have more information.

One of the things I think we could do in the coming years if we don't feel satisfied here, is ask people to provide more information. That is not very much to go on.

Also, the American Society of Pediatric Nephrology included Chlorothiazide in its list. They have listed quite a few drugs, so they wouldn't have helped us prioritize. They listed about 30 drugs to look at, but just to keep this in mind that there were many paths to get to this list.

PARTICIPANT: The other thing, if either Alan Shapiro or Dr. Rodriguez would like to comment on some of

the Thiazides, too, for hypertension?

DR. WARD: Could I defer that? Let's go ahead and discuss the Hydrochlorothiazide, and then we will keep this discussion on both, since they really are representative of the same class.

Go ahead and do Hydrochlorothiazide.

Review 3: Off-Patent Drugs (continued)

Review of Hydrochlorothiazide

Dr. Thomas P. Green

DR. GREEN: Ditto for what I said about everything else about Chlorothiazide. Again, the indication that is listed here is Hydrochlorothiazide for hypertension. The mechanism is expected to be virtually identical to that of Chlorothiazide. It is only available in an oral formulation.

As contrasted with Chlorothiazide, there is a reasonable literature in the recent literature and the data that was sent along on Hydrochlorothiazide, I think representing its more widespread use for several indications.

It is used as an adjunctive therapy in the treatment of hypertension, and it is used somewhat, I

think, without a lot of data in the literature about the same indications that we talked about before for generalized disorders of edema causing the naturally diuretic effects.

However, a lot of the literature that has been around for the last 10 years deals with the use of Hydrochlorothiazide for a number of other disorders in which, in my view, the thinking about this, the value of further study of this drug, would carry over to a lot of other and essentially orphan indications.

Disorders that lead to increased calcium excretion in the urine, such as renal hypophosphatemia and other genetic disorders that lead to hypocalcemia, are pretty widely treated with Hydrochlorothiazide and used for a long period of time and used beginning in early childhood.

In addition, disorders of nephrogenic diabetes insipidus where not dealing with a calcium excretion caused some changes in the renal handling of salt and water and thereby improved patients' long-term water balance, and have been shown to improve their long-term growth and general health.

So while those are really orphan indications affecting a very small number of patients, Hydrochlorothiazide is used in those several circumstances and I think therefore has wide impact.

Probably back on task, I think the real reason we are asked to look at Hydrochlorothiazide has to do with its use in the more common disorders. I guess no additional comments, or I will carry over the comments that I made about Chlorothiazide in terms of the rather paucity of studies in children. On the other hand, the perception of relatively wide therapeutic index and safety, except for the direct knowable disorders of deranged fluid and electrolyte imbalance.

So here, I would rate it somewhat higher, probably more -- and maybe this is not legitimate in terms of our task -- but more on the kind of carryover value of the knowledge to many other children with a variety of disorders for which there otherwise wouldn't be therapy.

DR. WARD: Thank you.

DR. STILES: Yes.

Alan, do you want to provide secondary review?

Secondary Review of Hydrochlorothiazide

Dr. Alan D. Stiles

DR. STILES: Not a neonatalogist comment this time. I think the other really important reason to consider this drug around anti-hypertensity cases is the obesity epidemic. We are clearly beginning to use this drug very frequently on multiple age children, where before, that was unlikely to be an indication that would be pulled out. As it is in adults, it is the first-line anti-hypertensive often pulled out of the hat with these children who have also type II diabetes and other issues.

So in my opinion, that raises this to a much higher level of concern, taking everything else. There is a gigantic literature here about calcium excretion and other things. There is not much literature about the use of this drug as an anti-hypertensity control.

DR. WARD: Actually, Larry, do you want to go ahead and comment from the FDA? I want to hear about the frequency of use for hypertension and obesity.

FDA Review of Hydrochlorothiazide

Dr. John Alexander

DR. J. ALEXANDER: I think it was an excellent comment. We definitely need to be aware of that. Just a

few additional comments.

As far as the literature with regard to HCTZ, it has been used or studied in combination with other drugs. So that is something we can be aware of in terms of usage.

Secondly, as far as the calcemia issue, one reassuring study I came across was that although it did decrease the calcium excretion in the urine, it did not decrease bone mineral density in non-ambulatory children. This was a group of children with mild malignancy. So that is reassuring in terms a positive sense in terms of its usage.

Also, in terms of other drug interactions, if it is used concurrently with Dopamine in certainly critically ill patients, it may in fact increase the diuretic effect of the Dopamine, or vice versa. Dopamine might affect the diuretic effect of the Hydrochlorothiazide. So needless to say, there are a number of drug interaction issues that will need to be taken into consideration.

It is mentioned in the fourth report as being one of the drugs being considered for usage in hypertensive children.

FDA Review of Hydrochlorothiazide

Dr. Alan M. Shapiro

DR. SHAPIRO: I'm Dr. Alan Shapiro. I'm from the Division of Pediatric Drug Development. I'm also one of these people with one kidney. I'm primarily an infectious disease specialist, but I have also spend some time in pediatric nephrology in some training.

I wanted to echo Dr. Stiles' comments about the use of the Thiazides. Right now, at this point, most of the drugs that have been studied for hypertension in children have been the newer drugs, which have been namely the ASE inhibitors. Yet the older category of drugs, as we know in the adults, have a lot of efficacy, and it is considered first-line.

When you look at the Joint National Committee Report No. 7, they pick out Thiazides as being the first choice or first line for someone who has what we would say stage one hypertension, which the fourth report has also treated with the same category in kids.

We are seeing larger amounts of hypertension due to the obesity and due other causes that we are not completely aware of, and I think the point about studying

these drugs, and specifically the Thiazides, we need to know what are good agents to work with these kids.

All the studies that have been done with anti-hypertensives look at the blood pressure lowering over a short period of time. We have no clue about the clinical end effects of putting kids on anti-hypertensives for a long period of time, whether it is going to change their cardiac damage, kidney, retinal disease, a lot of the things we think we see in adults.

Yet we also don't have any clue, looking at the hypertension versus the treatment, whether there are long-term effects on growth and development.

So I would be one in support of putting the Thiazides higher up on priority, because we need to know this information.

Open Discussion

DR. LAWLESS: I think that if you link this, part of the study is a link towards an obesity management program and it is part of the obesity management -- obesity is going to be a major national priority -- then, yes, you have to get the dosing of what is the effective dose to use. You can't base it on weight in obese kids

for the long term. You just can't do that.

If it is not linked to that, if there are going to be recommendations for obesity management and this is going to be out there, you have to study it. You have to link it together and not leave it open. If it is not going to be done, you can still have it a lower priority.

DR. SHAPIRO: I looked over this fourth report quite well, and I know that they have a stage management for the kids with pre-hypertension, those with stage one, and those with stage 2, which essentially very closely parallel what is in the adults. For a kid who has stage two hypertension, they are put on anti-hypertensives.

Like I said, we are still running into the fact we don't know these anti-hypertensives very well, and we are just picking what we are familiar, because the ASE inhibitors were newer. You could apply exclusivity to them and they could get a benefit for study. The older drugs do not have that benefit, and that is where we come in.

DR. WARD: Yes.

DR. KARKOWSKY: There are two issues I would like to raise. The first issue is that diuretics are a

very effective drug in adults for African Americans, in contradistinction to the ASE NARBs, which are not particularly good. Depending upon your target population. that might be a useful reason to increase the priority.

Second of all, the appreciation for the dose of the diuretic has markedly changed over the last decade. People were overdosed in the past, and the toxicity was markedly increased because of that. Even if you know that the drug does work, does anybody have any idea what dose to use in kids, okay. Is it worth that amount of work to better define what is a cheap and useful drug in a population that might need it.

DR. WARD: Other comments?

Yes.

DR. ZITO: I just was going to offer the observation that if one were to look at the history of Thiazides over the last 30 years, there probably has been a significantly greater utilization of Hydrochlorothiazide, which would argue then that the safety database would be significantly better for that drug than the other. It might help make the case for it.

DR. SNODGRASS: Yes, a couple of short comments.

One is, if there were an IV formulation of Hydrochlorothiazide, would you have any reason to use Chlorothiazide? Just something to think about.

The other is, with the dose issue, there is data from adults that six months after stopping Hydrochlorothiazide in adults, you still have an anti-hypertension effect the precapillary arterial resistance sites. So there are a lot of unanswered issues about those long-term effects.

DR. GROGG: From the general pediatric side of things, I would like to recognize Dr. George Giacoia. He has been one of my mentors in the past. George, good to see you.

From general pediatrics, really, do we utilize Hydrochlorothiazide for hypertension, because it is almost always used for hypocalcemia treatment in children, and kidney stones and those kinds of things.

DR. WARD: In which patient population? Are you talking about children with myelomeningocele incumbency?

DR. GROGG: Just in general. If they are passing RBCs in the urine and it turns out that it is a calcium problem, most of these kids with one milligram per

kilo of HydroDIURIL.

DR. WARD: Rose.

DR. HIGGINS: I'm Rose Higgins. I'm a neonatalogist from the Pregnancy and Perinatology Branch. Can you guys hear me?

PARTICIPANT: Yes.

DR. HIGGINS: We did have a newborn drug development initiative which occurred last March, and there were many experts from around the country that participated in that. One of the working groups was focused on bronchopulmonary dysplasia, and these issues of the Thiazide diuretics came up markedly.

The problem with determining growth and neurodevelopmental outcome in children with BPD is that it is so confounded by all the other factors that are going on in the nursery, and I think that is why this was moved forward for the hypertension as opposed to the BPD indication in order to get information for labeling.

PARTICIPANT: I can see exactly -- I'm a neonatalogist as well -- how that would have come about, but I think the reality is, in the NICU in the acute care setting, we very seldom would reach for a Thiazide as our

first-line treatment for hypertension, as opposed to the treatment of BPD. At least in our unit in our area in the west, many of these kids go home on long-term treatment and we really have very little information about electrolyte imbalance efficacy and also adverse effects.

DR. WARD: Yes.

DR. GROGG: Just a final comment from me is that you also need to monitor the electrolytes initially, and that may increase the cost.

DR. WARD: Yes, there is no doubt about it.

Okay. Other comments?

[No response.]

DR. WARD: I will try to get the order correct this time.

Should we go to Acetylcysteine for Acetaminophen poisoning.

Dr. Berquist.

Review of Acetylcysteine

Dr. William E. Berquist

DR. BERQUIST: Again, I want to thank you for inviting me. My bias is from pediatric liver transplant and pediatric TDI, so I guess I'm the only one. I'm also

biased towards the San Francisco Giants.

[Laughter.]

DR. BERQUIST: I wanted to use my time to have a little bit -- [off mic].

DR. WARD: Could you move the mic down a little bit closer?

DR. BERQUIST: Okay, thank you.

So, Acetylcysteine is actually a precursor to Cysteine, which is necessary for -- [off mic.] The charge was to look at Acetylcysteine and Tylenol overdosage poisoning.

So I think that the main reason for this is because Acetaminophen toxicity and poisoning is probably one of the most common overdoses that one runs into. Acetylcysteine is actually a fairly old drug because it has been around and studied, as a number of these, in the '60s and '70s, and from that came the guidelines that have been drawn up and have been fairly well established. So much of the use of it has been previously established and the application to children has been utilized.

There have been some controversies about the use of it in particularly Chinese formulation versus the world

formulation. In the United States, primarily the world formulation is used.

DR. WARD: Let's just pause a second. Do you want to go ahead and bring that file up?

[PowerPoint presentation.]

DR. BERQUIST: So one of the major issues with it are the side effects in its use. So one runs into a fairly substantial proportion of the children having problems with nausea, as well as adults. So this is the structure.

Again, Acetaminophen is only about 5 percent. So this is Acetaminophen, and it is converted to the sulfate of the glutathione. About 5 percent is detoxified through glutathione or conjugated, and this leaves a small percent which is down at the bottom -- [off mic] which is really the pre-form, which is damage.

This is another slide which shows that most of it is really excreted, but you have glutathione depletion which ends up resulting in hepatocellular necrosis.

So one gives the Acetylcysteine to provide the cysteine for glutathione. This is where this -- [off mic] is vitally used, again established predominantly in

adults, with the level of Acetaminophen in the blood guiding whether or not there would be hepatic toxicity.

Now, I might remind you that, again, in adults, most of this is from an attempted suicide. In children, they may be getting toxic doses over a period of time. These are the three forms of treatment. There is a 72-hour PO, a 20-hour IV, and a 48-hour IV regimen.

The labeling is such for pediatric patients that there is only one study, and that is actually in newborns, looking at the IV infusion of Acetylcysteine, but there are really no controlled studies in pediatric patients.

One does not find any randomized control studies because this is a fairly well established treatment. The only other option is what I do, liver transplant.

[Laughter.]

DR. WARD: It is a tough control group.

DR. BERQUIST: It is a tough control group.

I think the major issue here is the warnings of the anaphylaxis and the actions especially in IV, as well as the other adverse effects in the world, but these are the issues that apply. I think probably that this is a common problem that you have this toxicity, but really, it

is the only major treatment.

This was an open label study which was done by Perry and Shannon looking at the toxicity. Again, this reemphasizes that if you give the medication within 10 hours of ingestion that it is very effective, as compared to those who aren't getting it.

This study is acute Acetaminophen poisoning in children. Kids are not just little adults. This was a single case report recently from Chicago where this child had a very high level, a five-hour level, 863 micrograms a milliliter, and the point was this child did very well with hemodialysis and Acetylcysteine therapy. Their case represented the largest reported ingestion under 18 months who recovered.

This particular study was the one out of all the slew of articles which really looked at sort of a meta-analysis of what studies were available. It was from Buckley [ph.] I think that they are from New Zealand. They compiled over 900-some cases looking at outcome of IV versus oral and basically showing that they were fully effective in terms of the outcome.

These actually are the only studies that they do

compare, looking at the treatment delay and outcome with the IV versus the oral. They did a comparison of with and without hepatotoxicity, again showing that late presentation and high-risk concentration were major factors, especially the delay in receiving Acetylcysteine.

So their conclusion in these 981 occasions is that the differences probably are factual and relate to an appropriate subgroup analysis. A shorter hospital stay, patient and doctor community, and concerns over the reduction of bioavailability make intravenous preferable, but really, the differences are not really substantial.

So these are the adverse reactions. Again, they are usually manageable, but they represent about 60 percent or so of cases. Again, this particular paper looked at risk factors for adverse reactions to Acetylcysteine, and their conclusion was the major risk was in asthmatics. Again, most of these reactions can be managed very successfully.

This particular paper points out that one of the problems we run into in infants and children is that they may be given multiple doses rather than a single large dose of Acetaminophen. So they may accumulate a higher

dose and therefore trying to use it in those particular cases may not be appropriate. They devised a recommendation that you really look for hepatic injury. Those are certainly going to be your highest-risk patients.

So as I reviewed it, the number of cases that we see actually in infants with Acetaminophen poisoning where it really causes a problem is actually very few. In my experience, we actually did a three-center study, and most of our patients are easily managed with Acetylcysteine, either oral or IV, and we haven't had to do transplants except for in those particular cases where it was very delayed and where there were other drugs. So that pretty much mirrors what you see in the adult group.

So I think my ranking for studying this, at least for Acetaminophen toxicity, because it is not that common except for adolescents -- and there I think the data is such that you can pretty much use adult data -- is that I didn't see a big role for further studies. I think I gave it a score of three.

What I did think is that in our area of dealing with acute liver toxicity, increasingly Acetylcysteine as

a scavenger and to help scavenger free radicals to help the liver recover is more prevalent. For example, in neonatal iron storage disease, we are seeing a number of infants who have an iron overload, and in that particular case, that has been used. It may prevent liver transplantation. That is kind of a focused area.

You have a drug that is not going to be used in a very large number of individuals, at least not the way it is currently, and I think that there is a role in the future to study this, because in the area of acute liver failure, we do need other treatment protocols to kind of help get these kids through that and hopefully get the liver to recover. So that was my only concern, is we might shift the focus towards that.

So, thank you.

DR. WARD: Okay. Tom?

Secondary Review of Acetylcysteine

Dr. Thomas P. Green

DR. GREEN: Well, I really have pretty much the same comments as Dr. Berquist. Maybe just a little summary of my own thoughts about it is that I was struck in looking at the literature provided about this

discrepancy between the recommendation for IV use outside this country and the recommendation for oral use within this country of Acetylcysteine for Acetaminophen poisoning.

I guess those of us that are insecure about so many things that the insecurity about giving an oral medication in a nauseated, vomiting child who has a very high risk for potentially fatal outcome of the underlying poisoning, I'm pretty insecure about that. I think translates in other people's insecurities to long lengths of stay and just a feeling of not giving the best therapy for the child.

So that, in my view, the ability to study this drug and its allay of some of the concerns about the toxicity or the incidence of side effects of the IV preparation would be fairly useful and, in addition, in developing bioavailability information. So one could actually, perhaps, study better the oral medication and thereby be more confident about its use, even though I acknowledge that the literature does show pretty similar outcomes.

So that's where I come down.

DR. WARD: Dr. McCune.

FDA Review of Acetylcysteine

Dr. Susan McCune

DR. McCUNE: I can't add to Dr. Berquist's wonderful summary about this drug except to add that there are no adequate and well controlled studies documented in the label, which is a problem in that the PK information is only in 500-grammers. We try so hard to get studies in 500-grammers, and it is interesting that this was the one that we have.

[Laughter.]

DR. McCUNE: Speaking of BPD and those issues.

I think two of the interesting conditions that you talked about are, one, the chronic use and toxicity associated with that that has not been very adequately studied; and then, at clinicaltrials.gov right now, there is an adult study ongoing for acute liver disease not associated with Acetaminophen toxicity. So I think to then expand that into the pediatric population would be excellent.

Open Discussion

DR. LOPEZ: My name is Lolita Lopez, medical

officer from GI. I only have one comment to make, and that is to let you know that in the label it is stated that the elimination half-life for Acetylcysteine is longer in newborns, about 11 hours, compared to that in adults, which is 5.5 hours.

The PK information is not available in other age groups. So we have the adults and the tiny babies.

DR. WARD: Could I ask you both, and FDA as well, to comment upon the toxicity? I was struck with the New Zealand study that showed, out of 900 patients, I believe, there were two or three with hypotension. As a neonatalogist, my impression of the literature was that hypotension with intravenous therapy was more common than that and was actually a significant issue.

PARTICIPANT: Well, again, I think these particular patients are at risk for hypotension anyway with liver failure, so you have kind of a rough set to work with.

DR. WARD: Is there merit in a study that evaluates intravenous versus oral therapy? It sounds like you would say yes.

DR. GREEN: Yes, absolutely. Again, developing

the bioavailability information might lead to more confidence in the oral form, therefore the shorter lengths of stay, I guess, eliminating the IV use.

DR. SNODGRASS: We probably treat about 100 a year, adults mostly, with this, and the IV has come out recently. Of course, it is more expensive.

If you look at the oral use, 80, 90 percent or more, what you absorb early is going to go through the poor vein. So you get about 60, 70 percent oral at least absorption, and that is really markedly decreased for oral.

In the first 10,000 cases in the United States in the Acetaminophen trial orally, there was not one case of anaphylaxis. In the first 25 IV when it was given rapid bolus in the U.K., very rapid, probably disrupting sulhydra [ph] bonds and plasma proteins, they had a case of anaphylaxis. So I think that is one issue about the IV, is the slowness of the use.

The other is, if you have a six-fold difference, if it is six liters per minute output in an adult and it is one liter per minute going to the liver when you give it in IV, then only a portion of the IV is hitting the

liver. So you see your end of the curve won't show you what is getting into the liver from the oral. That is why the oral works so well, even though they vomit. They actually absorb it. It smells awful. It is rotten eggs.

So I think these are issues to be addressed, and they are important issues. I think the extension of this into the liver prevention areas or treatment areas beyond Acetaminophen, pediatric nephrology has some literature about interstitial nephritis. I know I have been called by nephrologists about the dosing, as well as other issues.

So I think there are other uses for this down the road, and the IV will have a real place. It is defining what those issues are.

PARTICIPANT: I think the portal circulation is certainly a pertinent issue with respect to the bioavailability.

DR. BLUMER: I guess we need to keep two things in mind. First of all, with respect to the pharmacokinetics, there hasn't been any link between pharmacokinetics and pharmacodynamics with this drug. So having that data I'm not sure is going to help us a whole

lot. I mean, it is probably easy to get, but it is not going to be as useful in determining the effectiveness or safety of the drug.

I think, to echo some of Bill's comments, the likelihood of significant toxicity in young children is really very, very small. I think that the literature that I'm familiar with would show that with exposures under 300 milligrams per kilo in children under 16 to have significant hepatotoxicity, you really have a very rare problem.

So I think we have to just keep those things in mind as we look toward this. Our experience in the ICU as well is that the oral is actually very well tolerated. The kids that do vomit respond fairly well to Noandanzitron [ph] or a drug like that, and then tolerate the medication. There are at least theoretical reasons why the oral formulation might be better, but I think at the end of the day, after the 20-hour regimen or the couple of days it takes you to give the oral regimen, you won't see anything in our patients.

So I just think we have to weigh all those things. I mean, there is a great desire to get data. I

think the future for Acetylcysteine is in other areas, and the other area, I think, is in terms of end organ protection and things like that, where there may actually be some good PK/PD models that could be developed. That may be a more important indication.

DR. WARD: Yes, Stan.

DR. GROGG: Good old Muco Mist. Those of us old enough to remember, they used it in the nebulizer, and the smell, and it actually made the asthma worse rather than better, but we didn't realize that.

Where I see its use is in the 18-month to three-year-old that Tylenol is the number one ingested overdosed or accidentally ingested medication in pediatric use. So I would like to see some more studies. I was surprised it hadn't been approved, because that is what we reach for immediately if we see a child with an overdose of Tylenol. I would like to see some studies on the safety and its use.

It has to be used somewhat not knowing what type of plasma values you may get if charcoal is already in the stomach, too. You tend to give charcoal immediately for any type of overdose.

DR. WARD: Wayne.

DR. SNODGRASS: The charcoal data was some years ago. It doesn't bind it very much, so that is not much of an issue for that particular aspect.

DR. WARD: That is charcoal binding and Acetylcysteine?

DR. SNODGRASS: Right.

PARTICIPANT: That does not affect it, so it still works.

DR. WARD: Steve.

DR. LAWLESS: I have a question for Dr. Blumer. I was struck by your comment about the pharmacokinetics and essentially the discordance there with this drug in particular. If you are calling for studies for that and that is a discordance, and given the idea that you have no other option, you don't give the option as liver transplant.

DR. WARD: Right.

DR. LAWLESS: Doing studies on it, if you are starting to compare it to other drugs in terms of prioritization, I'm trying to find out a real reason to highly prioritize the drug to study. What is the end

goal? I mean, would you put somebody in a study where the end point may be liver transplantation?

DR. BLUMER: I think the ethics of that are lacking, so.

[Laughter.]

DR. LAWLESS: We are in America.

DR. BLUMER: I think the real issue is whether Acetylcysteine at this point in time can be used safely and effective for Acetaminophen overdose or for oxidative protection with what we understand about it now, or whether our use and children's health will be improved by further study. That, I think, is really the issue. This is not on the list for placebo control trials.

DR. WARD: Any other comments or discussion?

[No response.]

DR. WARD: If not, let me just remind you, check your forms.

We will take a break. As Dr. Alexander pointed out, we are ahead of time. Why don't we resume about 10:45. I'll look to the boss. Okay.

[Laughter.]

DR. WARD: All right, 10:45.

[Break.]

Review of Clonidine

Dr. Julie Magno Zito

[PowerPoint presentation.]

DR. ZITO: I'm really delighted to be here. I wish I were better prepared. The events of the last two weeks have been incredible, with the FDA's announcement of the Black Box and child psychiatry is just in a frenzy out there about what are we going to do, what sort of monitoring, and so on. So I have been listening to a lot of that at your annual meeting for numerous things last week.

I have two approaches to what I would like to do here. First, I would like to show you some empirical data that, thanks to Dr. Lasky and Dr. Mattison, we at the University of Maryland -- and I want to acknowledge my colleagues, two of them who have helped work on data analysis are here in the audience: Dr. Dan Safer, who is in child psychiatry and more or less knows whatever I know, and then Mecale Menis is the research assistant.

I'm just going to say two things to remind ourselves of what our task is. One is to focus on the

value of funding and conducting additional studies, and then, secondly, to think of what scientific questions and what types of study designs we would like to do to advance the science.

So let's move now to the question of what is the story on Clonidine. The information you gave me mentioned autism and ADHD, and I think somewhere else that I saw hypertension, as diagnoses that you were interested in.

The Metaworks people did a huge printout. It is enormous and is quite a potpourri of uses of Clonidine across all varieties, including surgical, sedation, insomnia, and so on. I'm really going to stay much more narrowly focused on the mental health-related issues.

I have a Mid Atlantic Medicaid State Database on which I'm going to show you some utilization. Everybody knows Clonidine and Guanfacine are examples of drugs that are in the category of alpha-agonists. They pretty much have had very, very little pediatric use until recent years.

The first reports of Clonidine use for mental health problems came, I think, with Michael Hunt's paper around 1988. Beginning in the early '90s, all the curves

that we have shown in looking at trend usage, there is this huge increase in use of all psychotropics virtually, with the exception of narcoleptics, lithium, and some of the drugs that are nastier and reserved for more severe situations. But this group of drugs went from nothing into something on the charts.

The other point is really just these two examples that I know about that get any usage in mental health, and the second thing to say is that most of it represents the use of Clonidine and then, to a smaller extent, Guanfacine. That is sort of the way that they appear in the literature, and that is the use.

If we were to look at the children zero to 17 -- so look at the last set of bars on the table -- you can see that the use of an alpha-agonist runs with stimulant use. That is to say that some proportion of children that receive the stimulant are also now receiving an alpha-agonist to deal with some of the problems with sleep, the insomnia problems that occur in the evening. There is possibly, also, a small number of them that get Clonidine alone, but I think that group is much smaller.

Then if we split it out by age group, I would

make the argument that we are not looking at the occurrence of hypertension. There is no diagnostic information on the slide, so I'm making it all up as we go along here. But if you look by age group, you can make the case that since stimulant use really takes off beginning with the school-age kids, that pattern is pretty consistent with use for ADHD.

That is, again, just showing you that most of it is Clonidine.

Now, the nice thing about the Medicaid data set is that we have a variable that nobody else in commercially insured populations and HMOs has, which is very submissive, although that may be changing. I don't know, maybe HMOs are starting to do that.

There are very pronounced differences in the use of psychotropic medications according to race/ethnicity. I think many of you who have been in treatment service delivery for many years would understand that we have a problem in terms of getting and keeping people in treatment for chronic conditions over time if they are poor, under-educated, come from different cultural backgrounds, or have problems accessing services.

So all of those things probably contribute particularly in the area of mental health, where there are bigger disparities and bigger disagreements around how we handle children with problems in hyperactivity, school performance, getting along with their peers, aggression, et cetera. So there is good reason, then, to understand that most of the usage is white, and we should pay attention to that.

In the gender use we also have a bias, because we all know that boys are badder than girls. So there they are in much larger numbers.

That's it for that part of the show. The rest of the story is that I just ran out of time to get all that stuff on the task sheets into PowerPoint. I discovered at 10:30 last night that, oh, I guess the worksheet isn't going to work from a Word file, so it shows you how tired I was.

I will start my decision, and then we can work backwards to some of the rationale.

So I'm on Task 1, the scoring sheet for Clonidine, or Catapres, which is the brand. The indications are autism and ADHD, but there is actually a

whole range of neuropsych conditions. Anything that we can't fix with everything else we have in psychiatry, there is a tendency to use what else is out there. That is a messy statement, but it is a reality. I have been reading the literature for 25 years.

Clonidine came from adult use in schizophrenia. That is its root into child, which is really a pity because it didn't work and it was shown to be a considerably more dangerous drug.

You know what? I don't know how to do this. I'm very challenged here. Maybe you can move the screen for me.

My overall score is nine, so very high on getting this drug on the list. The reason for pharmacokinetics and pharmacodynamics, I had nothing to say. Basically, I really don't know. I didn't see in the literature I reviewed any sort of detail or attention to this, but the drug has been around a long time. Mecale, it was marketed what, since? I forget. We ran down the years. '80-something. No?

DR. WARD: Catapres as an anti-hypertensive was available in the '70s.

DR. ZITO: Yes, the '70s, so it is even longer. So when you have that long an experience with a drug, it is undoubted that kinetics have been done at least in adults. Now, what that means for us I have no idea.

The next category I can't see.

DR. WARD: Why don't you just go ahead and read from that list of criteria? I think we have all worked through them for our individual drugs, so I think we will be familiar with them.

DR. ZITO: I'm sorry.

DR. WARD: That's fine.

DR. ZITO: I was going to sit over there and just do it. I'm sorry.

So in terms of efficacy information, there is available data, and now I will go back to telling you about studies of this drug. There are 10 studies that I reviewed for these mental health purposes. So we did about 10 studies on a whole range of mental health conditions.

Now I'm back to where the neonatologists and others were talking earlier, which are small-end, open studies, short-term use, and very unconvincing results

that would be easily driven by the enthusiasm of investigators. So I'm not persuaded that the data are very strong for things like autism. There are two studies that are both open. Even the investigator's abstract reads with a feeling of equivocal findings.

In regard to the studies that deal with things like Turrets, again they have a large advocacy group, a research study group, so the end is larger, but a lot of limitations in terms of design.

A large set of concerns about safety of Clonidine in young children because of the developmental potential for changes in the cardiovascular system. There is also a very large concern around accidental poisoning and toxicities, which have been shown to be pretty serious, and growing because the numbers of utilizers in the pediatric population is growing.

So the younger sib of the child who has started on it is now able to go on the kitchen table and poison himself accidentally. So those are all big concerns and sort of rationale for why we would want to know more.

Of course, it is not a hospitalization issue except in cases like autism or very severely impaired

pervasive developmental disorders, stuff like that. On the other hand, it is a very large proportion. From my figure, it would be legitimate to guess that there could be as many as 700,000 children in a given year who get exposure to Clonidine.

Of course, for some of them it is going to become a chronic condition because ADHD or whatever may then move on and could be a harbinger of other severe mental health problems to come.

The other thing we have learned in studying these is that it is not even likely that we could stop with just a stimulant and Clonidine combination and say, wow, there have been serious questions about that. There was debate in the literature. FDA people were involved in wondering whether that was really a deadly combination.

The sort of general impression is, it is not a deadly combination unless you really mess up and come up with a very complex regimen in which all bets are off. So high-dose use of Clonidine with a high dose of Methylphenidate would predispose to that. Throwing in other drugs that are known to really have serious cardiovascular effects, like the TCAs, would be a good way

to find mortality.

So that's the story on the scoring. My general comments around it are that it seems like the trajectory around mental health is going in one particular direction, and particularly because so much of this usage occurs in primary care, we need to give pediatricians and family practice doctors as much help as we can in assuring them that we have a good literature about what they are using and then eventually good clinical monitoring that would go along with it.

I don't know what else I need to say about it at this point.

DR. WARD: Dr. Grogg?

Secondary Review of Clonidine

Dr. Stanley E. Grogg

DR. GROGG: I will start off. I'm a general pediatrician, and we feel like psychiatrists because we are now forced, because of the inadequate supply of psychiatrists, to learn about these drugs. We see a lot of kids with ADHD.

[Pause.]

DR. GROGG: Anyway, so we have a large

ambulatory clinic in Tulsa, Oklahoma, for which we see a lot of ADHD kids. Because of the lack of pediatric psychiatrists, we get to take care of these kids.

Just what is ADHD, so you know. I'm going to be a boxing promoter when I grow up. It is impulsivity, inattentiveness, and hyperactivity. Now, I don't think anybody in this room has these conditions but our associates do, so we have to work with them quite a bit.

First-line medications at present, just trying to figure out which medications to go with with the kids, are stimulants, the Ritalin compounds, and the amphetamine and extra-amphetamine compounds. We are the capital of the world in methamphetamine in Oklahoma, so we are kind of careful with amphetamine compounds there.

A lot of non-stimulants are now available. Seventy to 80 percent of the kids will respond to psychostimulant medication, but there are a lot of newer medications, such as Strattera, that are available as a non-stimulant, and Wellbutrin, Effexor, some of the other SSRIs. Catapres and Tenex are the drugs that are available for us to look at and try to decide which is what indication or those kind of things. It is very

difficult.

As was mentioned, Catapres, or Clonidine, is a centrally-acting alpha-agonist used for hypertension in the past. It has been shown to have central effects so that it has been utilized for ADHD and some other psychiatric disorders, as alluded to by Dr. Zito.

Plasma levels peak about three to five hours. Thus, it is at least a PID with a half-life of 12 to 16 hours of PID dosage, which makes it difficult if you are just using it specifically for ADHD.

Safety and effectiveness below the age of 12 has not been established. Most of the studies have been above five years of age, and younger than that there are very few studies available.

It needs to be so heavily hydrated because of the drowsiness and sedation, and this is where I have a difficult time recommending it. If you look at what I put there, it is very confusing, and it is very confusing to the PCP out there as to how they would utilize Clonidine. Not many PCP physicians who are overloaded with ADHD kids would probably utilize it because of its confusion. Three to five micrograms per kilo per day PO div tid-qid dose.

I just throw this in here not for you to know how it is utilized but how complicated it is.

On the other end of the spectrum, if the child runs out, sometimes insurance only gives you a month's supply and then forgets about it because they are ADHD or the parents are ADHD, too. At the end of therapy, there may not be enough medicines to go through the weekend and they can have a secondary withdrawal type of symptom of hypertension, a rebound effect of hypertension, so there are some safety issues here.

Hypersensitivity to the drug class. You have to use caution, since it is an adrenergic stimulant, in coronary artery disease, cardiovascular disease in the kids, or if they have liver function or renal function limitations. There are a lot of drug interactions. I won't list them all. I will just show you there are a lot of drug interactions with this particular medication.

Adverse effects. The number one thing, and it is what we use it for; a lot of us will use psychostimulants such as Ritalin and then give them Catapres at nighttime in order to help their sleep if they have a history of insomnia, and that is probably the

number one of use of it with ADHD.

So, the cost. It is not too expensive.

So, in conclusion, often used in combination for sedation for sleep with psychostimulants rather than a drug by itself. It is difficult in my trade if you are using it just for ADHD. There are many potential side effects. There were three to four deaths reported back in 1999, and in the autopsies, it did not look like the drug had actually caused those deaths, but there are some questions about that.

You must withdraw gradually, which is very difficult in ADHD kids, because if they run out, they just stop taking it.

So, 20 to 30 percent of the kids with ADHD do not respond to psychostimulants, and we need an alternative drug. I would rather see Tenex, or Guanfacine may be a better choice to look at rather than Catapres or Clonidine. It is the same class, but it gives you a longer duration of action and sedation. My recommendation is to look at something different.

Although I gave it a score of 10, that is because there are a lot of studies out there. Even though

I gave it a score of 10, my recommendation is that this drug and its indications be a low priority for future listings and discussions.

It seems to help more for autism. There were only two studies that I could find. It seems to help more if you have mental retardation associated with autism, which is usually not the case. There are too few studies. The two that were present did not show a significant efficacy, to my mind, to recommend that we look at it further, so I recommend that this drug and indication receive low priority for future listings and discussions.

With that, it is time out, folks. Effects of gas.

DR. WARD: All right. With that closing --

[Laughter.]

DR. WARD: Let's see. FDA, Dr. McCune again. You are on.

FDA Review of Clonidine

Dr. Susan McCune

DR. McCUNE: I think Dr. Sheridan is going to join me.

It is tough to follow that.

I think a lot of the issues have been brought forward, and there could certainly be a lot of discussion about this drug. The use is extensive from a neuropharmacologic perspective, but the label reflects none of that. The label only reflects the anti-hypertensive use of the drug.

I think it is also important to note that from a basic science perspective, alpha-2 adrenergic receptor subtypes change dramatically in the brain during development in rats, so I think that there is certainly a need to look at this over the course of development in terms of responses to this drug.

I would like to reemphasize the fact that there are significant safety effects that are worrisome, especially the cardiac side effects. The accidental overdose issue is not trivial now that this drug is being used extensively off-label. There are a lot of opportunities for siblings to get a hold of this. There are also reports of the patch version of this actually being associated with overdoses.

So I think that there is a substantial amount of use going on. There is no information in the label, and I

think that there are significant safety concerns that would worry us.

FDA Review of Clonidine

Dr. Alan M. Shapiro

DR. SHAPIRO: I certainly agree with all that. I think the two speakers have put out Clonidine very effectively for our consideration.

I would urge consideration for a high priority for this drug simply because it is being used extensively. I am pediatric neurologist whose background is mostly in epilepsy, but I know among my fellow pediatric neurologists and probably among general pediatricians, this is a medication that tends to be used not only for trying to calm down patients that require stimulants and can't sleep well, but also, in other developmentally disabled children that need some form of sedation at night in order to be able to settle down and sleep, Clonidine is often used.

As Dr. McCune has just pointed out, the more it is used, the more the potential risks, particularly when we go past specific pediatric safety data and we don't have a specific preparation for pediatric which might be

also be considered. We rely on the parent to chop the tablet in half and dissolve it, or whatever, putting it in applesauce, and so forth. There are more and more problems if you have multiple caretakers for a child, problems with accidental overdosing, and of course, the younger sibling problem.

Open Discussion

DR. WARD: So there is no liquid formulation at this point?

DR. SHAPIRO: Correct. We only have the 0.1 milligram tablets and the 0.2 and 0.3, that's it.

DR. MEYTHALER: I'm a PMNR doc, and there are drugs being used a lot more off-label based on adult studies than people realize. It is being used a lot in spasticity and chronic pain. It is actually being used in Europe for both pain and spasticity, and it is being compounded in the United States frequently for this. Some of it is filtering down now into the pediatric population big time.

The other thing is that there are alternatives, and nobody has brought up the issue. This is an alpha-2-agonist. There is a lot of off-label use for all the

indications you guys have been talking about with the Tizanidine. It is an interesting issue because Tizanidine is one-fortieth the alpha-1 effects of Clonidine on blood pressure, but most all of it is alpha-2 effect.

So both of these drugs are being used relatively heavily in the populations, but there is an alternative out there for alpha-2s. It is kind of interesting nobody brought that up. I thought I should just kind of bring that up.

There is a third thing. Clonidine is being used a lot for sedation in agitated head injury patients, and I'm a head injury doc. The problem is that there is animal data out there indicating slow neural recover in neurological conditions acutely.

DR. WARD: First, we can't bring up a new drug, I think, at this point.

DR. MEYTHALER: I know, I know, but you do have listed other alternatives as well.

DR. WARD: Exactly, right.

DR. MEYTHALER: One was Guanfacine. I saw on the list that some people are using Tizanidine too, I think.

DR. WARD: I think we are hearing a nomination for next year's list.

Are you suggesting that traumatic brain injury should be part of the issues studied with Clonidine?

DR. MEYTHALER: Not at this point in time, but I do think that you do need to add in the spasticity and pain because that has heavy uses and there wasn't anything brought up about that.

DR. GROGG: Just to mention, it is available in a patch that can be put on the child so that you can utilize it that way, but it is about a 25 percent incidence of skin reaction to the patch. They can't tolerate it.

I would agree; I think it needs to be investigated, just not for ADHD specifically. I think that there are other drugs available and it has been shown to be safe and effective for ADHD. For other conditions, that is a different story.

DR. BLUMER: I actually just have a question about what I just heard from the FDA. One of the motivations that I'm hearing for considering this is because it is used. I wonder whether that is a good

enough indication for developing a study. I would question whether, if it is being used and the use is inappropriate or wouldn't be recommended, should we promote it?

I look at the sedation with Clonidine as an adverse effect, and now we are almost advocating that because it is used constantly for an adverse reaction we should then study it. I wonder if we shouldn't say, "Stop doing that." I mean, it is a drug that in some respects has a narrow therapeutic index, certainly narrower than many of the other drugs we have considered so far this morning.

I just worry about using use data to drive a process like this if the use isn't rational.

DR. LASKY: I think this hits at one of the cruxes of what BPCA is meant to address, and I was going to ask Stan about this. It scores highly, and you seem to be recommending against studying it because you are not pleased with the way it is used, but maybe the question to ask is, do we need to do a study in order to tell people to stop using it.

If your instincts are telling you that it is an

improper use, then is studying it a legitimate thing to do in light of how many people are using it and believing that it is an option.

So I'm trying to say that we need to separate a little bit our judgment on the use from a judgment on whether we should study it. They are not the same thing.

DR. WARD: Dr. Sachs, and then Dr. Zito.

DR. SACHS: There is a place in the label that if there is sufficient off-label use and it is actually inappropriate, and there is evidence that that is the case, that you can change the label to state that.

DR. WARD: Dr. Zito?

DR. ZITO: I would like to respond to Dr. Blumer's question, because I agree with you that all of us with any training in clinical pharmacology come from a very structured approach to the use of drugs. In the last 15 years, there have just been innumerable examples that I can point to for the utilization of drugs whose adverse effect is really essentially the desired effect.

Now, having said that and being practical, we have over a half a million kids who are likely to get the treatment, and whether they follow the Blumer effect or

the Zito effect is questionable.

[Laughter.]

DR. ZITO: Because we can preach all we want. There are lots of folks now who are very comfortable.

So what I would urge us to do is to think about whether we really want to do efficacy studies in a sort of traditional way, whether we would want to focus on safety and say we are really going to follow a very large cohort of children and we are going to follow them over five years so that we could see the changes in development, the impact on development from age two to seven, something like that.

DR. BLUMER: Or, is the question really to look at the sedative effects in children with ADHD. I mean, the implication I got was that you are going to look at it as a drug for efficacy in ADHD, and that is my impression of the use, too. It is used almost as an adjunct to children receiving stimulants, to help them sleep at night, et cetera; should that be the focus of the written request.

DR. WARD: There was a Pediatric Advisory Subcommittee, probably three years ago, specifically about

children being treated with stimulants and is it appropriate to ask a company to study a soporific for aid in sleep. The conclusion was no, yet the reality is, if you are the parents and the child is off the wall, and it is about midnight, you're going to reach for something and you're going to call your doctor the next day and ask them for something.

DR. LAWLESS: The question, actually, just along the same lines, is, one of the problems that is going to come up as you start talking about this drug, or any other drug, is the specific setting, the IV form of this versus this, but you are using a rationality of disease management.

If the studies you are going to recommend essentially going to be disease management studies, how does it fit within ADHD treatment, or is it going to be the specific drug itself and a very limited focus on the drug.

DR. LASKY: I wanted to bring up the comments by the National Institute of Mental Health. They specifically recommended that the drug Clonidine be studied for the indication of ADHD. They suggested that

PK studies are needed to determine the most appropriate frequency of dosing. PK studies of both oral and TTS preparations are needed. PK, when the drug is given together with Methylphenidate, is also needed because Clonidine is often used in combination with stimulant medication.

They also said, in terms of the scientific questions, placebo-controlled efficacy and tolerability studies are needed to determine the therapeutic benefit of this drug in isolation and when added to stimulant medication.

General safety and especially cardiovascular-adverse events and sedation and possible impact on cognitive function. Also, presence and extent of withdrawal symptoms needed to be determined.

I think Dr. Vitiello was going to be here, but I don't see him.

DR. WARD: Stan.

DR. GROGG: Once again, as an ADHD drug, and I think everybody is hearing this appropriately, I personally do not think that it needs further evaluation. As an adjunctive therapy for its side effect of sedation,

I think it does need to have further study. It does need to be evaluated, but I was under the impression that the recommendation is based upon just ADHD.

I think there are other medications available of a similar type, such as Tenex, that have less side effects if you are treating just ADHD.

DR. ZITO: To clarify what you are saying, I think you are saying for the treatment of ADHD alone. In other words, as monotherapy, which I would agree with.

DR. SACHS: I was just curious. I know the place that I see this used mostly in my practice is in kids with tics. I know that really hasn't come up at all yet in the discussion, but I was actually curious about the experience from the experts.

DR. GROGG: I would respond to that just from the aspect that we have utilized Clonidine for kids with tics because we think psychostimulants seem to make them worse, but it seems that some of the newer drugs such as Strattera and Tenex would work better with less side effects.

DR. WARD: Do you feel like we have answered your questions about people's focus as far as how they

feel this should be studied?

DR. SHAPIRO: Yes. I think it is very helpful, certainly, from the point of view of the division. We want to consider all these aspects when we come up to a particular drug when it is recommended that may be mentioned in terms of one indication, but we would consider the other indications as well in crafting a request for study through NIH contracts. So all of this feedback that you are giving us is extremely helpful.

DR. MATHIS: I just quickly wanted to address the issue of studying drugs because of amount of use. We have actually looked at this several times and have decided that from an ethical aspect it is not right to simply study drugs in children because a lot of people are using it.

It becomes a problem for us, though, when it is in the common medical literature that a drug is used as an adjunct treatment and it is being used off-label and many people are writing about its effectiveness, especially when there is a huge safety concern like there is with Clonidine.

So sometimes we need studies to actually

determine whether or not it is effective. Of course, if we had negative studies or a stronger safety signal that we were able to identify, we would use that to educate providers and we would also be able to get that into labeling to prevent them from using it.

So some of the times, while we don't say it is the use that necessarily drives our desire to have these drugs studied, it is more a need for additional information on the efficacy and safety of the drug because of its being used so frequently that drives us to do the studies.

DR. WARD: I think those are important points to make.

Any further discussion?

DR. SNODGRASS: I just think that points out a real ethical dilemma. At what stage do you reach the ethical dilemma that we shouldn't do this. On the other hand, you would like to have data. If you predict pretty strongly ahead of time that this is going to be negative, would you want your child in that study.

DR. WARD: Given the use information, if it is likely to be a negative study, it sounds like there are a

lot of kids responding to placebo.

DR. SNODGRASS: A dangerous placebo.

DR. WARD: Given the hour, let's try to fit in one more drug before lunch. There is a second blue sheet beginning with Cefuroxime for infections in children with sickle cell anemia. Dr. Snodgrass, I believe, is presenting.

Review 4: Off-Patent Drugs

Review of Cefuroxime

Dr. Wayne R. Snodgrass

DR. SNODGRASS: This is an issue of Cefuroxime and specifically its use in sickle cell disease. I think this parallels to some extent Tom Green's earlier characterization of, you have a drug that has a fairly wide margin of safety where in fact there are essentially no data in this particular selected indication, and yet it is undoubtedly being fairly widely used in this group of patients.

So it is not the same degree as Ethambutol, where you have serious disorders, but you have perhaps a number of other options from Cefuroxime, whereas with Ethambutol in that setting, you may have fewer options.

On the other hand, this is a potentially serious disease. It is an infection that can be very serious, particularly beyond the first many months of life, and they can present and rapidly progress.

So I think it is fairly widely used. Its safety is probably not much of an issue here. Again, Cefuroxime is widely used in other soft tissue and other related endpoints so that I think it is well recognized.

So the real question in prioritizing this is, certainly from the point of view of this particular disease, a study would be valuable, perhaps because there might be some theoretical issues about renal function and nephropathy down the line and this would be altered, perhaps, or whether there would be less response in those who are somewhat less immunocompetent with the asplinism [ph] in particular. So there might be some reason to have some advocacy in this and then perhaps some PK data, particularly from the point of view of if it were handled differently somehow.

I can't give it an extremely high priority, but at least it would be, for those reasons, useful to do that.

The other general comment I will have is that in the labeling with regard to pharmacokinetics, it is stated in the PDR at least that under age three months there is no data, basically. Yet if you go to the USPDI, you will see that in brackets it is down to one month or less, and then between one month and three months of age, we have specific dosing changes and say three to five times slower half-life. So there must be data there which I haven't found that somebody has reviewed.

So that is official compendia on the one hand, but it is not in the PDR on the other hand.

So I gave it a score of seven based purely on consideration of sickle cell disease per se.

DR. WARD: Do you want to make some secondary comments?

Secondary Review of Cefuroxime

Dr. Gary D. Overturf

DR. OVERTURF: I think this is one of those drugs that was indicated for sickle cell anemia primarily based upon the fact that it was one of the earliest cephalosporins with activity against Haemophilus influenza and at a time that we did not have Haemophilus influenza

vaccines that were effective in young children.

The drug subsequently got a very checkered career against Haemophilus influenza because of some PK and PD data which really suggested that it did not achieve good CSF levels. Actually, in one very famous trial which appeared in the New England Journal of Medicine, it was paired with another third generation cephalosporin.

So I think this specific indication is very infrequently used because the rationalization for using it primarily was based upon known pharmacokinetics, known activity against the targeted infections in populations that you wanted to use it in, and then known susceptibility organisms.

Now I think there are better agents, and of course, now there is also the problem of increased resistance not only in Haemophilus influenza but also streptococcus pneumonia.

So I think this has become kind of a moot point. I think it is one of those historical indications listed that has no rationale for use anymore. So this is a question to me not whether you study it but whether it should be delisted based upon what we know in terms of the

activity of this agent against current strains of infective organisms. I'm trying to think of another situation.

When we talked about anti-tuberculous drugs, it was similar. You get to a point where there is such a great resistance or such great problems that the drug is no longer useful for what it was used for as a historical indication. That is my perspective on this.

I don't know how you do that, but it is just not a useful indication anymore.

DR. WARD: Let me apologize to Dr. Wiederman for my confusion.

DR. WIEDERMAN: No problem. I will give you the short version. I can't figure out why it is on the list, either.

Although I will say in the package insert that was on the CD, it was for the oral form of Cefuroxime, so I don't know if there is a specific question about that. Then I saw Dr. Lasky's slide at the start. There was a particular question about its use under three months of age in sickle cell disease. That is probably the age range where sickle cell disease is not much different from

any other under three months of age. So if that is the question, I don't see much reason to put it as a high priority, either.

DR. WARD: The recommendation for it looks like it came from NHLBI, and it specifically addressed under three months of age with sickle cell disease.

DR. WIEDERMAN: They probably need some more ID guys.

DR. WARD: Some more guidance, okay.

DR. LASKY: Well, that might be just exactly a great solution to a problem, because people in different fields don't necessarily talk to each other.

[Laughter.]

DR. LASKY: People put their names forward. It would be interesting to continue this discussion back and forth, because I don't like to disregard it.

DR. WIEDERMAN: I was originally thinking maybe there were some things in the older sticklers with the acute syndrome or respiratory things, but again, it is a question of you can likely extrapolate, given that there is such a wide margin of safety here, from other studies. It would be interesting information but I'm not sure a

high priority.

DR. WARD: Dr. Shapiro and Dr. Alexander, do you want to comment from the FDA?

FDA Review of Cefuroxime

Dr. John Alexander

DR. J. ALEXANDER: I found this a little bit confusing, too, to understand what exactly was the indication that was being sought. We don't actually have an indication for drugs for treatment of sickle cell patients or even for prevention of infection in sickle cell patients. So I sort of found this confusing as to what the goal was.

I agree with Dr. Wiederman's comment that the current label for Cefuroxime basically covers children down to the age of three months, and we are talking about the oral formulation Cefuroxime. The reason that it sort of stopped at three months was just because of the fact that at the time that this drug was approved and labeled, we were in an era where we weren't using oral drugs much in children under two to three months of age.

So that is why that sort of cut-off was there, is that they probably didn't have any data that they were

looking at in terms of the oral drug or its safety in children less than three months and weren't expecting to use it.

There is no population under three months specifically with sickle cell disease where I think that there is sort of a use for this. The question that I had was, if the purpose is just we think that this drug is valuable in treating infections that occur in sickle cell patients, well, we think that the label sort of covers this already because we don't necessarily treat those patients with different doses unless they have some level of renal impairment or something like that. So the drug the way that it is labeled sort of covers that.

If the goal -- and this may be the case -- of the NHLBI was to actually have Cefuroxime looked at as an alternative to Penicillin for prophylaxis of patients with sickle cell disease for sort of prevention of infection, that is one potential where this could be a valuable drug for study, but that would be looking sort of at the efficacy, and there are a lot of questions about just how valuable that would be in an age where they have Hib vaccine, they have PCB-7 vaccine, and we don't necessarily

know exactly in this day and age what the treatment effect of even Penicillin in those patients is right now.

DR. WARD: Their comments were for the indications for Group B strep, pneumococci, staphylococci, H. flu, E. coli, enterobacter, and clipsiella [ph.] It didn't sound like anything specifically for children with sickle cell.

FDA Review of Cefuroxime

Dr. Alan M. Shapiro

DR. SHAPIRO: I have to concur with Dr. Alexander and Dr. Wiederman. I think for patients under three months I don't see any benefit. I think for the most part sickle cell kids under three months are most likely normal kids. It is when they are older that they develop the complication base and many of the renal problems.

With the kids under three months of age, let's say for the IV form, we are concerned that this drug may not get well into the CNS. So if I was in the case of using this drug for a kid under those circumstances, I would probably stick with a third generation cephalosporin where I feel more comfortable that the drug is getting

into the CNS.

Open Discussion

DR. WARD: Jeff.

DR. BLUMER: If we are talking about the oral formulation, I think the one thing that hasn't been mentioned is the oral formulation is the worst tasting oral formulation of an antibiotic in existence.

[Laughter.]

DR. WARD: That always recommends it highly in pediatrics.

[Laughter.]

DR. SNODGRASS: Can I make a recommendation that we delist this?

DR. WARD: I think everybody gets a chance to vote. Dr. Snodgrass is recommending delisting.

Yes, Steve.

DR. LAWLESS: I think one of the criteria that you have to mention in terms of, is there any study looking at racial or gender differences in drug metabolism, I mean, if you talk about sickle cell being a specific racial disease. We are not addressing it, but is that one of the underlying reasons; are there any studies

that actually address that. This would be the one time that I would think there was a study, this would be the time, because it would show that.

DR. WARD: I come from Utah, and we don't take care of many kids with sickle cell.

[Laughter.]

PARTICIPANT: But you do have your genetic problems.

[Laughter.]

DR. WARD: We do have our share of recessively inherited disorders.

They quote those issues in here, but my recollection of sickle cell was that in the young infant it wasn't a particular problem. They didn't present with asplenia and they didn't have infarctions at that early age. So I think there is a disconnect in this.

DR. OVERTURF: Actually, can I?

DR. WARD: Yes.

DR. OVERTURF: The issue on when splenectomy becomes a problem in sickle cell is a debate. For instance, the Jamaican studies showed that half their deaths from pneumococcal substance occurred before the

first year of life.

So despite the fact that when you look at the total data on when kids get a splenectomy or have a functional defect, it is a continuum. So some children probably acquire this quite early, but I don't think it makes any difference in terms of this discussion because I think all the comments about this being the worst oral cephalosporin to take in the world are quite germane if you are going to use this for a prophylaxis, as an example.

The fact that it really does not have the best of activities against resistant pneumococci or Haemophilus influenza, it makes it a moot point. This is not a drug one should select or would select for prophylaxis in sickle cell, even if you believed any of these other issues were germane.

DR. ZAOUTIS: One additional comment to Dr. Overturf. I agree with him about the pneumococcus issue. When you compare the MICs against resistant pneumococci between Amoxicillin, Penicillin, and then Cefuroxime, Cefuroxime is inferior to those agents in terms of the time above the MIC.

The second is a paper that was published several years ago in CID looking at risk factors for mortality from pneumococcal sepsis by Victor Yu [ph.] Among the beta-lactams, the only risk factor for increased mortality was the use of Cefuroxime for pneumococcal disease.

DR. WARD: Wonderful. Other than that, it has a great therapeutic effect.

[Laughter.]

DR. WARD: All right. Stan, yes.

DR. GROGG: What else needs to be said.

[Laughter.]

DR. GROGG: It is very expensive, too, so if you are replacing Penicillin --

[Laughter.]

DR. LASKY: It tastes bad and it is expensive. There you go.

DR. GROGG: And it is ineffective.

DR. STILES: I was just going to make a comment that has nothing to do with the drug in particular, but more of a generic situation we have gotten ourselves into.

Part of what we are doing is talking about places where we actually have good information or

reasonably good information and best practices out there for pediatricians. They don't use it and wait.

One thing that maybe should be at the end of the whole session is that we ought to feed this back to other groups that ought to be dealing with best practices.

DR. WARD: That is a good point.

DR. LASKY: I just wanted to also throw out that this is our first time doing this kind of outreach with the NIH institutes, and hopefully, over time, when people respond at the outreach, they will provide more information. It is a little hard to know.

Some time was put into this. NIH sent it out to a pediatrician professor at a very good university, and either they didn't put enough information down or they are off base, but this process will have to develop so that we have the information and the full thinking behind it and be able to respond to it.

At a minimum, I think after this meeting we could have a conference call just to make sure we are not missing anything on the thinking here, but at least we can respond to these people and say, "Look, we had these people, we talked about it, they didn't see it, and you

can come back with more information or move on," that kind of thing.

DR. RODRIQUEZ: As a personal participant in the development of Cefuroxime both for the oral and for the IV, I'm sitting here enjoying this.

[Laughter.]

DR. RODRIQUEZ: We even had adults who volunteered to have their sinuses perforated after Cefuroxime to demonstrate that there was a decrease in the amount of bacteria, including streptococcus pneumonia in the '80s.

See, this is the big point. I mean, in other words, we used to talk about Cefaclor before? Okay, that was some time earlier. In other words, the drug had its time, and it is time to move forward.

DR. WARD: Thank you, Bill. I thought I was going to have to say something really retracting a negative statement.

[Laughter.]

DR. WARD: In the discussion so far, I guess I have not seen more unanimity of negative feelings about a drug this morning.

DR. RODRIQUEZ: By the way, I used one in a drink to my daughter who had sinusitis. She was better within 24 hours, but I had to pay her quite a bit of money for her to take it.

[Laughter.]

DR. RODRIQUEZ: By the way, the only being that liked it was my brit dog, who loved it. But I haven't found a kid who likes it yet.

PARTICIPANT: And the dog has no sinusitis.

DR. RODRIQUEZ: No.

DR. WARD: I think on that note, it is time for lunch.

[Laughter.]

DR. WARD: We will resume around 1:00 p.m.

[Lunch recess.]

+ + +

A F T E R N O O N S E S S I O N

[Reconvened 1:01 p.m.]

DR. WARD: So I think we are down to Cephalexin, with Dr. Overturf and Dr. Zaoutis.

Review of Cephalexin

Dr. Gary D. Overturf

DR. OVERTURF: I think I will not use the computer.

Cephalexin. I was asked [to review] oral and respiratory infections, basically. Actually, a lot of the infections -- [off mic] and streptococcus -- [off mic], which are two respiratory pathogens -- [off mic] indications specifically for all pathogens.

So there is abundant data regarding Cephalexin. It is a very old drug. It has been used mostly in skin and soft tissue infractions, and primarily in treatment of bone and joint infections.

For respiratory and oral infection in general, there is relatively little data, except for some respiratory infections, like pharyngitis, which I will just mention briefly.

Actually, in looking for pharyngitis studies, I

found five randomized control trials, of which, one was a prospective randomized, controlled, blind trial which had about 500 patients -- [off mic] equivalent, microbiologically speaking. It is a relatively recent study.

As a result, there is a good deal of safety data also for Cephalexin, but for other respiratory infections other than pharyngitis, there is no data that is really prospective and controlled for such infections like pneumonia, oral infections of any kind that I could find.

Obviously, some of the respiratory infections can be of high morbidity or are associated with infections of high morbidity.

The other thing was that there are many other agents which are comparable, but with the exception of the bone and joint infections, there has been no empirical trials of any other drug, any of the other cephalosporins, that might be useful.

So I gave this a total point of seven, but mostly for relabeling. I don't really think this needs to be relisted. I think the data is available, but much of the data needs to be relisted in the indications, which

does include bone and joint infections, but it needs to be expanded to include PK and safety data on larger doses, because the stated dose is still 25 to 50 milligrams. So most of what needs to be done, I think, for Cephalexin is a relabeling based upon available data, which I think is adequate to support it.

On the other hand, if one were of the opinion that we needed this drug for respiratory infections other than pharyngitis, it would require a study. Its spectrum of activity is not adequate for most respiratory infections or for infections like sinusitis and other infections in childhood. So that I really don't think it needs to be relisted.

The other place where it is used a great deal in pediatrics is for urinary tract infections. It is a useful drug. It does have an indication, although it doesn't say it specifically, in children. I would give it a low priority because the standard dose is -- [off mic] a wide acceptance over many years.

So in summary, I really felt that the specific indication we are being asked for of oral infections, I think there are no data, and I don't think there should

be. So I wouldn't recommend studying that because, based on spectrum and based on other drugs, it would probably be not suitable for that indication.

For labeling, there probably needs to be a change in some of the labeling, just based on available data.

DR. WARD: Thank you.

Secondary Review of Cephalexin

Dr. Theoklis E. Zaoutis

DR. ZAOUTIS: I agree with Dr. Overturf, specifically addressing not the respiratory infections but the oral infections. The task was oral?

DR. WARD: I believe it was nominated by the pediatric dentists, actually, so they are, I'm sure, focused on gum and sinusitis.

DR. LASKY: If you want me to read what it says, "First-generation cephalosporins are not first choice or even good alternative agents for the management of acute oral infections, particularly because they lack significant activity against oral anaerobic pathogenic microorganisms. However, there are many

anecdotal reports of use of this agent in dentistry.

"Since the safety and efficacy for this use in children have not been established, the prevalence of these uses of Cephalexin should be assessed, and further reports on its appropriate and inappropriate use should be promulgated."

DR. OVERTURF: I think it is another example where a placebo works well for non-existent conditions.

DR. WARD: So sort of addressing their comments.

[Laughter.]

DR. ZAOUTIS: I think the safety and efficacy of the drug has been established in children even of other diseases.

They sort of made the statement that I was going to make up front, that oral infections are usually polymicrobial and oral anaerobes are a big part of those infections. Cephalexin has minimal anti-anaerobic activity in contrast to Penicillin and other drugs, so from a drug-drug match, it doesn't seem to be appropriate. I think the cases that have shown resolution have probably been resolved because of the host or other

factors.

So I actually gave it a three, but that was stretching it.

DR. WARD: Okay. So we have a stretched three.

FDA will speak to this.

Dr. Alexander.

DR. J. ALEXANDER: I'm not sure how much more to add to that.

[Laughter.]

FDA Review of Cephalexin

Dr. John Alexander

DR. J. ALEXANDER: I realize that Cephalexin is a fairly old drug, and so many of the indications and the way that the label reads is a product of the fact that it is older even than Cefuroxime. The way that the label is written, it actually has dosing recommendations on the dose that is meant to be given for children for treatment of the indications that are listed.

I accept the comments about the fact that now much higher doses of Cephalexin are being recommended for bone and joint infections and that that is still sort of an off-label use, but I think that that is potentially a

use that could be sort of studied separately where you get information on PK penetration into bony tissues with a higher dose in safety, and that would probably be sufficient for putting in more information on the label about that sort of use.

When it comes to oral infection, I don't really see that there is a great need for this, and I agree that the idea of its activity against anaerobic bacteria, which are what you would be concerned about with oral infections, doesn't make it a particularly good choice for that.

Open Discussion

DR. SACHS: The only thing that I was going to add was that this is on the list for drugs that should be recommended in SBE prophylaxis for Penicillin-allergic. The alternatives are Clindamycin, Clarithromycin, and Zithromax. Of the group, it is pretty much the best tolerated and least expensive. So my question was whether or not SBE prophylaxis would really be a reasonable indication.

I will say I was surprised at the nomination, particularly when you look at the approved spectrum of

organisms that it helps. The microbiology didn't seem to match, but at least as far as SBE prophylaxis, I think it is actually not an unreasonable indication to look at.

DR. OVERTURF: Actually, you open a real can of worms if you are going to open the whole issue of SBE prophylaxis, because virtually none of the drugs that are actually recommended for SBE prophylaxis are based upon actual data that suggest that you even can change the instance of bacteremia post procedure. They are based upon activity and likelihood that their PK and PD and the antimicrobic spectrum that they are treating will be adequate to maintain a low count or eliminate bacteremia, but there is no data that that is true.

So I think you are right, it is a reasonable drug. I would like to make a comment about this issue of the septic arthritis and osteomyelitis. That is a prescription that I have to write about two or three times a week because PEDEs ID [ph] people take care of that condition almost exclusively these days. At least once a week, I get a call from a pharmacist who looks this up and won't fill the prescription because the label is 25 to 50 milligrams per kilogram.

So if it is studied and felt that there is adequate data to support the safety of that, then I think it ought to be on the label, because it would actually save me at least one telephone call a week.

DR. ZAOUTIS: Two points, one regarding the SBE prophylaxis. I was recently informed that the AAHA, when they meet again, will be actually changing those recommendations for prophylaxis to minimize antibiotic use in the prevention of SBE prophylaxis significantly. So I think the recommendations are going to be change and there will be minimal antibiotic use post dental procedures for SBE prophylaxis, although I don't have that formal information.

DR. WARD: So we can be in front of that curve.

John, could you comment about whether the label specifically indicates its ineffectiveness for anaerobes?

DR. J. ALEXANDER: No, not usually. I mean, what usually happens is that we list the organisms for which there is known activity related to the particular indication that they have. So the organism goes into the list if the drug shows that it has activity against that organism and that it is used in a specific indication in

which that microorganism is known.

DR. WARD: So if I were a dentist and I knew that there were anaerobes in the mouth I wanted to cover and I knew what anaerobes those were, I wouldn't find it in the label, but I wouldn't specifically say "does not cover anaerobes."

DR. SACHS: It does say it is not active against anaerobe coccus and that there is really no activity against asinadobacter [ph.]

DR. RODRIQUEZ: An interesting thing is that in a manual for dentists it says "third drug of choice for oral -- [off mic], for acute dental infection of -- [off mic] gingivitis, periodontal abscess, and periodontitis." They give it in combination for both children and adults with different dosage regimens. So again, another area that we need to educate.

DR. OVERTURF: Do we try to educate through study? I think we need to educate through education.

DR. RODRIQUEZ: This drug is pretty well known in the area of anaerobic infections in the antimicrobial therapy guide for dentists. It is an article from 1999, and he put it down as the third option.

DR. WARD: Yes, Stan.

DR. GROGG: Just a comment. It is cheap and it tastes good, versus Cefuroxime.

[Laughter.]

DR. GROGG: But in this day and age of resistant and community environment and so on, resistant staph, at least in my area of the country where about 50 percent are resistant to first generation cephalosporins, I think it needs stronger labeling in the indications. Right now, it lists susceptible strains of this microorganisms, and they include Haemophilus and staph and M. catarrhalis, which it really doesn't have any effect at all.

I think I would go along with that it needs to not be researched further but relabeled.

DR. OVERTURF: I would agree with that. I actually had a point -- I had it in my write-up, but I didn't mention it at the podium -- that in most localities now, particularly skin and soft tissues infections, well over 50 percent of them are community acquired MRSA, and this would not be an agent that would be active.

DR. WARD: Can that be taken back, then? We would recommend relabeling of it based on published

information.

All right. Place your votes for it.

Jeff, do you want to talk about Acyclovir for hepatic infections?

DR. BLUMER: Yes, that is like talking about Penicillin for infection.

[Laughter.]

Review of Acyclovir

Dr. Jeffrey Blumer

DR. BLUMER: So Acyclovir is an antiviral agent that works through intracellular mechanisms of phosphorylation. The charge to look at hepatic infections wasn't entirely clear because the Acyclovir package label that was given was for the clinical formulation, and many of the references were for gingival stomatitis or for prophylaxis.

But overall, I think if you look at this for the one pediatric label indication, I think there was adequate and well controlled trials done for herpes simplex encephalitis in the newborn, for herpes infections in the newborn, and the carryover with herpes simplex encephalitis both in children and adults.

So I think that there is adequate pharmacokinetic data, not that the pharmacokinetic data, once again, in this particular area is all that useful because the activity of the drug is intracellular and in many respects the Acyclovir requires metabolism in order to be activated.

So that, I guess I looked at the data that was there. I didn't think that there would be much gained by looking at Acyclovir in a variety of these different indications when the parental drugs specifically were dealing with serious and life-threatening infections. The drug has been documented to work and work in our most vulnerable populations.

So I felt that while it is an important problem, it is a life-threatening problem, I think the drug has been demonstrated to work, and I didn't think that we would learn much more by doing more long-term or well-controlled studies of either the pharmacokinetics or efficacy.

The safety profile is, the risk benefits seem to be well defined and well worked out, and so, again, there didn't seem to be much in a way that would be gained from

further safety evaluations.

DR. WARD: Is the label currently up to date with correct dosing?

DR. BLUMER: No, no, no.

Secondary Review of Acyclovir

Dr. Gary D. Overturf

DR. OVERTURF: That was actually my point. The current dosing is 20 milligrams per kilogram qid 8 hours, so it is over twice the label dose, which I think is 10 milligrams per kilogram qid 8 hours.

I agree that there are many less well established treatment use of Acyclovir both in the oral and the IV formulation and primarily for prophylaxis in children for current non-genital infections, primarily with type I herpes and also some what I would have to call hepatic associated conditions like arigamulitformine [ph] and Bell's palsy, in which children are often treated for those two conditions with little or no data.

But again, since it is not labeled for that, to me, I don't think I would put those in the label. I would not encourage their use for conditions that I think are poorly established as links with hepatic infection.

I think there does need to be updating of the labeling of the dose for neonatal herpes.

DR. LASKY: I just wanted to make two points, and we will have to deal with this at the end. I think if NICHD is going to take literature and use it as a means for asking for a label change without doing additional study, it still will have to be on the priority list. So we may have to add a category that we don't see the need for clinical studies but we do see the need for studies or efforts leading to relabeling. I'm not exactly sure, because we haven't really worked this issue out.

Second, Gary, this is a nice example, because we have been wondering how these drugs and conditions have gotten on the list. We have this letter that you signed here from the Pediatric Infectious Disease Society.

[Laughter.]

DR. OVERTURF: I actually signed it, but I actually wrote it. I can't remember what I said.

[Laughter.]

DR. LASKY: Yes, I was recognizing some of your comments. So you at least need to confess to that.

[Laughter.]

DR. WARD: Do you want to comment from the FDA?

FDA Review of Acyclovir

Dr. Melisse Baylor

DR. BAYLOR: My name is Melisse Baylor, and I'm a reviewer in the Antiviral Division. When Acyclovir was approved for IV for treatment of neonatal herpes encephalitis back in '98 I think it was, in June, they had had the kind of big study that was done by the Colebbeter [ph] Antiviral Study Group. It had been published in the New England Journal, and they had that data to go on.

They knew the second study from the CASG was going on, which was the 45 versus 60. They had a little bit of preliminary data for review, and they looked at it, and they got no safety data from it. It looked like mortality and morbidity were going to be lower, but they had very little data.

So what they comment on is that they had encouraged the patent holder at that time to submit that data and justify the higher dose. After that, in fact, they were also asked to submit some data for a higher dose, and that data was never submitted.

So the FDA did try to get the higher dose data,

but the sponsor chose not to. It actually says in their review -- which is FOI-able, so I can say -- that the applicant preferred the 10-per-kilo-per-dose rate to be in the label.

So I think that we figured it was one of those things where everybody was comfortable using it, it was happy, but they didn't have to worry about it and didn't have to give us any money to review a new supplement, and they could move on. It saved costs.

Open Discussion

DR. OVERTURF: In the redbook, it is listed as 60. I know, because I helped write that.

So at least within the pediatric infectious disease community, that has been the accepted dose, and I think within the neonatal community as well.

DR. BAYLOR: That is one of the reasons that we haven't pushed it lately. We felt like everybody knows how to use it. It is accepted to use it. It is in the redbook. Yes, the label is out of date.

DR. WARD: The reason to discuss this out loud, I think then in that situation on our ballots you can go ahead and write in something about that, and we will let

the NIH and the FDA figure out how they are going to approach the company about this.

I personally and philosophically object to having incorrect data there, especially if it may be inadequate and which makes it dangerous.

DR. BAYLOR: Well, there was a justification in the review of leaving it at 30, and they did say that they were never studied head to head. The 60 versus the 30 were never studied head to head, that the disease itself had changed, and there was an article saying how HSV encephalitis had changed a little bit during the time, and they felt like there was a little bit of difference in the populations. They felt like they couldn't compare them, and with the company objecting to going to it, they felt like they were comfortable leaving it at that. So they did realize that.

I think that if it is something that you can do from the literature review, from the article that was published in multiple forms, to update the label, you could do it. Unfortunately, in the CASG study, there were a smaller number at the intermediate dose at 45, and almost all the PK was done at the 45. So we could update

the label to reflect more the pharmacology results from the 45, because it doesn't have that in the efficacy from the 45 and 60.

DR. OVERTURF: One of the problems with changing the labels, particularly, is this area is not static. For instance, the duration of therapy still has not been defined. They are still gathering data for the 21-day regimen as opposed to the 14-day regimen, which has a different outcome measure which is primarily the instance of relapse in disease after treatment.

So it is problematic. It is different than the Cephalexin that we just mentioned. That data was established a long time ago and hasn't changed now in 20 years, but this is still a static area where there is not a complete revolution. I don't know how to handle that.

DR. BAYLOR: I think it is doable. The question is, can we do it with data from the literature without companies cooperating. It is certainly doable to write in the label that people who get treated from this length of time to this length of time and the ideal treatment to prevent relapse.

So we can do it. It is just we have never had a

cooperative company.

DR. WARD: Is the data about 21 versus 14 robust enough that we can expect it to be definitive?

DR. OVERTURF: I would have to ask Rich Woodley [ph.] I don't know.

DR. LASKY: This also raises some issues that we have been struggling with, whether it is important to have labeling changes or it is important to have an increase in knowledge and information. Of course, they are both important, but we do get measured and evaluated by Congress with respect to numbers of label changes.

That doesn't mean we have to put that ahead of actually getting new knowledge, but I just wanted to lay that out there as a reality and something that we have to deal with to some degree.

So if there is a reason to make a labeling change and it isn't that costly, that is something that Congress wanted to see accomplished, and that is actually almost why not go ahead and do it if it is not that difficult to do. I think the issue of what published data meet the criteria is going to be addressed somewhat by our contractors who could be working on the systematic

literature reviews and meta-analyses. It is really an unpaved, unregulated area, but I think we have the resources there to actually do that.

DR. WARD: I think that is a very important collaboration between the FDA review officers and NIH to determine what serves public health the most.

DR. LASKY: Well, it also doesn't take funds away from the clinical trials, so it is not actually an either/or kind of thing, because the labeling changes will cost some money both from a literature assessment and regulatory process, but it won't cost the kind of money that a clinical trial will. So it will not take away from the clinical studies that we can do.

DR. WARD: Yes, Jeff.

DR. BLUMER: I was just wondering, is there a provision within the FDA to add to labels based on expert opinion? Because this is going to be true for all the anti-infectives, whatever class they are in. As Gary points out, these things never are static.

Yet whether or not you find data in the literature that would satisfy your review criteria, if you took all the pediatric infectious disease specialists in

the country and asked them, "What dose of Acyclovir do you use?", I think you would have fair unanimity at this point in time.

DR. OVERTURF: It has been my practice to never get more than three infectious disease people together at once.

[Laughter.]

DR. BAYLOR: Three is too many.

[Laughter.]

DR. OVERTURF: You probably won't get the same answer.

[Laughter.]

DR. OVERTURF: But I agree.

DR. LASKY: I don't think, from our end, that we are talking about expert opinion. We are talking about credible meta-analyses.

DR. BLUMER: I understand that, but you may not find it, and yet the literature may still not be reflecting what is now standard practice. I think the bone and joint infection treatment with Sublexim [ph] is a good example of that. You may or may not find enough compelling data in the literature to support that.

DR. BAYLOR: There are provisions in the regulation that allow literature to be used for updating labels. So that is not a problem. The thing that I don't know -- maybe John can shed some light on this -- if the company is not very excited about it, can we still do that.

DR. BLUMER: That is going to be true for this entire process.

DR. BAYLOR: So how to finesse that part of it, I don't know.

DR. J. ALEXANDER: I think that that is going to be part of the issue. When we go through this in terms of getting new information from this off-patent process, I think that the way that it is going to end up working -- and maybe some of the PEDE's people can correct me if I'm wrong -- is that we are going to sort of review this information that NIH collects from their studies, and based on that, we would end up publishing a Federal Register notice that tells companies to "Come on in with your drug and relabel it this way."

That is going to be in part difficult to do if a company is just going to decide, "Well, I'm just going to

drag my feet. I'm not going to do that because I'm not particularly interested in having that information in the label the way that it is presented.

Going back to the other question about the data in the literature, we do have to be very careful that we aren't doing things based on solely the opinion of experts, because FDA has gotten burned by that in the past. So we are supposed to be basing things on data that is supplied to us.

We do have instances where we have done literature-based NDAs, literature-based reviews of particular uses, and then gone ahead and labeled that. That has usually been with the cooperation of companies, but we have to be careful about the quality of the data that we get from being able to look at those literature articles, and oftentimes have had to go back and actually ask for the source data on which those articles were based in order to provide us with enough data that we could review to say that a labeling change is justified.

DR. LASKY: I think we see it exactly the same way, or that is my vision in terms of using the literature. I think in terms of describing practice, I

don't think we could consider a description of practice as a demonstration of efficacy and safety.

So the fact that every pediatrician or every whatever in the country is prescribing at a certain dose doesn't really demonstrate that it is the best dose. It is an important piece of information, but we would want to go beyond that.

DR. WARD: Lisa, go ahead.

DR. MATHIS: I just wanted to go ahead and clarify that the BPCA actually does have a provision where the sponsors must incorporate this information within a certain time frame. If they don't agree to do so, we take them to advisory committee. So we do have a mechanism in order to get this information into labeling.

DR. WARD: It would seem to me that there is the force to make this happen if there is adequate literature to support that dosing.

So what I would like would be that, for Acyclovir, if you want to recommend that relabeling be carried out to reflect the current level of information, write that into the side or somewhere on your form. Then we will at least have the opinion of this group in support

of that.

A wonderful drug, Amantadine for influenza.

Dr. Meythaler.

Review of Amantadine

Dr. Jay M. Meythaler

[PowerPoint presentation.]

DR. MEYTHALER: Amantadine is a small molecule. It has been around for a long time. The drug was developed originally as an antiviral agent. It is not recommended as a substitute for influenza vaccine. I want to point that out this year with the vaccine shortage.

The dose has generally been five milligrams per kilogram for kids older than 10. It tends to vary between 4.4 to 8.8 milligrams per kilogram for children. It is an approved use by the FDA, but the studies weren't so motivated. It was more a pharmacokinetic study in kids, where most of the research was really done in adults and in isolates. It is generally used for influenza A. It is not useful in influenza B.

I think these are just the kinetics. I'm not sure that anybody really needs to see all that.

It is a stable drug. It comes in tablets,

capsules, and a syrup. The last count I had -- actually, I just looked it up on the website -- it is 10 manufacturers that are active in the United States, some of which produce a syrup and elixir. So it makes it available for kids.

The interesting point is, there is a large market for this medication, obviously. That is the interesting point.

Mechanism of action. As I said, its antiviral action is not clear. It appears to prevent release of infectious viral nucleic acid into the host, interfering with the function of the -- [off mic] protein. In certain cases, Amantadine is also known to prevent virus assembly during virus replication. As I said, it is really only activated in influenza A, not B. The subtypes are H1N1, H2N2, and H3N2, which are generally other versions.

An interesting point [off mic] in kids -- I have to bring this up because [off mic] -- is that Amantadine's biggest use is probably in [off mic].

Amantadine -- [off mic] has effects similar to [off mic] which, by the way, is nothing more than a dimethyl ester of Amantadine. Actually, in vivo and in

vitro research indicates a possible blood-brain barrier at similar concentrations. They attach to all the -- [off mic] similarly.

For the summary, in my opinion, the FDA [off mic] the United States -- [off mic] $1 billion. The Europeans don't allow -- [off mic] versus Amantadine.

It is also related to another drug we are going to review called Rimantadine, which has much less dopaminurgic effects.

The side effects of Amantadine are generally also related to the CNS suspects, and it is profound. However, it has been reported to improve alertness and facilitate neurologic recovery in patients with brain dysfunction of various kinds. There are also similar points in review -- [off mic] patients both acquired and progressive, like in Alzheimer's disease, Parkinson's, or even traumatic brain injury.

Amantadine is a tricyclic. As I said, it affects the reuptake of dopamine. It has some weak serotonurgic effects and weak NMDA effects.

Now, the drug is predominantly metabolized in the kidney. It has advantages over Amantadine, and it

does [off mic] liver function. It is pretty much linear pharmacokinetics. That is an advantage in this situation.

It distributes pretty evenly through the body. As I said, 20 milligrams through the day of Amantadine in an adult will give you the same CNS concentration as about 40 milligrams of Amantadine, which [off mic] doses.

Side effects are incredible: acute psychosis, disorientation, nightmares very frequent. If you have ever taken Amantadine for [off mic] prophylaxis action. I did once about six years ago. The nightmares are real. It is incredible: hallucinations, behavioral disorder, CNS depression, dystonia, and uro-endocrine effects, particularly SIAVH.

[Off mic] -- pure anti-epileptic effects. I only cited pediatric references. There are also some adult references. High doses will of course, because adult [off mic] threshold.

Parkinson's disease in adults. It has an indication on Parkinson's disease -- [off mic]. It also has an indication in adults for drug-induced reactions -- [off mic] off-label, usually.

These are some of the off-label uses it has

brought in pediatrics [off mic] this drug in the United States is used for CNS depression. The biggest in this [off mic] is brain injury. Based on a number of studies that have been coming out, there are about four open-label and one randomized control equivalent to a level 2 trial that has been done on the drug, and now there is a multi-center trial, funded by NIDA for the next three years, in the United States to see whether it really does enhance recovery from coma.

So this drug is being used hugely. I just came from Neural Trauma. There is a lot of research being done on this drug, partly because -- [off mic]. So they want to go to Amantadine because it is cheaper.

These are all the other indications it is being used for. It does have some technical effects in the liver, too, for hepatitis C. It is being used in adults, and there are questions about whether it is being used in kids.

Pharmacokinetics are well known to be short-term in children. They are not that much different than adult. The problem is that it has not been studied in all these other diseases neurologically it is being used in, and --

[off mic] has been used for over 12 weeks, now two weeks. This is one issue.

The pharmacology kinetics and side effects of long-term use in children has not been well established. The interesting point is that it is rapidly falling across -- [off mic] malignancy, which is frequently not recognized because of its dopamine effects.

Traumatic injury is the leading cause of disability in children right now, and in adults, actually, according to the CDC. It is not stroke, because its prevalence is so much greater.

The issue is, is the off-label more than it is. If I had to score this, I would give it a four because of influenza. I would give it a six for taking a look at the short-term issues. It clearly hasn't been looked at for the long-term issues. It is not as high a score as some people would be giving it. As I said, it has been used in adult trials, recently in a randomized trial.

DR. WARD: Wayne.

Secondary Review of Amantadine

Dr. Wayne R. Snodgrass

DR. SNODGRASS: I have very little to add,

except that long-term use of agents that affect the dopaminurgic pathway can lead to tardive dyskinesia, which is irreversible. I am aware of cases with Metaclopamide [ph] as an example, which we don't think about that.

So I think the long-term issues clearly have to be studied if you are going to use this type of an agent.

DR. WARD: Let's hear from the FDA, then. I think the FDA needs to address this issue of the totally different indication than that listed.

FDA Review of Amantadine

Dr. Melisse Baylor

DR. BAYLOR: The antiviral edition typically reviews it only for its influenza use.

[Laughter.]

DR. BAYLOR: So I'm going to take that out. I will say, as far as influenza, we are not real interested in any more studies with this drug.

After listening to that, I think it needs more neurological studies.

Open Discussion

DR. WARD: Jeff.

DR. BLUMER: I guess, going back, personally, I

agree with both parties. I think we have missed the mark here totally.

Going back to influenza, this is an interesting scenario, because even though we do know the pharmacokinetics in children, once again, the pharmacokinetics were performed, if you will, in a sterile environment. So they have been related to nothing.

DR. SNODGRASS: That's true.

DR. BLUMER: If you go back even through the short-term use of Amantadine in influenza infections, I have no idea whether any of those adverse events that occur with short-term use are concentrated in the label. I mean, we have something that is relatively cheap and is widely used. Can we more safely use this drug if we knew of a relationship between the pharmacokinetics and the pharmacodynamics, specifically safety, not efficacy.

So there may be some reason to look at it in that regard, but I agree with you wholeheartedly. The overwhelming need is to now look at this as a CNS actor.

DR. LASKY: My conclusions that I'm coming to are that next year we are not going to have an outreach process because I hate to tell you which agency suggested

this drug. But we did this outreach and, I don't know, we are going to have to discuss it tomorrow and see how we can make it better. There is either a disconnect between all these different agencies and the group of experts here, or there is information that hasn't been explained.

The Office of the Director of the National Center for Infectious Disease at the Centers for Disease Control nominated both Amantadine and Rimantadine, and I will just read to you what they sent. They have several pages here, but they give a little background on what Amantadine is, what we have heard so far.

They say,

"Data Needs. Further randomized double-blinded placebo-controlled clinical trials of Amantadine for treatment in chemoprophylaxis of influenza A virus infection is needed, especially to examine the potential to reduce influenza A among healthy and chronically ill children. Randomized double-blinded controlled clinical trials comparing Amantadine with other antiviral medications and placebo when used for treatment and chemoprophylaxis of influenza A are also

needed.

"There are limited pediatric data on the efficacy and adverse effects of Amantadine when used for treatment. More data are needed about potential gastrointestinal and central nervous system side effects of Amantadine when used for treatment of influenza A among children.

"There are no data on the efficacy, adverse effects, and pharmacokinetics of Amantadine for treatment of chemoprophylaxis of influenza A in children under one year old."

It is kind of perplexing to me. It is going to be something we are going to have to mull over. Something is not connecting between our different institutes, agencies, and groups.

What they said for Rimantadine is almost the same. When we get to it, I will read that as well.

DR. SHAPIRO: I would like to make a comment. This was an issue that Dr. Baylor and I had talked about, was that we have a hole for those under one year of age. Basically, Amantadine is approved for the use of those older than one year of age, and so is, also, Tamivir [ph],

which is a neuromidase inhibitor which affects both influenza A and influenza B. You are using them in kids that are older rather than those under one year of age who have the highest morbidity and mortality due to influenza.

At this point, because of the safety signal that was reported out generally about, also, Tamivir, we have no agents to use for those under one year of age. It is not clear in talking with the Antiviral Division whether either Rimantadine or Amantadine would really fit this group because, number one, we were worried about Amantadine and its toxicity, and Rimantadine has really shown most of its efficacy for prophylaxis rather than treatment.

I think we have a therapeutic call that we need to address, but I'm not sure that these two agents are going to do it.

DR. ZITO: I was just going to make a comment in response to Dr. Lasky that it might be useful to look at the utilization data in terms of the diagnoses and so on so that you could make a case that utilization isn't there and that would sort of end the story.

DR. BAYLOR: Just to kind of reiterate, the

Review Division feels like we have more specific drugs now with fewer side effects, easier to tolerate, and active against A and B.

DR. MEYTHALER: This is more of an off-label issue. I will tell you, I have run past the pharmacies at a couple of children's hospitals as well as our adult pharmacies. This drug is not being used for an antiviral very much at all. In the adult population, it is over 80 percent it is being used in CNS, and in pediatric, it is over 50 at least, I safely can say. It is all off-label now.

There is a big market. There are 10 manufacturers out there. They are obviously selling it.

DR. LASKY: Well, I think this shows that we do need to find out. If it is being used in kids under one, we aren't going to have the conditions associated with the drug use data. We haven't put that completely together.

The CDC statement was a bit longer, and I didn't read it. They said during the 2003-04 influenza season in the U.S. there were 142 pediatric deaths with laboratory confirmation of influenza reported to CDC. So it doesn't have the ages there, and it doesn't have a rate.

I think it is safe to say that influenza affects the under-ones and affects mortality, but we don't know if Amantadine is being used to treat it.

DR. BAYLOR: Interestingly enough, in the MMWR, those influenza deaths were primarily in teenagers. The reason was really unclear whether they didn't receive treatment early or what happened, but they weren't the typical population that you would expect of influenza deaths, being small children, ex-preemies, or BPD. It was very much a surprise.

I can't address how much Amantadine or Rimantadine were used last year during the outbreak. I know that our Drug Shortage people worked with the influenza companies to make sure they got as much drug as they could.

DR. LAWLESS: Two things, actually, may help here. You were reading the rationale behind some of these reasons. Having some of the rationale behind it, not just saying, "We think these are the ones to be studied." There are certain risk data that people are saying is the justification we are putting forward on this as far as there were 1,000 kids who died last year, or something.

That adds a little bit of a different flavor to some of the review and what we are doing with it.

The other thing is just a more editorial comment. I don't know how everyone else feels, but having prescriptions without real indications of why someone is writing a prescription, I think there may be some loss on that. I think the idea of maybe, perhaps, from an FDA standpoint or something else -- I know in the Medicare world they do this -- is, you have to put an indication of why you are using a drug so you have a better idea of what the uses really are. That is pretty cheap.

DR. WARD: Dr. Pursley.

DR. PURSLEY: First, what is troubling is this gap where the vaccination isn't available to infants until six months. Although there is global vaccination for kids between six and 23 months, what do we do for those kids who are at greatest risk who are less than six months, and what do we use in the meantime.

DR. BAYLOR: Oh, there is a huge need. I agree totally. There is a huge need for the less-than-one-year-old. Our problem with the questionable efficacy of Rimantadine, there is not the strongest evidence to

approve it, and it actually was pretty much equal to Tylenol in treatment studies. The CNS toxicity was borderline efficacy for Amantadine, which makes us uncomfortable identifying either of those as the agent to go for.

Then we are left with two more drugs that are approved right now for the A and B, which are the Osotanavir and the Zanamivir. Osotanavir has some troubling preclinical data, the animal data, which has been made public in the "Dear Healthcare Provider" letter, where very high doses that were much higher than you should see in real humans, they had some CNS toxicity.

As the FDA, we can't really force them to study at lower doses in animals or in children, and I don't think that too many parents would be excited about the informed consent.

Zanamivir is our last choice, and frankly, it is being used so little right now that even though there are nebulizers and intravenous formulations that have been studied through the CASG, it is being used so little that the sponsor is really reluctant to put any more money into its development.

So we are in trouble. There is a huge need. I just wish somebody would make a good drug.

DR. PURSLEY: One of the problems, of course, is the ability to make the diagnosis and quite a bit of inference about respiratory disease in the first couple years of life is primarily due to respiratory syncytial virus.

I think it would be a difficult thing to study, but maybe there are some opportunities for it, because I understand that as of this month there is mandatory surveillance data being sought for influenza in kids. Is that true?

DR. OVERTURF: Yes. In most states now, at least deaths from influenza are reportable, and in some other states, hospitalization of children with documented influenza are reportable as well.

DR. ZAOUTIS: Tami's comment about at least reading the list of gaps in knowledge, would this be one where a systematic review of the literature trying to address those specific questions, bringing the two sides, bringing the gaps closer together?

DR. LASKY: Actually, this is one that from our

first look that we can't do from the literature because when we looked at the Metaworks review, although there are a lot of studies on Amantadine, there were only, I think, two on influenza. That is really not enough to do a meta-analysis, unless they are just outstanding studies, which I don't think they were.

So we tried to keep this group confined to ones where the literature was a little bit smaller. The ones with a large volume of literature we culled out before handing this group to you. So we cannot use the literature for this.

DR. RODRIQUEZ: I just had a question in terms of antivirals for influenza. I thought that Ribavirin had activity, even though it is still a pain in the neck when it has to be given. Essentially, if the person is sick enough to be in the hospital, could we offer that preparation?

DR. BAYLOR: Right. Ribavirin has activity against everything in vitro.

DR. RODRIQUEZ: No, there is in vivo data, actually, in the Journal of Pediatrics. There was almost a 36-hour difference in fever compared to the control.

DR. WARD: So, when you are in vitro, it is terrific.

Let me suggest this. The issue had to do with interest in its study for influenza. That is really the question that is on the table. So vote with respect to that. If you feel like we should bring it back to the Neurology Division -- Dr. Sherman is gone right now, I think, when I looked around -- we can write that in and we can at least express ourselves about traumatic brain injury. It sounds like this is a brand new area. Maybe it is not so new, but at least new to me as a neonatalogist. That can move forward through the process. But today, I think we need to vote with respect to influenza.

Yes.

PARTICIPANT: Can we write in also the need for Oseltamivir or some other drug to be studied in the first year of life?

DR. WARD: Yes.

DR. LASKY: Please do.

DR. WARD: Dr. Pursley, should we talk about Rimantadine?

DR. PURSLEY: I think I will avoid going to the podium. That will save everybody some time.

Review 2: Off-Patent Drugs

Review of Rimantadine

Dr. DeWayne M. Pursley

DR. PURSLEY: This should be pretty quick and easy here, because there doesn't appear to be the extra respiratory indications that Amantadine has had. It has been more limited in that it is not recommended for a prophylaxis in additional treatment.

The good news is that it should be a pretty easy meta study because, from what I can gather, there was only one trial of 37 patients done by Carolyn Breeze Hall [ph] that suggested that there was any efficacy to begin with.

So I think that what you heard for Amantadine you can assert as well for Rimantadine.

FDA Review of Rimantadine

Dr. Melisse Baylor

DR. BAYLOR: Interestingly enough, on the FDA analysis of Dr. Hall's review, Tylenol and Rimantadine were equal. It happened that on day 2 Rimantadine was slightly better. By day 5, Tylenol did better and

Rimantadine had built resistance and 41 percent bounced back with more symptoms. So they approved it anyway, but I wasn't around. What can I say.

DR. WARD: Two votes for Acetaminophen.

[Laughter.]

Open Discussion

DR. WARD: Again, let's vote on this with respect to influenza, as indicated on the ballot.

DR. LASKY: I'm not sure; are you saying that these aren't effective for influenza or haven't been demonstrated to be efficacious?

DR. BAYLOR: They have had some minimal efficacy. I think Amantadine was the first one approved for influenza, and at that time there was nothing else on the market. It had some minimal efficacy in not-that-impressive studies, so it was approved based on the minimal efficacy.

Rimantadine, on the other hand, was approved for prophylaxis only because the treatment study wasn't impressive.

DR. LASKY: Because one of the issues when we talk tomorrow again about it is the idea of clusters of

drugs, and this is kind of coming up as a cluster of drugs. The CDC actually named six drugs, and some of them were on-patent and we couldn't respond to them, and some of them have been mentioned here.

If the efficacy isn't demonstrated so CDC is asking for a study to evaluate efficacy, what we have to judge is, is this an important question, not whether we think the answer is one or the other. Just to remind people, is it an important question to study, rather than, do we think the outcome is a negative finding.

DR. BAYLOR: It had minimal efficacy in the studies for approval, and at this point I think, with other agents available, the toxicity outweighs the benefit.

DR. WARD: Dr. Wiederman, do you agree?

DR. WIEDERMAN: Simply put, Amantadine forget about because of the CNS side effects. There is no use wasting time on that for influenza.

Rimantadine, the studies for efficacy were not as good as Amantadine. So it is a maybe, but both of those agents are only active against influenza A. If we are going to do something, and I think we should do

something, for the under-one-year-old population, it should be Oseltamivir and whether you can get a study done or not. So I think I'm in agreement with Dr. Baylor.

DR. WARD: Wayne is suggesting and you are making the very same suggestion that if you want to write in something about Tamivir, to go ahead and do that.

DR. BAYLOR: Is Oseltamivir on-patent or off-patent?

PARTICIPANT: On-patent.

DR. BAYLOR: Okay. We can't use BPC funds to study on-patent drugs, folks.

DR. MATHIS: You actually can. I mean, there is a process for referring studies to the NIH. The question is, would we need to do animal studies, which we can't issue a request for. We can only issue written requests for pediatric studies.

So we could ask for human studies of Tamivir or Oseltamivir, but we would first need some animal studies to clarify the animal studies that have already been performed.

DR. LASKY: I think that is getting way off the task, but the task today is to come up with a list of off-

patent drugs for study under this provision with this pot of money.

What happens in many of these discussions is everybody just says there is a more current drug that needs to be studied, but that is not what this day is about. This day is about studying off-patent drugs, whether there is something of value in studying it, and we shouldn't get too far astray, I think, from that.

DR. WARD: Let me just clarify. Rimantadine still is only effective against influenza A.

Am I wrong? A and B or just A?

DR. BAYLOR: No, both drugs are influenza A drugs.

DR. OVERTURF: I understand you can't ask for patented drugs here to be studied, but what if we are asking for these drugs off-patent to be used as the comparator against patented drugs? In that sense, we are still studying them.

For instance, you could conceive of a trial where you actually looked at one of these drugs with Oseltamivir against placebo. One of the things that will facilitate studies now and one of the reasons that we

don't have data on these is because we didn't have a facility with diagnosis, and we do now. It is the same thing that plagues influenza vaccine studies, because we have to use influenza-like illness in large studies and, in that case, because you have to look at it every year because of the different strains. Here at least you can look at influenza A strains year after year.

You could make a recommendation, it would seem to me, to include off-patent drugs to be compared against patented drugs.

DR. LASKY: Yes. That is one of the issues and one of the solutions that we are going to have to engage in, I would think. The way the written request is written, in my experience, is about an off-patent drug and an indication.

Now, in some of them FDA has specified it has to be placebo-controlled or active-controlled. I think more of these you are going to want active-controlled, and we can suggest an on-patent drug as a control comparator.

DR. OVERTURF: It is the same thing for peer review, the case for things like Acyclovir or Famcyclovir or Valcyclovir, where you have newer generation drugs or

essentially pro-drugs for another compound. There would still be some virtue. You might find that the cheaper, older drug actually is equivalent to the more expensive drug.

DR. LASKY: I think it is good that you have brought this up because it is not enough to say we should study this. We have to think through, how do you really go into today's environment and ignore current drugs. You can't do studies on 30-year-old drugs, when that is actually what we have to do.

DR. PURSLEY: Oseltamivir isn't approved for kids 12 and under. Is that because it hasn't been studies or because it isn't effective?

DR. OVERTURF: There was a comment here that it has been studied.

DR. BAYLOR: It is one and up.

DR. PURSLEY: For prophylaxis?

DR. BAYLOR: Oh, for prophylaxis.

DR. PURSLEY: I'm sorry. I wasn't clear.

DR. BAYLOR: Yes. I'm not positive; I think it has been studied. It has not been turned down, so I'm not sure about that. I know there wasn't a cut-off because

there was a problem, so I thought it was approved.

DR. WARD: So what I think I'm hearing is another hybrid essentially and a recommendation that studies of a placebo and an on-patent but active comparator be considered. I think that is a fascinating design that has feet in both the on-patent and off-patent worlds.

So if you favor that, you can write that in in the margin of the ballot, and we will let Tami figure out how these are going to be tabulated and paid for.

[Laughter.]

DR. LASKY: For the record.

DR. WARD: So Amantadine, Rimantadine. We are down to Methadone.

Go ahead.

DR. LASKY: I wasn't going to ignore them, but I think also these comments are going to be in the transcript, which is really where they are going to have their greatest benefit. We will tabulate the scoring. It is hard to tabulate comments, but the comments having been part of the transcript will be used in developing written requests and RFCs. So all these ideas are going to be

drawn upon.

DR. LAWLESS: I have a question for the FDA people. This year, with the purported shortage of flu vaccine, are you guys going to be tracking the use of these drugs this winter in particular before we even start studying them to see whether the utilization of these drugs is increased and whether, again, other side effects are noted or not? It almost seems like it is a forced study going on indirectly.

DR. BAYLOR: In influenza, we have a mini team, which I am not on, for influenza preparedness, and they have been keeping track of drug supplies of the drugs and they know how much is out there. We certainly can get records of prescriptions by month, and since Amantadine is used so much in neuro, you wouldn't expect a spike, but you could follow for the flu months when we know flu is in the areas of the U.S. what the prescription rate did, if it jumped or not.

DR. LAWLESS: Because if it is done that way, by the time you get the recommendation you may see some early trends of the use of that and other side effects which may change some voting later on.

DR. BAYLOR: We certainly can track that this flu season.

DR. WARD: Interesting comments.

Alan, do you want to talk about Methadone for opiate-addicted neonates?

DR. STILES: Sure.

Review of Methadone

Dr. Alan D. Stiles

DR. STILES: This probably wins the prize for the longest label. It is 19 pages long, and there is not a lot in there. In fact, there is a line or two that basically say it can be used and there is no pediatric information. So I will summarize the label right there.

I think there are several issues to be considered here. One is that there is a wide population of variability with this. We have the fetal group. Those would be the maternal Methadone treatments that lead to neonatal addiction. We are evolving a different group now where we have opiate use in neonates that then need to be withdrawn from opiates. Then we have the use of Methadone now in some of the older children as an analgesic. So we actually end up with three different groups of folks who

deal with this.

We also have the cultural issues that move from unit to unit, and the usual problem we have in neonatal studies that the last line is this needs a well-controlled study to take a look at the question. That is true across the board with this sort of thing. Everyone has their favorite and every unit does it a little different way.

There are no studies looking at pharmacokinetics that I could find or that we received looking at this particular drug in neonates, so I think that is just an unknown. Like all opiates, it will depend on when you happen to go after this how much it takes to get it through.

One big question is, how do you transition to Methadone from whatever you happen to be on. If you are Morphine or you are on Fenmil [ph] or on some other medication, how do you transfer someone over to Methadone. There are risks with that with over-sedation and even death associated with transitions in these drugs.

To try to deal with this study, you have to figure out how you are going to measure the effect, because that is almost as variable as the number of

studies and the number of units are, because everyone does this a little different way and everyone is certain they are right.

Then finally, there are some questions raised in the label and other places about increased incidence of Sudden Infant Death Syndrome with patients who have been exposed to Methadone, and then certainly death would be the worst outcome you would expect just from using this medication.

DR. WARD: Steve.

Secondary Review of Methadone

Dr. Stephen T. Lawless

DR. LAWLESS: Actually, ditto to everything Alan just said. Actually, I think the usage is not just in the neonatal ICU. The pediatric ICU is the second place for iatrogenic withdrawal. How to get kids off ventilators is growing as an issue, so it is not just the neonatal population. I would actually assess the younger kids there, also.

The other thing, in terms of the impact of prolonged hospitalization of kids who go cold turkey, let them go versus put them on methadone for a couple of weeks

while they are in the hospital. There is a cost issue in utilization, and no one knows also the long-term impact on neurologic status of these kids. The brain is developing, fat solubility; what is actually getting in there long-term. So I think there are lots of long-term issues, and short-term, with this drug.

DR. WARD: Now we are back to Clonidine.

[Laughter.]

DR. WARD: Dr. McCune, are you going to discuss this? Who is going to discuss this from the FDA?

DR. MATHIS: I actually think that I'm going to cover it, because Dr. McCune had a meeting to go to.

FDA Review of Methadone

Dr. Lisa L. Mathis (for Dr. Susan McCune)

DR. MATHIS: I think that one of the concerns that Dr. McCune had was that the neonatal intensive care units are actually using another drug preferable to Methadone now for neonatal withdrawal. There are also safety concerns with this drug.

I think I have given what has already been said. We didn't have too much to add, other than there were large safety concerns and there may be other drugs that

are better for this indication.

Open Discussion

DR. STILES: Not to steal Dr. Pursley's thunder about sedation and Morphine, the way all of the information that was on the CD about this came out is actually maternal addiction leading to neonatal problems, and we really have this drug in use differently than that now. So we need to think about it again if we are going to continue to use it, as opposed to just the situation where you have the maternal addiction to Methadone and a baby we are trying to get off of it.

DR. LASKY: I did the literature search for it, and I found it very, very hard to find articles about the infant. That says to me that it hasn't been studied. When I see that something hasn't been studied, I interpret it as, well, it needs to be studied. I don't think we had the use data. It would be an inpatient issue. So there may be more things we need to learn, but it is not there in the literature, that's for sure.

DR. WARD: I would agree 100 percent. I work with a fellow who is actually studying it in the PICU, Ralph Lugo, but in the neonate, I am hard-pressed to find

any kind of a guidance for dose, even in a therapeutic concentration range.

What you said, Alan, I couldn't agree more. Some of the kids become so sedated, and if they are not adequately monitored and resuscitated from that, they get into big trouble.

How are we doing for time? 2:15.

PARTICIPANT: Did we have a score on that?

DR. WARD: I'm sorry?

PARTICIPANT: Did we have a score?

DR. STILES: Do we have a?

PARTICIPANT: A score.

DR. STILES: A score. At least when I scored it, I think I came out with a five, which didn't reflect anything about what I think about it.

DR. LASKY: Nobody's score reflected what they thought about it. It was just an experiment.

DR. WARD: Tami and I were talking about this. The scoring system is very difficult. I have wrangled with this issue, and there are two ways to score it, I think. You can score it based on exactly the tabulation as indicated, or I think you can even score it and say,

look, from zero to 10, do I think this is a two or a three, or I think this is an eight or a nine and really needs study.

DR. LASKY: This is part of developing the process. The science of scoring things and scaling things is a whole separate science. You are our first pool on this scoring instrument, so you are unconsenting subjects in a non-controlled trial of a scoring tool.

I think one of the things about a scoring tool is that it doesn't necessarily pick up the same thought process that one has when one asks how important do you think something is. This is a different kind of question, which is why it seems that it doesn't seem to fit with people's sense of how important it is, but it does pick important criteria.

So for me, who likes to study this type of thing, it is an interesting kind of process to observe, but I think an important piece of information as well, even if you don't agree with your own assessment.

[Laughter.]

DR. WARD: We have another comment.

MS. KAHN: Yes. With regard to Methadone in the

peripartum population and the problem of neonatal withdrawal syndrome, there are, as far as I know, only four very small-scale studies of the amount of Methadone which passes into the breast milk in lactating women and how much Methadone has been measured is very small an amount, highly variable, and based on a paucity of information.

Nevertheless, the old obstetrical recommendation of avoiding lactation in women who are using Methadone after they give birth has recently been reversed just based on a fair amount, some of it formal, but mostly informal safety experience and the observation, again mainly a clinical rather than a study observation, that the incidence of neonatal withdrawal syndrome is lowered by breastfeeding early in women who are taking Methadone and have just given birth.

On the other hand, because there is a lot of variability, that has really been an observation of what appears to be a safe practice rather than actually being recommended that there is an actual reduction in the incidence of neonatal withdrawal.

I think that that is a very, very difficult

clinical question that needs to be answered and that is not being answered right now by the investigators who are studying women who are in the peripartum period. I would like to suggest that with the recent advent of Buprenorphine, it is now possible to look at a study where we can look at both Methadone and Buprenorphine in this patient population and the implications that it has for breastfeeding and for neonatal outcomes.

DR. WARD: Would you clarify what you mean by studying the Buprenorphine as a comparator? You would give that to the mother in place of Methadone?

MS. KAHN: Yes, that's right, that's right.

DR. WARD: I think the last Committee on Drugs' statement about breast milk drug excretion said that Methadone in therapeutic doses did not pass enough into the breast milk to be a contraindication to breastfeeding.

MS. KAHN: Right. It is not a contraindication. It appears not to be a contraindication of breastfeeding, but there isn't a lot of certainty about how much Methadone there is actually passed to the neonate, and that may actually be variable depending on the relationship between the time of lactation, the time of

taking Methadone, and the actual period of early milk versus late milk during the lactating period.

DR. WARD: It is a very long half-life, so I actually don't think that the variation in maternal concentration will be significant during one or two, or three even, breastfeeding cycles, but the whole area of breast milk drug excretion is dramatically understudied.

Wayne.

DR. SNODGRASS: Yes. I think there is newer data that the Buprenorphine-Oxone combination is better than Methadone in terms of preventing heroin addicts getting a euphoria. Methadone is long-acting, so that that is the issue here. If during pregnancy it is given, it is long-acting, and withdrawal during pregnancy can lead to fetal death. So the issue then post-birth is how do you deal with that withdrawal.

By contrast, with Morphine as an example, we have dealt with some very high-dose, one-gram-per-day type doses in adults of Morphine by IV, and the withdrawal there is 10 days, 10 percent a day, and you don't have what you have with Methadone because it is prolonged. So it is a different phenomenon with Methadone.

DR. WARD: I don't know what to make of that infant death after perinatal addiction with Methadone. It was, as I recall, 23 days or something after birth, whether it was SIDS or whether it was Methadone-related.

This is a commonly used drug in the NICU or in the PICU, and certainly, everything that is used in the PICU gets to the NICU sooner or later.

People's wishes. Do you want to break now for a break, or shall we just head on down the list? Let's go, okay.

Let's do Bupropion for depression and smoking cessation.

Dr. Zito?

DR. LASKY: I just want to add that these are two on-patent drugs and they come to NIH through a different process. These are drugs for which FDA has already written written requests, and copies of the written requests have been circulated on the tables. The written requests have gone out to industry. Industry has declined the opportunity to do the studies. It gets passed to the Foundation for NIH, which then refers the drugs to us. So they are not competing with the off-

patent drugs for the same pot of money, but we are asked to review them.

Review 2: On-Patent Drugs

Review of Bupropion

Dr. Julie Zito

[PowerPoint presentation.]

DR. ZITO: We can skip down to the story on Bupropion, and I will bring back some Medicaid-insured child utilization data to help you frame the issue of how much exposure kids have to Bupropion.

If you look at the first bullet, you see that about 3 percent of the kids zero to 17 years of age received one or more prescriptions for an antidepressant in the year 2000 in this Medicaid state population. So we are growing, particularly when you add, of course, the older age group, 15 and up.

The bulk of that is represented by SSRIs, which should be no surprise, and now, since the news and the chaotic events that have been second place and the black box warning, it has reframed the way I'm thinking about presenting this drug to you today.

TCAs have been demonstrated in younger age

children to be not effective to treat depression. Younger age kids are 12 and under, typically. So there would be no falling back to TCAs as an alternative to SSRIs.

Now, the group called "Other Antidepressants" is where Bupropion is hidden, and so when you separate out Bupropion from the other members of that group, you see that the bulk of utilization for the other antidepressants is in fact Bupropion. So there was substantial use of this drug in these data.

Now, we split it out by age group. Of course, the 12 to 17 are the largest users of Bupropion, but five to 11 is pretty substantial. That is where we get into concerns about differential effects, because it is pretty easy to demonstrate that depression, if we are talking about depression -- and already I have skipped over a whole bunch of issues about the fact that there is no diagnostic data there, so I shouldn't be making those big assumptions. It could be ADHD, it could be comorbid depression with ADHD. But the five to 11s are pretty substantial.

Now, if we look by race and ethnicity, again, the predominance there is pretty substantial. So there is

a good race/ethnicity basis for examining data by race/ethnicity. Of course, in gender again, it is the bad boys who are seen to be pretty substantial in use.

So that's it for that.

So in deference to my husband, who is a chemist, I actually got the structure, and you can see that in contrast to the promotional material, this drug is different from any other drug in the category. It has very much comparable activity, although slight differences in terms of dopaminurgic reset and reuptake blocking.

Bupropion has, I put up there, indications for major depression, ADHD, and comorbid depression. The smoking cessation, I guess, we could add in since you did suggest it.

There will be drug interactions that we might worry about if it were to be used in combination with drugs that typically are competitive inhibitors of metabolism.

We have a long half-life, so a long half-life after chronic use means about essentially a 24-hour half-life, elimination half-life. It does pass into breast milk, so we have to think about those 16-year-old mothers

and young women who are out there that might be on the drug.

The good news is no cardiac conduction relays [ph] have been demonstrated, which has been a big problem we see with TCAs.

By 1985, Bupropion had been evaluated in over 3,000 adults, and there is substantial experience with this drug in adults. I think the initial enthusiasm for the drug was very much dampened by the fact that it has a substantially higher risk of seizures, and we will talk about that more in a minute.

Pediatric studies, according to the label, have occurred in a very small number of six- to 16-year-olds, and so there is insufficient data.

So in '85 for depression for Wellbutrin tablets. Then in '96, the SS and the SR, and in 2003, the XL, and since '97, smoking cessation.

Contraindications. People with anorexia, bulimia, or at higher risk for seizure would all be people that should not use this drug except in very limited circumstances.

Drug interactions I'm going to skip over, but

essentially the more you combine seizure-lulling potential drugs, the higher the risk would be. We have learned a lot about how to reduce the risk of seizure with this drug. So if we keep the dose below 400 milligrams a day, the incidence drops down to comparability to a TCA. Unfortunately, use of combinations now is becoming so prevalent that we really have to worry about the way we use it.

A lot of the data that we are looking at would suggest that comorbid depression in kids who have ADHD and are being treated with stimulants explains combination use with some antidepressants, typically with an SSRI, and now, what are we going to do about that.

The warning is around seizures, which I mentioned, and the increased risk when you add in other drugs that control the seizure.

I noticed in looking at the handouts that you gave us, the package inserts, that the company has put in a new statement beginning in April -- it is dated April '04 -- which states the following, and it is all about the suicidality issue. I have listed it here. You can read it for yourselves.

It is a very convoluted problem. I don't know how we are going to get around it because it seems to suggest that treatment, and in some instances people are saying effective treatments for depression and for suicide, would increase your risk because you are getting better and you are getting well enough to harm yourself.

I don't know how to explain this stuff to the public and really get them to believe that we know what we are talking about, but there is a strong tradition within psychiatry to say people have experienced it and people have gotten well enough to kill themselves, so I don't dismiss it. I just find it incredibly difficult for us to deal with.

Precautions are all about how much in a single dose because of the risk of seizure.

Now, the agitation anxiety is one of those problems that the SSRIs have. It would be really nice to know if we could do a better job in seeing lower rates of emotionability or agitation or anxiety, the kinds of things that they are worried about with the SSRIs.

Skin rash shows up over and over in the studies, and sometimes hypertension occurs, and that seemed to me

to be more in the adult literature.

So there are a bunch of symptoms here that are called neuropsych symptoms that fall under the category of behavioral toxicity. It will be hard to tease apart whether this is the underlying illness or whether it is a symptom that has broken loose, so if we study this drug, a good bit of effort ought to go into being able to look at those things.

I didn't really find anything about kinetics in the information here, except that they do mention that the drug has been studied in about 104 children.

So my recommendation on efficacy is based on the fact that this is not an SSRI, not an nSSRI. It could become more important as an alternative drug for the treatment of either major depression or comorbid depression.

It represented about 22 percent -- [off mic]. So it is not insignificant in its use. The racial stuff is interesting.

A brief review of the drug by Connors and others, and a number of studies were done to evaluate it for the treatment of ADHD. I don't know if it is a world

leader or not. Some of the studies imply improvement. There is a subgroup set of kids who do not respond well to stimulants, and of course, Strattera is available now and that is in the same category and class of drugs. So there is probably something to it as an ADHD treatment for the child, and there is at least one study on ADHD.

Again, those neuropsych symptoms. Side effects: anxiety, agitation, hostility. All of them really need to be considered in studies that we would use to evaluate children.

Now, the next one here is telling you to go to the FDA website. There you can find a vast amount of information that fed into the FDA's reporting to the public on how they got to where they are on the SSRI issue.

There are actually two studies mentioning Bupropion. Neither one of them seems to be real or at least to appear in the report. One had no evaluable risk information. There was no suicidality reported. Then in the other one, they said the study wasn't available.

Finally, a very recent 2001 paper suggested that the sustained release form for adolescent depression

comorbid with ADHD was an open study. So the science of this study really leaves a lot to be desired, but they have come out saying they find the effects they are looking for. There is an effect there.

The hypothesis that I would pose to be evaluated is an antidepressant, in particular focusing on younger age children versus older age children, because there is a good deal of data to suggest that depression does not respond well to meds. So that would be really helpful if we could do that.

And then, paying some attention to tolerability and acceptability. So getting at efficacy, not very short-term but over the course of a year, and of course, really measuring epileptic effects, would be essential to satisfy ourselves that we know how to use this med better now than we did when it first was marketed. Is it a reasonable alternative to the SSRIs, is one question that could be addressed.

Finally, thinking about a large cohort study, because seizures are not that common and suicidality is extremely difficult to study. So we have some practice networks, volunteer networks, and then we have very large,

organized treatment settings, like HMOs, that seem to be reasonable settings in which we could collect the type of information that would be ultimately most helpful.

DR. WARD: Dr. Woo.

MS. WOO: I'm not a doctor yet. I haven't finished my Ph.D. quite yet. I'm almost done.

Secondary Review of Bupropion

Ms. Teri Moser Woo

MS. WOO: Anyway, I just want to note that the labeling says that "It should be noted that Wellbutrin is not approved for use in treating any indications in the pediatric population." That is what their label says.

Now, those of us that are in pediatric primary care know that this drug is being used, and it is kind of concerning when you get into the literature what it is being used for and the fact that there is very little data to support its use.

There are very few studies about its use in depression, and the studies are small sample sizes without adequate power to really prove what they are trying to say that they want to use it for. It is being used for ADHD with very little data to support that, and it is being

used in younger kids without data to support that.

It is a real concern, especially with the seizures. The seizures are dose-related, and there is no real clear dosing guidelines for younger kids supported by good RCT studies.

There is also concern that they are taking a stimulant such as Ritalin; does that decrease the seizure threshold, taking these drugs together. That is a concern for me.

There is no dosing really in the literature for ADHD, even though it is being proposed in some studies for use. Once again, those studies were small.

I think the main things that we need to look at is the PK/PD in younger kids. We are using it in kids that are six- to 12-year-olds, and we are not really sure what is going on with Asitacome B450 2B6 [ph] at that age and how this drug is being metabolized in that age group. Luvox, was that relabeled in that age group? The dosing was different in that specific age group based on the pharmacokinetic studies.

My recommendation, I gave it a seven-plus. I think this does need to be studied. I think the group

really needs to push this, and it is unfortunate that they have already addressed it with the drug company and they have kind of not wanted to relabel it for pediatric use, because it is really concerning to me that we are using it in pediatrics with so little good, solid data for it.

That's it.

DR. WARD: Do we have representation from the FDA?

DR. SACHS: That's me.

FDA Review of Bupropion

Dr. Hari Cheryl Sachs

DR. SACHS: I'm glad you clarified that. It is actually approved in adults for both major depression and smoking cessation, but not in kids.

While there certainly are some alternatives for depression in children, only one is approved. There are some alternatives for smoking cessation. Again, none are approved in kids. Most of them are over-the-counter. Of course, the big concern in studying this would be the seizures.

As far as depression goes, I think people are pretty much in agreement we need some good drugs in

depression. Whether this is the drug is not necessarily clear. As far as smoking cessation is concerned, there are 3.8 million kids under 18 that smoke. Again, whether they are addicted is another story. This drug, it would seem to me, would need to be used in kids who are addicted, especially if there is some risk of seizures.

Obviously, the FDA Review Division, we did issue a written request for both these indications, and so from the FDA point of view, this would be a drug that we would be very much interested in studying.

Open Discussion

DR. WARD: Did the Review Division discuss ADHD?

DR. SACHS: ADHD was not discussed. As far as I know, in the written request, they did indicate that if we had to choose between these two indications they would rank depression over smoking cessation.

DR. LASKY: I don't think everyone is aware. As I mentioned, these are on-patent drugs, so FDA has already written a written request. The written requests were handed out at lunchtime. Our reviewers, when they were asked to review the drug, were asked about Bupropion and depression, and we didn't ask about the smoking cessation

indication.

I think at NIH we would prefer that the two indications be separated, and maybe they should be separated on the scoring sheet.

We actually, at NIH, didn't really understand that aspect of the written request, so if you can elaborate on it a little bit, and if the group could react to that specific indication as well.

The indication of depression is a little more clear and comprehensible, but the idea of pharmacologically treating children for smoking cessation as young as 10, as is suggested in here, is a little harder to understand.

DR. MATHIS: Just as far as addressing what indications are in the written request, as we are formulating written requests for on-patent drugs, we are forced with making the choice between on-label and off-label indications. We cannot combine the two in a written request. That is a legal decision that has been made. So that may be why ADHD does not appear on this written request. These are the two on-label indications.

The other thing is, we don't generally issue

written requests with just one indication on it when there are two labeled indications that we are interested in, because that would give industry the opportunity to choose which study they are going to do, and frequently, it ends up not serving the pediatric population because they tend to go where the easiest study is or where the smallest study could be rather than studying that population where there is the greatest public health benefit.

So that is why you see these two indications showing up on this written request and no ADHD.

As this moves into the arena of NIH, how they handle it from a contract standpoint can be very different than how we can handle it as a written request that is going out for an on-patent drug.

DR. WARD: Let me just push that a little bit, then. If the NIH requested ADHD in addition to depression and smoking cessation and data were obtained with respect to ADHD, yet it has never been labeled for ADHD, how would the division or how would the FDA be able to handle that?

DR. MATHIS: Well, any study that is done, if people plan for it to be incorporated in the labeling, would have to be submitted as a labeling supplement or an

efficacy supplement. This would have to be an efficacy supplement because it would be a whole new indication.

That would be very difficult to do without the sponsor, unless of course the FDA issued a separate written request for ADHD, which could be something that the division could consider at this point.

DR. SACHS: You asked one question about smoking cessation and why, maybe, this drug would be chosen. We talk a little bit about a concern in depression, of course, would be if you have weight loss, that could affect growth of kids. That may be a significant thing. We certainly found that to be true for Veloxitine.

If you think about it for smoking cessation, weight loss would be a little attractive, because most people that discontinue smoking are concerned about weight gain.

DR. WARD: This looked like it was 2B6 metabolized, and I will ask Jeff, do we know whether it has similar ethnic diversity in its polymorphism as far as slow metabolizers as 2D6 does?

DR. BLUMER: Well, 2B6 doesn't have the same ethnic differences. There are three isoforms, one of

which is a NO isoform. So you would expect there to be slow metabolizers. Of course, this is the barbituric response to the isoform of B450.

DR. WARD: Other discussion?

Wayne, yes.

DR. SNODGRASS: Are there any patients, adults, with depression that don't respond to SSRIs that will respond to Bupropion? Is that a known entity? In other words, where does Bupropion come in on the drug choice list?

DR. WARD: I just don't know. You are certainly out of my arena there.

DR. MATHIS: I'm not aware of any data.

DR. WARD: There is the issue of considering a different mechanism of action.

DR. SNODGRASS: Well, I'm also thinking of just risk, benefit, and risk.

DR. SACHS: This drug does still have a black box warning, too.

DR. WARD: With respect to seizures?

DR. SACHS: Well, no, with respect to suicidality, which I just mention, again, because there is

a part of me that says if the speculation is there is any increased risk because of the underlying disease, if you are studying a group for smoking cessation and you saw an increased risk of suicidality, that would definitely let us know it is the drug. On the other hand, is it unethical or risky to study a population that doesn't have a risk of suicidality with a drug that might.

DR. WARD: But is the black box warning a "me too" because of the SSRIs, or is there direct data?

DR. SACHS: It is part of the whole warning.

DR. WARD: It is the "me too" thing.

DR. SACHS: All the drugs got labeled.

MS. WOO: Also, there was a study about using this with kid with comorbidities and they were talking about asthma, but I am also concerned with some of the other comorbidities our adolescents have, like OCD and some of the other drugs we are putting some of these kids on, and we are adding in Wellbutrin.

I think we are seeing a lot more drug interaction and psychotropics in adolescents, which used to be an adult problem. I think we really need to look at this drug as well. We need to start looking at

comorbidities.

DR. WARD: I would just observe that polypharmacy with psychoactives in children seems to be the rule, not the exception.

PARTICIPANT: It is scary.

DR. WARD: Yes, I would agree with that. "Scary" is the right word.

DR. ZITO: There is a not-so-funny joke. You can't be on more meds than your age.

[Laughter.]

DR. WARD: Let me suggest that we do what Tami recommended, and that is that we handle votes for depression and for smoking cessation independently of each other. If they are the same, obviously they are the same.

PARTICIPANT: And ADHD?

DR. WARD: I'm unclear what to do with ADHD. The issue is exactly as Dr. Mathis said, and that is that if we want to propose a new indication, it requires a full-bore efficacy trial. I think we would probably be able to rely on previous PK studies, but efficacy, safety, et cetera. Dose ranging, probably.

PARTICIPANT: And two. You need two.

DR. MATHIS: We could take information back to the Review Division as well. I mean, if people felt very strongly about that, we would be happy to share that with the Review Division.

DR. WARD: So the answer would be, if you feel that it should be studied in ADHD, write that in. Let's go ahead and vote at this point on the two that are before us of depression and smoking cessation.

Yes.

DR. ZITO: Let me make a complication here and think about a study design in which depression is a comorbidity of ADHD. There is a very substantial pool of kids out there like that. So you could be brought in because you have depressive symptoms, but MDD might not be the only criteria for entry into the evaluation. So like the early suggestion, we might get more bang for the buck.

DR. WARD: I think that is probably best carried back through the recorded comments and transcribed comments as a study design issue.

DR. ZITO: I also want to make a comment around the smoking cessation. I have two big concerns there. One is that the older you get, the less like pediatrics

you are, or the less likely are concerns about pediatrics there. So smoking cessation just isn't as big a problem for me as is defining efficacy and safety in a pre-pubital population. That is one issue.

The second is, I was trying to think about how you would engage kids, because here is an example where the behavioral pattern is very peer-driven, it is very age-driven. It has almost nothing to do with pharmacology except I see it as a big deal for really long-term addicted smokers that you use pharmacology to get them through the early stages of coming off cigarettes.

I am wondering what scenario we have here in terms of who we want to study for smoking cessation. Not that it isn't an important issue in teenagers, but I just don't know what is new here that would be different and how you would be certain that you would not be just describing or mandating pharmacologic studies in the absence of behavioral intervention.

DR. WARD: That is a legitimate question, but I think that is also back to a design issue.

DR. SNODGRASS: I'm going to ask, along the same line, how strong is the data that Bupropion is effective

in smoking cessation? I thought it was only in conjunction with significant behavioral input, 20 percent or 30 percent without.

DR. MATHIS: The current labeling does put it in the context of behavioral therapies as well, and the written request does that, too. I mean, that is a major component of treating smokers.

DR. SACHS: Like I said, I was trying to raise the difficulty of identifying a group of smokers and adolescents who are truly addicted. I know one cynical thing that I read in some of the studies was that we might as well wait until they are 18 and then you can really study them as adults.

DR. LASKY: They not only have to be addicted, they have to be interested in quitting.

[Laughter.]

DR. LASKY: And motivated and willing to participate in such a study.

I know one of the things we are going to try to do is quantify the underlying conditions that we are trying to address here, and I'm very curious about the number of kids who are truly addicted and motivated to

quit at the same time.

DR. MATHIS: But I think that we have to be really careful not to underestimate the public health benefit of getting kids to quit smoking, because people who are lifelong smokers have usually picked up the habit before they are 18 years of age. If we can break that cycle, perhaps we can prevent some of the long-term illnesses that come from lifelong smoking.

Kids can become addicted to nicotine just like adults can. It is no less addicting in children than it is in adults.

DR. WARD: Yes, Bill.

DR. RODRIQUEZ: Dr. Zito, your comment about depression and ADHD, how frequent is the depression in the ADHD patients?

DR. ZITO: I don't know the answer to the depression. Maybe Dr. Vitiello could answer that. I do know the utilization data, so I know that there is increasing use. So my assumption is that the depressive symptoms are there.

DR. VITIELLO: Right now, Bupropion for depression could be like a third-choice drug. It is very

difficult because of the issue about the black box and if this would change. But right now, the first choice is an SSRI. The second choice, if the SSRI fails, is another type of SSRI, and then the third choice is probably Bupropion or something in that neighborhood. So right now, it is the third choice, but this may change.

DR. RODRIQUEZ: That was my question. If this were to become effective, the indication would be depression in patients with ADHD, right? It would be depression?

In other words, if the patients that are studied with depression have depression with ADHD, that would be the indication?

DR. VITIELLO: Yes.

DR. RODRIQUEZ: Okay. Thank you.

PARTICIPANT: I just want to comment that I think there is a study in teenagers that, after two weeks of a pack a day or more, you are addicted. It doesn't take long and it doesn't take much. I don't think there is any comparator to the inhaled prescription nicotine approach.

DR. WARD: I personally would not underestimate

the health impact of young children starting smoking. You can just walk down the street, and it is pretty young.

So we are back to write-in candidates for ADHD and Bupropion for depression, and smoking cessation handled separately in the scoring system, okay?

Morphine for sedation. Dr. Pursley?

Review of Morphine

Dr. DeWayne M. Pursley

DR. PURSLEY: We have had a number of discussions about Morphine over the last few hours. One of the problems that we first encountered was that there was a discordance between the agenda, which was suggesting that the indication was sedation, and the actual letter, which suggests that the indication was analgesia. That is okay, because it reflects what is going on, I think, in some of our intensive care units.

Further, it was complicated by the fact that the label was for the oral form, although the 19 studies that were referenced and provided on the CD were for IV, epidural, and sublingual for indications as disparate as spinal surgery and mucositis, and with outcomes that not only included pain but nausea, vomiting, and pruritus.

I think in this situation is probably helpful to at least start with what I am familiar with. I think what is happening in neonatal intensive care units is mirrored in some ways with the rest of pediatric care.

It might be helpful just to take a step back and talk a little bit about how pain management has evolved. I think talking to some of the older neonatologists it seems like we have started with an era where there really wasn't a concern about pain management in newborns. There was a presumption that their central and peripheral nervous systems were immature, if not primitive, and that pain wasn't really appreciated by newborns.

Thankfully, we got away from that era, but we sort of went the other way, and things really jumped when we discovered IV phetinol [ph], I think.

Probably, more recently -- and by more recently, maybe the last five years or so -- we have entered into a period of introspection where we are trying to understand what the right thing is and understanding that there is a difference between using pharmacologic agents for sedation and using pharmacologic agents for analgesia.

About four or five years ago, the AAP came out

with a statement on pain control in newborns which encouraged the use of validated measures for pain. One of the problems, of course, is that it is difficult to discriminate between pain, stress, and normal variations of behavior, and awake and sleep states in newborns.

My kids cry, they scream, and they have variable behavior, but I have found that behavioral and environmental interventions are effective, and I haven't had to resort to pharmacologic agents.

So the ADP sort of got us, I think, refocused on pain management in newborns and suggested that environmental and behavioral interventions should be utilized as much as possible and pharmacologics used as a last resort. They also suggested that only pharmacologic agents with proven efficacy and safety be utilized, whatever those might be.

There is a consensus statement that came out about three years ago in which they focused, thankfully, on specific interventions, what interventions in the NICU actually require pharmacologics. Their consensus was that it required nothing more than lidocaine, either topical or injected, and sucrose on pacifiers has proven to be a

prevalent intervention in neonatal ICUs.

In fact, the only indication for opioids mentioned in that statement was for thoracostomy tubes. I think that most neonatologists would agree that that is something that required fairly aggressive pain control.

Then, more recently, in fact a year ago, JAMA published a study that was done by a large group of NICUs examining the routine use of narcotic infusions in their units, because in the era in which we assumed that all babies were in pain, many NICUs were actually managing their babies with intermittent Morphine dosing, if not continuous narcotic infusions.

They found that there was no measurable analgesic effect with the narcotic-managed babies as opposed to placebo. There didn't appear to be any effects on neurologic outcome, and they expressed a concern about what the long-term use of these medications might result in.

Then, six months ago, another group of NICUs, a group called Neopain, published their study, in which they examined differences in outcomes between babies who were managed with continuous infusions and not. They found

that not only did the infusions not appear to be helpful, of any benefit, but for those babies who were receiving placebo and received open-label Morphine, there actually appeared to be worse neurologic outcomes in that group.

The Committee on Fetus and Newborn has embraced this issue and is looking at this most recent published data. My sense is, and I have plenty of people to ask here, that neonatologists and NICUs are trying to sort of move away from this and trying better to distinguish between appropriate sedation, which might in fact be better managed with appropriate behavioral and environmental controls and analgesia, where analgesia is needed in an aggressive manner, such as with a thoracic tube placement.

So that is at least one neonatalogist's perception of what is going on with that age group. I would invite other people to educate me as to what might be happening in pediatric ICUs and within the ORs.

So I will just stop right there for right now.

Secondary Review of Morphine

Dr. William E. Berquist

DR. BERQUIST: Yes, thank you. I agree there

was a little confusion about what we were trying to do, but the letter was very helpful to clarify that.

First of all, the premise is Morphine Sulfate is commonly used for analgesia in the intensive care units. I think with that premise, then you say, well, how best to use it. Actually, when I reviewed all of those different studies, this is a great drug to do PK/PD studies on. You can see that come through. I mean, our anesthesiologists and pain people have a great forum to do those kinds of studies.

Most of these studies are, again, what are we doing; what is convenient; how much you study it. So they pick different groups, and then they look at the different doses. The problem is, they combine it with different combinations, but at least they are able to get some data as to dosing.

So I would gather that the question is, even though they have done a number of these studies, we are still not absolutely sure about what is the sort of proper dose to use and to recommend for Morphine, again, as a single agent.

As such, I think there is probably room to

pursue that, because it is a very definable kind of question. So I think once you look at the letter, then you could say, well then, now maybe I understand what you are after. We were given an oral preparation, and that got me confused. Then I looked at the literature, as did DeWayne, and I think that really helped me to understand.

DR. WARD: The written request is actually specifically stated for analgesia, even though the yellow ballot form says "for sedation."

Dr. Sachs, are you going to comment from the FDA? Or, Dr. Mathis?

DR. MATHIS: Dr. Beckman was actually scheduled to cover, but had to go to another meeting.

FDA Review of Morphine

Dr. Lisa L. Mathis (for Dr. Hari Cheryl Sachs)

DR. MATHIS: Basically, what she had put together was very much in the vein of what we have just heard, that there is some data out there now from the Neopain study and from the previous study that questions the efficacy, we don't have good PK/PD or dosing, and based on these three things and the large amount of use, it would be a very good drug to study.

Open Discussion

DR. WARD: We were in the middle of planning two studies of Morphine in neonates when Sonny's paper came out, or when it was about to come out, in the spring. You have to read it very carefully because the kids who had the neurologic injury were generally those, exactly as Dr. Pursley said, who were receiving it in the placebo group outside of the infusion but also had hypotension.

So I think the issue about -- I have a slide about it -- it is the dose, it is the dose, it is the dose. This, I think, is a classic example where we probably don't have the dose right. We may not even have the right indication, but it is used widely.

Jeff and Steve, I think it is growing in use in PICUs as well, but I don't know that. No? Fetanil [ph] is still the standard?

DR. LAWLESS: Jim, you know a lot more than I do about it, but I mean, the use of Morphine, actually, is probably decreasing. Fetanil has taken over in the operating room. I can't remember an OR sheet that I have seen for years that has actually had the word "Morphine" on it. They are way beyond all that stuff.

DR. BLUMER: When we surveyed groups in preparation for the Lorazepam trial, it turned out that it is about 50/50, and it varies. The indication is pretty interesting because when you talk to people about how they use it, I mean, to some extent we are treating ourselves. I mean, it is not clear that we are treating patients.

We believe that patients have pain, and it depends on what your current religion is. So those are the patients that get opiates. It is a real problem.

DR. WARD: Dr. Higgins.

DR. HIGGINS: One of the other issues that underlies the charge of this committee but goes along with what Dr. Blumer is saying is JCAHO has issued some guidelines for pain being either the fifth or sixth vital sign, depending if you count oximetry as a vital sign. So that is one of the overriding issues that is facing intensivists and folks that work in the OR that probably should be sort of kept on the radar screen with this drug.

DR. WARD: Let me just echo, also, this issue about validative scoring tools. SciAnon [ph] has a second edition of a book called "Neonatal Pain," in which Bonnie Stevens states probably five times there is no gold

standard for determining when a neonate is in pain. We still struggle with that. We do the best we can. We try to follow JCAHO's requirements to monitor it, and it enters into how you design a study, certainly, for testing these drugs.

DR. LAWLESS: Again, this is a part of the JCAHO, and even their latest thing about using disk monitors and everything else, I mean, there is a nice element of consumerism there. It sounds really nice, but in terms of practicality, it is sending a false sense that this is actually very easy to control.

DR. WARD: And to measure.

DR. LASKY: Just to help clarify this, the written request asks for kids from one month up to 16 years. Are there any comments from the reviewers on the age distribution? Is this too wide; is this appropriate?

DR. PURSLEY: I would think that the issues would be different for the one-month-old than the 16-year-old.

[Laughter.]

DR. PURSLEY: Conducting a study, I think, would be very difficult for the reasons that have been expressed

here and in children that can't tell you that they are in pain.

DR. MATHIS: Just to clarify, that is the pediatric patient age group. However, there is also a neonatal patient age group. If you look right above that in the written request, there is preterm infants and term infants to less than one month of age. So all age groups have actually been covered in the written request.

DR. PURSLEY: I think I understand what started this, but my impression is that what is happening in the section and what is happening in our NICUs right now in terms of their focus on this as illustrated by our chair's interest, is what should be happening, that sense of self-examination.

I'm wondering if, after some time, there would even be sufficient equipoise to do a randomized control study of this.

DR. WARD: Well, the Neopain study, as well as the previous one, No Pain, were randomized and controlled, but there was the escape mechanism, if there was pain detected, the child got treated outside the study. That is really the issue, as Jeff points out. Are they in

pain, or what are we treating.

DR. LAWLESS: Unfortunately, or fortunately, I come from a hospital system where we have a cardiac ICU person who used to profess that he does not give or did not give any analgesia to his post-op patients.

Now, the trouble is, his mortality rates were far less than everybody else's, his length of stay, all quality measures were tremendous. So a hard pill to swallow.

DR. BERQUIST: This actually is an area of conflict. In liver transplant, we run into the same issues. The same thing with GI patients. You start pushing opioids and then you run into all the side effects and problems. It just reemphasizes the importance of studying and looking into pain management.

I think the premise, though, that Morphine is the most common is perhaps a question. Is that the drug we should choose or not. I think the idea is very good, though, that these things really need to be looked at, especially with the giant commission pushing.

DR. WARD: Jeff.

DR. BLUMER: Two other comments. One, if you go

back to the issue with sedation, then it becomes an important issue because, given the various receptors that exist for opioids, it is not clear that all of them or that the new receptor, for example, is the receptor for sedation. So when you start thinking about the way that we use these drugs in both intensive care units as an adjunct to sedation in many cases, they are generally not used alone.

That's fine, if you think about using them with a benzodiazepine, but if you are using them alone, then there may be -- I shouldn't say there is -- there may be a difference between Fetanil and Morphine.

The second thing, and one of the things that confounded the Neopain study certainly -- one of the two -- where you begin to look at long-term outcomes. Despite the group that you are randomized to, if you have that escape clause and if those patients get non-protocol opioid, unless you drop out all the patients who get put on the placebo arm, for example, you will never be able to look at these long-term outcomes. It seems to be one of the driving forces behind a lot of these issues.

DR. WARD: I have thought at length about how do

you analyze such a study. I think at some point you have to get out of the intention to treat mode and look at total dose and response and outcome.

DR. SNODGRASS: There is no PCA for neonates because they can't give it to you.

DR. WARD: We are the PCA.

DR. SNODGRASS: Right. So they can't be telling you. So that is one issue that is fundamentally different than the older age group studies.

The other is that 30 percent of patients in any placebo group in these adult pain trials get some pain relief, and then if you measure endorphin and keflin [ph], they rise, because they have the expectation of pain relief.

DR. WARD: That may be the whole mechanism of sucrose, also, if there is an opioid receptor component to sucrose.

Fascinating and helpful discussions, I think. Any other comments?

Dr. Buckman, I apologize. We sort of cruised ahead here. Do you want to make some comments?

DR. BUCKMAN: I think if everything from the

discussion has been supportive, we have no further comments. We really felt strongly about getting this written request out there into the foundation, and we would like to see these studies accomplished.

Adjournment

DR. WARD: All right. We have beaten the clock again this afternoon. I think it has been a very productive discussion. First, you have done your homework, which we all truly appreciate. There has been a lot of information to go through, and I think it has really helped illuminate the discussion.

So we will resume in the morning at 8:00. Thank you very much.

Oh, yes, turn these in or leave them there and we will pick them up.

[Whereupon, at 3:15 p.m., the meeting was recessed, to reconvene at 8:00 a.m., the following day.]

+ + +

CERTIFICATION

This is to certify that the attached proceedings

BEFORE THE: NICHD Best Pharmaceuticals for Children Act (BPCA)

HELD: October 25, 2004

were convened as herein appears, and that this is the official transcript thereof for the file of the Department or Commission.

DEBRA DERR, Court Reporter