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# Best Pharmaceuticals for Children Act (BPCA)

# List Prioritization Review Panel

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**VOLUME II**

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**P R O C E E D I N G S**

[8:00 a.m.]

DR. WARD: I was going to call this Infectious Disease Morning, but Dr. Wiederman pointed out this is really Infestation Morning.

[Laughter.]

DR. WARD: So we will lead off with Dr. Grogg talking about Albendazole in place of Dr. Orenstein, who had a family crisis.

**Review 4: Off-Patent Drugs**

**Review of Albendazole**

**Dr. Stanley E. Grogg (for Dr. Susan Orenstein)**

DR. GROGG: Thank you, Bob.

Now that I know Bob has his roots in Oklahoma, we are the best of friends.

I don't know whether to do a high-pitched voice and be Susan, or just kind of be myself and report what she had to say. Dr. Orenstein sent us an Email, so I have her information that I will report to you, and then I'll give you a quick report for myself as a secondary reviewer.

[PowerPoint presentation.]

DR. GROGG: Giardia, is an infestation, as we are told, but it is the most commonly diagnosed intestinal parasite in the United States. We see a lot of kids that do end up hospitalized for failing to thrive and abdominal bloating and some diarrhea. The national average is about 10 per 100,000 population. It increased in certain areas, such as New York City. Rates are highest in young children, zero to five years of age.

Sources are domestic and wild animals. I know I had a dog that had giardia, and the veterinarian told me that it was contagious to humans. So this is one of those things that people can get, actually, from animal sources. Most commonly in day care, fecal-oral -- parents love that when you tell them -- and it can be food-borne.

Low infection dose. It doesn't take a lot to infect you, and symptoms include diarrhea, cramping, weight loss, nausea, flatulence, and bloating, and can be asymptomatic and mild and yet contagious.

The CDC MMWR Surveillance Summary of 2002, Metronidazole Flagyl in most often prescribed in the United States. It doesn't come in a liquid form, but the

tablet can be crushed up. Furazolidone was, although less expensive, available in the United States by suspension form, but it is no longer available in the United States. There is another drug that is available.

Quinacrine is effective and inexpensive and is available -- I haven't utilized that myself -- and some of the other agents.

Albendazole, which is the drug that we are talking about today, has been reported to be as effective as the Flagyl with fewer side effects in two- to 12-year-olds. Puromycin is not absorbed. Aminoglycoside is less effective but used in pregnancy because it is less likely to cause cancer. Flagyl can be combined with other substances to help in the treatment.

Albendazole is poorly absorbed, and you need to take it with a fatty meal. The benefits of Albendazole: it is better tolerated than some of the alternatives. It has a wide spectrum against potential coinfections with other types of parasites.

In Africa, it is used every six months in combination with other medications to deworm, if you will, and that is probably where it came as a proposal to

be utilized for giardia.

Disadvantages. It requires at least several days of dosing to obtain 90 percent effectiveness. There are lots of studies that have been done, so it has been looked at and evaluated.

In Task 1, Dr. Orenstein gave it a score of one for information on PK. Unavailable, no studies, but you do have quite a few studies that are out there. And zero all the way through.

I will just go straight to the summary part.

The comments were, it has been studied in a number of large pediatric RCTs internationally where cases are more prevalent than in the U.S. Its efficacy and safety appear relatively assured in children greater than two years of age at doses of 400 milligrams for five days.

You need to treat for a somewhat extended time period for giardia, especially if dosing compliance is assured by observation. That is part of the problem, is the compliance, giving it five days in kids and 400 milligrams per day for five days. It should be given with a fatty meal, so you send to McDonalds first.

Sustained efficacy is most likely if infestation is prevented. Its benefits include low rate and severity of side effects and concomitant therapy for coinfection with other ailments or parasites.

The U.S. prevalence in children less than two years of age is somewhat unclear. If there is a sizeable population of such potential patients, further information establishing dosage and safety in this group would be worthwhile. Again, it is the most common parasite infestation.

So she didn't make any particular recommendations except to say only for limited study in zero to two years, if there are enough children in this age group who would potentially benefit by this drug's availability.

So with that, on Table 2 she has some comments. Dr. Orenstein says, indication to giardia. Pediatric use, expand the use data on treatment of giardia and other ailments. Adverse events, add column for giardia treatment using the data from studies by Pengsaa and Escobedo. Dosing for giardia in children and determine and define dose in less than two years of age. Method of

administration to children unable to take tablets should be specified. Can it be turned into a liquid form, in other words.

You could use endpoints of giardia from the stool. It is tough to find giardia in the stool instantly. Those infectious disease people know that it takes at least three stools a lot of times, and most of the studies were done with two negative stools. They did not use the INSOC test.

A rigorous RCT comparing Albendazole and Flagyl and Furazolidone in children in the U.S. at doses now believed optimal, including children less than two years of age, would be useful to assess the efficacy and comparable safety of these three medications.

So that is her recommendation.

**Secondary Review of Albendazole**

**Dr. Stanley E. Grogg**

[PowerPoint presentation.]

DR. GROGG: This is not a canned presentation. I just want you to know that.

Albenza is the other name. It is approved in the United States at the present time for hepatic

disease, which is echinococcosis -- I haven't had enough coffee yet -- of liver, lung, and peritoneum caused by the dog tapeworm in greater than two years of age and neural cysticercosis -- I call my infectious disease experts for these kind of diseases -- which is the pork tapeworm, in greater than six years of age. So it has some FDA approval in the United States at the present time.

Giardia -- we always think of the board question that I teach our residents -- is a teardrop-shaped protozoan that you would see. You can see the picture of it here. It lives in the small intestine and is transmitted primarily when infective cysts are ingested in water, fecal-oral contamination, and actually from animals.

Clinically, it is passed via the fecal-oral route. You have a little better diagram of the organism. It causes severe abdominal cramps. I tell my residents, it is a disease without fever, unless you have coinfection, but they have a lot of gas passing, as in my picture yesterday, and abdominal cramping. It is the most frequent non-bacterial cause of diarrhea in North

America, so it is prevalent.

Albendazole is an anthelmintic type of agent. It is a white powder. In Oklahoma, we are worried about that statement for other reasons. It is practically insoluble in water. At best, it is not very well absorbed in the intestinal tract or from the intestinal tract due to the low solubility. Negligible or undetectable in the plasma, so you have to take it with a fatty meal to get any systemic effect.

The systemic effect, though, is due to the primary metabolite Albendazole sulfoxide. Again, you need to go to McDonalds before you take it.

Maximum plasma concentration is two to five hours after dosing, with an average of 1.31 micrograms per mL following oral doses of 400 milligrams, and the half-life is eight to 12 hours.

It is widely distributed throughout the body, and it is excreted both in the urine and bile and broken down in the liver. It can actually be found somewhat in low quantities in the cerebral-spinal fluid.

It is converted in the liver primarily, as I said, to metabolite, and urinary excretion is a minor

elimination pathway, with only 1 percent in the liver. Most of it is in the biliary tract, where it is excreted.

So in pediatrics, it looks like there have been some studies done that indicate at 10 milligrams per kilogram, five patients six to 13 years of age, the pharmacokinetics and the efficacy were similar to adults. In less than six years of age, there were no problems encountered safety-wise in a limited study.

Sixty-two children with giardia treated at 400 milligrams once daily for only three days only showed a 50 percent parasitology cure. That had a good P value in this limited study with no major side effects.

So here are 150 children, two to 10 years of age that received a single dose of 400 milligrams suspension that they converted it into, with 22.5 milligrams per kilo per day, compared to the Flagyl three times a day for five days.

For the five-day treatment, they got a 97 percent cure, so it looks like it does work if you give extended treatment.

Three Albendazole and 20 of the Flagyl had side effects, which included diarrhea, abdominal pain, nausea,

vomiting, weakness, and anorexia, but it did not discontinue the use of the drug.

A pediatric giardia study in 165 Cuban children treated with Chloroquine and Albendazole at 400 milligrams per day for five days, and Tinidazole, which is not available in the United States. The Chloroquine and Tinidazole cure rate was 91 percent and 86 percent respectively, whereas the cure rate for Albendazole was only 62 percent.

Microbiology. It has an inhibitory effect on the tubulin polymerization, resulting in a loss of cytoplasmic microtubials, for those that remember microbiology from medical school. In the United States, as I said, it has pork tapeworm and dog tapeworm as indications for its use.

Contraindications. Rare fatalities have been described, with granulocytopenia or pancytopenia, so CBC monitoring at the beginning of each 28-day cycle is indicated. Fortunately, this is quite rare in kids in the studies that have been performed.

It is a category C. In pregnancy it may cause fetal harm, and it has mild or moderate elevation of

liver transaminase when utilized, which is reversible when discontinued.

Dexamethasone is a drug that causes changes in drug levels. Adverse reactions include abnormal liver function tests, abdominal pain, nausea, vomiting, headache, dizziness, vertigo, reversible amnesia, versus what some of us have, and fever.

So rare adverse reactions, as I mentioned, are leucopenia, rashes, pruritus, allergic reactions, acute renal failure. Again, rare in children, at least as it has been studied so far.

Flagyl has been used in children and is available in the United States. It is three times a day. In the teenagers, you can't take it with alcohol, which is a good thing. The potential cancer-causing effects, though, are a concern for the pediatric population.

We do have a relatively new drug, Alinia. It is a suspension approved by the FDA. I have used it a couple times with very good success. It is approved for giardia and cryptosporidium, so since Furoxone is not available in the United States, this has kind of taken the place as at least my drug of choice. I don't know

about infectious disease or giardia. So we do have something else that is available.

Just looking at the cost, Albendazole is cheap and can be crushed and turned into a liquid form. Flagyl is somewhat more expensive, but Alinia is $36 for a bottle, which is pretty much a treatment course for kids.

In conclusion, we need to monitor liver function studies and CBCs if using Albendazole. It is not available in the suspension, but we can crush the pill. It appears to need five days of therapy for giardia, which can cause problems with compliance, possibly.

So although Albendazole is somewhat efficacious for giardia with only mild and transient side effects, other drugs are available -- Alinia -- with better cure rates and fewer side effects.

I was having a hard time scoring, Tami, these particular score sheets, which I think they are good because they bring to our attention what to look for. I gave it a 10, but I recommend that this drug and indication receive low priority for future listings and discussion, whereas Susan gave it a three. It is just a

matter of, I read all those articles and I thought there was a lot in the literature just because I looked at all those articles.

With that, I would say if it was later in the morning it would be time for a snack, but that is the end of my presentation instead.

With that, whoever is next.

DR. WARD: Dr. Beckman, are you going to speak for the FDA, or someone else?

**FDA Review of Albendazole**

**Dr. Joette Meyer**

DR. MEYER: I'm Joette Meyer. I'm a clinical reviewer in the Division of Special Pathogen and Immunologic Drug Products.

I would just like to mention that there are actually two drugs approved in the United States for the treatment of giardia in children. As was mentioned, Nitazoxanide, or Alinia, was approved in November of 2002. It is available in a suspension form, and the indication does go down to children one year of age.

The study in which Nitazoxanide was approved was a clinical trial comparing three days of Nitazoxanide

to five days of Metronidazole, and Nitazoxanide was shown to be non-inferior to Metronidazole.

Also, earlier this year, in May, the FDA approved Tinidazole, or Tindamax, for the treatment of giardia in children greater than three years of age. Tinidazole is available as a tablet, but the tablets can be crushed and dissolved in Karo syrup. There are actually directions in the label for the extemporaneous pharmacy compounding of the drug.

There are some articles in which Albendazole has been compared to Tinidazole in the literature, and actually, Tinidazole appears to be more efficacious than Albendazole. There are also articles comparing Albendazole to Metronidazole, and the two appear to be more equivalent.

I think those are all of my comments.

**Open Discussion**

DR. WARD: Yes, Gary?

DR. OVERTURF: A couple of comments. First, you don't need three stools to diagnose giardia any longer and for at least a decade, because we have molecular tests. Nobody recommends three stools for

giardia anymore. So it is actually a fairly easy disease to diagnose because the tests have sensitivity way over 95 percent on a single stool.

DR. WARD: Are they PCR?

DR. OVERTURF: No, they are usually antigen tests looking for one of the specific giardia antigens. Most labs actually will not do full O & Ps which use a microscope exam unless you indicate that you have a patient from outside the United States in which you are looking for anthelmintic pathogens.

One of the reasons why the Pediatric Infectious Disease Society was interested in Albendazole is that Albendazole is very useful. It is the only drug available for a few things like echinococcus and cysticercosis. Because that market is small in the United States, we want to keep it licensed for giardia, but we also would like to know how effective it is.

The other thing is that, practically speaking, when you are treating patients with giardia, its failure rates are very high with any single drug regimen. You often have to use a second drug regimen. Albendazole, if nothing else, provides one of those alternatives, and it

is a very well tolerated alternative.

The other thing is, we had made the comment that we were a little bit surprised Metronidazole wasn't on the list because it is a drug that really has not been studied. It is another one of those situations that we talked about yesterday which could still be used as a comparator for many of these trials.

The biggest issue about Metronidazole that just keeps coming up over and over again is based upon the Ames pseudomonas test, which is this a carcinogenicity issue. As far as I'm concerned, it is a non-issue. It really has never been proven to be of any importance at all in human biology as far as I'm concerned.

DR. WARD: I think it was also found in rats in the bladder. That is my recollection.

DR. OVERTURF: Right. I think you are right.

So I understand these are problems, but they remain on the label. They are problems that everybody pretty much ignores, actually, clinically.

So I think Albendazole should be given a higher priority. I don't know if it needs to be on the list this year, but I think it needs to stay on there until we

have it appropriately niched. Maybe we need more data before we make a final decision.

DR. WARD: Dr. Meyer, would you comment on extemporaneous formulations of Albendazole? You indicated Nutrasol, there are directions on the label for that.

Have stability and solubility, and so on, been looked at with Albendazole?

DR. MEYER: No, there is no information in the Albendazole label, as far as making a suspension. I think it's only -- I forget the tablet strength.

DR. WARD: It is 200.

DR. MEYER: Two hundred? And the dosing in pediatrics is 15 milligrams per kilogram per day. So it would have to be adjusted to the 200 tablet.

DR. WARD: I guess a related question would be Nutrasol for cysticercosis. Has that been looked at? Here we already have a suspension form, right?

DR. MEYER: Nitazoxanide is in a suspension form.

DR. WARD: Has that been looked at for the tapeworms?

DR. MEYER: No.

DR. WARD: Thank you, Dr. Grogg and Dr. Meyer.

Again, same scoring system as yesterday. Blue sheet today. Put your names at the top and register your votes for Albendazole.

DR. WIEDERMAN: Can I just ask, we are voting on Giardiosis, not neural cysticercosis?

DR. WARD: Correct.

DR. WIEDERMAN: A Trojan horse from the Pediatric ID Society.

[Laughter.]

DR. MATHIS: I'm going to go back to the Pediatric Infectious Disease Society to ask two questions. First of all, Metronidazole is off-patent, so if you have recommendations that it appear on the list, you may want to provide that input to NIH next year for the 2006 list.

Then, on top of that, are you saying that you were hoping that Albendazole would stay on the list to make it remain available for other indications other than giardia? So, you want to see it remain on the market for other indications, not for giardia?

DR. OVERTURF: Actually, I think both. Some of the data that we reviewed by Dr. Grogg I think is interesting in that it has had a checkered past. I guess I would have to examine those studies a little more carefully, because there are two issues here.

This is very much like dealing with Streptococcal pharyngitis. Some studies look at microbiological success, and so eradication of the organism. Other studies look at elimination of symptoms. I suspect that most of those studies that showed low rates were primarily looking at eradication of the organism. That may not correlate with symptoms.

The background rate of giardia in developed countries is in some places just a little less than 5 percent. In other words, 5 percent of us around this room are sitting here with giardia and living with it quite well, thank you very much.

[Laughter.]

DR. OVERTURF: So the issue would be, who is having symptoms.

The tapeworm infection is probably much less, but most of you will not be symptomatic with tapeworms

until I tell you you have one.

[Laughter.]

DR. OVERTURF: So I would like to leave it on the list for both continued examination and studies. I hate to say eliminate it for other indications.

That was actually a confusing issue of the whole process here. We had to address drugs in a very specific way, and then when we got requests to review and come here on the panel, we got very focused reviews at times that I thought sometimes we didn't think were even pertinent, like the issue of Cefuroxime and sickle cell disease and Cephalexin and oral infections and so forth. Yet there are broader issues for those drugs, and I think that is true for Albendazole.

DR. LASKY: I just want to clarify a couple of things, because it is becoming clear to me the problems that we are having in the process.

When we sent the outreach, we were required to have the outreach to the public go in a very open manner so that it does not appear to be a survey. If it is a survey, it has to go through clearance to the Office of Management and Budget, and it could be held up by over a

year, apparently.

So we were told in wording the outreach that we had to make the outreach as open and voluntary. Basically, if you care to take this opportunity and share your thoughts with us, please do. I have been thinking about this since last night as well. The outreach really needs to be more structured, but then it comes into conflict with this OMB regulation that we are not allowed to go and survey the American public, basically is what that thinking is.

So we may be stuck with an open-ended outreach that then gets funneled into this much more specific process, which is, I think, one of the problems that we are dealing with.

The other point, Metronidazole was mentioned by the Pediatric Infectious Disease Society in this letter, and I think we discussed it. I'm sure in our notes we can find out why we didn't put that on the list but did put Albendazole on the list.

What we tried to do is when we did receive the outreach is, we did review it not only in the working group but FDA went back to the review divisions. There

were conversations that took place, but it is clear then that this is an area of interest and needs further thought, if nothing else.

DR. WARD: I have a couple of things. One is that at the end of the day we want feedback about process. One of the things that has arisen since the beginning of this BPCA process is that those in the clinical arena and carrying various hats of expertise in specific therapeutic areas may have in mind specific drugs that need to be studied in a specific area or in general areas. Then, when it gets translated to requests for studies by the FDA divisions, that focus may miss the mark that we had in mind.

I think to the degree that we can figure out how to reconcile that disconnect we can improve things, again, to serve the needs of children better, so that we can encompass what we see in the clinical arena but the division reviewers may not be as aware of.

Yes.

DR. MATHIS: I have to admit I was talking to Don about how we could feed this information back to the review divisions and then next year possibly have them

come back for indications that we have heard around the table over today and yesterday.

So, yes, this information can be used. I'm sorry.

DR. WARD: I didn't mean to put you on the spot.

DR. MATHIS: That's okay.

DR. WARD: Stan.

DR. GROGG: Just a final comment. One of the endpoints of the studies that I reviewed, they all did stool evaluation, and since the cyst is found in the duodenum, it may not be present in the stool. So whether they were really cured or not is a question. Now that we have better techniques for diagnosing giardia, I would suggest that any studies that might be done use the newer techniques.

DR. WARD: Let's move off of the infestation area.

Dr. Zaoutis, do you want to discuss Clarithromycin for oral infections in dental patients?

**Review of Clarithromycin**

**Dr. Theoklis E. Zaoutis**

DR. ZAOUTIS: Our task was to evaluate Clarithromycin for oral infections. Clarithromycin is a macrolide class antibiotic that is available in several formulations: extended tablets, regular tablets, and the granules for oral suspension.

There is very good PK and PD data in children, including dosing guidelines based on weight that appear in the label.

The Metaworks group has put together a nice review of the studies, and they identified 82 pediatric studies in which Clarithromycin has been evaluated. Included in those are 14 randomized clinical trials, two non-randomized trials, and 14 cohort studies.

The current indications for use in which efficacy has been established include pharyngitis, tonsillitis, community-acquired pneumonia, sinusitis, otitis media, uncomplicated skin and soft tissue infections caused by Staph aureus and Group A strep, and disseminated mycobacterium avian infection.

PARTICIPANT: And H. pylori.

[Laughter.]

DR. WARD: Here comes a small voice from the

right. Any other voices?

[Laughter.]

DR. ZAOUTIS: It is a relatively well tolerated drug with the most common side effects being gastrointestinal: vomiting, diarrhea, and abdominal pain. There are rare severe events, including cerzapoints and ventricular tachycardia associated with prolonged QT interval with the macrolides, as well as with this macrolide, specifically.

It is an inhibitor of the P450-3A isomer, so it has potential for interactions with other drugs.

Specific to oral infections, as we discussed yesterday with Keflex or Cephalexin, oral infections tend to be polymicrobial and include anaerobes. The label lists several anaerobic bacteria that Clarithromycin has activity against. The label suggests that the data is in vitro only, and the drug has not been evaluated clinically for the treatment of infections caused by anaerobes.

In addition to the Metaworks review, there is some literature in the treatment of oral infections, and the studies break down into two categories, one looking

at in vitro data against anaerobic bacteria and the other sort of case reports and less rigorously done studies.

The in vitro data, including one study looking at Clarithromycin's activity against anaerobic bacteria identified in pediatric patients suggested that it has some activity against some of the anaerobes. There are several other papers using adult isolates of anaerobic bacteria that suggest that it has, again, reasonable activity against some of the anaerobes.

Clinically, there is a double blind randomized control trial that appeared in the Japanese Journal of Antibiotics which revealed a response rate of 77 to 88 percent for Clarithromycin when used for oral or dental infections. There is also a dental study that was non-randomized of 41 patients that suggested it worked well, although the details were not available.

The Journal of the American Dental Association has also published a systematic review which mostly consisted of case reports anecdotally reporting success in the treatment of oral infections with Clarithromycin.

Finally, the Cochran Group looked at one study for the prevention of mucositis in cancer patients, and

used Clarithromycin to prevent mucositis and found borderline significance.

So in filling out this task scoring worksheet, I had a little bit of difficulty, as mentioned by the other reviewers. There is a lot of PK and PD data for this drug, although not for this indication. There is a lot of safety data and a lot of efficacy data for this drug, again not specifically for this indication.

I'm assuming that the request from the Dental Association had to do with the treatment of panallergic patients, but that is an assumption.

In looking at the rest of the questions on this list in terms of the severity of the disease and whether this is a leading diagnosis that leads to hospitalization, prolonged hospitalization, chronic disability, I do not feel that was important. It does have a very good therapeutic index, and there are other alternative therapies that are effective and safe.

So I scored it as a priority three and did not recommend that it appear on the list anymore.

DR. WARD: Dr. Woods?

**Dr. Charles R. Woods**

DR. WOODS: I think I don't have a lot to add to that. I wasn't sure what the indication was that we were looking at.

For oral infections, I guess I would just echo, I don't see that this has much of a role unless there is some interesting in panallergic patients. I think there may be a role to study it for other indications: cystic fibrosis where actually in biofilms it may actually have some potency against pseudomonas. There may also be some immunomodulatory impacts, some thinking along that line, although I sort of suspect it actually is an antibiotic more than an immunomodulator in that condition.

So that would be the place I would say it might be deserving of further study, but I also gave it a priority three, the same score.

I would, maybe, recommend it for study for another indication but not for this indication. So for this indication, I would not recommend it.

DR. ZAOUTIS: The voice from beyond became the hand from beyond and handed me the book from the request for this. Actually, in their request, they say that

"The recent literature for adult dental patients suggests that the susceptibility of oral pathogenic organisms to Clarithromycin is low and the propensity of macrolide impacts to inhibit the CYP3A4 across a multitude of pharmacokinetic adverse drug reactions mitigate against routine use of this class of antibiotics."

Then they go on to say that it should be studied.

DR. WARD: With EKG monitoring.

[Laughter.]

DR. WARD: Who is speaking for the FDA? John, okay.

**FDA Review of Clarithromycin**

**Dr. John Alexander**

DR. ALEXANDER: I don't think I have much to add to this, either. I mean, Clarithromycin is a drug that is available as a syrup. It is labeled. It has a funny metallic taste to it. It has the same issues with Erythromycin with regard to potential for QT prolongation and SIP 3A4 interactions. The only sort of advantage to it over the Erythromycin is that it has a longer half-

life and it allows for BID dosing of the drug.

The activity against anaerobes is variable. The information on the anaerobes that is in the label to which the reviewer referred was basically information that we have on in vitro data that was submitted for some of those organisms. When I was trying to look into some of the information on other anaerobes, the data there are variable. So there are some reports where for peptostreptococci and some of the oral floor that MIC50s and MIC90s are a little bit higher.

So I do think that there are other drugs that are available as alternatives for treatment of oral infections.

**Open Discussion**

DR. WARD: Gary.

DR. OVERTURF: Again, the request is misplaced because there are needs for Clarithromycin data, particularly for, for instance, pertussis prophylaxis in neonates, where there are virtually no data. There are no data, and there is really no PK and PD in that group.

One of the things that was not mentioned is its safety. Nobody takes 14 days of Erythromycin, nobody,

zero. You might get it down a kid because you can just stuff it down them.

The major advantage of the new macrolides is that they do not cause the GI distress that is caused by Erythromycin, and they have no potential to do so. So for those indications which are prolonged treatment regimens, they both shorten the course of those treatment regime, or potentially, and they may avoid some very serious adverse events, like some of the problems we have had in neonates with Erythromycin.

So again, this is a drug that needs to stay on the list but for a different reason. This oral infection has nothing to do with anything. I agree it should be off the list for oral infections.

DR. WOODS: The other comment to make is that, in pediatrics, in terms of macrolides, Azithromycin has sort of supplanted Clarithromycin in many ways, partly because of taste and the shortened course, but there are rising concerns that, I guess, the kinetics of the white cell and its persistence inside white cells at sub-MIC levels may drive resistance to macrolides.

So I do think we need to have different types

of information for this, not for oral infections.

DR. WARD: Another word from the FDA.

DR. SNODGRASS: If I might add another comment, I don't know how many years you can keep a drug on a list. Clarithromycin was dismissed last year.

DR. MATHIS: We can come back every single year and discuss this drug.

DR. SNODGRASS: Until 2007.

[Laughter.]

DR. SNODGRASS: It was dismissed last year as a "me too" drug, if you will remember, but for another indication. There have been some post-marketing reports on Clarithromycin, and those include some allergic reactions as well as some dental discoloration. So certainly, those people who are prescribing it will see some of these adverse events, but it is reversible.

Otherwise, I agree with the other remarks made by the reviewers and Dr. Alexander.

Thank you.

DR. WARD: Gary, could you comment about Azithromycin for pertussis in neonates?

DR. OVERTURF: Actually, there is more data on

Azithromycin in general for things like pertussis prophylaxis. Most of it is European data, some of it is Canadian data. I think the Canadian study, though, was with Clarithromycin, if I'm remembering right.

So again, this may be nothing more than an issue of labeling, except for some of the PK and PD data that affects neonates, which this is a frequent indication because that is the group who needs pertussis prophylaxis the most.

So I just reviewed the pyloric stenosis and I'm totally convinced that Erythromycin is associated with pyloric stenosis.

DR. WARD: Actually, that is not a new issue. If we hadn't been in this process, we probably would have known that in the 1950s, because the data on that is that old.

DR. OVERTURF: The first report I found was in '76, and it was actually very poorly done.

DR. ALEXANDER: Actually, that is a point here, because, I mean, in terms of Clarithromycin, what Clarithromycin is is 6-O-methyl-Erythromycin. It is the same drug with a methyl group on the end of it.

There are studies that we have requested for Azithromycin, based on this off-patent written request process for two different indications. So it's not pertussis prophylaxis but it's ureaplasma infection, and for chlamydia. They are both including PK information on Azithromycin down to pre-term neonates because of the ureaplasma question. So we will have more information that will be available on the PK of that drug.

I think that in terms of trying to select drugs for priority, I would still look at the potential for Azithromycin as the drug to use for treatment of pertussis over Clarithromycin just because of the concerns of its relatedness to Erythromycin and the pyloric stenosis issue.

DR. MATHIS: Just real quickly, I would like to say that even though one year we might decide that a drug should not be placed on the priority list for the indication that we looked at it for that year, that we need to keep the discussions open. We learn new things and we develop new resistances or new use patterns.

So even though we may dismiss a drug from the priority list this year or last year, there is no reason

why we may not discuss it again next year. So keep giving us your ideas about how you would like to see these drugs used, and we will keep discussing those issues. We need to keep reevaluating all of these drugs as we go through this process.

DR. WARD: One of the things we did yesterday was to have write-in aspects about indications. I think having those recorded is helpful to the agency, and it preserves our thoughts and our discussion in a very clear fashion. I would suggest, as Dr. Overturf pointed out, two of these, the tapeworms for Albendazole and other indications for Clarithromycin, to feel free to write those in if you feel that those need to go back to the agency as potential areas that need to be studied in the future.

DR. MATHIS: To write them in after scoring the current indication.

[Laughter.]

DR. WARD: Yes, Stan.

DR. GROGG: I hesitate to say this because my son works for a pharmaceutical and part of his salary comes from --

PARTICIPANT: Full disclosure.

DR. GROGG: Full disclosure.

In addition to the metallic taste, it is kind of back to the septum issue. You get that first dose down, but that second dose, unless you like to eat sand, it is almost impossible because it gives that sand-like consistency in the mouth for at least three hours, I can tell you personally, having tried it, thank you.

DR. WARD: Wayne.

DR. SNODGRASS: So there are studies on taste, particularly young children's preference for taste. There was a study in one of the pharmacy journals several years ago, and black cherry came out first, as an example. My point is this, that for oral antibiotics and other oral drugs, this is a real issue in pediatrics. If you are in the position of prescribing for children, they will come back to you that day maybe upchucking, and you have to deal with it. These are big problems.

DR. WARD: The whole issue of compliance. It is not like you are going to reason with them.

DR. SNODGRASS: No, no, you are not.

[Laughter.]

DR. SNODGRASS: Is there any kind of discussion with drug companies or through the agency about dealing with this in some more general manner?

DR. MATHIS: We actually do at times ask for palatability, and then we also do the intent to treat studies. So if a kid can't complete a course of therapy because they are throwing it up, that becomes a review issue for us.

But you are right. We have actually done some internal studies on palatability for things like --

PARTICIPANT: Doxycycline.

DR. MATHIS: Doxy we did; for iodine we did. So there are different compounding reasons why we have looked at palatability, and it is a big issue.

DR. WARD: In about I want to say '98 or '99, there was a meeting about formulations for pediatrics specifically about that, and that may warrant redoing the whole issue of taste as a special science.

DR. MATHIS: It really is in the best interest of industry to make their formulations palatable because otherwise people start talking about their drug like we have been talking about the drugs around this table. We

are all practicing pediatricians, and we know what not to give our patients so they don't come back throwing up.

DR. ALEXANDER: I do think that you need to recognize that this is a difficult issue for the industry as well. I mean, I have dealt with them on a lot of issues with regard to the tastes and formulations of different products, and sometimes it doesn't matter what flavors that you add to something, a drug just tastes so bitter that you are not going to mask that poor taste.

So there is only so much that you can do that is going to provide both the drug being able to get into the system as well as covering the fact that you have the taste issues and palatability of the drug.

DR. MATHIS: Dr. Alexander, I'm sure, can share the experience that industry has had with HIV medications. Everybody knows about Prelone, which is cherry-flavored gasoline. The HIV medications have been a real challenge for the division.

DR. WARD: There is an organization, U.S. Pharmacopeia Convention, that has some superb formulation chemists. This sounds like an opportunity for a role.

Stan.

DR. GROGG: Just a suggestion to the pharmaceutical companies that we might refer back. If they make it taste like gasoline or furniture polish, kids seem to like those.

[Laughter.]

DR. WARD: Let's return to the infestation world and talk about Ivermectin for scabies.

**Review of Ivermectin**

**Dr. Lisa L. Mathis**

DR. MATHIS: Ivermectin was new to me. We don't have much of a problem with river blindness in Portland, and so I was looking it up and thought, oh, this is an interesting drug.

If you are not familiar with it, which I wasn't, it is in the class of the Ivermectin broad-spectrum parasitic agents, and it binds selectively with high affinity to the glutamine gated crotamiton channels in invertebrates. It does not cross the blood-brain barrier.

It has been used extensively overseas. It is an antiparasitic used to treat strongyloides and onchocerciasis, which are worms, I think.

Anyway, there are lots of studies overseas: India, Brazil, et cetera. The only thing that has been studied in the United States is some case studies for using it for scabies. It has been used overseas. Over 19 million doses have been used worldwide. It is a pretty safe drug. In some countries, they just pass it out on a regular basis to treat people for their worms.

The reason that they are using it overseas for scabies in India and the other published studies was that it was easier to use than the liquid formulations and they had higher compliance.

The case studies from the United States are the same thing. It has pretty good efficacy. It works 70 to 100 percent of the time with two doses to clear scabies. It works very well for crusted scabies and people that are resistant to repeated topical applications of Permethrin. The main thing is that I don't know why we would want to use an oral agent for scabies.

It has been used extensively in people over 15 kilograms. It is not indicated for pregnancy, but overseas a lot of people use it and there has no fetal toxicity or teratogens.

Let me see. I gave it a score of three because, yes, there is no PK data on younger kids and there is no efficacy data in the United States about using it for scabies, but I don't think that is a high priority to study. I just don't see why we need to have an oral agent for scabies.

DR. WARD: Let's let Dr. Woods comment, and then Dr. Epps.

**Secondary Review of Ivermectin**

**Dr. Charles R. Woods**

DR. WOODS: I think I would echo that largely, except that I would like to see more data on this for lice, maybe, even than scabies, which I think is a potentially bigger problem for us in the end. So for scabies maybe not, but I might give it a four.

It won't rank a high score in terms of hospitalizations or chronic disease, but in terms of a problem that is out there in pediatrics at least in terms of perhaps growing resistance, there are difficulties with lice. I would say it might be more useful there. Scabies, maybe not. It would be nice to have as an option but not necessarily a lot of further study for

that indication.

So I might give it a four in terms of score and say we ought to look at it, but again, coming back for a different indication, more for head lice as another agent.

DR. WARD: Dr. Epps.

**Tertiary Review of Ivermectin**

**Dr. Roselyn E. Epps**

DR. EPPS: Good morning. As a pediatric dermatologist, I can tell you we would need to study this drug. I think it would be extremely helpful not only because there are a lot of children. It is a school problem. It goes through the schools and people who live in crowded conditions. It goes around and around and around. As a subspecialist, I am referred patients who have had scabies for months and months and months. It is very helpful for people who have atopic dermatitis or skin problems who cannot tolerate topical preparations.

So a little bit more data would be very helpful. Maybe it is not appropriate for infants, but sometimes the infant has it, somebody holds the baby, everybody holds the baby, everybody has scabies. So we

need some alternatives other than just topical Permethrin and some of the topical sulfurs and some of the topical things that don't work in people who are sensitive to and cannot tolerate them.

DR. WARD: I knew nothing about Ivermectin, so I found it interesting to read. The issue about secondary infections in scabies appeared to me to be a significant health problem in children. The difficulty with compliance with topical treatment, I think, poses a problem as well.

**FDA Review of Ivermectin**

**Dr. Lisa L. Mathis**

DR. MATHIS: I'm going to be the FDA representative on this.

You may know that I discussed Lindane last year. As we look at the indication of head lice, we have multiple treatments for head lice. There are many approved therapies and there is no problem getting sponsors to come in to apply for new drug applications for new drugs to treat head lice. We don't have a problem.

In addition to that, head lice might be very

annoying and something that we need to treat because it does interfere with schooling, but it is not a public health problem. Scabies is. If you look at parts of the world, like third world countries where you don't have adequate medical care, scabies accounts for a very large percentage of the morbidity in children.

When we look at scabies in the United States and we look at approved therapies, we have Permethrin, which is actually very effective and is our first-line therapy.

Outside of that, we have Crotamiton and Lindane. Crotamiton has less than a 40 percent efficacy rate, if you believe the current literature that is out there, and there is resistance, documented resistance. If you look at Lindane, it is a second-line therapy, so if a patient fails Permethrin, they have to go to Lindane. We know that there are problems with toxicity with Lindane, especially in patients who may have scratched their skin or have atopic dermatitis.

While we would rather see a topical formulation for Ivermectin, we have to start looking at safer alternatives for the treatment of scabies, and that is

why we strongly recommended that Ivermectin make the list.

There have been a lot of patients in the world that have used it, but most of them have been out in Africa and there hasn't been very active surveillance of safety. You only see what you look for, so when you hand out the drug and then you disappear from the village, you are not going to identify safety risks with the drug.

In addition to that, the doses that you need for infestations are higher than what you need for river blindness. It is also two doses. So we do need to evaluate this drug for both safety and efficacy, and we need safe alternatives for the treatment of scabies.

I can tell you -- perhaps somebody from the division can comment -- we don't have sponsors knocking on our doors with alternatives to treat scabies. It is a condition of poor children who are living in crowded conditions and there is not a lot of interest in it. That is one reason why we think this would be a very good thing to have studied.

**Open Discussion**

DR. WARD: Dr. Zito.

DR. ZITO: A question on its patent status. This is off-patent?

DR. MATHIS: Yes, it is.

DR. WARD: Yes, Dr. Sachs.

DR. SACHS: If I can just add, in India for example, 7 percent of all kids hospitalized for any condition have scabies. So it really is a huge public health problem.

I do want to mention that there was a recent warning in MedWatch about difficulty in standing or walking in toxic epidural necrosis.

DR. MATHIS: I should add, with Ivermectin, too, everybody really does assume that it is a very safe drug, but we have case reports in the New England Journal of Medicine that actually talk about elderly patients who are given oral Ivermectin for the treatment of scabies, who ended up dying within several days because of neurologic reasons.

DR. SACHS: I thought that was after six months.

DR. MATHIS: Some of the cases were after six months, some of them were very short-term. It does

attach to the P proteins, and so it increases the permeability of the blood-brain barrier.

Actually, going to you, it has been used as an adjunct. There are studies of it being used as an adjunct to Baclofen for spasticity because it does hold open those P proteins and increase permeability of the blood-brain barrier.

So while we assume that it is a very safe drug, and it is being used off-label for scabies, I think we really need to assess the safety of it. Perhaps this isn't going to be our safe alternative, but I think that we need to determine that.

DR. WARD: Gary.

DR. OVERTURF: The other point is that it has also been used in Filariasis prophylaxis as well. The difference is that those prophylactic regimens use these drugs very infrequently. I mean, the doses are much lower, and you really can't extrapolate safety data from many of the prophylaxis treatment regimens that are used in Africa for what we might expect with scabies.

I personally think that it is overkill for most scabies, but it is not a disease I see. I feel the same

way about lice. I think a lot of lice is overemphasized, and I think a lot of the turmoil about issues about resistance really don't appreciate the biology.

Regardless, if it is going to be used, safety data really is, probably, needed.

DR. ZITO: I want to make the suggestion that we think about, if we were to support additional research here, that it be focused on safety, that we could think about ideas like a registry or a protocol that shows that the individual was resistant to safer alternatives as a first step, and then a defined protocol in which safety could be assessed.

DR. MATHIS: We actually would have to look at efficacy as well to label it because we don't have any efficacy data. So we always have to look at safety in balance with efficacy.

DR. ZITO: What I'm alluding to is the fact that the tradition of our trials has been that the safety data is generally inadequate to answer many questions because of a lack of standardization of the way the data are collected, definitions, and what symptoms you would look for. Also, because there has always been a sense of

under-reporting. You don't really go aggressively looking for bad things when you are trying to demonstrate effectiveness.

DR. WARD: I think that simply underscores the need for careful study in which safety is collected thoroughly.

MS. WOO: One thing that did come out in the studies in the United States, all the cases in the case studies were immunocompromised patients, and immunocompromised patients who get scabies, it turns into crusted scabies. This has been very effective in clearing them up very quickly, but then you also have to deal with safety with the immunocompromised patient, too.

DR. WARD: Dr. Epps.

DR. EPPS: Well, unfortunately, a lot of this isn't reported because it is common or people recognize it. They don't need to report it because when it is diagnosed, quite simply, with oil and scraping, then you move on and you treat everybody.

I will also say that there may be even more of a public health issue when these people are admitted to hospitals. There was a recent outbreak at a local adult

hospital -- not at our facility -- and these patients had gone home and they had scabies and nobody realized it until later. They had to call back and get the health personnel treated.

So it is a problem. Of course, that is not going to be part of their PR campaign, that you come in and you get scabies, so people don't really talk about it. They are embarrassed about it or they don't discuss it, but it is not like having an ear infection.

DR. WARD: Steve.

DR. LAWLESS: We actually don't, obviously, see much scabies in the ICU, but in the NICU, maybe.

[Laughter.]

DR. LAWLESS: The question I have, actually, is on two things, just because it is new here and it is getting intriguing here. If you treat it with this oral medicine and you treat it for a certain period of time, how long does it last in terms of the therapy? If you go back to the living condition and you are being reexposed, you are just going to be getting it back again. So you are treating the public health matter of cleaning up the area.

The second question is, is it in use right now? I'm trying to do a tradeoff in my mind of one drug versus another. You study it, it gets used, and now it is actually sold as this is a new use for this drug and expanding the market, versus a lot of drugs we are looking at right now are already in use and we are trying to decrease some morbidity that may be associated with them.

So I have those two questions in terms of how long does the effect last, and then, also, how big of a market is there right now?

DR. MATHIS: Yesterday we were talking about smoking cessation. A drug therapy isn't going to cure the problem of overcrowding. It is not going to cure the problem of poverty in the United States. So the drug therapy has to be used in conjunction with other scabies eradication programs.

That being said, a lot of patients do have reinfestations. The problem is that then those patients are identified as treatment failures and placed on Lindane, where they have seizures.

So you are right, it is a big problem. I don't

know if any drug therapy is going to cure that, although we do put this as part of a drug treatment program. In some of the Lindane labeling, we actually go through details about how to get rid of the scabies in clothing, and head lice, too, since it is indicated for that as well.

The other thing is, you are right, we may be creating a new market for this drug, which then you have to worry about safety, because you are going to increase the use. When we look at the alternatives, Lindane is safe and effective when used as labeled. The question is, are people using it as labeled, because we are still having serious reactions: seizures, death, even when used as labeled.

So while you might increase safety concerns for Ivermectin in itself, it may be relieving us of the safety issues from Lindane or other alternative therapies.

DR. WARD: Yes.

DR. ZITO: How much latitude in writing the label do you have for it appearing as a second-line treatment? What we did with Clozapine was indicate it

for treatment-resistant schizophrenia.

DR. MATHIS: I think that that would have to be a review issue. If we found significant safety problems, we would want to probably label it as a second-line therapy. If, however, we didn't find significant safety issues, I'm not sure why we would want to do that.

DR. WARD: Yes, Wayne.

DR. SNODGRASS: Related to that would be risk of developing resistance for other therapies.

DR. MATHIS: That has always been a big concern of ours. Now, there is documented scabies resistance to both Lindane and Crotamiton, although there is no documented resistance to Permethrin at this time. However, bugs are a lot smarter than we are, and eventually, I'm sure, they will figure that out and develop a resistance.

Head lice, it depends on what part of the country you are in, of course. I mean, head lice are resistant to everything.

DR. WARD: On that note, why don't we go to Malathion for lice, Dr. Snodgrass.

[Laughter.]

**Review of Malathion**

**Dr. Wayne R. Snodgrass**

DR. SNODGRASS: Malathion is an organophosphate insecticide, and it is used in tonnage amounts in the United States in agriculture and other similar uses.

I have a hard time recommending an AK-47 for lice. In the labeling, it is under age 12, I believe. Maybe it is age six.

PARTICIPANT: Greater than six.

DR. SNODGRASS: Six, maybe it is. Manufacturers do not recommend it, and there are concerns about increased skin absorption in young infants.

It is an organophosphate. I guess I'm coming from a different spectrum, but I treat those kind of poisonings. So to create them I think would be a problem. You would have to be in a position to say if you are going to study this drug in young infants that you are going to monitor cholinesterase and look for some adverse effect there.

This then gets back to, well, it is head lice. How do you deal with head lice. When we talk about resistance, how is resistance measured, and what about

mechanical methods. That gets into motivation, and there are all the issues about setting and social setting and all this.

So I don't think this has a good safety profile to recommend it be studied.

DR. WARD: Ms. Woo?

**Secondary Review of Malathion**

**Teri Moser Woo**

MS. WOO: Once again, I saw this as one of my drugs, and I was like, "What is this? Why are we using Malathion again?" I thought that was like an old thing. It went off the market and it came back on.

I was here last week for another pediatric pharm meeting and talked to a pediatrician from Tennessee who said they use it all the time for head lice in Tennessee. So I guess this isn't such a dead issue.

PARTICIPANT: No pun intended.

[Laughter.]

MS. WOO: It is a little scary to me to be using an organophosphate. There is no PK or PD data for children under age five. There are real concerns about toxicity in infants and young children.

There are many studies showing efficacy. It works really well. It is like 100 percent effective against lice. It is really great stuff. It is over-the-counter in the United Kingdom. You can go down to your local drugstore and buy it and use it there without any concerns for safety there.

My big concern is just toxicity in young kids. So if we have all this resistance in lice and people are out there using it, I would give it a three on the scoring sheet, but the problem is, if people are using it, we really do need safety data for the younger kids. People just use it for everybody in their family, even if the label says under age five not to use it.

**FDA Review of Malathion**

**Dr. Lisa L. Mathis**

DR. MATHIS: I would almost say ditto to my Ivermectin comments. Again, when we look at the safety of this drug compared to the safety of Lindane, it is an organophosphate, so we do have to be careful about checking acetylcholinesterase levels in the blood, that and our PK/PD, especially when you are talking about scabies, which is from the neck down, rather than head

lice, which is just on the head. Again, head lice isn't really our big concern. Scabies is.

So the studies would definitely have to demonstrate no systemic toxicity, and I'm sure Dr. Epps can give you a good lecture that the fact that it is topical doesn't mean that it is not absorbed and seen by your body. All these drugs are absorbed, and we do have to worry about systemic toxicity.

**Open Discussion**

DR. LASKY: I also wanted to throw out that we have visited some of these issues because Lindane was on our first list. We have struggled with the issues around Lindane, and one of the issues is, well, if you take this off or you limit its use further, what will you use instead. I think later this afternoon it will be interesting to talk about the issue of groups of drugs -- and these really suggest themselves -- Lindane, Ivermectin, and Malathion, that really would have to be studied together or in context of each other because the use is related.

DR. WARD: Stan?

DR. GROGG: There may be two mechanisms of

action on this medication. One is the pesticide activity, but the second, it is flammable. So if you put it on and you light a cigarette, it may take care of the head lice.

I think they are phase 3 studies, but occlusive dressings that are coming out that should be available soon for head lice that basically suffocate the head lice, like the old mayonnaise that we have used frequently in the pediatric practice.

So I think there are going to be some new things available for head lice avoid the toxicity of medications.

DR. MATHIS: But I do want to emphasize that we are not discussing the indication of head lice. Remember that scabies is under the stratum corneum and you can't suffocate it like you can head lice. It is already approved for use in head lice.

DR. LASKY: But not under age five.

DR. MATHIS: That is correct.

DR. WARD: So I assume that the real issue is five and under, do we feel this needs to be studied in the young child to determine just how much it takes to

cause them to seize.

DR. MATHIS: Well, yes. You would have to have greater than 50 percent of cholinesterase inhibition to start seeing seizures, so that is probably -- uh oh, Dr. Snodgrass is going to get me for that.

DR. SNODGRASS: No, no, no. You're right, if it is used according to the directions. The problem with Lindane is it doesn't get used according to the directions. That is going to happen here as well, no matter what you try to do. That is where the problem comes in. They reuse it, they pour on 10 times as much. They keep using it for several days in a row, never wash it off, and all those issues come up. That is where you begin to get into trouble.

DR. WARD: Dr. Sachs.

DR. SACHS: The other thing is, again, head lice is very common. Up to 30 percent of kids get infected. I can tell you in my practice it was the number one after-hours call. People freak out when they get diagnosed with head lice.

In a nice study of prevalence, they found that there are a lot of prescriptions written for this

product. Malathion and Permethrin were the top products. In some comparative studies, it looks like Malathion may have less resistance than the Permethrins and Lindane, so there may be that potential benefit. The adverse events certainly can't be understated.

DR. WARD: Granted it will probably be misused, as you said, Wayne. So in an epidemiological sense, what is the frequency of significance AEs with Malathion?

DR. MATHIS: There is a pretty low rate of reported AEs, and there is a very low rate in the clinical studies that were performed for the approval as well. I mean, it appears to actually be very safe when used as labeled.

DR. SACHS: I found 12 adverse events in the database, 12 since this was approved, and it looks like the prescriptions written, it said the prevalence was like 12.1 per 1,000 affected kids.

DR. MATHIS: Dr. Sachs, correct me if I'm wrong. All 12 of those weren't in pediatric patients, is that correct?

DR. SACHS: No, I looked just for pedes.

DR. MATHIS: You did, okay.

DR. SACHS: They may be duplicates. I didn't actually analyze them further.

DR. MATHIS: Were they severe? I mean, some people actually report treatment failure as an adverse event.

DR. SACHS: It was mixed.

DR. MATHIS: It was mixed.

DR. SACHS: And a very superficial look at the adverse events.

DR. ZITO: Could we just get a little clarification on that? How many years since marketing experience is represented by that data?

DR. SACHS: Since approval.

DR. MATHIS: That was in the early '80s, so it is over 20 years.

DR. ZITO: And we are aware of the great under-reporting?

DR. MATHIS: Absolutely. In the best of situations, we see about 10 percent. That is the number that is thrown around.

DR. ZITO: In the literature, all I found was allergy and respiratory NI symptoms, in addition to what

was in the label.

DR. SNODGRASS: It seems that head lice and perhaps scabies are prime candidates for new mechanisms of action for new agents that have a better safety profile. That is a longer term goal.

DR. MATHIS: Dr. Snodgrass, if you know of any of those, encourage those sponsors to come in.

DR. SNODGRASS: And all of the economic issues.

DR. LASKY: It is a money-maker, so actually, we hear there are quite a few drugs out there, I mean, over-the-counter, so this should be an incentive.

MS. WOO: I had one mom tell me she spent $150 trying to get rid of the head lice. I'm like, "What did you buy?" She went and bought everything off the shelf. I mean, the one thing about having prescription medicines is we really do control the amount that they get, and it is a much more controlled situation, but the over-the-counter medicines can't hurt them.

DR. LASKY: We had a talk on Lindane and someone came in with a slide showing about 20 feet of the over-the-counter aisle for lice preparations.

DR. MATHIS: And again, alternatives for head

lice treatment are not a problem. We have sponsors coming in regularly with head lice treatments. The problem is scabies. I don't know when the last time was that we had an application submitted for a scabies treatment.

MS. WOO: The information I got was that this was for lice. Are we talking about using Malathion for scabies now?

DR. MATHIS: I think that if it is on the list for head lice, we have to look at it for that. You're right.

DR. WARD: You can write in "for scabies."

[Laughter.]

DR. WARD: It can be advice to the agency.

Yes.

DR. ZITO: This is not the venue, but I hear a call for people to go back to their various associations and to argue for better education around these issues.

DR. WARD: If there is no more discussion, we are going to move to a group of dermatologic drugs, or some related, some topical steroids. We will try to deal with all those together, I believe, before we go for a

break.

We will start with Aclometasone dipropionate cream for dermatitis.

Dr. Epps.

DR. EPPS: I will talk about all the topical steroids together, if that is okay. Fortunately, in dermatology, we have progressed beyond "if it is dry, make it wet; if it is wet, make it dry."

DR. WARD: I have to go back to school, then.

[Laughter.]

**Review of Aclometasone Dipropionate Cream for Dermatitis, Desonide Ointment for Dermatitis, and Hydrocortisone Valerate Ointment and Cream for Dermatitis**

**Dr. Roselyn E. Epps**

[PowerPoint presentation.]

DR. EPPS: Topical corticosteroids have been available since the 1950s, so they have been around for about 50 years. They are widely used in pediatric dermatology, and they are generally safe if used as directed, but we will talk a little bit more about them.

They are frequently used in pediatric dermatology practice for many dermatoses. The most

common examples would be atopic dermatitis, or eczema, contact dermatitis, seborrheic dermatitis, and psoriasis. Atopic dermatitis and psoriasis bear special mention because they have early onset. Atopic dermatitis frequently presents in the newborn period. Some people will say the patient was born with eczema, just popped out with eczema, but they are chronic and they are recurrent.

Atopic dermatitis, the prevalence has been increasing over the last few years or decades. In the 1970s, they said perhaps, maybe, 1 to 3 percent. It has increased over the decades, and it is now estimated perhaps as many as 20 percent of American children are affected.

Now, perhaps the numbers were higher before. Perhaps the reporting is better. Fortunately, in atopic dermatitis, with age the prevalence decreases. They are pretty equal as far as gender is concerned. You will find some differences between different countries or nationalities, but generally, it is quite prevalent in the United States.

Psoriasis is another condition that we do see,

which has more of a bimodal peak as far as prevalence, or onset, I should say, in childhood and in adult populations. Psoriasis prevalence in children is thought to be perhaps 4 to 5 percent. You may hear higher numbers. Contact dermatitis, the prototype is, say, poison ivy, nickel dermatitis, other more limited conditions. Seborrheic dermatitis we often see in the newborn period as cradle cap, but we also see it in other children as well.

The effects of topical corticosteroids are anti-inflammatory, antipyretic, as well as vasoconstriction. The vasoconstriction that can occur is the basis for a lot of the studies of potency which we will discuss.

The mechanism of action is thought to induce lipocortins, which is a group of proteins which inhibit phospholipase A2, and consequently, because of increasing levels of arachidonic acid, it affects inflammatory mediators such as the prostaglandins and leukotrienes. So that is the current thinking as far as the mechanism of action for topical corticosteroids.

Biochemically, they are bound to plasma

proteins, are metabolized primarily in the liver, and are excreted by the liver into the bile, as well as by the kidney.

When using topical corticosteroid, there are several patient factors to consider. One, of course, is patient age. You wouldn't use a super-potent steroid in a young infant or a small child. The body surface areas involved, you must consider that, the body site that is being treated. Different parts of the body or different skin areas have different thicknesses, for example. The thinner areas would include the eyelids, the groin area, face, whereas thicker areas would include the palms and soles as well as other parts of the body.

It is also important to consider the condition that is being treated. Some respond better to more potent or milder corticosteroids. The skin integrity is important, whether or not there are excoriations or open areas that can increase the absorption. Skin type and pigmentation can also be a factor because with people of color or darker pigmentation, sometimes it can result in hypopigmentation as a side effect.

When considering the medication, you consider

the potency; the vehicle -- which means whether it is an ointment or a cream. We will talk more about potency and vehicle -- the application method; the frequency of application, whether it is once a day, twice, three times a day; the amount of product that is being applied; as well as the treatment duration, whether it is days or weeks or months.

Now, when considering the potency, they are classified according to vasoconstriction studies. The original studies were done in the '60s. There have been some later studies along the way as new medications develop and as the process for determining vasoconstriction has been modified.

Class 1 is super-potent. An example of that would be Clobetasol. Class 7 would be an over-the-counter corticosteroid, CortAid or your hydrocortisone. Most of the others also fall in between.

Now, regarding the vehicle, the ointment, cream, lotion, gel, solution, and foams are available for topical corticosteroids. The potency within a particular class can depend on which preparation you use. For example, most people consider ointment to be a little bit

stronger than the cream, which is stronger than the lotion, although that is not always the case.

Various concentrations of an active agent within a similar vehicle doesn't result in a different vasoconstrictor assay. In other words, 0.5 percent and 0.01 percent for the same chemical may be the same strength vasoconstriction in the same vehicle, in the same cream. It is also important to notice that all vehicles are not created equally, and we will talk a little more about that, too.

Now, what are the local side effects we see. In order of frequency, we see itching, irritation, dryness. Folliculitis can occur as a side effect of topical corticosteroids. Hypertrichosis, particularly with the stronger ones or fluorinated ones. Acneiform eruptions, hypopigmentation. We do see perioral dermatitis when it is used on the face.

Allergic contact dermatitis can occur. That does bear special mention. Some people are actually allergic to the active agent, the steroid.

Some people are actually allergic to something in the vehicle. In other words, some of the creams, for

example, have preservatives such as parabens, particularly in over-the-counter medications. Some of them are allergic to tixocortolpivalate, which is in a lot of hydrocortisones. There is a whole family of preservatives and emulsifiers and things that people can develop contact sensitivity to.

Also, if you are allergic to a topical corticosteroid, there are groups A, B, C, and D, according to the contact dermatitis people, where you may cross-react within a particular category. So sometimes the treatment isn't helpful.

There may also be maceration or secondary infection, which would include bacterial and fungal and viral infections. Not only your typical bacteria, but also more unusual ones. The viral would be molluscum and HPV, as well as candida and other fungals. Atrophy and striae are the ones that most people become very concerned about. Obviously, they are much lower as far as incidence is concerned, but atrophy can be reversible. Striae are not.

The systemic side effects are what we become a little bit more concerned about. You can see

hypothalamic pituitary axis depression, adrenal axis suppression, Cushing Syndrome, as well as linear growth retardation.

Last year, the Dermatologic and Ophthalmic Drug Advisory Committee held a whole-day meeting concerning topical corticosteroids and their possible side effects. Some of the results we will be talking about in the next few slides.

So as far as the HPA axis suppression, which I consider to be the most significant, adrenal suppression occurred with systemic absorption of the drug. This is particularly true of more potent varieties as well as people who applied it to large surface areas. The suppression occurred not only with the higher class but also the lower classes, which might be the four or the five, even when used properly sometimes.

I alluded to the surface area, which contributed. Some patients were applying it head to toe. A little is good, a lot is better, so they applied it everywhere. But the axis suppression was usually reversible within 14 days. A lot of these were performed by stimulation tests to assess that.

The HPA axis suppression occurred with routine use at times. Those children are at risk for adrenal crisis. Now, minor HPA axis suppression can occur. We don't really know what the clinical significance of that is, whether they respond under stress or not. It is hard to know. A lot of people don't think about it, so it is probably under-recognized and under-reported. You only see the people who crash, unfortunately.

Now, today we are considering Aclometasone -- there is an extra L according to the insert -- dipropionate, Desonide, as well as Hydrocortisone valerate and the studies that were done.

Now, Aclometasone, there is no specific data as far as pediatric -- oh, I'm sorry, as far as how frequently they used it. They had some Express Scripts data which was relayed to me this year. So it may not be from 2004, but that is when I received it.

Desonide. There are 0.4 prescriptions per 100 children enrolled, whereas for Hydrocortisone of all types -- we will talk about the family of Hydrocortisone topical applications -- there are 1.62 prescriptions. So at least 2 percent of the children enrolled with Express

Scripts received at least two of these drugs, and perhaps more when you include the Aclometasone.

Now, Aclometasone goes by the trade name of Aclovate. There is a generic. It is generally prepared as a cream or an ointment and 0.05 percent strength. It is a synthetic corticosteroid, and it is mild. It is group 6, so it is a little bit, as I tell patients, above the drugstore, which is a seven.

It is approved for patients over one year of age, according to the insert of GlaxoSmithKline. Safety and efficacy in use over three weeks had not been established, which means it hadn't necessarily been tested according to them. It is not recommended over a large body surface area of 20 percent, and it is useful for most dermatoses.

Now, there were several clinical trials that had been indicated. There was an open study of healthy volunteers. Thirty grams of cream were applied to 80 percent of the body surface area twice a day, so that is 60 grams of cream. Then, in addition, they put on a plastic suit to provide occlusion for 12 hours a day, and no HPA axis suppression occurred, so that is pretty

useful data. Although it doesn't translate to pediatrics, certainly that is a significant amount of medication over a period of time.

A second study was a randomized control trial comparing Aclometasone and Hydrocortisone 1 percent ointment in children with eczema, both in the ointment form. It was applied twice a day for three weeks. No telangietasias or atrophy were seen, and they were equally effective.

Most of the clinical trials are done with ointment because then you eliminate those compounding factors of the vehicle. Now, there are some that are coming up with creams, but most of the time ointments were utilized.

In another randomized double blind control trial, there were 33 psoriasis patients, which is a little bit different than the atopic dermatitis, where the Aclometasone and Desonide were applied twice a day for three weeks. Rapid improvement was seen, and there was no statistical difference between the two. So that was useful as well and flows into our discussion of Desonide.

Its trade name is Desowen. Another company, Fougera, has also sold or manufactured Desonide. It comes as a cream, ointment, and a lotion. It is a non-fluorinated corticosteroid, which is very helpful, and it is also of a mild potency.

The safety profile has been looked at. In a particular study that came out this year, the Adverse Event Report Database was surveyed, as well as trials published regarding the cream, ointment, and the lotion. The data was collected from 1992 in all countries where the drug was available.

Now, only 62 adverse event reports were made. They were primarily consumers. I am sure this is more of a tip-of-the-iceberg phenomenon. A lot of times when something doesn't work or there is irritation, they don't use it anymore and they throw it away, and it is not reported. They were local reactions, but none was serious.

As far as HPA axis suppression has been evaluated regarding Desonide, this was specifically for children with atopic dermatitis and was randomized and controlled, comparing Desonide and Hydrocortisone

ointments for four weeks. No HPA suppression occurred for either group.

Next, there was a randomized double blind right/left study, which means one cream was put on the right side and the other is put on the left side on the same patient. They compared Desonide but at different strengths, one with a 0.05 percent and one with a 0.1 percent. There were 40 patients hand eczema, and there was no statistical difference in the vasoconstriction or the clinical responses. So that would go along with different concentrations within the same vehicle.

A multi-center randomized investigator-masked parallels group study was also performed with Desonide compared to Hydrocortisone, 1 percent ointments, twice a day for five weeks, and in a small subgroup up to six months. There were 113 children enrolled, which is a good size study for pediatric evaluation. The Desonide, as one would expect, had greater efficacy, more rapid response, but was equally safe.

Next was a randomized double blind study comparing Desonide cream versus Betamethasone valerate cream, which was a predecessor. It is halogenated, but

it is still of the same class. Patients ranged from one to 80 years. I didn't see specifically how many children were in the pediatric group, but they didn't see side effects of clinical significance. This was an older study, 30 years old.

Now, regarding Hydrocortisone, which many of the drugs were compared to, there are different structural analogs. Some people or clinicians don't always realize that there are different strengths, even though they all say "Hydrocortisone." So sometimes the Hydrocortisone is methylated, halogenated, hydroxylated. Oxidation can occur, which is dehydrogenation -- this is basic chemistry -- esterified, and if there is a glycol group present, acetamide form can be formulated.

Now, how does that affect the strength. Well, Hydrocortisone valerate ointment, which is what we are talking about today, is considered a class 4, whereas the Hydrocortisone valerate cream is class 5. Hydroxycortisone buterate ointment and cream are class 5, whereas the lotion is class 6. So it drops down as far as vasoconstriction studies are concerned. The Hydrocortisone 1 percent, on which most of the trials

were done or compared to, is a class 7. So different potencies within the same family.

Now, some people or some practitioners will prescribe the 0.2 percent, thinking that that is weaker than the Hydrocortisone 1 percent because the percentage is a different number. Patients often make that mistake as well. In fact, the Hydrocortisone valerate is actually mid-potency Hydrocortisone.

So the brand name is Westcort. It is cream and ointment in form. It is not fluorinated and synthetic. As I stated before, the ointment is a class 4 and the cream is a class 5.

Unfortunately, the studies in Hydrocortisone valerate were extremely limited. This one is from 1978, which was a randomized double blind bilateral paired study which compared Betamethasone valerate and Hydrocortisone cream and placebo against Hydrocortisone valerate. Twenty-five of the 68 patients were under 14 years. They all had chronic atopic dermatitis, and a four-week trial was undertaken.

The Hydrocortisone valerate was equal to the Betamethasone valerate but of course superior to

Hydrocortisone and placebo.

In another multi-center randomized evaluated blind and parallel group trial, Hydrocortisone valerate cream was compared to the Mometasone furolate cream, 0.1 percent -- for those of you who are wondering, that is Elocon, which is a group 4 potency -- once a day for three weeks. They had 219 pediatric patients, and the Mometasone was superior to Hydrocortisone valerate cream.

It was also indicated on the paper that it was under a generous grant from Sharing Plow [ph], so you have to take that into consideration for this multi-center group. Consider the source.

So topical corticosteroids are widely used in pediatric dermatology. They are generally safe. There was no documented HP axis suppression for Aclometasone, Desonide, or even Hydrocortisone 2.5 percent, but there were very limited studies regarding Hydrocortisone valerate, particularly in the age group where the onset occurs.

Using the evaluation list, I would give it perhaps a 3.0 to a 3.5. I think where data might be helpful would be in patients under one year old, where we

frequently have the onset. I think although patients are not frequently hospitalized, when they are hospitalized, they are hospitalized because they are superinfected and bacteremic or they have eczema herpaticum, where you have herpes infection on top of the eczema. That is pretty serious. It can be quite a threatening infection.

Although there is not high mortality, the prevalence is huge and increasing. I think there are a lot of studies as far as Aclometasone and Desonide but not as many in Hydrocortisone valerate. That may be useful as far as HPA axis suppression is concerned. I think there is a lot of hesitancy not only in the medical community but also in the population about steroids. Everyone thinks that they are equal and that you are going to grow a beard and run a marathon, when in fact, as I said, they have been around for 50 years.

I think a little bit more data as far as suppression is concerned would be helpful, especially since we are finding that this is a class 4 and some of the suppression occurred in similar populations. Certainly, there are plenty of patients out there to test it for.

I don't know if there are any questions.

DR. WARD: Before we have some secondary presentations, in your clinical practice, is there an age range, for example six months or one month, in whom you would only use, for example, 1 percent Hydrocortisone and you wouldn't use a class 4 level of potency?

DR. EPPS: Well, usually, by the time they have come to me, something has already been put on them and they are beyond the drugstore.

I usually don't jump that high. I mean, there are 20, 30 different topical corticosteroids out there. I might use something mild within the same class. I tend to emphasize more topical care issues, avoidance issues, but there are some people who use it very sparingly and there are some who use it as a moisturizer.

I think if we had a little bit more data, maybe it would be reassuring, or at least we would have a little bit more information that could be helpful. Certainly, I don't jump to potent ones because of the ratio of the body surface area to the weight. You can't safely use a potent steroid in a young baby.

Also, I meant to mention, the diaper area is

particularly problematic because the diaper effectively creates occlusion. When you have the moist environment which is occluded, the absorption is much higher. So sometimes that is a problem as far as diaper dermatitis is concerned. Those patients are particularly much more likely to have absorption and the systemic side effects because of the occlusion of the diaper and the moist, warm environment.

DR. WARD: Dr. Winer, did you want to make some remarks?

**Secondary Review of Aclometasone Dipropionate and Desonide Ointment for Dermatitis**

**Dr. Karen K. Winer**

DR. WINER: Basically, looking at the data that was provided, I came to the conclusion that overall the topical glucocorticoids in the lower dose is probably generally safe in adults. However, it looks like in children we don't have the data to say it is safe in the very young kids.

As an endocrinologist, I'm not only looking at adrenal suppression, I think that there are other issues that have not been addressed in any of the studies that

have been done to date. First of all, it is linear growth, which goes along with adrenal suppression, HPA axis suppression, and also impairment of bone accrual, which no one mentions at all.

I would say, if there is an impairment of growth, there is probably an impairment of bone accrual as well, so I think that those three things, not just the HPA axis, are very, very important in growing children and have not been adequately addressed so far.

It is interesting; I just in general did a search on eczema, and I noticed that there are several reports that kids with eczema or chronic eczema are generally shorter. One report said that 22 percent of children with eczema have a height of less than the third percentile. So one would conclude that these glucocorticoids that are used on a chronic basis are having a systemic effect.

I thought it was interesting that a lot of the data that was provided was on a very small number of kids, so it is really hard to really come to a conclusion.

In the Aclometasone, as Dr. Epps mentioned,

there was one study in 28 kids that said there was basically no effect on the HPA axis. However, you have to look at how these studies are done. Some people look at just the plasma A and plasma cortisol and some, I think, do it correctly, where they are actually looking at the HPA axis by doing a chlorotyrosine stimulation test.

I think there was only one that I could find, or two, actually, that used the chlorotyrosine stimulation test. They both were not in the packet. One was by Tom Moshang in CHOP [ph.]

It is interesting; the largest study, that multi-center study of over 100 kids, Bowman, Gray, and Baylor, they didn't even look at the HPA axis. They didn't measure the kids' heights or weights. They just looked at the lesions. So to say that it is safe and there is no systemic effect, if you are not even measuring these things, it is really hard to really come to any conclusion.

As far as the actual FDA-approved label, I think it is appropriate. It provides the warnings that I think should be there. However, the Aclovate, I didn't

understand why they chose one year as the cut-off. They say in children over one year old. I assume it is because of the kids less than one year are in diapers, but kids greater than one year are also in diapers.

So the studies have not been done, and it is really hard to say that kids greater than one year can use these drugs with caution and kids under one year cannot. So that is, I think, just a very arbitrary cut-off in the label for Aclovate.

Pretty much, the labeling is all the same. I think the data that they are citing is by Monroe and the 1970s studies. It is old data, and one wonders about the validity of that data now that we have better assays available to us and better ways to ascertain adrenal insufficiency.

So I agree. I think I would score it a three. We need more studies in this area. It is a very prevalent disease, and it is not just adrenal suppression which can cause death given certain circumstances. Adrenal suppression is not really reversible quickly. I mean, it is reversible in many of these studies because it is given to these individuals for less than a month.

However, if the child is taking steroids for one, two, three years, they will have adrenal suppression after you stop the drug for as long as one year. So that is a very dangerous situation, especially if the physician doesn't know about it and there is no Hydrocortisone therapy given to that child.

So I think basically more studies should be done in this area.

DR. WARD: Let me push you on that aspect. Should all age ranges of children be studied, or is it particularly under a year of age?

DR. WINER: I think all age ranges, simply because we are not just dealing with adrenal suppression. I think adrenal suppression is very important, but we are talking about linear growth and we are talking about bone accrual. I think that even in the adolescent age or in the school age, those are very important issues. It just has not been measured at all.

DR. WARD: Dr. Epps, I want to ask you, we have been trying to assign a degree of rating that we feel would be appropriate with respect to whether it needs to be studied or not, low being not much need, up to 10,

needing study. Would you commit yourself?

DR. EPPS: Well, I certainly feel that there is a need. I would say perhaps maybe a six or a seven is reasonable. Generally, they are pretty safe. Honestly, I don't see that many side effects with this group, but as she has pointed out, there can be systemic side effects.

These are chronic diseases. I mean, there are people who have atopic dermatitis their entire life. It is not something that is just going to go away. The same is true for psoriasis, and I guess some people believe that they react differently, different conditions respond differently to different medications. So certainly, you could start with atopic dermatitis. There is a huge population.

I guess, certainly in my population in my practice, it is pretty important. I know in the scheme of things this isn't malignancy, but it is important.

DR. MEYTHALER: Which one of the three would you choose?

DR. EPPS: Hydrocortisone valerate. I mean, it is very sparse, and it is old. I mean, the studies are

almost 30 years.

DR. MEYTHALER: Yes, but it is also, you said, the one that is used the most frequently.

DR. EPPS: Correct. So you want to test that. And it is the strongest. The potency is the highest.

DR. NIKHAR: Can I say a few words, please?

DR. WARD: Please.

**FDA Review of Aclometasone Dipropionate, Desonide Ointment for Dermatitis, and Hydrocortisone Valerate Ointment and Cream for Dermatitis**

**Dr. Bindi Nikhar**

DR. NIKHAR: I'm Bindi Nikhar from the Division of Derm and Dental Products at the agency. I heard Dr. Epps' talk, and generally we agree with most of what Dr. Epps had to say, and what Dr. Winer pointed out.

Dr. Winer pointed out about growth studies and so on in children. I think the division has debated about whether growth should be looked at in children, especially when they have been on topical corticosteroids.

Unlike the studies that were done in children involving inhaled steroids and steroids for the nasal

preparations, in children it becomes somewhat difficult because it is atopic dermatitis. Chemical cause can wax and wane, and children who don't improve then go on to stronger steroids. So it is difficult to basically have them on that same agent for a long period of time.

We do realize that growth is a very sensitive indicator. Sometimes growth can be suppressed without actually having HPA axis suppression, but I think that is something that is within the consideration of the division.

I also wanted to point out that Hydrocortisone acetate, the class 7 steroid that is available over the counter, we actually have concerns about that because there are no pediatric HPA axis suppression studies on Hydrocortisone acetate. Actually, what we were going to propose was that this drug should be studied and this drug should be incorporated on the list.

In fact, I was going to talk about that, but this is widely used. It is available over the counter. It was originally marketed as a prescription drug in 1952, and the agency classified it as being generally safe and effective in the OTC monograph in 1983. Right

now, there are three concentrations, the 0.25, the 0.5, and the 1 percent concentration.

It can be used three to four times daily by adults and children over two years of age, and the label just indicates warnings directing consumers to stop use if symptoms get worse or last longer, and that children less than two years of age should not use it.

In 1973, based on the insulin stress test in adult patients, it was deemed that there was an HPA axis suppression, but of course, a cortisone stimulation test was not used, and the division uses that test for assessing HPA axis suppression now.

We have concern there could be prolonged periods of use, including the diaper area and, of course, under occlusion. So we think it would be in the interest of public health to actually study Hydrocortisone acetate 1 percent in pediatric patients. The current safety information is very limited about this drug.

**Open Discussion**

DR. WARD: Why wasn't that on the list? Seriously. I mean, there has been a big process to obtain information to make this as relevant as possible.

DR. NIKHAR: Sure.

DR. WARD: We have three fairly potent products on here, and if the least potent one available over the counter is the one that the division feels we should study --

DR. NIKHAR: Actually, I would like to point out that the sponsors who would like to take their topical corticosteroid products over the counter, they are compared to Hydrocortisone acetate when, actually, we have no suppression studies.

DR. WARD: Gee, I think we can get those studies done.

DR. LASKY: The drugs came to us in a large group, and we winnowed them down. We did consult with the division, and we did have FDA input in this, and we used it in combination. We did not want all 19 drugs on the list, but we looked for high frequency of use. I think we went for the more potent than the less potent.

DR. MATHIS: It was, actually, one of the drugs we did look at, and just because we had to limit the number of drugs that we considered for the final list, it didn't make the cut. However, it is certainly something

that we can consider in light of the discussion today.

DR. WARD: If a study were designed of one of these three, could the Hydrocortisone acetate, as proposed, be the comparator, or would you want a placebo?

DR. MATHIS: Never say never, right? I mean, you could even have more than just two arms if you did need the placebo, and I think that that would be something that we would need to take back.

Also, it would be something that we would need to talk with NIH about because, of course, they are the ones that have to issue the contracts, but we can certainly consider that.

DR. LASKY: My inkling is that, because we are looking for long-term effects and very subtle effects, this would need large numbers and long periods of time. My personal prejudice is it would have to be an observational study or something closer in between, because people are not going to sit within the structure of a randomized clinical trial unless there are many, many options and secondary treatments, which will result in a multiple-sell kind of design anyway.

So my feeling all along is that this is going

to produce information about a number of topicals at once, but it is something we have to deal with.

DR. WARD: Let me ask one other question. What is your feeling about the three? Do you agree with Dr. Epps that the Hydrocortisone valerate would be the most important of those three that are on the list? I understand the acetate, but of the these three?

DR. NIKHAR: Yes, I agree, I think, with the ointment we do need more information out there. I agree with that.

DR. WARD: Our obligation is to provide guidance for practicing pediatricians. They have to go through, frequently, the pediatricians and family practitioners before they go to you.

Bill.

DR. RODRIQUEZ: I just want us to remember that there are drugs where, after exposure for as little as four to eight weeks, you see differences in the growth and you see differences in the weight of the kids that were exposed to those drugs. There were systemics, but some of these things have been absorbed.

So therefore, what I'm trying to say is that

the effect on growth may actually be noticeable for a segment of the population after a relatively short period. Short means if you took it over a lifetime, you are talking about one year, for example, et cetera, if you are actually concentrating on looking at those things with the appropriate monitor and all those things that need to be done that most people don't use in their practice.

DR. WARD: Dr. Mathis, let me ask you about this issue of the Hydrocortisone acetate as comparator or as one needing study, because it is over the counter and quite old. How can we handle that, again to serve pediatrics?

DR. MATHIS: Well, I think there are several different ways that we can handle it. It is, of course, off-patent, so it is difficult for us to ask the sponsor for studies, although we could do that.

The other thing is to consider using it as a comparator arm. I do agree very strongly with Dr. Nikhar that here is the drug that we are holding up as the gold standard for being safe, and yet we have no current data on it. The data that we have, of course, are testings

that we would never use today to assess the safety of the drug, and they are not very relevant as their means of cortisol levels. We know cortisol levels have meaning for an individual patient, but it is difficult to draw conclusions on mean levels across a whole group.

We will take this back and consider it, and there is a potential that you may see this for evaluation next year.

DR. WARD: Dr. Zito, then Dr. Grogg.

DR. ZITO: There have been some really good suggestions raised in the last few minutes, and I just wanted to endorse that all three drugs, obviously, could be studied as different arms in a very large study.

Now, obviously, you can't do that very expensive testing in thousands, but you could do them in subsets. You could do fancy stuff in subsets which would not be as costly. That is one thing.

The second thing is a focus on chronic use. That is, looking at the prior history or the prior use of steroids would help you to define children who are at much greater risk.

Going across all the age groups makes a lot of

sense because then, as you get into those adolescents, you may have kids with eight, 10, 12 years prior experience using steroids.

I was also very interested in the issue around flaring, around the fact that the use sometimes is encouraged by the fact that it appears to some individuals they can't stop using some of these external products, and how you deal with that in protocols.

Then, finally, to think about design issues. I know it is very hard for us to change and to go forward in the way that we think about what is, quote, unquote, "robust" or "highly internally valid" studies, but we are in a different place than we were 40 or 50 years ago in terms of having very large, organized, clinical practice treatment settings. I think of Kaiser as an example. All their docs are well trained to use the computer and to enter information, for example.

So if you were writing a contract that would encourage responses from quasi experimental design issues, it would encourage people to think that way.

DR. GROGG: In this world of bad news, it is some good news. I think we are seeing some steroid-

spearing because of the immunomodulators protopic. Maybe some of the studies might be concerning diaper rashes and the use of short-term steroids followed by Elidel or protopics.

DR. NIKHAR: Well, topical immunosuppressants have their own problems, but we won't go down that road.

DR. LASKY: They aren't approved below two, first of all.

PARTICIPANT: They are on-patent drugs, so we can't talk about them.

DR. NIKHAR: Those drugs, yes, two years and up, and they have their own issues, but we won't go down that road.

DR. MATHIS: I think, to quote Dr. Epps, better the devil you know than the devil you don't. I think she said that years ago during an advisory committee discussing some of these.

You're right, we are seeing some steroid-spearing, but there is a reason why those drugs are labeled as second-line and none of them for patients under the age of two.

DR. LASKY: I think last year at the hearings

people mentioned ad hoc compounding of immunomodulators with the corticosteroids.

DR. WARD: Dr. Sachs, then Dr. Woods.

DR. SACHS: I just wanted to make sure as you thought about this that, and correct me if I'm wrong, either Lisa or Bindi, but two of the drugs, the Desonide, I guess, it says, "Safety and effectiveness are not established in children at all," whereas the Aclovate coverage says under one, as you prioritize the three.

DR. NIKHAR: Right. There is no as such pediatric safety information for Desonide yet.

DR. WARD: Dr. Woods.

DR. WOODS: I'm generally not worried about topical or inhaled steroids being overly immunosuppressive in terms of risk for infection, but I guess in terms of the use in young children, one question that at least might be explored is, if you are absorbing enough to alter your growth, could you be absorbing enough to at least maybe down your response to vaccines.

DR. WARD: Good point. One of our difficulties is, if there were 19 products that came, the sieving of that to get down to sort of a precious few to go on this

list maybe missed some of the focus needed. I think there may be a way to handle that, as you pointed out.

Of those three, I think, again, in a practical sense, we are not going to be able to study under BPCA all three of these products. There simply won't be enough funds to support that. So I think we should make some effort at evaluating what we think is the greatest priority.

DR. NIKHAR: I would also like to point out that the age group for the HPA axis suppression test, we have encouraged going down to as low as three months, and there are different cohorts of children. So children as young as three months are being studied.

DR. WARD: All neonatologists are familiar with how unreliable serum cortisols are in the neonate.

Good. Thank you very much.

Wayne?

DR. SNODGRASS: One small question, Dr. Winer. Is there any data that any steroids have different potencies for bone accrual or linear growth versus, say, vasoconstriction or inflammatory actions?

DR. WINER: Well, we understand what the

different potencies are. Endocrinologists look at glucocorticoids in terms of their action and their ability to suppress, so you have the Hydrocortisone and the Prednisone group, Prednisone being about four times the potency of Hydrocortisone, and intermediate acting would be the Triamcinolone, and then the very long acting, more potent would be the Dexamethasone and the Betamethasone.

We know the longest acting causes adrenal suppression for sure, and Cushing syndrome. There is a lot of data on that. Along with Cushing syndrome comes osteoporosis, poor bone accrual, and lack of growth.

The gray area is the shorter acting, the Hydrocortisone for children or adults who use that on a chronic basis. I think that is really the question that one should ask right now. What happens with a shorter acting, even the over-the-counter Hydrocortisone, really used very liberally, frequently, on a chronic basis. What happens to those people. I think that should be the question.

DR. NIKHAR: Can I also point out that although the potency determines how effective a drug is and side

effects are directly related, it is not always the case, because it depends what is in the vehicle. For example, propylene glycol, which can be an additive in some of these vehicles, that increases the absorption of the active chemical moiety and therefore side effects.

DR. WARD: Let's take a break, and then we will come back.

[Break.]

DR. WARD: There has been a request from the FDA to go ahead and move up a couple of the drugs, Sevelamer and Zonisamide, in anticipation of the arrival of some of the FDA reviewers for some of the others.

**Review 2: On-Patent Drugs**

**Review of Sevelamer**

**Dr. Robert M. Ward**

DR. WARD: Let me talk -- it is actually going to be quite brief -- about Sevelamer. There were only two references included, and one of those was a textbook about renal failure.

Sevelamer is a phosphate binding agent. It is a polyamine, and it is available in 400- and 800-milligram tablets. Its importance is that it does not

contain any aluminum, so that it frees us from the aluminum toxicity that accompanies virtually all of the other phosphate binding agents.

The other aspect of it is that it is a lipid binder and will reduce LDL in cholesterol, sort of as, hopefully, a benefit.

The average dose in adults is 14 grams a day. So if a child is old enough to swallow tablets, they are potentially treatable with this because of the lower dosage forms of 400-milligram tablets. It has been shown to be effective at lowering phosphate to normalize the calcium phosphate product.

What has been interesting is, when you look at the literature, the effects on parathyroid hormone, the secondary hyperparathyroid hormone that accompanies renal failure and phosphate retention, does not seem particularly to be corrected by this, yet it improves the periostitis and the other bone findings.

A written request was made to the company to study this drug in six- to 18-year-olds, and they turned it down. My understanding at this point -- somebody from the FDA can correct me -- is that this is actually the

only phosphate binder free of the accompanying aluminum, I think. Is that true? Okay.

So that is its importance, I think, in pediatrics. These children are not dying from hyperphosphatemia, but they certainly have chronic morbidity and symptoms from it and their growth velocity will be slowed. They simply need treatment, and it will be either with this or with something else.

Dr. Zaoutis?

**Secondary Review of Sevelamer**

**Dr. Theoklis E. Zaoutis**

DR. ZAOUTIS: Not a whole lot more to add. I sort of agreed that in terms of assessing the worksheet or the score for it, it is a problem in these children. It has chronic morbidity and may lead to visits and repeat follow-ups, so in those areas I thought it would be important to give it a priority score. There is no data on any of the other parameters, efficacy, safety, and PK/PD.

I thought it would be important to consider studying this drug further, and I thought the letter by the FDA was appropriate. I gave it a priority score of

eight.

DR. WARD: I gave it a priority score of seven. I really think this is one of those very difficult issues in therapeutics that everybody around the table probably realizes. Widespread but low toxicity or low morbidity disease or an infrequent but high morbidity/mortality disease. How do you make that tradeoff.

I think in pediatric therapeutics we have to make that tradeoff and we do need to serve children's interests the best way we think we can.

Any other comments?

Dr. Grylack was here. I don't know if he wants to, or Dr. Temeck from the FDA?

**FDA Review of Sevelamer**

**Dr. Lisa L. Mathis (for Dr. Laurence Grylack)**

DR. MATHIS: Actually, Dr. Grylack gave me his comments, and we discussed this. We really don't have anything in addition to add.

**Open Discussion**

DR. WARD: Yes, Jeff.

DR. BLUMER: A question. It would seem that

with something like this, and considering that it is an on-patent drug, the formulation isn't going to work. I mean, this is just sort of a point of information. I'm just curious.

DR. MATHIS: For the on-patent drugs, as well as, actually, for the off-patent -- but it is a little bit easier with an on-patent because there is a pharmaceutical company that has that infrastructure -- we can require that they make an age-appropriate formulation. If they are able to demonstrate from a chemistry standpoint that they cannot make an age-appropriate formulation, we can ask them to give us a compounding recipe that we can include in labeling. We have been able to do that in the past.

As far as the off-patents go, we can still require that, and we ask that, but maybe Dr. Mattison can address this a little bit more. It is more difficult as we are asking private investigators to study these drugs to have them also have the chemistry infrastructure to come up with new formulations.

DR. MATTISON: I know that you all are frustrated by the lack of pediatric formulations. There

are several different approaches that we can take. One is through our SBIR activities. We can try to stimulate that.

So we are working to try to develop formulations for off-patent drugs that are still used fairly extensively that make sense in terms of pediatric dosing.

You are looking in the right direction. That guy back there with the red tie is one that has been stimulating our discussion in that direction, Jeff.

DR. ZITO: Let me ask a question around that issue. To what extent do you promulgate information about the need for it to departments that would cut across chemistry, pharmacy, et cetera?

DR. MATTISON: Are you asking me? We have done it to some extent. We need to do it more.

DR. ZITO: The website, for example. It would be so nice to see one-pager that says there is a great need.

DR. WARD: As Dr. Mattison pointed out, this one is of those special situations where this is still on-patent, and with hyperphosphatemia with renal failure

in infancy, they are certainly not going to be swallowing 400-milligram tablets. So we can, I think, express ourselves that a formulation is needed because renal failure will start shortly after birth in some of our kids, unfortunately.

Alan.

DR. STILES: So, what is the question to this group about this drug?

DR. WARD: The question is, is this a priority for study in pediatrics. If it is and a formulation is needed, I would ask you to go ahead and write in to the side "liquid formulation is needed." That request can be made by the agency to the sponsor, even though the sponsor has turned down studying this drug under the request as issued to them.

Rosemary, do you want to comment about this? I think I'm correct, but have I made a mistake?

DR. MATHIS: Our office director, Rosemary Roberts, is here, and so I was just deferring to her to see if she had any additional points to make about formulations or if we have made them all.

DR. ROBERTS: I would just say that we share

with you the frustration over the formulation issue. Ideally, we would like to see commercially available pediatric formulations for all the products that are used in the pediatric population.

That said, it is not a commercially viable option for many companies to take and put in the work. Sometimes these are extremely difficult formulations to make in a liquid preparation. Taste is always a problem. Then, once they do make it, if they put it on the market, then they have to maintain that line and undergo all the CMC that is necessary.

So recognizing that, we have indicated and we have seen, especially in the area of some of the antihypertensives that have had studies since the FEDAMA and the BPCA were passed, pharmacy compounding recipes that we are putting directly into the labeling.

I think prior to FEDAMA and the BPCA, the agency was really negative on the thought of putting anything other than a commercially available formulation in-house supply, but we recognize that as long as these are done appropriately and we get some stability information on how to store it and how long it will be

stable, that this is much better than having nothing for these children.

Unfortunately, we have seen studies done and then, in the end, there is no appropriate formulation available for children. So that is certainly a down side to that.

So anything that you would suggest that could be helpful to encouraging industry to do formulations for children, we certainly would appreciate. I think the suggestion to put up on the website that a formulation for this particular product would really be advantageous for our children would be a good thing to do.

DR. WARD: In another life -- we live many lives -- as Committee on Drugs chair, we tried to use that sort of bully pulpit to pressure some companies into providing formulations that we felt were very important for children. I think we can continue that effort. Maybe it will be extemporaneous, but at least we can encourage them to make the effort.

DR. SNODGRASS: Is this an orphan drug relatable to a small enough population or not? Just for the particular age group?

DR. MATHIS: I actually don't know if this has orphan drug designation, although the fact that it is getting a written request doesn't necessarily preclude that. If we were requiring them to do these studies under PRIA, we would know that it wasn't an orphan.

I don't know what the status of it is, although I don't remember reading that it was orphan. That goes unknown to us sometimes, unless we actively ask.

DR. WARD: I don't know the frequency of chronic renal failure in pediatrics, particularly young infants below the age of two.

DR. CLARK: I'm Mary Beth Clark from GenSci. I want to just make a very brief statement.

No, it is not an orphan indication that we filed for at all. Just to give a very brief update, I think your thoughts on the liquid formulation are very important, and you should make note of that. There are certain things that I can't discuss here in an open forum, but there are things that we are looking at.

We did receive a written request from FDA on a protocol that we sent them. They had wanted an extended safety follow-up that, based on problems we saw in

earlier studies, we didn't think that we could meet the timeline that we were given by FDA. We went ahead with our study as designed, which didn't meet the written request.

We have just completed the study. We are submitting it to FDA. We are in discussion with FDA about future studies as well, just so that you know that.

DR. WARD: Thank you. Appreciate having the sponsor here to hear our comments.

Let's move to Zonisamide for epilepsy. I believe it is Dr. Woods.

**Review of Zonisamide**

**Dr. Charles R. Woods**

[PowerPoint presentation.]

DR. WOODS: This is a drug I have had to learn about, at least in a capacity as a general inpatient attending. At times we admit children for our neurology service with various types of seizures, so this is an antiepilepsy drug.

It is classified as a sulfonamide. It is unrelated to other drugs in the class, and this just gives you the basic structure. It is supplied in capsule

form only.

It has been available in Japan and South Korea since 1989. That is where almost all of our pediatric data comes from. They have a lot of experience with it. It appears well tolerated in reports. It is effective against a broad range of seizures, or a broad spectrum anti-convulsant agent.

There have been 14 studies amongst Japanese children, although basically all of them have been open-label, with only one in which there was a small randomized component.

No RCTs in children in the U.S. or Europe. Again, it has fairly broad potential and may be even most important in some of the much more difficult seizures types we see in children, infantile spasms and linitis gastric syndrome.

The precise mechanism of action is not completely clear. It appears to block both sodium and calcium channels. It may stabilize membranes. It does bind to some GABA benzodiazepine receptor complexes, but it doesn't appear to potentiate GABA synaptic activity. It has some weak dopaminurgic and serotonurgic

neurotransmission effects. It also has a weak carbonic anhydrase enzyme inhibition activity, which may be important in some side effects that I will review in a minute.

There are some animal models suggesting it may have some neural protection against hypoxemia, although it is not completely clear that would translate into infants or children.

Interestingly, it does not inhibit or induce the P450 cytochrome system, which is a nice feature of the drug. It is both acetylated and reduced. I will show you a little more on that in a second. Certainly, liver disease can reduce its clearance.

Drugs that induce liver enzymes can increase its clearance, also, so while it doesn't necessarily impact other drugs, other drugs can impact it.

Half-life is low, like many of the anticonvulsants, 50 to 70 hours. It could be shorter in children, and maybe shorter dose intervals are required, but we really need more information on that topic. The Japanese data suggests younger children may need higher doses, and the dosing, maybe, should be based on surface

area rather than weight.

This may be more in the pharmacogenomic arena, but at least in terms of the acetylation, there are differences in frequencies of poor acetylators in different populations. So it may be that if you acetylate rapidly and you clear it better, you might have less acetylate build-up of toxic levels. So it may be safer in Japanese children and Chinese children than it would be in other groups. This would be something that needs to be studied. Although it is not completely clear if you acetylate poorly, you may still clear it just fine from the reduction aspect, but again, this is something that needs further study and in different populations.

Adult data from the package insert. I think probably most of this is based on the U.S. showing reasonable both reduction in partial seizures and response. Response generally is taken as a 50 percent or more reduction in numbers of seizures in a specific time period in epilepsy studies.

As usual, read the instructions very, very, very carefully.

[Laughter.]

DR. WOODS: Adverse effects. These are the adult data, again. Compared to placebo, some slight increases in a number of issues, anorexia being one that may be of importance and may be relevant to growth or weight gain in children.

Dizziness and ataxia seen somewhat more than in placebo recipients. Also, in adults, a little bit of tendency towards some confusion. Maybe some difficulty concentrating. Who knows if it would work for ADHD in some other way.

Can see depression and occasionally even psychosis, but these seem to be fairly rare events overall. Fatigue being another side effect seen in adults.

A couple of things to note about this, at least in adults. There seems to be some predisposition toward kidney stone formation. Not quite sure if this is a sodium channel, a calcium channel, carbonic anhydrase inhibition issue. It does seem to occur, at least in the things I read on this, in people who might be predisposed to have stones anyway. I'm not sure that this would be as big an issue in children as it would be in adults, but

again, it would be something that would need to be looked at.

Its current indications in the U.S. are for treatment of partial seizures in adults with epilepsy. It probably, again, has a much broader spectrum than that, and probably is being used in children, and is being used in children, off-label in this country, especially for refractory seizures. We really don't have much data, or no data, in Europe and the United States in kids under 16.

My wife found this on a greeting card years ago, and it applies to most of my life, I think.

[Laughter.]

DR. WOODS: Amongst Japanese children, we do have some pharmacokinetic data. This study shows basically you get higher levels in older kids, and then it shows, I guess, on the top quarter that there is really no impact of using Zonisamide on Carbamazepine, but there can be an impact of Carbamazepine on Zonisamide.

You probably can't read this very well, but the next few slides are summaries of the Japanese studies in

children, five studies looking at Zonisamide as monotherapy for partial generalized seizures. Amongst those with partial, they saw some impact in about 78 percent, and in those with generalized, about 71 percent. Fairly large numbers compared to a lot of things we have in kids. These are not randomized. These are open-label data.

If you look at Zonisamide as adjunctive or mixed therapy -- meaning, I guess, mixed where they had some kids open-label, some randomized, but primarily adjunctive therapy here -- a little bit less response, 34 percent, 15, and then, when it was mixed, slightly better numbers. Probably a lot of these kids are having it added as an adjunctive therapy because they have more refractory seizures in the first place, so that may be why their response rates are a bit lower there.

Then, in children with infantile spasms, there were five studies that looked at this. Twenty-two to 36 percent response rates, which is pretty good for that disorder. You will take just about anything. ACTH is the primary therapy there. It has lots of side effects and is difficult to administer, so if this were to be of

benefit in that group of children, it would be a good addition.

One study in the U.S. on this showed a 33 percent impact on infantile spasms. So again, within that range. Again, these are observational studies.

Then, on the kind of wastebasket linitis gastric syndrome, which is also very refractory, response rates in the range of 26 to 50 percent, which if that were to hold up, would be a nice benefit. Even if that is just reduction and not elimination, that would be important for those children and their families.

Progressive Myoclonus epilepsies, which I really don't know much about except apparently they progress and they are severe and they don't respond well to much of anything, there may be some effectiveness of Zonisamide in some of these disorders. Again, this is a heterogeneous group. Some may respond, some may not, but again, anything that helps, even for a year or two, is a useful part of our inventory.

Adverse effects in pediatric studies. Again, not huge numbers in these trials to pick up severe rare events. You can't read this very well, but some of the

ones, 13 to 18 percent, maybe even up to 34 percent in some of the trials, anorexia being in there. Rashes do occur, and maybe salivation issues in a few. Not that different from the adult data.

This was the one sort of randomized trial or part of a trial in Japan that actually systematically collected side effect or adverse event data, showing similar numbers of about 23 percent somnolence, 15 percent or so ataxia, some cognitive impairments in a few. That may be more severe in children who already have underlying cognitive issues. Irritability also seen in there.

Then there is something called oligohidrosis, and this may be due to the carbonic anhydrous inhibition activity that reduces sweating. This is apparently a fairly common side effect, although it is probably not clinically significant most of the time. There are a couple of reports in the literature, I think, in 18-year-olds and maybe adults with heat stroke perhaps attributable to this. It will be something that will need to be looked at.

So in summary, at least in the Japanese

experience, they feel that it is well tolerated under gradual titration to target dose. That is considered to be about 8 milligrams per kilo per day. Adverse effects seem generally mild or in line with a lot of the other anticonvulsants. That is not to say there aren't adverse effects with this.

I guess there would be two ways to look at this, ultimately, as monotherapy or, I guess, new epilepsy issues. Would we look at that first, or with that more as an adjunctive agent for refractory seizures. So certainly, in the latter case, some of these side effects may be more tolerable than they might in the former.

Frequency of adverse events. Interestingly, many of these children were on other medications, so it is lower for Zonisamide alone. When you have one other AED, 37 percent; two or more, up in the 40 to 50 percent range. I don't know that this speaks to drug interaction, but maybe the action of the side effects that were caused by the other agents.

In the studies in Japan, about 12.5 percent discontinued for either adverse event or the combination

of drugs they were on either wasn't working or they were having side effects.

Target serum concentration, at least so far, would seem to be 10 to 40 micrograms per mL, start at 1 to 2 kilo per day and work up over several weeks to that 8 milligram per kilo per day dose.

Since we are having flu problems, I thought you might like that. "The company is giving free flu shots, Wally. The shots will be delivered by wealthy stockholders who will hunt you down and shoot you with flu darts." Wally is initially optimistic, thinking, "Well, at least I won't get the flu."

[Laughter.]

DR. WOODS: We could probably manufacture this kind of flu shot more quickly.

[Laughter.]

DR. WOODS: I hope you feel this way.

"I just had a good meeting." Dogbert says, "Well, maybe it just didn't last long enough to reveal the incompetence of the attendees," which is me in this case.

I think we are having a good meeting so far.

[Laughter.]

DR. WARD: So we will keep on pace.

DR. WOODS: I guess, to answer the questions, we need more information on pharmacokinetics. We need more information on efficacy, more information on safety. This is not necessarily a leading cause of mortality, the seizures, but a fairly leading cause of morbidity in pediatric patients.

There is a fair amount of hospitalization for seizures in general, maybe smaller for the more refractory ones and maybe less than we are used to seeing, but I think I would still give it a one there.

Not necessarily lengthy hospitalizations very often, although that might not be true for infantile spasms early on, depending how we define "lengthy."

Frequency of physician visits. It keeps our pediatric neurologists and neurologists in general very busy, so a lot of pediatric seizures. It does account for a fair proportion of our total pediatric hospitalizations.

DR. WARD: I blinked. The formulation, liquid formulation?

DR. WOODS: We need a liquid formulation, also. It is only in 25-, 50-, and 100-milligram tabs right now. Probably, you could look at issues of metabolism in different racial/ethnic groups. It may not be a big issue but it needs to be explored. There are alternatives, but I would give it a one there still, because for some of the kids with refractory conditions we need more agents in those.

So I come up with a score of 10 in my look at this for epilepsy in general.

DR. WARD: Dr. Zito?

**Secondary Review of Zonisamide**

**Dr. Julie Magno Zito**

DR. ZITO: I will talk while Glen is loading in the numbers so I can show you the utilization data for this drug from a Medicaid population.

I'm not as enthused as Dr. Woods. I know that there is a great need for more information on every new drug, or relatively new drug, but this, for my priority list, would go pretty low.

I do have a little bit of experience learning how to monitor antiepileptic drugs. When I was at the

University of Minnesota, I worked for about a year and a half with Ilan Lepic [ph], who is an expert in the field. I learned a lot about the complexity of managing seizure disorder, including the over-use of meds, which then becomes a new problem in itself.

So the whole field focus on adjunctive treatments becomes a really difficult issue, and this is only approved for adjunctive use. So already your enthusiasm should be a little bit different than if it were, say, for mild therapy.

I want to go back to the point that Ilan is interested in, I guess. They have written a letter to the FDA saying, so I guess there is a six-month marketing exclusivity there, or related to that. Why would they be writing you a letter?

DR. LASKY: Unless you have something else, I think it is the other way around. FDA has written a letter to them, and they turned it down.

DR. ZITO: So their response, I thought, was positive, was it not?

DR. LASKY: Is there a response?

DR. ZITO: The way I read the letter and my

interpretation is that they would be interested in conducting efficacy and safety studies. So that tells me something. There is interest in marketing, and there is a market need there.

The second point relates to efficacy. I think the data are incredibly weak for adjunctive use, 20 percent, 25 percent responders. Even in psych studies we do better than that. So I thought the numbers were not persuasive in regard to its role as adjunctive.

The third point I would like to make, also, then around in vitro efficacy, there also wasn't such good stuff.

The fourth point I would like to make, and it relates, really, to my main issue of why I am not enthused, relates to safety. The Japanese issue is really important because American physicians prescribe drugs much more intensively, at much higher doses almost than the rest of the world. So you need to immediately think that people who don't see a response are going to push the dose.

Already, we have now a good indication of the clinical pharmacology that is very suggestive that

oligohidrosis and fever, while maybe hasn't killed anybody yet, is a potentially serious thing where there isn't good, close clinical monitoring to recognize that that fever is actually related to meds rather than to just cough and cold or flu.

So the carbonic anhydrous inhibition, which we have had those drugs for many, many years. They are not world leaders in the world of epilepsy.

Then, of course, there are the skin rash issues with a number of these drugs that have come out as adjunctive therapy in recent years. We worry a lot about Steven Johnson syndrome and toxic necrosis syndrome. So there is a potential there.

Then, the final point I will make is that the anticonvulsants are now no longer for the treatment of seizures. We have, wow, mood stabilization for aggression conduct disorder in children, but aggression in adults and failure to get mental health drugs to fully control people.

So you should expect that there will be some experimentation for the purpose of mood stabilizer certainly at least in the teenage population, and then

that would mean that you could be looking at kids on regimens that include stimulants and perhaps even an antidepressant and this drug for that purpose. That will have nothing to do with the use in seizures.

So having said all that, now I will show you that nobody is using it in the data set that I had. But then, new drugs don't get used. They get adopted slowly, so it is not surprising.

DR. WARD: If the data actually show essentially no usage, we are probably okay without seeing it.

DR. ZITO: I mean, it is stark, so stark we couldn't provide a prevalence. The numbers were too small. We had, actually, 10 less-than-18-year-olds in the year 2000. Now, I'm sure that through '01, '02, '03, each year we have grown by another 30 kids, something like that.

DR. WARD: Your denominator for that 10 or 30 kids in that database is roughly?

DR. ZITO: That is what I could show you. I haven't memorized it.

DR. WARD: If it is that low, that is okay.

DR. LASKY: It is the entire Maryland Medicaid population, which is one-third of the children pretty much in Maryland.

DR. ZITO: Oh, you wanted to know the total denominator of enrollees?

DR. WARD: Yes.

DR. ZITO: It is 301,000.

DR. WARD: So we are talking 10 or 20 or 30 over 300,000. That is a small number.

DR. ZITO: I was reaching for the number of anticonvulsant users. It is 10 out of 20,000 or something like that.

**FDA Review of Zonisamide**

**Dr. Lisa L. Mathis**

DR. MATHIS: Just from the FDA perspective, one of the reasons why this ended up being referred to the foundation is just people feeling like there is a small population of very desperate patients that need alternative therapy. So I think nothing in addition to what has already been shared by the experts, but just to consider that these are patients that don't always have something else.

**Open Discussion**

DR. MEYTHALER: I just have a couple of questions on that. There are a number of other drugs that have been used in pediatric seizure control off-label. Ten have come out in the last six years, like Topiramate and Lamictal, some of which have first-line indications as well as second-line or adjunctive indications.

I'm surprised that these weren't recommended, unless the companies are proposing them right now, because those tend to be used second-line. I helped write some of the guidelines for seizure prophylaxis in head injuries. So that was one of my issues with it.

The second issue, though, is, I will tell you there is a real secret use of this drug off-label for weight and obesity, both in kids, adults, et cetera. This drug is being used heavily in weight control because it does drop it. You brought that up, but this is under the guidelines that there are a lot of people using it.

One of the docs in my clinic used up our whole supply of this drug that we had as samples, and it was all in weight reduction, not in seizure control, and we

had a lot of seizure patients.

DR. GROGG: For his patients or himself?

[Laughter.]

DR. MEYTHALER: So that is another issue. It is being used off-label. In fact, a lot of people feel Zonisamide may be selling almost 50 percent of the drug now for that. It is not being used as much for anti-seizures, and that is why I think the drug company turned it down.

DR. WARD: Charles.

DR. WOODS: Let me just comment, my enthusiasm for this drug is more that we should study it because I think we do have a need in kids for at least adjunctive measures.

I do share Dr. Zito's concerns about some of the side effects, and certainly, they may be more severe in some populations than others.

DR. MEYTHALER: The side effect profile, though, is very when you compare it to Tegretol, Depakote, or even Dilantin.

DR. WOODS: That is why, also, I am not as worried about that, because these other medications are

toxic and this may not be much more severe. The other thing that gives me a little encouragement, even if it is not highly efficacious, is that it doesn't have much interaction with the other agents. So those are things that, to me, say I would study it, but I don't know that it is going to be useful.

DR. ZITO: I think the safety profile deserves a delay in conclusions. It is a thirteen-fold difference between the occurrence of oligohidrosis and fever in U.S. kids than in Japanese kids, so they didn't have it over there. They didn't experience that problem.

My thought is that unless you do something to really know that you can control this by appropriate dosing, I think it is going to happen again in United States children. In western Europe, the same thing happened.

DR. WARD: We just study it in Minnesota.

DR. SNODGRASS: Just from a general point of view, I think that there is this subgroup of patients. The benefit-risk ratio considerations of a drug like this are in favor of certainly studying it. I mean, yes, you look at the side effect profile, you certainly would, but

there is a group of patients out there that clearly need anything else you can bring to bear on that therapy.

DR. WARD: Dr. Zito, I was impressed with this issue about adjunctive treatment. The reason it is adjunctive is because they fail the first line, so if it does add something to a population that is relatively desperate for seizure control and their function in school or life is compromised, it may be an important adjunct.

Your issues about safety are pivotal. Why would there be a thirteen-fold difference. Is it failure to look at that and recognize it and search for that in the original studies? Quite possibly.

Charles.

DR. WOODS: The other thing is, average ambient temperature in an area may impact that issue.

DR. WARD: Absolutely. I wasn't facetious about studying it in Minnesota.

[Laughter.]

DR. WARD: Dr. Epps.

DR. EPPS: I have a question and a comment. Question: Would this have any effect on those who were

G6PD deficient, and is that something that is done at baseline?

DR. WOODS: That is actually in the package insert already that if used that should be looked at. So I think that would be addressed.

DR. EPPS: Secondly, since we are faced with Generation O for obesity and it is a huge problem, and although I don't advocate drug loss for weight loss in young people, you may want to add that as an indication for study for those who are really a problem.

DR. WARD: Bill.

DR. RODRIQUEZ: I also have a question about the kidney stones. Those were the ones who demonstrated severe enough blockage, et cetera, for pain, I assume. That is the way they were actually following. The question is, I wonder how much of these patients do have this classification in their kidney area.

DR. WOODS: I didn't see any specific information on that aspect, but it would be something that should be looked at.

DR. WARD: Nephrocalcinosis.

DR. LAWLESS: In any of the reports, did any of

these kids go to surgery?

DR. GROGG: I think the kidney stone data really are from adults.

DR. LAWLESS: That is where the confusion is. Anybody that has a tendency to have fevers or not to sweat, you go to the operating room and the first thing they will start talking about is relieving hyperthermia. So especially in a high-risk group like this, we are going to be looking at it anyway. The idea that if all of a sudden you have this group with this high prevalence and you go to surgery, I will guarantee you that most anesthesiologists will probably recommend that that definitely has to be studied, because they will stop the case.

DR. MEYTHALER: Is this oligohidrosis a warning in the label at this point in time for adults, do you know?

DR. MATHIS: Debi Avant says yes.

Is it in labeling?

That actually is a concern with Atropine and Atropine-like drugs, because you have patients on Scopolamine or Glycopyrrolate that go to Disneyland and

they overheat because they can't sweat.

It is not always Disneyland.

PARTICIPANT: Yes, it is.

DR. WARD: It is, okay.

Other discussion?

Has everybody discovered the extra sheets, the yellow ones? These are for rating of these medications.

We will move on backwards to Griseofulvin. Dr. Grogg will present, and Dr. Blumer will discuss.

DR. GROGG: I would suggest to you that having a kidney stone could give you a seizure.

[Laughter.]

DR. GROGG: I would also suggest that you do not get to massage each other again. Not during this lecture at least.

**Review 4: Off-Patent Drugs**

**Review of Griseofulvin for Tinea Capitis**

**Dr. Stanley E. Grogg**

[PowerPoint presentation.]

DR. GROGG: Tinea Capitis. Clinically, symptoms vary. We have a dermatologist here that probably sees some of the resistant forms, but vary from

minimal pruritus with little or no hair loss -- so mine, again, is not from Tinea Capitis -- severe tenderness, oozing, and permanent scarring can occur. I think the permanent scarring is the reason primarily for treatment.

Systemic treatment is required because of the hair shaft and the fungus getting down into the hair itself. Topical antifungal agents cannot penetrate and sufficiently eradicate the infection. They may help with transmission and contagiousness, but they do not help with treatment.

Available brands. Grifulvin is in the micro-size tablet of 250 and 500 milligrams, and there is a 125-milligram suspension. I would suggest to you to put on the bottom of the list there whether you recommend further study or not that it be available in the 250 for 5 cc concentration, because 125 requires a lot of drug intake.

Gris-PEG is also available, which is the ultra micro size, and it comes in 125 and 250. The reason it is a smaller dosage is you do not have to have as much of the ultra.

So in the micro size, the dosage is 10 to 20

milligrams per kilo by mouth. According to the insert, two to four weeks, but that doesn't seem to work in therapy any longer with a maximum of one gram a day. Again, going to McDonalds before you take the medication seems to help. This is not against McDonalds, it is just indicating that a fatty meal helps to increase absorption.

Comments. Because of resistance, many studies recommend 20 to 25 milligrams, which is what we have been using in our continuity clinics for some time, for six to eight weeks of therapy rather than the original recommendation of 10 to 20 for two to four weeks.

Tablets can be crushed, and that is a reasonable mechanism of giving a higher dose in a smaller amount.

Now, the ultra size or the ultra micro size, such as Gris-PEG, the efficacy of GI absorption of the ultra crystalline Griseofulvin is approximately 1.5 times that of the micro size. So you get a little better absorption with a smaller dosage by using the micro size, and this too can be crushed and mixed with food, but it is a little more expensive.

Contraindications and cautions. Hypersensitivity to the drug class components, porphyria, URIA in there. Pregnancy, caution. It is derived from Penicillium mold. However, there has been no evidence of any type of significant reactions if a patient is allergic to Penicillin, but I would hesitate to use it if you had an anaphylactic reaction to Penicillin.

Caution if impaired liver and renal function, which is apparently more of a problem in adults than in kids.

Possible drug interactions. I have just listed a few, but some of your antiepileptic agents. It can have drug interactions, increasing or decreasing dosages. Contraceptives, bad situation for teenage girls. The other thing, you can't drink alcohol. The drug doesn't work as well.

Some of your other antifungal agents will affect the drug concentrations, like Warfarin. Some of your transplant patients may have problems in hypocholesterolemia people.

Some of the other drugs that are used are antipsychotics and even aspirin can have an effect.

Serious reactions are quite rare in kids but include granulocytopenia or hepatotoxicity. That is the recommendation in the brochure to get CBCs and liver functions, but at least in my reading and my experience, rarely do we get CBCs and liver functions in these kids unless they are going to have to be treated for more than two months.

Common is rashes, urticaria, nausea, headache, confusion, vomiting, and all the other things that you see in most of your drug interactions that can happen.

This is a picture of my wife just recently. She had a 103 temperature and a rash, and I knew she had West Nile virus. She was on Lamisil. The Infectious Disease person came out to the house to make a home call because I was in Washington, D.C., at the time, and told me no, if we take her off the Lamisil and put her on a course of Prednisone, she will feel better fast, which she did. So you can get drug reactions.

She told me not to show that picture, by the way.

[Laughter.]

DR. GROGG: Griseofulvin PK/PD information.

Variable absorption. Twenty-seven to 72 percent of the oral dose. Increase, again, with fatty meal, and also 100 percent with the ultra size formulation.

Can be given once a day, but if you are giving something for two months, once a day is bad.

Don't dare tell her I showed that.

Needs increased milligram per kilo because of increasing resistance that is present, and treatment is now recommended, as I said, for six to eight weeks instead of the four weeks.

There are many studies available. Thus, I gave it a high ranking. The more I read, the higher the ranking.

It is fungistatic rather than fungicidal, like Lamisil is fungicidal. It seems to interfere with mitosis, inhibited by disrupting the mitotic spindle structure and arresting cell division at a meta phase stage -- I think you think I know what I just said, don't you? -- and inhibits nucleic acid synthesis and possibly antagonizes chitin synthesis in the fungal cell wall. Now we know what it is.

The two common forms in the United States are

the Trichophyton, which represents the highest amount, and Microsporum. We used to use the Woods lamp for diagnosis. Well, that is only good for the microsporon, and that is less than 20 percent, more like 10 percent of the cases now.

The skin, a PK/PD continuation here. It is excreted mainly in the sweat and, to a lesser extent, the sebum. In serum levels, the big concentration is about four hours, with a half-life of 24 hours. Thus, we can give it once a day.

It is markedly reduced within 48 to 72 hours of actually stopping the drug and metabolized in the liver and excreted in urine and feces. Thus, if a patient forgets to take it because they go with dad over the weekend, it may drop to zero and then be a problem.

Pediatric information and efficacy, abundant reviews in the literature. Used basically in Express Scripts of two and a rank of five safety. Available for United States. It is the only drug indicated for Tinea Capitis for kids two and above, and it has been shown to be very safe. You should consider CBC and liver function studies.

I think the reason it is on the list is because two and below is where we don't have an indication at the present time. Most of the kids are over two years of age that have Tinea Capitis, but I do see them as young as six months.

It is associated with a high frequency of physician visits for children, mostly pre-adolescents. Most common infection in young urban children, crowded situations again, and it is a chronic condition with possible scarring if not treated, thus giving lifelong implications of psychological types of interactions.

The instance does seem to be increasing. Daycare helps with different things.

Increased incidence in African Americans. It tends to be more prevalent in African Americans than in Caucasian populations.

Just to give you an idea of the various costs, you can see the ultra micro size is not utilized in my Medicaid practice because the increased cost is not covered on the formulary, but it is about $85 or $86 per treatment course, versus $49, and the suspension is $43.

Again, because of the large volume required, I

would recommend that it be put on the bottom of the sheet. A 250 for 5 cc suspension would be nice.

Alternative therapies are available. Lamisil, in particular, has a shorter duration of therapy needed. Four weeks with greater than 80 percent efficacy. It is fungicidal in its action rather than -static, and perhaps cross therapy could be utilized, where you give it for a week and stop for two weeks and repeat.

Others that might be available but in the literature didn't appear to work as well as Griseofulvin in the higher concentrations were Sporonox, the Diflucan, and Nizoral.

Griseofulvin and Terbinafine in tablet form are comparable in price and the least expensive. A liquid form of Fluconazole, or Diflucan, is slightly less costly than Griseofulvin if given for only 20 days, so if you were using it short term. Itraconazole is the most expensive of the agents.

So, comments. The availability of an oral suspension and the absence of blood test monitoring support Griseofulvin's use in children, especially if it was available in the 250 for 5 ccs. Presently, it is the

only drug indicated by the FDA for Tinea Capitis, but it is only approved for greater than two years of age.

The comments against its further evaluation would be the increasing duration of therapy and the increased dosage necessary for treatment. With the increased dosage, a big problem. You are talking two tablespoons a day for some of these larger kids who are crushing the tablet up. With the larger dosage and the extended time period, we may need lab monitoring of the CBC and liver function. There is no standardized sensitivity test that I'm aware of that is readily available.

So I think this is somewhat confusing, whether you are a dog or a chicken walking behind the dog, as to what is going on.

[Laughter.]

DR. GROGG: So even though I gave it a high score, everything is high for me. I'm a very optimistic person, if you can't tell. Because of the reasons in the previous slides and the availability of new drugs such as Lamisil, even though my wife had a reaction to it, I would recommend that Griseofulvin receive low priority

for future listings and discussions for the reasons I have mentioned.

That completes mine for the day. Thank you.

DR. WARD: Stan, let me just ask you, are there liquid formulations of Lamisil, if you know?

DR. GROGG: No.

DR. WARD: Any of these other alternative treatments have a liquid formulation?

DR. MATHIS: Fluconazole does, but remember that none of these are approved or tested for safety and efficacy for this indication.

Wait. Dr. Nikhar is going to update us on Diflucan, which is Fluconazole.

She can speak, just to clarify.

DR. NIKHAR: Diflucan was actually studied under a pediatric request at doses of 6 milligram per kilo per day, and Griseofulvin was 11 milligrams per kilo per day for Tinea Capitis, and Diflucan did not win. It wasn't approved against Griseofulvin.

DR. ZITO: And that study was conducted by?

DR. NIKHAR: The sponsor. It was a pediatric request.

DR. ZITO: By the winner?

DR. MATHIS: No, it was done by Pfizer.

DR. NIKHAR: Pfizer, yes.

DR. ZITO: Well, sometimes it is helpful because sometimes there are design modification issues that would lead to a better response.

DR. NIKHAR: What I am trying to say is, Griseofulvin was a very low dose and still Diflucan did not win.

**Secondary Review of Griseofulvin**

**Dr. Jeffrey Blumer**

DR. BLUMER: I guess I came away from this with a different conclusion. I had occasion to review Griseofulvin a couple of years ago, and I'm struck with a number of things. First of all, second to Albuterol, this is the most prescribed drug in our outpatient clinic. It is major in our city university hospital.

I mean, I have to believe that there is an epidemic of Tinea Capitis out there because it is constant. Every time we go to study something in Tinea Capitis, we can fill these study quotas in about a day and a half. So it is a very, very common problem.

When you look at the literature, there are a zillion papers on Griseofulvin out there and treating Tinea Capitis in kids. I mean, what was provided to us just was the tip of the iceberg.

When you track back and see if you can find the basis for the recommended dosing and duration of therapy and whether or not the target populations were ever studied, the answer is, I can't find them. That doesn't say that they don't exist.

So in some respects, I come away with a feeling that part of the changes in practice that have resulted in changes in dose and duration are really reflecting us groping to treat this. I don't know that any of these newer antifungals, even though they are fungicidal as opposed to fungistatic, will necessarily offer any advantages. I think part of the difficulty is, we simply don't know how to use these drugs for this indication.

I think the uptake and the presence of these drugs into the sebum and into the hair follicles is something that hasn't been fully explored. I mean, there are some data on it and it is an interesting pharmacologic model. How that model then translates into

drug efficacy is not at all clear.

So I think that there really is a need to look at this. It is a drug that I think pediatricians or pediatric practitioners are in many respects more comfortable with than some of the newer antifungals, but I think that we really don't know how to dose it, how long we need to treat, and what the proper endpoints are.

Especially since in urban populations we do see this more in African Americans, I don't know that any of these studies, at least in terms of the pharmacology -- certainly, the efficacy studies have been carried out using the target population, because that is sort of who shows up -- I don't know whether the experience in general pediatric practices reflects what happens in dermatologic practices. I would be curious what Dr. Epps has to say.

So I think there is a real need to study this. I would give it a high priority, but I almost think we need to start over.

**FDA Review of Griseofulvin**

**Dr. Roselyn E. Epps**

DR. EPPS: I agree with a lot of the comments

that have been made. I think there are a couple points I would like to make, also.

With the increased immunocompromised population, whether it be HIV or chemotherapy, we are seeing a lot of Tinea Capitis that is not dermatophyte. Griseofulvin and Lamisil are most helpful for dermatophytes. We have a lot of yeast, there are a lot of saprophytes, there are a lot of mixed infections out there. Griseofulvin does not help. That would be one point.

Second of all, a lot of times we don't culture. I mean, I tend to do cultures because I'm a specialist. They are referred, it is not working, or something is not right. So we see plenty of Trichophyton, but Microsporum also it is known that you need to treat longer. The standard treatments are not long enough.

Sometimes we have to resort to other medications, but obviously, you like to have something in your hand saying this is what I'm treating. You see them back frequently. Sometimes you get baseline lab tests. It is nice to have alternatives.

I agree with the previous comments. I think we

need to study all of them. I don't think it is simple. Over time even, the causes of Tinea Capitis have evolved. Now we see a lot of Trichophyton species. Before, we had a lot of immigrants; there were a lot of other species. Now we are having other waves with this mobile population. We are seeing all kinds of bugs for Tinea Capitis. So all of it is not the same.

I would also advocate the liquid form for Lamisil. I understand that there is one circulating that is not available. That would be wonderful. I think the doses that are published where a lot of times you see 10 to 15 per kilo for Griseofulvin, they just aren't high enough. I mean, most people go 20. Some of the pediatricians or some of the dermatologists are going into the 25 range, but you are careful.

I mean, you watch those kids, and you don't use it on all of them, or you might get baseline labs just in case, especially if they are on a lot of meds or there is a potential toxicity. You have to see them back, because sometimes six to eight weeks still isn't long enough. I mean, there are some stubborn bugs out there.

So I think we need to look at all of them. The

Fluconazole, I guess, is the 6 per kilo per day, which is nice. It is a once-a-day thing. It supposedly stays in the skin a little bit longer. It is very helpful. That is also true, I guess, of Lamisil. You can open up the little caplets and sprinkle it on ice cream or whatever the favorite is to get it down.

So there are options out there if you have to use other things, but all Tinea Capitis is not the same, number one. Number two, there are a lot of patients who have other issues, and I think we need to look at all of it.

**Open Discussion**

DR. WARD: Yes, Stan.

DR. GROGG: I would agree with everything that has been said. My suggestion would be that it be studied at the increased dose and the longer duration of therapy for both efficacy and safety and in kids under two years of age, not for the present dose at under two years of age.

DR. NIKHAR: Can I say something?

DR. WARD: Yes, please.

DR. NIKHAR: I heard the previous comments, and

I think pediatricians are very comfortable using Griseofulvin. I do think from the division's point of view, we would like to see further dose ranging studies performed, especially in the younger children.

DR. WARD: So there is agreement about the need to study Griseofulvin. Great.

DR. LAWLESS: Question: How badly did Fluconazole lose?

DR. NIKHAR: It didn't win on any of the criteria against any of the bugs. It was actually used in two different regimens for three weeks and for six weeks.

DR. MATHIS: Dr. Nikhar, was that a non-inferiority study, or was it a superiority?

DR. NIKHAR: Yes, it was a non-inferiority.

DR. MATHIS: So it was a non-inferiority study against the 11 milligrams per kilogram of Griseofulvin.

DR. LAWLESS: So it wasn't a four-game choke.

DR. NIKHAR: I stand corrected. It was a superiority study.

DR. MATHIS: Superiority? Thank you.

DR. WARD: It may have been an 11-inning game,

though.

DR. LAWLESS: A question for you, actually, just in terms of, when we make final recommendations later on, you are talking about some of these studies that look like they can be done relatively inexpensively. Some would take a lot more time and effort. Is there going to be a recommendation after this -- and we can talk about this later on -- two drugs versus here are all the ones we reviewed, the top ones, and if we have money left, we do the rest?

DR. LASKY: You mean sitting around the table with like poker chips and cigars and horse trading? I don't think we are figuring in the cost right now.

DR. WARD: Green eye shades and smoke, yes.

DR. SACHS: The only question I have is, in looking at the literature, I didn't get a huge sense of this huge population under three or under two. I was curious from you guys' perspective.

DR. LASKY: I just also wanted to throw something out. It is off track, but CDC did recommend a look at Fluconazole. Then, in our review, I think we pulled it out, and I can't remember what the reasons

were.

DR. MATHIS: It was still on-patent.

DR. LASKY: Oh, okay.

DR. BLUMER: I would just emphasize that I don't think limiting it to the younger children is important. Just to add some spice to this, we actually had a senior resident for her senior project last year study Griseofulvin, and there were two things that we discussed and were put into the design.

One, I was so impressed with the amount of Griseofulvin prescribed that we underwrote doing cultures, and it turned out that 30 percent of the time that someone was prescribed in our clinic -- now, it may be peculiar to Cleveland -- there was no evidence either based on culture or any other evidence that they had a dermatophyte, interestingly enough. So there may be an element of overuse.

The other thing was that I did convince the general pediatrician and resident who were doing this to use label doses. In fact, in the study protocol, they got a very high cure rate, which didn't fit with anybody's experience. Now, is it because we are setting

them up to use this "forever," I mean, quote, unquote, for two months and they are not taking it at all.

I don't know what the answers are, but I am just struck by the fact that this does not seem to work as well as it should, and I haven't a clue why. So I'm not sure I would limit it to these young kids. I think if there is an opportunity to look at it, we really should look at all of the target patients.

DR. LASKY: Were those data published?

DR. BLUMER: No, they are still in abstract form. I think that they may have been presented at AMP, though.

DR. LASKY: It seems like the data need to be looked at carefully before we would go forward.

DR. WARD: I think he makes some very good points about not all Tinea is dermatophyte, Dr. Epps' point. I would suspect that many times treatment is undertaken without culture confirmation, and so failure would be anticipated.

MS. WOO: The cultures take so long to come back. I mean, I culture all the kids I start, but it takes like two weeks sometimes before you get your

cultures back.

DR. GROGG: I might add to that culture part, our Medicaid system in Oklahoma doesn't pay for the cultures. I'm told they are extremely expensive and take a while. Thus, we are not allowed to order a culture. That is, I think, silly. But you can't order a culture unless they have been on a course of Griseofulvin for two months.

DR. WARD: Back to toxicity, I think.

DR. GROGG: We can do KOH preps.

[Laughter.]

DR. ZITO: I have a question to follow up, Dr. Blumer. Are you alluding to the fact that what we see under research conditions differs from clinical practice experience?

DR. BLUMER: I think that is not new, obviously, because it happens all the time.

DR. ZITO: Because it is a big problem.

DR. BLUMER: Sure, but it is a striking difference because in general practices, those escalated this to two and sometimes even three times what was initially labeled. Why it was initially labeled that

way, as I said, I can't discern. Then, the durations just keep extending, so at least general pediatricians seem to be treating for three times as long.

So the difference that we generally see under study conditions compared to general practice is now being really amplified in this particular instance. While the safety of the drug is documented, at least in the label it is based on much lower doses. I have no idea what happens when you start dose escalating and exposing patients for this period of time. Obviously, there is not epidemic toxicity that is discernible, but who knows.

DR. MATHIS: If I could just add one more point, we have the Diflucan studies that are posted on the Web, I assume, because they were submitted under a written request under the Best Pharmaceuticals for Children Act.

So if the Fluconazole is not any better than Griseofulvin and if we know that Terbinafine has a boxed warning for rare cases of liver failure, maybe it is a good option to study Griseofulvin, which we do have some sense that works, and to get just a better idea of how

that compares from the safety standpoint as well.

DR. WARD: So it sounds like low dose/high dose may be consistent with clinical experience at this point.

Yes.

DR. WIEDERMAN: Along those lines, I think I noticed on one of Stan's slides a half-life of 24 hours, which would indicate we don't need to give it every day. So that would be Monday, Wednesday, Friday.

DR. BLUMER: It sort of depends on what it takes to get it to the target site. The dynamics are complex.

DR. EPPS: Certainly, Itraconazole, some people do pulse dose one week out of a month or something, but it is all anecdotal.

DR. MATHIS: Poor Dr. Epps has had to deal with a lot of my treatment failures when I did practice in D.C., so she knows. She was always able to cure them.

DR. WARD: Shall we move on to Hydroxychloroquine for lupus.

Dr. Meythaler.

DR. MEYTHALER: I'm not the reviewer.

DR. WARD: This has you listed, but if not, I

will be happy to discuss that.

DR. MEYTHALER: Why don't you go first.

**Review of Hydroxychloroquine**

**Dr. Robert M. Ward**

DR. WARD: At this point, hydroxychloroquine is really only labeled for malarial use in the U.S., yet the preponderance of data are for its use in autoimmune disorders and chronic inflammatory processes: lupus, JRA, chronic interstitial pneumonitis that was reported from Canada from Toronto beginning in infancy.

All of these disorders for which this is being used have a small range of dosages. My recollection is they are 4 to 6 milligrams per kilogram per day.

Hydroxychloroquine has a retinal disorder that can lead to blindness. It appears to be dose-related. When the dose is exceeded 10 to 15 milligrams per kilogram per day, the frequency was higher.

A wonderful group from Cleveland acting under Karen Olness' direction has just completed a randomized control trial for reduction of HIV viral counts in Uganda, and I agreed to serve on their Data Safety Monitoring Board. In that, there were two dosages, but

they were 5 milligrams per kilogram per week versus placebo. The code is not broken, but none of the groups has an increased frequency of retinal disorders, which is, I think, a terribly important safety issue.

At this point, I think that the issue has to do with, this is a set of very serious disorders: SLE of different forms of cutaneous lupus, more of a renal, and more of a disseminated lupus; and then JRA, Sjogren's syndrome, all of which have been treated successfully with Hydroxychloroquine before they would move on to 6 MP and some of the more potent immunosuppressives.

I think this actually is a difficult conundrum because I think it is hard to evaluate and it is not a widespread disease, but it is a terribly serious set of diseases in pediatrics.

For that, I thought it actually deserves study.

**Secondary Review of Hydroxychloroquine**

**Dr. Jay M. Meythaler**

DR. MEYTHALER: I'm sorry I wasn't totally prepared, but I do actually have a fair amount of experience in this from my rheumatological days.

Hydroxychloroquine has some serious side

effects, as a lot of people know, for long-term usage. It causes retinal deterioration and other problems. It can cause some platelet and hematological deficits for long-term uses.

Of course, its initial use is in malaria, but it is being used as adjunctive medication in all the rheumatological disorders, so rheumatoid arthritis, SLE, et cetera. It is used as a second-line drug.

The studies in pediatrics, I agree with you, are fairly weak. There is some data out there on the drug if you read the material for short-term use for malaria and things like this, but the long-term pharmacokinetics aren't known for people who would be on it for weeks and months at a time.

We have no idea how it affects a developing retina. There has been no systematic ophthalmological evaluations of these patients over a long period of time.

So there is a fair amount of need, and the drug is used frequently by the juvenile rheumatoid arthritis folks, fairly, fairly frequently.

This drug, actually, when I was reading over the material, would, I think, have a fairly high

priority. I mean, I did score it fairly high when I was reading over the materials. I think it would definitely rate about an eight on the scale, because it is used fairly frequently.

DR. WARD: The rheumatologic disorders are not an area that neonatologists encounter very often, but it appears that there are some very specific antibody monitoring tests that can be carried out to show responsiveness -- I will defer to those in the room who have treated these more than I -- so that the endpoint could be actually fairly distinct.

DR. LAWLESS: Are they using it where there is a rescue therapy second-line, or are they using it as a maintenance therapy second-line?

DR. WARD: It is more of a rescue, but then they do tend to keep you on it for a long time. Yes, but it is more of a rescue, it is true. After steroids and some of the other things have failed, Hydroxychloroquine is one of the drugs they will use. They will use some other drugs, obviously. Methotrexate has been used, and some of the other immunosuppressants have been used as well, but Hydroxychloroquine has been successfully used

in lupus for over 25 years.

Dr. Epps and Dr. Zaoutis.

DR. EPPS: I agree with the comments so far. We also use it in dermatology for other connective tissues disease, like morphia, scleroderma. Even though eventually they burn out, a lot of people feel it does greatly decrease the course.

For those who aren't familiar, it is a kind of hardening of the skin. It can be generalized. It can be asymmetric, and certainly if it is asymmetric like on a leg, there will be a limb length discrepancy and other problems. Sometimes, if it is on the face or the head, you can get seizures or something.

So there are some significant sequelae that can occur. Unfortunately, the numbers aren't huge. So it will be much easier to study lupus patients and perhaps maybe translate that over, but it would be nice to have some study period.

DR. ZAOUTIS: I don't know the answer to this, but specifically thinking about lupus, the age distribution of lupus patients tends to be older. They tend to be the teenagers. It is the adult data that

become more relevant to that population. Is there such a small number of lupus patients that are younger and require specific studies?

DR. WARD: This surprised me. I trained in Baltimore and thought I knew about lupus. As young as eight in some of the series, but there were specific manifestations of lupus. They were focal cutaneous sorts of forms.

**FDA Review of Hydroxychloroquine**

**Dr. Carolyn Yancey**

DR. YANCEY: Carolyn Yancey from the Anti-Inflammatory Division. Just to add to the comments, I agree with all the different comments. Just on the PK side and dosing, the half-life for Hydroxychloroquine is about 40 days. So it is challenging, and there is no anecdote. So I sort of talk about the risks before I speak to the benefits, which I think are significant. So I'm certainly pleased to hear the initial impressions of the information that people have reviewed.

It is used extensively in pediatric rheumatology, specifically for preventing lupus flares and treating and managing the skin manifestations. I

would say it is most successful in those two categories.

Now, how is that done? We don't tend to think of it as rescue. It is more, maybe, a way to balance a child who is on high-dose steroids where you would like to start to taper those steroids and you need something else that you believe is going to prevent this multi-system autoimmune disease from flaring. That is where it is most successful.

In terms of the visual effects, the blindness with this drug can occur. It is extremely rare. What we do in pediatric rheumatology, and I think we have done an exceptionally good job of it with guidelines that were actually collaboratively created from the ophthalmology section as well as the rheumatology section over 12 years ago, we rarely use this drug in children under seven because part of the six-month screening that we require is visual testing, and color vision as well as visual fields. There are some six-year-olds and five-year-olds that can do this, but just as a guide, we rarely use it in kids under seven, but we have definitely used it before.

Whenever I have personally seen some

abnormality in that six-month screen by a pediatric ophthalmologist, we have either stopped the drug or reduced the dose and it has been resolved. Blindness is reported. I haven't seen that in the kids, and I have definitely seen improvement.

Frequent uses, again. For serositis, dermatologic findings, as well as arthritis. It is not usually used by itself. It is usually used in conjunction with something else.

One of the studies that was done in the late '70s was Hydroxychloroquine, Dipenicylinide [ph], and placebo. For some of you who have read the literature, they all looked fairly equal. The Hydroxychloroquine performed as well as placebo, and it was a very, very difficult study to explain the results.

When you looked at secondary endpoints, and it wasn't quite that rigorously designed at that time, it was most successful for decreasing pain, the arthritis, and the skin findings.

The dose is usually once a day. It can be BID, but it is usually once a day. It is usually a dose of 6 milligrams per kilogram per day.

**Open Discussion**

DR. WARD: Would you comment about the use in JRA?

DR. YANCEY: We use it in JRA. We have used it extensively in dermatomyositis, and as Roselyn commented, in other, more rare rheumatic diseases, like scleroderma. It decreased the thickening and the stiffness of the skin, and that is even harder, I think to even describe anecdotally. But with dermatomyositis, lupus, and then JRA for arthritis as long-term medication. In pediatric rheumatology, we have been rigorous about the eye exams.

DR. WARD: The kids in the study -- I was given permission to discuss this -- they started at six months and went to 12 months, and Dr. Blumer will actually be reporting the kinetics, I think. That is my understanding.

Yes, Dr. Zito.

DR. ZITO: Just a quick comment from a rheumatoid arthritis patient. I have been on this drug. I have had the eye exams. After about a year, you get into multi-drug regimens, and it really becomes very unclear when you are adding something new.

So it is curious. My rheumatologist didn't even want me to go on it. I said, "Let's try it. What do we have to lose?" So the adult people, that I'm in touch with anyway, this is like a third- or fourth- or fifth-line.

The other concern I have is whether Medicaid is going to pay for that, since someone brought up the fact that some Medicaid systems now are restricting, because without that eye exam, we really set up for a serious risk.

DR. WARD: Dr. Sachs.

DR. SACHS: I was just curious if there was any data about kidney problems with kids with lupus that get this. Does it help?

DR. YANCEY: I don't have data.

DR. MEYTHALER: I haven't seen anything in the literature, specifically, with lupus. It is a very, very common problem with lupus, whereas in JRA, juvenile rheumatoid arthritis, you don't get the kidney issues.

I do want to state, though, I think it is probably more used in JRA than it is in lupus, and the pediatric population is generally over seven that would

develop it. So you see it more frequently used in JRA.

I don't know if there is any data with regard to kidney function and how it rescues kidney function in lupus in kids. I didn't find any.

DR. WARD: We have several new agents for JRA both in study and recently approved. Are we likely to see a growing use of Hydroxychloroquine, or the same, or decreasing? I will make it multiple choice.

DR. MEYTHALER: I think it is decreasing for the reasons that you said, due to the eye exams. It is a pain in the tail to use it, both in the adult as well as the pediatric population. You have to have the eye exams. You can't use it without getting it every six months. It is in the literature. Everybody knows they could get sued if they don't get the eye exams every six months.

DR. YANCEY: I also just think in terms of the approval process and the progress, the approval of Methotrexate as well as the increased knowledge and the safety monitoring and when to lower the dose, the ease of titration, the different formulations that allow you to use different administrations, has made a difference.

Yes, the eye monitoring is a challenge. I believe the challenge as far as insurance coverage could be overcome without question. There are guidelines from the American Academy of Pediatrics that state very clearly the way in which a person on that medication should be careful.

I agree with your point in terms of adult rheumatologists and the approach. Certainly, Hydroxychloroquine is further down on the list with low-dose Methotrexate and Arava. Thought not approved as an indication, it clearly had an acceptable study.

DR. MEYTHALER: My one question I have is, Methotrexate is well studied in children, obviously, and particularly with cancers and other things. Some of the other drugs, why haven't they been looked at, some of the other immunosuppressants? Why didn't they make the list as well as Hydroxychloroquine? That is the one thing that caught me by surprise in this.

DR. WARD: They may be on-patent.

DR. MEYTHALER: Some are, some aren't.

DR. YANCEY: A fair question. Lupus, of all the pediatric rheumatic diseases, we are particularly

challenged for approved, well-studied drugs for lupus. So it is a challenge.

DR. WOODS: I was going to ask, for lupus specifically, it sounds like you want more information, but it sounds like you have very good guidelines for use of the drug, and certainly in JRA or other rheumatologic conditions have a great comfort with the use of it. So I guess one question is, if you had limited resources to study, is this the one you want to have studied for that particular item?

DR. YANCEY: I would say we would like to look at the efficacy more clearly. I think on the safety monitoring, we have sufficient information to know how to monitor a child who is taking it, but in terms of efficacy, well-studied information, we really don't have it.

DR. MEYTHALER: Would you want to limit this just for lupus or not go to juvenile rheumatoid arthritis? That is the other issue. I mean, that is my question. Why is it limited just to lupus? JRA is an issue, and it is a fairly big issue.

DR. YANCEY: Correct.

DR. MEYTHALER: So you really need efficacy data more than safety data at this point.

DR. WARD: Yes.

DR. WIEDERMAN: So, why is our charge to look at lupus rather than JRA?

DR. MEYTHALER: I didn't understand that.

DR. WIEDERMAN: Aside from lupus, it is mostly adolescents. We all want more information on everything, but that would seem to be low priority. We could extrapolate that adolescent information more easily from adult studies.

DR. WARD: I think it is. I think if we feel the greatest pediatric use and gain is in studying JRA, put it in the margin.

DR. MATHIS: I would ask Dr. Yancey just to comment on that, too, because it may be an additional study that we want to do.

DR. YANCEY: Because of the paucity of approved drugs for adult lupus as well as pediatric, it was the decision of the division to encourage study of Hydroxychloroquine in pediatric lupus.

I would agree with expanding the recommendation

versus contracting it. It is just amazing to realize what is still not approved for even adult lupus, much less pediatric.

Just a comment about pediatric and those that are in big inner city hospitals. There is a huge amount of pediatric lupus in this country. The classic prevalence demographics that you see in adults are different. In children, it tends to be equal between boys and girls. We see four-year-olds with lupus, five-year-olds with lupus, and it is a quite serious disease.

DR. WARD: Other discussion?

DR. LASKY: Well, I just wanted to say, I went back through the history, and the FDA input does say juvenile rheumatoid arthritis, so there must have been some back and forth on this. I think this conversation is reflecting it.

DR. MATHIS: I actually do think that we had been considering all of the options, and then I believe an expert committee wrote in and requested it for lupus.

DR. LASKY: I think so, but I haven't been able to find it. So let's look at it as it is and write in the additional one, and we will resolve it.

DR. WARD: All right. Dr. Berquist will talk about Sulfasalazine for JRA.

**Review of Sulfasalazine**

**Dr. William E. Berquist**

DR. BERQUIST: It comes right on the heels of the last discussion, so I'll be very interested to hear what the rheumatologists say on this. As a gastroenterologist, I'm very familiar with this medication. This is Sulfasalazine, and the topic, really, is its use in rheumatoid arthritis.

What I'm going to do is go through the label, which actually is rather impressive because there is quite a bit of information about it.

[PowerPoint presentation.]

DR. BERQUIST: This drug actually is two molecules. One is the sulfa part and the diazo bond, and then your 5ASA. The way this works is, you ingest the drug, some of the sulfa is released, which causes a lot of the side effects, and when it gets down to the colon, that bond is broken and releases the 5ASA, which has been shown, at least in ulcerative colitis in adults, to be the agent responsible for its efficacy.

Now, as far as pharmacodynamics, the label actually is quite correct in saying we really don't know how this drug works. There have been studies done, but actually, the relative contribution in rheumatoid arthritis in terms of its PD is unknown. It is thought, actually, that this may in part be due to the prostoglandins.

In the pediatric population, in fact, it has been studied down to the age of four years. I think one reason for this request is the use of this has been shown all the way down to two years, but there is very little data in the children under four years of age, so to date comparative PK data have not been conducted to determine whether or not there is a significant pharmacokinetic difference between children with rheumatoid arthritis and adults with rheumatoid arthritis.

There is a genomic factor, an acetylator status, so 60 percent of Caucasians actually are slow acetylators, which results in a longer half-life. So there is a factor which might result in a higher incidence of adverse effects, so that is a factor that needs to be considered.

For indications, it is listed for ulcerative colitis and for prolongation of the remission for ulcerative colitis. It is also used in the treatment of patients with rheumatoid arthritis, and you can see down here it is also indicated for the treatment of pediatric patients with juvenile rheumatoid arthritis who have responded inadequately to salicylates or nonsteroidal anti-inflammatory drugs. So actually, it is on the label for use in rheumatoid arthritis children.

Also, it is even more complete at saying when you use it in rheumatoid arthritis you may have to wait for its effect. They even indicate that, and that concurrent treatment with analgesics and nonsteroidals is recommended. So it recognizes that it may take a while for it to work.

Now, precautions. Those also go into pediatric use as well, and this is probably one of the key slides that indicates why we are looking at this. The safety and effectiveness in pediatric patients below the age of two years with ulcerative colitis has not been established.

Then, in the second paragraph, it goes into the

safety and effectiveness for juvenile rheumatoid arthritis, and it covers the ages of six to 16 years, but not under six years. So again, it raises the issue of, how many children are we talking about under six who this might apply to.

Again, as far as the extrapolation from adults with rheumatoid arthritis to children, it is based on similarities in disease and response between these two patient populations. Published studies support the extrapolation of the safety and effectiveness for Sulfasalazine for juvenile rheumatoid arthritis.

Then they point out some of the problems in juvenile rheumatoid arthritis, including a serum sickness-like reaction. Of course, all of the side effects, which we are well aware of, including fever, nausea, vomiting, headache, rash, abnormal liver test -- it doesn't mention colitis, which actually does occur -- and treatment of systemic course juvenile rheumatoid arthritis with Sulfasalazine. So if you have this sort of systemic reaction, you don't use it, obviously.

So adverse reactions in general. The adverse reactions are similar to those in juvenile rheumatoid

arthritis, or the same as adults, including the serum sickness.

Also, there is one paper which I will show you about some immunoglobulin suppression in a few patients, and it also includes the dosing for children as well. It indicates, again, how you can actually use the medication but to watch for diarrhea and to sometimes reduce the dose because you can start with a lower dose and gradually increase it. It has the doses for juvenile rheumatoid arthritis listed, and the desensitization regimens have been reported to be effective to cut down on some of the side effects.

What we do when we are using this drug is, often, we will start with a low dose and gradually increase it, also watching for any sulfa reactions.

So this label is actually quite good and very complete. I might mention there is only one randomized control trial that is listed, and we will try to go through these really quick.

The use of Sulfasalazine in rheumatoid arthritis began in adults, and then it was extended to children. This study came from Prague in the early '90s.

What they showed was that there was a definite improvement in about 47 percent of their 21 patients, but they also had 19 percent, or four, that had to discontinue. They were comparing it to a hydroquinolone and basically commented right early that there were a lot of side effects.

This actually came from another article in the early '90s. There were about four studies in children. It is a little over 100 patients total. Most of them had a favorable response, anywhere from about 40 percent up to 90 percent. Again, side effects in about one-third of the patients on the average. So about two-thirds respond, about one-third have significant side effects.

This study here showed a 73 percent improvement. Again, these are all open-label studies sort of following, again, as you would know, what the adults did. The conclusion that it was an effective primary or second-line therapy for JRA and should be studied in a multi-institutional placebo control study. This is 1996.

All of these are pretty much similar in showing that there is a high number of side effects with the

drug. This shows they are looking at the response over time, showing with time that there is improvement in all of the parameters.

Now, there was an Australian multi-center study which looked at 105 patients. These were randomized to coated Sulfasalazine or placebo for six months. They had 65 patients, so they had a fair number that dropped out. Again, they looked at a variety of indexes, and they had a lot of side effects as well. There were 14 in the Sulfasalazine and four in the placebo group, and again, had a lot of side effects.

This study was the one on immunoglobulin levels. There were six patients, and these five patients here all had low IGA. These had to be less than two standard deviations, and they all got better once you stopped Sulfasalazine. I haven't seen too much of that in the ulcerative colitis group, so I was struck by that.

This was the randomized double blind placebo controlled multi-center study from the Dutch multi-center group, and basically they treated with 50 milligrams per day of Sulfasalazine and concluded that it was effective and safe, but it was not tolerated very well in one-third

of patients. This was sort of a summary of looking at the various scores.

What was interesting to me when I read this paper is that what they did was they looked at the exit outcome and actually did not find a significant difference. It was pretty close, a P value of 0.06, but they couldn't find the difference between placebo and Sulfasalazine until they redid how they scored it, and then they got a significant score. So I thought that was kind of interesting.

This shows about how close it is.

Anyway, so my comments about this are, when I first read through, I was sort of struck, and as we have talked about it, there are a lot of other drugs available for treatment of juvenile rheumatoid arthritis. I can certainly understand the reason for looking at it. It is just like we do in ulcerative colitis. I mean, this is a horrendous problem to deal with chronic illness and stay away from steroids. So when it works, it is a great drug.

I have sort of a love/hate relationship with Sulfasalazine. We are pretty much forced to use that as

a first-line drug in ulcerative colitis, and I always do it with sort of trepidation because if I don't do it, I can't use the other options. There are a lot of other options for ulcerative colitis, which I'm surprised haven't been really looked at in JRA, as just a comment.

I don't even understand why this drug is even looked at in JRA, except that the adults did it, because if you look at the rationale for it, very little of this drug actually gets absorbed. It is probably about 15 percent.

So, I mean, from a hypothetical standpoint, why does this drug even work? So in other words, it makes sense for ulcerative colitis because it is released in the colon and there it would have a topical action, but why would it work in JRA is beyond me. At least looking at the studies as I reviewed the literature, I think it is pretty bad. I don't think there really is a good study that shows that this is efficacious.

In fact, if I were going to say anything, it might be useful to do an efficacy study. We already know this drug has a lot of problems in terms of its side effects and safety, so if I were going to do anything, I

would say, is it really worth anything in JRA, and why don't you spend your time looking at something else.

Of course, I am very biased. I would rather see it looked at in terms of ulcerative colitis because that is where we are pretty much forced to try to use this drug.

The reason I don't like this drug and I often have a lot of my patients on it is, they get so many side effects, they have problems with colitis that I just cringe to recommend it. I always have to kind of go up, warn people about it, and watch it. So my preference is to try to use it just to see if it will work.

When it works, that is the love. It is a great drug for ulcerative colitis. If you can just have them on that alone and not use any steroids. So we at least have these other agents available.

I would also urge, if you are going to spend money for something as per our discussion, I would think you would want to put it into Methotrexate or perhaps 6MP or something else, but that is my thought about it.

DR. WARD: Dr. Woods?

**Dr. Charles R. Woods**

DR. WOODS: As I was reviewing this, I wasn't quite sure whether I was looking at it for inflammatory bowel disease or JRA. One of my questions was, did we actually even have enough information about it in inflammatory bowel disease. It sounds like we could use additional information there if we were going to study it.

I don't think I have anything else to really add, except I wonder if some of the side effects during acute inflammatory bowel disease exacerbations, are you more likely to absorb it during severe inflammation, or less likely perhaps? Pharmacokinetic evaluations in those situations might be useful in trying to help use the drug better. I don't know. I didn't see anything in the material to review on that.

Just one other minor question I had just in terms of how readily we label anything remotely related to aspirin as needing flu shots. This doesn't have that kind of labeling. Maybe it is not absorbed enough to matter. Maybe we don't need to complicate that further, but I just had that question about the drug as well.

DR. BERQUIST: There is some absorption from the colon. If it gets absorbed at all, it is about 60 percent from the colon. Probably once you get really bad colitis, though, you may not absorb anything. It is just exuding, and so probably very little gets in.

I think the problem has been that we know there are a number of patients -- it is fairly well documented, although it hasn't been well studied -- that you get a colitis with it, which is really a problem. It is sort of a hypersensitivity. We really don't quite understand that. Once we stop that drug and take them off, we are better able to control their colitis.

So there is a need to better understand it.

DR. WARD: Dr. Yancey?

**FDA Review of Sulfasalazine**

**Dr. Carolyn Yancey**

DR. YANCEY: Just a few comments. I think it is has been a very thoughtful review, and I agree with all your comments. There is more information in that label than in many, many others that I'm certain the audience has listened to over the last two days.

How did it get started. It got started from

the initial concept of, is arthritis an infectious process. Would it be beneficial to treat people with arthritis with an anti-infectious agent and an anti-inflammatory agent.

There was actually, also, historical learning from gastroenterology that the arthritis that you can see with inflammatory bowel disease improved in those individuals on Sulfasalazine. So the clinical history is quite fascinating.

In pediatric rheumatology, we use it most often with reactive arthritis, psoriatic arthritis, which is a real entity, and to some extent in JRA. It is definitely not a first-line agent with JRA, but with reactive arthritis, psoriatic. It is questionable with ankylosing spondylitis in terms of that etiology, which can be very difficult to sort out in that middle age group.

The incidence of adverse events is about 30 percent in the studies. It is significant. The skin is quite significant. The hypoalbumin anemia, the decreased IGA deficiency, is what we see in the kids with arthritis. I can't explain it, but that has certainly been my experience.

Other risk factors. There has actually been a sperm count, if you look at adult studies. In studies five years out in children, and there are not many, it hasn't been an issue, but that is an unanswered question. it definitely is an adverse event risk factor that has to be very carefully explained at the beginning.

DR. WARD: That is probably an advantage in teenagers.

**Open Discussion**

DR. MEYTHALER: Isn't there some question about its transitive effects, too, though? I mean, it doesn't seem to be as long-lasting as Hydrochloroquine or some of the other immunosuppressants in rheumatological diseases both in adults and kids, so consequently, Sulfasalazine is not our first choice for a second-line drug in either population anymore for rheumatoid arthritis.

DR. YANCEY: For juvenile rheumatoid arthritis, I would agree it is not first-line. I would say for reactive arthritis or psoriatic, it would be a first line. That is an even smaller population. It is a small population.

DR. WARD: Charles.

DR. WOODS: One other thought, too, is looking at some of the studies, when they used a 30 milligram per kilogram per day dose, there didn't seem to be as much effect noted as maybe at 50 milligrams per kilo per day. I'm not completely sure those are fair comparisons, but that may get to the issue of how poorly absorbed it is. You don't see as much benefit in rheumatologic conditions until you go to a bit higher dose. That would need to be explored if the drug is going to be used.

DR. YANCEY: In terms of prescribing it, the off-label part has been that you have to get to a higher dose. It usually takes about four to eight weeks to do that. To really get an effect clinically you need the higher dose.

DR. WARD: Bill?

DR. RODRIQUEZ: It is fascinating. If you are here with the process long enough, you see cycles. On December 10, 2002, this drug was brought up to the advisory group. It is fascinating. The division that was suggesting that it be studied suggested ulcerative processes, the colitic process. At that time, it was nixed.

It is fascinating that in this meeting we are getting now some of the same feedback that, quote, unquote, we would not have expected in December of that year.

DR. WARD: Brownian movement.

[Laughter.]

DR. WARD: Yes, Dr. Zito.

DR. ZITO: Two very quickly. One is what the protocols are within the specialties, and another is what the utilization is in the field. We ought to really pay a little bit of attention to that, or the likelihood of adoption, and so on.

The second point, quickly, is that with Zonisamide I think I totally forgot to say something about sulfonamides and their restrictive use in certain populations. I think there has been information suggesting restrictive use in blacks, and I didn't know how much that should affect both of these. At least it is a point to consider.

DR. WARD: I think the other point that you made that I think probably would escape many of us is the concern about treating psoriatic arthritis, a disorder

that I would not even be aware of.

Folks, I think we ought to break for lunch. We will come back and do Cyclosporine, and then have some discussion about the process. Tami needs some feedback, and Don as well, about what has worked, what hasn't worked. I think she may even provide some of the scores from yesterday. We will see.

I have 12:30 now. I see the nomination for 1:00. One-fifteen, something like that? As soon as people can have lunch.

[Lunch recess taken at 12:30 p.m.]

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

[Reconvened 1:20 p.m.]

DR. WARD: Not everyone here has scores compared to how we rank things. This, sometimes, disconnect has arisen in discussions about how we will rank drugs for neonates that we have worked on for the last year, and culminated in the meeting in March.

It is difficult to know whether the criteria we are using really select what is more important to study, so we will compare the two ranking systems.

Steve, do you want to talk about Cyclosporine?

**Review of Cyclosporine**

**Dr. Stephen T. Lawless**

DR. LAWLESS: Let's talk about Cyclosporine. Actually, as opposed to a lot of the other drugs, there has been a lot in the literature on Cyclosporine and its use in pediatrics and pediatric transplantation.

In terms of background, Cyclosporine has been purported to be the drug which essentially revolutionized organ transplantation back in the '60s, '70s, and '80s when it was first used.

In terms of the organ transplantation for both

pediatric and adults, instead of having essentially no survival or an occasional survival, we are talking about survivals now in the 80 percent range, 90 percent range, depending on the transplant. The same regimens are being used, whether it is heart, lung, kidney, multi-organ, intestinal, whatever. You name it, they are all there.

As part of the regimens of steroids, OKT3 and thiaminositic seroglobulin, and a newer drug, which is FK-506, or Tacrolimus, which essentially is a competitor to Cyclosporine.

The reviewers have been asked to look at Cyclosporine against the indication of heart transplantation or its use in heart transplantation, but it is hard to sort out that versus other things. There have been some studies there.

In terms of the mechanism of action with Cyclosporine, the real true mechanism is not known. It is excreted in the urine. There are about 15 different metabolites. If you do an assay on it, Cyclosporine does break down, and there is a whole slew of metabolites. Some of them may actually have anti- or may have immunosuppressive properties, but not all the 15 have

been fully studied.

The absorption of Cyclosporine is both in IV form and PO form. The absorption by PO is very erratic. The newer form has a little better absorption but still has been hindered in terms of the pharmacokinetic and pharmacodynamic data. There has to be a lot of care of how it is given and what medium and what not.

In terms of the side effects, there has been a lot written about Cyclosporine, a lot during the studies. Even though the label hints that there have been studies done in pediatrics, there just are not well done pediatric studies. It is not that they have not been done, it is just kind of declarative.

The side effects, however, are pretty significant. One of the reasons why it is written up so much is because of the side effects. They are not hard to find. Anywhere from giving an agent which is very nephrotoxic for kidney transplants. Hypertension is a severe problem. Having thrombocytopenia with a hematolytic anemia reaction and thrombosis is a problem. Some electrolyte abnormalities, seizures, encephalopathy, mostly with higher levels of

Cyclosporine. Rare cares of anaphylaxis.

The two big things are actually herkisisom and gynecomastia, which may not seem like much, but in adolescents, they are probably the two biggest reasons why adolescents stop their medicine. It is hard to get prom dates when you have hair all over your body. That issue is a real issue for a lot of them. They will stop taking it for those reasons.

The other thing, actually, is that in terms of the dosages, even though the pharmacokinetics have been really worked out, a couple of things which are trouble or hard with this are that there are multiple ways of passing Cyclosporine. You can do it by HPLC or radioimmune assay, and depending on the conditions you are using, the levels of the serum or plasma levels have to be interpreted in different ways.

Most immunologists also gear towards levels, aiming for a certain level, rather than saying, we can give this dose and walk away from it. They will measure sometimes twice a day the levels initially of Cyclosporine to balance out to a certain level.

I think the interesting thing, and one of the

reasons for the heart transplantation study in particular -- this is going back a little bit to my days in Pittsburgh -- were that, depending on the transplanted organ, you were aiming for higher levels of Cyclosporine because you would think that if you had a kidney transplant, you could aim for lower levels in the long term, less nephrotoxicity, less side effects. You can go back to dialysis if you have to.

Liver transplantation, a little bit more intermediary. However, for heart transplantation, they were going for higher levels. So at higher levels, you have a higher incidence of having side effects, including nephrotoxicity.

However, the studies on what is the optimum level versus rejection are not as easy to come by, because even though some of the articles submitted said, here is a table which says nephrotoxicity or organ damage from Cyclosporine versus rejection, which is the thing we worry about, trust me, it is not as easy as determining one has vacuoles, one has inflammatory reactions. You can have five pathologists look at the same slides and come up with different answers. It is a very, very

difficult thing.

So there are various different ways of doing it. Some people avoid IVs, some people give the IV. A lot of problems with conversion from IV to PO and balancing things. Sometimes the therapeutic window is narrow and sometimes the therapeutic window doesn't seem to be narrow. So it is not an easy drug to play with, though it is very popular.

Now, adding on top of that, you have FK-506 now, which has become also very, very popular. Essentially, it is the competitor. You don't use Cyclosporine and FK-506 at the same time. It is one or the other.

FK-506, in most of the studies shown, has been used in kids. Some of the articles reference double blind studies done, randomized clinical trials done in pediatrics, though not on the summary sheets.

It seemed to have less side effects than Cyclosporine, but the trouble is that there is also some evidence that FK-506 causes more nephrotoxicity. So there is a little bit of a question mark there.

Now, on top of that is the reason why, also, it

is important to look at this from the short-term, which is preventing acute and hyperacute rejection. There is also the new long-term issue which is coming out, which is that it was initially thought that kids who got the transplant at the same time they got introduced to either Epstein Barr virus or CMV had a lympho-proliferative disorder that would develop, post-transplant lympho-proliferative disorder, which was responsive to taking away your Cyclosporine. You would get better from it, but then you would reject.

So you have this balance, and sometimes it would become malignant. The incidence initially was about 0.4 percent a year when they were sort of discovering this event.

The trouble is, it is every year. It is cumulative. So there is about a 1 percent chance of getting this every year. So now that you are seeing survivals of 10, 15, 20 years, now you are seeing about 20 percent incidences of lympho-proliferative disorders popping up in these kids, and in adults, too. So there is the short-term toxicity and now there is the long-term toxicity coming up, also.

Now, initially, when I reviewed this, when I reviewed this, my recommendation was a high score, thinking they have a lot of data here, a lot of studies done. Yes, we should study this, this is a big population, big push for organ transplantation, especially because it is now being used in things like the nephrotic syndrome, arthritis, a lot of off-label stuff. People are trying to use it, just trying to go for lower levels.

There is a lot of data out there which hasn't been really compiled into almost like a summary statement. This is what we think should be done.

The New England Journal had an article in its infancy on Cyclosporine, which is still probably the best article ever written on Cyclosporine, and it was 20 years ago.

The problem is there that all these new problems are popping up and you have these new drugs to play with. I gave it a high recommendation for study because it is such a difficult drug and people are actually flying by the seat of their pants a lot of times with it. It is a dangerous drug, but it can also be a

very, very powerful drug.

DR. WARD: Would you characterize those limited pediatric studies? Are there RCTs in that, or are there various ages?

DR. LAWLESS: Actually, yes. Actually, I was surprised because I was looking at some of the articles. They were even describing RCT in a heart transplant. So when you are comparing Tacrolimus versus Cyclosporine, which is the only way you really can compare it because it wouldn't be steroids versus non-. I mean, it has to be something to something.

They said in terms of efficacy of immunosuppression and rejection, they are probably equal. The Cyclosporine has more side effects overall than the FK-506 because it still has the same incidence of leukemia and lympho-proliferative as Cyclosporine. So there is a choice now working with that. A study would almost be a hand-in-hand.

There was a mention of some of these studies, but they weren't summarized, necessarily, in the overall picture that I got.

DR. WARD: Bill.

**FDA Review of Cyclosporine**

**Dr. William E. Berquist**

DR. BERQUIST: Thank you.

I am very familiar with this drug because I have had to deal with it since 1984. I think we talked about this last year, too, if I'm not mistaken.

There actually is a lot of work on pharmacokinetics. Pharmacodynamics, there is also a lot of work. We do understand the calcium inhibitors work in a particular area in terms of the immunology to decrease IL2, and so there is a calcium binding protein for Tacrolimus, or FK-506, there is also a separate binding protein.

What we really don't know is we don't know what really induces tolerance and how to sort of monitor it from an end target. So we end up measuring drug levels of Cyclosporine as well as Tacrolimus to sort of guide us as to how to use it.

I think most people in transplant are very familiar with the toxicities, and most organ transplant groups have moved away from Cyclosporine. If you look at the data split in these studies in Pediatric Liver

Transplant, which I am a member of, we looked at the trend in liver transplantation, and you see a shift from all the centers using Cyclosporine over to Tacrolimus.

The reason for it is really the side effects of toxicity as well as the efficacy of the drug. So the reason that Tacrolimus got approved for use in children in liver transplant is they did a large study comparing it against Cyclosporine.

So the fact is, we have a lot of data already for Cyclosporine in kids in terms of why we are using it. In talking to the cardiologists, which I recently did. I talked to those at UCLA, where they are not using Cyclosporine anymore for their heart transplant patients. They indicated to me that most of the cardiac transplant groups are still using Cyclosporine.

So I think the reason this was chosen, if I'm not mistaken, is that you have a few groups that haven't moved over in part to using Tacrolimus, and so that may be one impetus for it.

The other issue is, Cyclosporine, as you know, is now off-patent. So there are some questions which would put it under the purview of this prioritization

process. Most of the issues that I think have been talked about, including PTLD, are big issues. Actually, with the monitoring that is done now and with the antivirals that we use, we had an incidence where we were in around 15 percent, especially in intestinal transplant.

In cardiac transplant, where you run very high levels, again that is kind of a learning you do in transplantation. You take the risk of these complications and you learn how to do it. I find our cardiologists a lot of times seeing their patients with really bad CMV, occasionally PTLD. I think if you do the right protocols, there is a good body of knowledge of how to manage that.

So we have cut down on the degree of PTLD, especially in liver, and it may be more difficult, say, in heart transplants. It is more of a problem, actually, with the Prograf, which I think has a greater risk of causing PTLD, but it was first reported with Cyclosporine.

It is sort of like, well, what is really the question. The question is Cyclosporine for heart

transplant. You don't need that. We know it is used for that. They already have it.

So I think the question has more to do with understanding some of the safety issues long term, not efficacy. We know how effective the drug is, so I think that if we were going to study anything -- and this would not just be for heart transplant, it would be for anybody using Cyclosporine on a very, very long-term basis -- what kind of studies would you do. As you know, that is kind of a tough area.

We also know Cyclosporine has an effect on mitochondrial function, so it turns out it may have a role in learning problems and there may be some other areas that we are not looking at long, long term. Remember, these kids are stuck on this drug basically their whole life and they have to keep a certain level. They are running into these side effects.

So I can understand why we might want to look at some of the long-term toxicities, but I think you have to start narrowing down the focus of what the question is. Are you going to look at learning problems, are you going to look at kidney problems, are you going to look

at PTLD, and are you going to have enough patients to be able to do that.

I think, in a way, the attention is moving away from Cyclosporine and moving towards Tacrolimus, but that is, I believe, still on-patent.

**Open Discussion**

DR. WARD: Let me ask the superficial question. What is the age range for labeling at this point?

DR. LAWLESS: For cardio transplants, it is infancy up, actually, newborns or first month.

DR. WARD: I wasn't sure whether we had taken that step to get a label down to neonates.

Bill, it sounded like your major question would be one of long-term outcomes and toxicities that may not be identified yet.

It sounds like both of you have said that the link between efficacy or effectiveness and concentration may be not as tight as we would like.

DR. BERQUIST: Again, I sort of reviewed this last year. We really looked at the PK data, and that has really been well done in kids. I think there are some excellent reviews on that, and a good knowledge of some

of the moderate, even somewhat long-term safety issues, is how better to kind of deal with that.

DR. LAWLESS: The PK is good. I agree 1,000 percent.

PARTICIPANT: That is a lot.

[Laughter.]

DR. LAWLESS: I was going to say 1,000 percent, but.

[Laughter.]

DR. LAWLESS: The only clincher is that you still end up with the management of the transplant surgeons. At 4:30 in the afternoon the Cyclosporine levels or the FK-506 levels are back, do we leave them alone; add 10 percent, 5 percent. So it is a lot of the seat-of-your-pants type of a thing. So it is more like clinical pharmacodynamics you are trying to link to. If the kid's fever is up or has a fever, let's adjust and play with it.

So the pharmacokinetics are good because you can get it to the level you want, but it is the management of, now what do I do if the clinical situation changes.

DR. BERQUIST: To me, that is like Transplant 101. I mean, you have to do that stuff. If you don't, your program isn't going to do well. So to me, that is kind of a basic thing.

The thing that is strange in the label -- I just wanted to comment on that -- is the label actually says not to use a second immunosuppressant agent with Cyclosporine. I don't understand that. I know where that may have come from before, but one way we are using this is to actually lower the dose of Cyclosporine and use a second agent. That actually allows us to run fairly low levels, decreasing the renal toxicity, because you can use Rapimmune or you can use MMF.

That is a little bit of a problem that I have with the label.

DR. WARD: We will turn it to Dr. McCune. You can answer that.

DR. McCUNE: No, I can't answer that. I totally agree with that. I think a lot of the literature has advanced since the time of the label in terms of combination therapies in order to do exactly what you are saying, which is to decrease the steroid load and to

reduce the risk of renal disease.

I also wanted to clarify a point about labeling. Although we are using it in transplant patients that are in the neonatal period, the label actually says that there are no adequate and well controlled studies conducted in children, but patients as young as six months of age have received the drug with no unusual adverse effects. So in theory, it is really only down to six months in the label.

I just wanted to add a couple of points. In addition to the Tacrolimus, we are now getting a number of other agents as well: Sarolimus and Everolimus, I guess it is. There are three current trials that are ongoing in pediatric patients with renal transplant with those agents.

I think that this drug wound up on the list this time for a couple of reasons, although heart transplantation was the indication that you all looked at it for. I also believe the reason why it is in with those other two drugs that you just discussed before lunch was that the Anti-Inflammatory Division had also wanted it discussed from a rheumatologic perspective and

for its potential rheumatological use. I think Dr. Yancey can probably speak a little bit more to that.

DR. WARD: Does it correct obesity?

[Laughter.]

DR. MATHIS: Lice. If it deals with lice.

PARTICIPANT: It takes away the side effects of Clonidine.

[Laughter.]

DR. YANCEY: There are very, very, very few pediatric rheumatology trials with Cyclosporine. The only ones I have been able to find have been open-label and anecdotal. It has been successful. It is usually used with very sick children who are recalcitrant, resistant to everything else.

In the Anti-Inflammatory Group, we are proposing that this be studied in children with pediatric lupus. Again, there are very, very few drugs approved with a specific indication for lupus in adults or children, but I would urge consideration of this for pedes lupus.

DR. MEYTHALER: There is a fair amount of work going on in the adult side that hasn't come down to the

kids, but it is being used hugely now in neuroimmunology. It is being used in CIDP, other inflammatory neuropathy issues. I just came out of Neurotrauma and Neuroscience, and they are looking at it in Neurotrauma in general. It may be protective against neuroimmunological effects in acute head injury, spinal cord injury, et cetera. There were at least six posters and about two presentations last Thursday and Friday on this drug, so its use is going to expand very rapidly.

DR. BERQUIST: That is a very interesting use of it. As I mentioned, it affects mitochondrial function, so it actually --

DR. MEYTHALER: Caspase pathways. It affects the caspace pathways, yes.

DR. BERQUIST: So there are these other actions which we are beginning to become aware of, but they may have other importance in terms of learning and other kinds of function.

I'm just surprised, if you are going to pick a drug for immunosuppression, I mean, we have moved away from Cyclosporine and moved towards Prograf.

That is my thought about it. I guess it is

reasonable to study Cyclosporine.

DR. LASKY: I just wanted to throw out that the American Heart Association asked us to take a look at Cyclosporine for heart transplant patients but didn't provide any other information. They listed about 10 drugs and conditions.

The other comment that I had is that in taking a quick look at the literature before we sent it out, it looked like many of the RCTs were for kidney transplant patients but not much for heart transplant patients.

This seems like a good situation where we would want to do a meta-analysis of the kidney transplant literature and then take a look and see what can be extrapolated to the heart transplant situation and what can't be.

DR. LAWLESS: I think there were a few. At least one I know of. I saw one reference in one of the articles on heart transplant in particular with kids.

DR. McCUNE: Yes. We looked at both, and there really wasn't a substantial difference between the two, and the recommendation being, if you are a transplant center that prefers Cyclosporine and you are used to it

and you know how to monitor it, don't change horses in midstream. If you are not, you can develop your program with Tacrolimus.

DR. BERQUIST: Again, this is the phenomenon we see in kidney and we see it in liver. In intestinal transplant, they tried to use Cyclosporine, and that is where, I guess, it becomes very obvious. Cyclosporine was really tried at the very beginning and was very unsuccessful. So all of intestinal transplantation now is done with Tacrolimus for that very reason. So it is just not as effective an immunosuppressant agent.

DR. LASKY: The point I wanted to throw out is that perhaps we need an intermediate step of this more systematic review of the literature before deciding to undertake what would be an extremely challenging and expensive clinical trial.

We don't have this option on the paper, so I'm throwing it out for the column, but it just seems like we need to look at the literature in a very careful way.

DR. WARD: It sounds like both of you have indicated it is fairly extensive, especially in renal transplants.

Dr. Epps and then Dr. Zito.

DR. EPPS: Just to piggyback on some earlier comments, we use Cyclosporine anecdotally in dermatology, also, for erythrodermic psoriasis, things where topical things aren't options, or severe recalcitrant atopic dermatitis.

Anecdotally, I don't know how it would fit into your study issues, but it seems at times that the generic is not the same as the trade. I would presume those studies were done at some point, but in talking to some colleagues, when the pharmacy switched them over, you have an erythrodermic hospitalized kid because the levels are zero. Whether it is an absorption issue; I don't know what the issue is, but in different fields, people have mentioned the same incident.

DR. BERQUIST: It is really an absorption issue. Again, in transplantation, we have already learned that. I guess a lot of people are not aware of it, but we really have to monitor those levels, and that is a given responsibility. When you are using this drug, you need to know that and you need to know how to use the drug.

DR. EPPS: I'm saying it is a pharmacy issue as well.

DR. BERQUIST: Right. We are aware of it. It might be a thing you could study, brand versus generic.

DR. EPPS: That was my point.

DR. WARD: Have you had the same experience Dr. Epps describes from a proprietary to a generic?

DR. BERQUIST: Oh, yes. The San Francisco Chronicle had a wonderful article about that.

DR. WARD: I'm sure it is in the bibliography.

[Laughter.]

DR. WARD: Yes, Dr. Zito.

DR. ZITO: I was just sitting here wondering about registries or about organizations in which all the transplant people talk to each other, because a quick and dirty survey would shed a lot of light on who is using what and what the need is.

DR. LAWLESS: It is not like a CCSU or a POG [ph], where here are the protocols you really know and you are really tracking this thing diligently. It is more of a registry with a lot of political overtones to it.

But if it had more of a structure like a CCSU or a POG or something along those lines, or the Cambridge Study Group, then you would be able to do this very, very nicely.

DR. WARD: Frankly, a survey about dosage ranges and concentration ranges used and outcomes could be beneficial.

DR. BERQUIST: Just so you know, I mean, there are some organizations that can help facilitate various studies. I don't know what they have in heart, but there is Naportex [ph] for kidney and split for liver.

So what we are doing in transplantation is sort of getting together, just like oncology or other areas, so we can look at various protocols to sort of make that easier to kind of do multi-center trials.

So we have a database. This actually is NIH-funded right now. It is the SPLIT database. So we have 39 centers which are contributing.

I think that transplant is trying to develop an infrastructure, so it may be the kind of thing you could come back and say, well, we would like you to do such and such, as well as have a dialog.

DR. ZAOUTIS: There is a pediatric database as well.

DR. WARD: For hearts. I know there is a JRA multi-center trial group.

Is there anything related specifically to lupus that brings people together?

DR. YANCEY: Lupus is covered in two collaborative groups, the Pediatric Rheumatology Collaborative Study Group, which has been in existence longer, but the second group, CARA, Childhood Arthritis Rheumatic -- I forget the acronym, but there are two groups, and yes, lupus is definitely covered.

DR. WARD: I think usage as well as a little bit more detailed information about the relationship between outcomes and concentrations and your style of management gives us at least a range to shoot for as well.

DR. BERQUIST: Again, it comes from what is the PD. I mean, we know the PK. The question is, what is the PD. What you end up doing in transplant is cause and effect. If they are not rejecting and you can use a lower dose, then you have less side effects.

That took a long time. It was this curve that you had when you first got that drug that came out. People had all kinds of disasters. You learned from it, and gradually you achieved what tended to be a standard trough level.

That is really the criticism, that as you get farther out, can you lower that trough level and cut down on the long-term side effects. That may be the area to focus on.

DR. MATHIS: Do we also need to focus in on where the drug is used with another immunosuppressant, like Tacrolimus. Do we need to look at it in conjunction with another drug?

DR. BERQUIST: Probably not with another calcium inhibitor, but that would be another thing I think would be very good, is to cut down on the nephrotoxicity by using it with either Rapimmune or Sarolimus and Mycophenolate mofetil or CellCept. So I think you could use those.

DR. WARD: Do you see any problems with biliary problems in your patients? You are in the liver transplant group.

DR. BERQUIST: Biliary?

DR. WARD: Yes, with Cyclosporine.

DR. BERQUIST: Not really, because most of ours are biliary atresia. They don't have a biliary tract.

DR. WARD: Okay.

[Laughter.]

DR. WARD: I was curious.

DR. BERQUIST: But actually, you don't. There is an issue about bile flow and absorption.

DR. WARD: Yes, biliary stasis.

DR. BERQUIST: So that is a big factor in terms of absorption, yes.

DR. WARD: Go ahead.

DR. HERNANDEZ: My name is Arturo Hernandez from the Immunologic Drug Products, FDA. I have just a couple comments.

I mean, registry data show definitely that the transplant community, which is the one that we have more experience with Cyclosporine, is moving from Cyclosporine to FK, the alternative calcium inhibitor.

For me, it looks like in all the kind of transplants, which reflects also what is happening in

pediatric patients, more than 60 percent of the programs are using FK, with the exception of heart transplant, which approximately 60 percent are using Cyclosporine. The rest are using FK.

So for me, we just have two alternatives for calcium inhibitors. There is FK or Cyclosporine. Cyclosporine has been on the market since the early '80s, '72, '74. We know a lot about Cyclosporine, so for me, it makes sense.

The trends in the scientific registry point to that approximately I would say in five or 10 years we will see the usage of Cyclosporine, at least in transplantation, is going to be a minimum. As you said, for example, the units are using FK in all transplants, I mean, at least in the areas of major transplant centers such as Washington Hospital Center in Fairfax and Georgetown University. They are using predominantly FK.

So for me, it makes sense if we are going to spend any resources to try to learn a little bit more about how to use the drug in kidneys. We have two alternatives, either FK or Cyclosporine. It would make even more sense to use those resources in trying to learn

a little bit more about FK.

DR. WARD: Other discussions?

[No response.]

DR. WARD: I would ask you to score these sheets that were sent out, Task 1 and 2 as well as the three Sheets 4, 5, and 6 from today. We will pick those up if you lay them out.

Tami, do you want to go ahead and discuss the good, the bad, and what we need to do differently.

**Summary of Day 1**

**Dr. Tamar Lasky**

DR. LASKY: Well, yesterday I said I wasn't going to thank anybody until after I saw what kind of job everybody did, so now I can say thank you all so much. You did a fantastic job.

Thanks, first of all, to the members of the Expert Panel. You just did a great job in your areas. You did a great job of being able to think about questions that were outside your areas. You have been very supportive as we go through our developmental stages.

I think our first two years we were in our

infancy, and this year we are in our toddlerhood, so if you are patient, we will grow up and mature and we will have a great process and great impact on pediatric health over time.

Thanks to Bob Ward for serving as chair. You did a great job. You kept us on task and on schedule. We want to renew our contract with you for the same high rate of pay.

[Laughter.]

DR. LASKY: Maybe we should give him a raise.

DR. WARD: Right. Make it double.

DR. LASKY: We can't afford a raise, but we can give him a lot of job security.

[Laughter.]

DR. LASKY: Thanks to the FDA and NICHD members of the working group who met over the different months and helped hash this out. They are all seated at the table.

I wanted to thank my boss, Don Mattison, who is the branch chief and the leader of all these activities, especially for his perfect mixture of sound advice and support and a little bit of neglect in there. That just

works out perfectly.

The contracting people did a great job. They are not here to hear our thanks, but we are glad that we had support there.

Thanks to everybody who attended and participated, and who care about this process.

Before we get to the discussion of next year's process, or maybe by way of bringing us to that discussion, last night I couldn't resist. I was taught in graduate school never to take peek-looks at the data, to bring it all back, clean it, review it, and do all this stuff, but I didn't follow the teachings that were given to me. I did take a look at the data, and I really wanted to share them this morning.

I have a preliminary tabulation of the drugs we reviewed yesterday. We will see what people think of them. I'm not sure what I think of the whole thing.

[PowerPoint presentation.]

DR. LASKY: This is how it worked out. I scored it this way. I tallied up the marks that were given for study for the drug in 2005 in one column. Then, in a second column, I tallied the recommendations

for study of that drug a year later.

So in my quick and dirty look with no statistics, it looked like either way we look at it, just looking at the first column or the second column or the two combined, we get the same drugs being at the top of the list.

I have the on-patent drugs in a separate category, but in the off-patent drugs, there was a lot of unanimity. Hydrochlorothiazide for hypertension, and you can read this.

If we go down the list to Flecainide, you have plurality, or a majority of the experts recommending it for study. Then, below that, we have a little weaker recommendations and support.

As I said to Bob earlier, I'm going to compare this to how the scores worked out on the sheets and see if there is any logic here or if we could just next year save money and just do like some Monte Carlo imputation and just generate like a random set of numbers.

[Laughter.]

DR. WARD: The wrong Monty. It was Python.

DR. LASKY: Monty Python, yes. That would be

good.

[Laughter.]

DR. LASKY: These are very small numbers, but people clearly think the on-patent drugs are important to study. It is something we are going to have to bring back to our congressional liaison and all of our policymakers.

People want us to study the on-patent drugs, in addition to studying the off-patent drugs, but there was very strong support for the study of Morphine for analgesia and for Bupriopion for depression, a little weaker for the smoking cessation.

So those were the peak results for yesterday, and of course, I don't have today's. I will probably run home and do that right away, but we can use that when we are discussing.

**Plans for the Coming Year**

**Dr. Tamar Lasky**

DR. LASKY: This will just take a couple of minutes. I will talk a little bit about what plans are in the works, and then we will just have an open discussion. I think I will ask Bob to moderate the

discussion.

[PowerPoint presentation.]

DR. LASKY: This is a diagram of what the process was this year and the input we put into it this year and what we are planning for the coming year. It just seems to have turned out that we have divided the year into these quarters: February to April, which is a kind of outreach period of time where we are sending out the mailings, soliciting comments. This is when we receive the suggestions for the drugs and indications.

Once we got that material in hand, it does take a certain amount of time to sift through it and sort it through and incorporate it into whatever we are using, a spreadsheet or now we have a database set up to keep track of this and review the comments, rank it, and have a preliminary list.

So for people who are interested in having input in the process, and if you know other people, this is the time to really get the information to us. Anytime it is welcome, but February to April is especially effective.

This year, we published the preliminary list in

the August Federal Register, and from that time forward, we planned for this meeting. That is not a good time for input because we are trying to process the material.

This year will be our first time with this process. We will take the information from today, we will summarize it, we will look at it, we will discuss it, and we will see how it looks and what we are able to do. We will consider what things are feasible, what things are expensive, how it cuts across different disease groups.

I have gone over the middle column of the material we brought in. Actually, the two last boxes are really going to bring this input into next year's process, because we haven't gotten the results yet. We are going to have information on hospitalizations. We are going to have the Maryland Medicaid Outpatient Frequency of Use, and we are going to have some inpatient data from Dupont. That will go into next year's process, which will repeat.

We may do the outreach exactly the same; we might change it. That is one of the things we need to discuss, what changes would we make this year.

We are going to have many more literature reviews, more substantive literature reviews, and we have already set aside 12 drugs that had an abundant literature that did not reach the process this year because we felt it was necessary to have literature reviews. They should come to the process next year because we will have invested so much in studying them at least from a literature point of view.

There will be more data coming in from RTI on the frequencies of condition and from Westat on the frequencies of outpatient use. It might, again, in that last quarter, really feed into the following year process.

So we are really putting an emphasis on increasing our knowledge base, continuing to increase our knowledge base, but this time we are also going to try to look for areas in the literature that we can feed into the labeling process and save time and money for these other areas in which we can't rely on the literature.

These are some of the activities underway. We are finishing a purchase order with the University of Maryland, this interagency agreement with the Agency for

Health Research and Quality, a purchase order with Dupont. We are going to have a colloquium on November 9th and start to talk about inpatient use, because that was missing this year. It is much more difficult to obtain.

We are just beginning a contract with RTI looking at the frequency of conditions. The project director is in the audience, and she has been taking notes of all the conditions we are interested in, all the lice, all the skin conditions, and everything else we have talked about.

Westat is going to go beyond the Express Scripts data to give us more information about outpatient use, and then we have two contracts with two organizations, CCS Associates and Metaworks, both of whom are here today. We will try to meet with them and talk with them.

These will do professional, scientific-level, publishable literature assessments, systematic literature reviews, and meta-analyses wherever possible.

So I'm going to list a bunch of questions, and then I'm going to sit down. People are free to bring up

additional questions or to, even better, try to answer these questions, because I think we know many of the weaknesses but we don't have the answers. So help us by showing us our weaknesses, but also help us by coming up with some solutions.

There are many criteria to be considered, and we are all aware we need to think about severity, we need to think about racial/ethnic disparities and differences, therapeutic index, availability of alternative therapies, and here I am talking about operationalizing these criteria in a way that can be measured so that people don't just weigh it in an intuitive sense but we can rank things and quantify things.

I think with severity we are going to use some of these measures: mortality, hospitalization, physician visits, chronic conditions, and limitations on growth, independence, and development. Those will be some of our measures of severity.

We are doing this analysis with AHRQ, and I just wanted to put before you the top 10 diagnoses associated with hospitalizations in this era, the 17-year-old age group. This is from 2000. We have an

extensive analysis here that will be coming out. We have broken this down by age groups and by race and sex, as well as payer status.

It is clear, for example, we have these three respiratory conditions: pneumonia, asthma, bronchitis. We have epilepsy as a discharge diagnosis across all age groups, and we have affective disorders up there. So these are some very critical issues in pediatrics, and they help us know what diseases we need to have an impact on in addition to the others. When you break this down by age group, of course, there are different diagnoses.

BPCA does address racial/ethnic differences, and as I understood it, originally this was interpreted as genetic variation in response to drugs. We know that there is variation in the occurrence of indications or conditions as well as variations in our ability or success in diagnosing conditions, and additionally variations in treatments of conditions, which translates into frequencies with which drugs are given to different racial/ethnic groups.

I think as a byproduct of the work we are already doing, without additional cost we are going to be

producing some very interesting data in this area.

This follows exactly what Dr. Zito presented about drug use, but these are hospitalizations for affective disorders by race/ethnicity per 100,000. You see the number is much higher in whites, lower in blacks, lower in Hispanics, lower in Asians.

We don't know if this is because of a difference in the underlying incidence of disease or differences in diagnosis, or I don't know if this is a success in treatment or a failure in treatment, to tell you the truth. So there is a lot we don't know.

The same here for the patterns for pneumonia, bronchitis, asthma, these three top respiratory diagnoses. Patterns are very different. We know about the increase in asthma in blacks, but it looks like Hispanics have a different pattern, with the highest levels of pneumonia and bronchitis being in the Hispanic population. Lower levels, it seems, of everything in the Asian population. So there is much to be looked at here.

This is going to be one of my pet projects because I fell across this, and as an epidemiologist, I thought this was very interesting. Why would one

racial/ethnic group be more likely to be hospitalized for burns. Actually, there are a whole bunch of good reasons related to cost of housing, the age of the mother, whether the mother is a smoker, and urban/rural living. It actually fits together so that we see that black children are at higher risk of being in the hospital because of burns and thus in a group that would be treated with all the different treatments related to burns.

Shifting now, one issue we have with BPCA is to coordinate the process that takes place here with the Oncology Subcommittee. We know we have to do it. We haven't figured out how to do it, so it is on our to do list for this coming year.

We want to continue expanding our contact with different medical specialties. I think this year we brought in Dermatology, and I hope we stay in touch with Dermatology. I don't know how many other groups we need to bring in. We may need a dentist, and there are other groups that we might want to think about.

I guess I'm taking advantage of having the microphone. This is one of my little issues.

It seems when we study these off-patent drugs that because they are older drugs, some of our concerns are more on the safety side than the efficacy side. What this is doing to us is driving up our sample size requirements by an order of 10 at least, which translates into cost and decreases the number of drugs that we can study.

As an epidemiologist, I really think the appropriate way to study safety endpoints is through observational studies rather than through randomized clinical trials. I think it is at least an alternative we have to review and consider. It is very compelling because the safety issues are so dominant in so many of our discussions.

It is also interesting, and I think we were talking earlier, some of us, about the difference between thinking about a disease and following from disease to drugs rather than following each drug individually. The dermatologics is a good example. They are used interchangeably and in combination with each other. It makes sense to me.

I can see the kind of massive study that would

just cover all the dermatologic drugs at once, but we could also have a similar kind of study that looks at the whole scabies/lice question and all the treatments at once and sort of gets the whole issue taken care of. We do have to break them down because of the written requests, but it would be nice to be able to coordinate these issues to some degree.

Then, opening it up for other issues and comments. I'm going to go sit down and now I'm turning it over to all of you.

**Comments and Discussion of the Process**

**Dr. Robert M. Ward, Moderator**

DR. WARD: Let me ask people to start with the comment on information provided to you and requested from you. Are there some specific, concrete areas where we could have improved that?

DR. BERQUIST: I thought that it is helpful for us to know more specifically why we were reviewing a particular drug. What I found was helpful was this book here, where you have the requests. I know that might introduce some bias in and of itself, but I still think it helps us to sort of focus. I would encourage more

specificity about why you are choosing a particular drug.

DR. WARD: Bill?

DR. RODRIQUEZ: I have a bias, and you are going to hate me for it, but I think each one of you should give us some information, because you all had your own personal experience on the subject. Believe it or not, everything that you went through is valuable to us, so don't minimize it. So share with us your thoughts: what would be the ideal; what would be the dream process for you in terms of information. We want to hear from everybody.

DR. WARD: The thing that struck me as I was going down this list and looking at the final ballot as it comes out is that there are specific age ranges that frequently impact our decision-making. Those could have been listed. We could have known that.

For the FDA people who are, maybe, out there also, I would ask that the FDA folks be here for both days, the whole group. There is a lot to be added. You have a vast experience in pediatrics and therapeutics to share with us as well, and I think it helps the process.

Steve.

DR. LAWLESS: Yes, two things. One is just a general comment and the other is thinking out of the box.

The general comment actually is, it would have helped a little bit when doing the evaluation to have almost like a tradeoff analysis. Everybody can be very passionate about their different specialties, and so whoever can mix with the rheumatologists or neurologists or dermatologists or intensivists and how convincing their argument is.

So a tradeoff so people put it in that perspective would be kind of a nice way in terms of their evaluation.

Thinking out of the box actually is, a lot of us have actually gone to an electronic medical record. So the backbone of a lot of this that is going on can be written as specifications in any electronic medical record.

So if you are putting in things like what is the indication, why are you using this drug, and linking it and having the programmers actually behind the scenes link it to some of the other side effects and that kind of stuff. There are a lot of us doing national efforts

on this kind of stuff, but thinking out of the box, a lot of what you are doing in terms of the meta-analysis could be done with a query of a database, and that could save a lot more time and effort, rather than having to back and reinvent the wheel.

DR. WARD: Can you convince your medical staff to do that?

DR. LAWLESS: Yes, actually, we are.

DR. WARD: Okay. I have heard of others that are doing that, and if you can, you are absolutely right. We actually have a database that has every dose administered in our children's hospital per year. You just have to go query the right population.

DR. LAWLESS: Absolutely. The thinking-out-of-the-box part of it in terms of putting people to do that would make it so much easier. Then you will see where the off-label things are coming from and you will see the side effects. It really is at the fingertips.

DR. WARD: Yes.

DR. ZITO: Just a few comments.

DR. WARD: Go ahead.

DR. ZITO: Steve, I'm not really clear. I

think it is not as simple as you are presenting, or at least I'm not sure where you are going with that. What goes on in Hospital A could be very much a regional issue.

So I don't know whether you were suggesting that frequency of information would be provided to that?

DR. LAWLESS: No. Actually, the key word, which you hear more about in electronic medical records, which is actually the thing that is making them difficult, is the word "integration" of them. If you have your pharmacy system that integrates with your order entry system which integrates with your laboratory system, they all get linked nicely.

What drives up the expense for most people is creating those interlinkings, because you have the best system here, the best system there, but with a little bit of writing of specs and the interfaces, you actually can have labs interfere with the order entry which interfaces with some of the other electronics.

When you do all that together, then you are almost having a system of pharmacokinetics and pharmacodynamics being set up.

DR. ZITO: So if I hear it, then you are pushing an agenda in which we could evolve really good community-based treatment information through this contract process. Is that what you are saying?

DR. LAWLESS: Yes.

DR. ZITO: Great.

DR. LAWLESS: Actually, the different parts of the FDA and the CDC are actually working with the HL7 groups to do something along these very similar lines to create those languages.

If you do it with a mind set of saying, how are we going to do it for this, with the forethought of doing it because pediatrics is very specific, you can actually start getting these things: how the CDC is changing, if you change this drug versus something. You have the numbers, which you don't have normally. So you are dealing with millions of records at a time rather than a couple of hundred.

DR. WARD: And they have diagnosis-related prescribing.

DR. ZITO: I have a couple of quick comments in relation to Dr. Lasky's comments about the dimensions

that you are interested in us for reacting to and the difficulties we all experienced together in trying to fill out the rating form. So probably, the rating form is something that you are going to be looking at.

I wondered as I went through it, I guess the problem is that it is really organized a lot about what the FDA needs in order to add to the labeling. Maybe that is not the problem, that is the mission. I shouldn't be saying it in a negative way.

But for some of us, as Dr. Lawless just expressed, traditionally there have been dimensions that have been radically missing from the information that is given to the clinician. We have tried to fix that in sort of small fix-it, band-aid ways.

For example, you might see an epidemiologic statement that says, well, the occurrence of neuroleptic malignant syndrome in this drug is one in 65 billion. So that invites the clinician to turn around and say, it is not me, it is not important.

So there have to be fixes that go beyond that. So in our ratings, maybe we could come up with a way of assessing the impact on quality or the need for better

quality assurance on this drug, or if we add this information to the label, what is the public health impact, maybe something like that.

The second point is, best practices which go on very well in the academic centers and never get promulgated to very many of the people that are out there that are too busy or not being paid to perform best practices as opposed to usual practice, which I think needs to be a driver here. In other words, if it is being widely used, we need to make some assurances that the labeling additions would either lead to abandoning it or the other way.

The third point is comparative trials. It seemed like we could fix a lot of the problems in the drugs on the list by setting them up as comparative trials, which is much more important in the public sector because traditional trials against placebo response are necessary but not sufficient to make a decision for us to use the drug and to use it in a cost-effective way.

The final point is long-term use. I would beg that the trials that do get conducted not stop at four weeks. For any drug that needs to be chronically used,

at least some one-year outcomes should be urged.

DR. WARD: Alan.

DR. STILES: This is sort of a mom and apple pie comment. Excuse me for making it.

First, I have to react to the best practices in academic centers. You are absolutely wrong about that. Each academic center is each academic center, and each practitioner, unfortunately, by and large functions as an individual without knowing what their benchmarking is and without actually doing best practices. Although to ask them, they will tell you they are doing best practice. So that, I think, is a really big issue, and something we have to address.

I would suggest we add somewhere on the evaluation sheet something to measure the view of the reviewers as to clinical relevance of the drug that we are deciding to look at. It even started coming out in the discussion one way or the other, but often being able to get that particular point across may make a difference in how it ends up on the priority list.

DR. MEYTHALER: I would also like to favor adding in what he is saying on the relevance. Having

almost a tiered number, like a five or six, a set number of this is an orphan drug, and then population numbers, and literally a check-off of the number of incidents and then prevalence and then mortality issues, those three categories. Maybe you have a five-level tier issue with population.

You need to put your money where you are going to have the biggest effect.

DR. MATHIS: Just to piggyback on this, the BPCA was indeed passed to fill gaps in labeling for drug products. That is why we look at the gaps in the current labeling, because that is what our congressional mandate is.

When we are trying to decide for on-patent drugs, which is under the BPCA process, one of the things that we try to do to assess whether or not we should issue a written request is to determine the public health benefit. We go through this process every time we are writing a written request. One of the ways that we determine that is the number of patients affected.

Previously, under FEDAMA, we looked at 50,000 as the number of patients that we thought was

significant. Although that is not written under BPCA, it is still kind of the number that we use, but then we balance that against, is this going to be a significant improvement in treatment for even a small number of patients.

So either a significant number of patients or a significant impact even on a few patients would make a public health benefit.

We also balance that against current alternatives. If we have newer, safer drugs that are much better than the older drugs, we are not going to issue a written request for the older drug because it is yesterday's story. It is not what we want to use in practice any longer.

Then, the third point about what we get into the labeling as far as education goes, I do think that we need to be very careful with that, because as you know, the FDA does not regulate the practice of medicine, and we don't want to start doing that. We want to give physicians a little bit of freedom to use their judgment when they are treating patients. However, we could all join together in a broader effort to educate physicians

about drug use.

DR. WARD: I think some of the more recent labels listing frequencies of various adverse effects and real incidence, number affected divided by number prescribed, are so useful. I really found the dermatologic products a fascinating discussion because they are widely used in children by lots of different prescribers. The more definite information that we can provide them about effectiveness and toxicity, the better kids will be treated.

Yes, Bernie.

DR. WIEDERMAN: Just a couple things. One, to re-echo in terms of the scoring system, when I look back, and I think I remarked yesterday, my point totals almost were the reverse of what I felt was important. I think it had to do with the fact that, are there alternative therapies available; or where does this drug fit in the vast scheme of things. It got lost because everything is assigned an equal value on that score sheet. So to sort of lend support to the combination of your scale of things.

The other thing is what to do with those

comments and input. I think it would be helpful to the reviewers to get that information along with everything else that is said, but to have some kind of vetting process so that if someone wants to study Cefuroxime in under three-month-old sickle cell disease patients and somebody says, "Wait, I'm not sure I understand that," and they are literally calling the person and asking, "What did you mean by this?"

I still worry that we are missing something that was important and we just didn't get it. So it is tough.

Then, just one comment for Tami. I noticed on your Top 10 Diagnosis List acute bronchitis, which I think most of us would say there is reasonable discussion that it is a diagnosis that doesn't exist in pediatrics. I don't know what that is representing, but it is not acute bronchitis hospitalization. There is coding for bronchiolitis, so maybe that is it, but before you get sold on that, make sure what it really is.

DR. LASKY: I see a whole Ph.D. dissertation for someone who wants to look at the patterns of assigning the different respiratory diagnoses and which

ones appear with which other ones in what order. It is really a complex issue, and it is definitely inadequate in many ways, but this is a database that is a probability-based sample of the United States and so has the advantage of being standardized, if not adequate from the other points of view.

DR. ZITO: A question on that. Are they ICD 9s, then?

DR. WARD: But in each hospital, a coder in medical records frequently is the one assigning that code looking at the chart.

DR. RODRIQUEZ: Could I say something? One thing that we have dealt with before with this is specifically finding out what is actually included under bronchitis. That information should be available because it should give us the bronchiolitis, it would give you acute viral respiratory infection, low respiratory infection, and they are all lumped together.

But I agree that bronchitis is not a pediatric diagnosis.

DR. LASKY: Just returning to this, what we are going to do is use the database as it is and basically

produce a listing. People need to comment on it and go to AHRQ and ask them about any of the data definitions, because they are published. They have come up with this clinical classification system which groups together related ICD 9s, so you have 259 categories instead of all the ICD 9s.

In some cases what they have done is changed the name of the illness to a kind of vernacular.

DR. WARD: It may be bronchiolitis.

DR. LASKY: I think, on one hand, it needs in-depth exploration, but I don't think we are going to be able to do it.

DR. WINER: Tami, is this the kid database?

DR. LASKY: Yes.

DR. WARD: Yes, Dr. Epps.

DR. EPPS: First of all, I just wanted to thank Dr. Mattison and Dr. Mathis and Dr. Lasky and Dr. Ward for a very smooth meeting, as well as the staffs of the FDA and NICHD. It was a very interesting meeting.

Basically, I guess one thing that I feel just generally is, I think information is powerful. I think when I'm trying to decide, I usually err on the side of

more information. I think the more information that practitioners have, the more information patients have, the better.

When I participated in one of the advisory committees, sometimes the feeling was that, well, let's approve the drug and get the post-marketing data. We see how that goes with Vioxx, okay. It doesn't always go very well.

DR. WARD: Got it.

[Laughter.]

DR. EPPS: Certainly, I mean, we found it quicker, sooner than later, in that regard. Certainly, dermatology is not like pneumonia, where you have a nice X-ray. Everyone can't even agree on the diagnosis all the time. I mean, they are still trying to define atopic dermatitis, the North American group versus the Europeans, and on and on.

So sometimes we have those problems, which is why sometimes it is very difficult when we are assessing dermatology studies and deciding, well, did that person really have eczema anyway when they were testing it.

To put on my pediatric hat, I think

pediatricians mean well. I think they try to do what is right for their patients whether they are at an institution or in private practice. Parents are very savvy. They are on the Internet. You have to keep up. They are reading the same studies you are, and some other stuff that is probably floating around in cyberspace.

DR. WARD: That is not a study.

DR. EPPS: Correct, that is not a study, but because it is typed out and in writing, it could be true from their perspective. So I think everyone is trying to pay the best attention.

As far as data that we may need, certainly, like age of onset, whether it is acute or chronic, prevalence, certainly mortality is important, but morbidity is extremely important. I mean, a lot of conditions that we have talked about cause chronic disease, a lot of illness, may impact the whole family, days lost from work and school. They are very expensive if not treated properly.

Perhaps we can get some data from N. Hanes, I don't know. We have been fighting to get acne put on there. They don't think it is important, but just

prevalence of some common diseases may be there. Without going through the Kaiser or the whatever, I don't whether we are up to four by now for N. Hanes or if it is in process. Who knows. Anyway, that may be a source. I know N. Hanes-3 is out there.

I agree with whether it is clinically relevant. I think that is very important. That would be paired with incidence as well.

Back to the dermatologic issues, unfortunately, we do have some tools that people have tried to use. Some of them are SCORAD and some others which are controversial, but there are efforts being made to try to uniformly assess some of the dermatologic conditions if you decide to go that road.

I do think one of the more important things is certainly the public health benefit and trying to find the best result for society in general.

DR. WARD: One of the things that has come up in discussions about neonatal outcomes is long-term follow-up. One of the challenges in pediatrics is sorting out the effects of the various disease processes from the effects of the drug long-term. I think that

will always remain a challenge for us.

DR. STILES: Plus, we have changing therapies that affect outcomes between the times you are trying to look at the question. So we remain several years behind.

DR. PURSLEY: Plus, we have the issue of socioeconomics overriding all of those medical and conditional effects.

DR. WARD: Not that it is difficult to do.

My final slide in the talk about perinatal substance abuse is that if you did not assess the underlying socioeconomic condition the child was reared in, you miss the predominant effect. So we can attribute it to any number of drugs or complications if we create a superficial analysis.

Yes, Dr. Sachs.

DR. SACHS: I was actually kind of curious about you all's opinion a little bit of the input process from the experts. One of the other things that I'm privileged, I will say, to do is serve on the Academy of Pediatrics Committee on Drugs.

As you guys may know, the Committee on Drugs, for example, issues statements periodically about certain

things, and right now there is a statement that is in the works on emergency drugs that all pediatricians should have in the office, for example. That has a list of many, many, many drugs, some of which -- I will daresay most of which -- are not labeled in kids.

That is a very pragmatic source right now of drugs that are being recommended by, presumably, an expert group for everyone to use. It just kind of occurs to me that there may be similar things that you all as experts are aware of that we may not be that would kind of be useful, especially if we are not hearing from that group.

If we didn't hear from the American Heart Association, I mean -- this time we did, but let's say we really wanted to look at SBE prophylaxis. It would be silly not to look at their recommendations, and I think we would consider that.

But just as a starting source, instead of an individual nomination, if you have this statement, I was just curious what you guys thought about that type of input.

DR. WARD: Steve.

DR. LAWLESS: If you look at risk management data and liability data, I'm not an advocate for creating more work for lawyers, but if you look at what has gone on in risk management, what have those drugs actually been associated with: product liability with risk. If you use that as a guide, you can actually see sometimes a little bit more of a different slant on things.

A lot of it may not be the drug itself. It may be what you are talking about.

The use of Epinephrine. In the use of Epinephrine, the indications for the drug are proper. However, the mechanism of how it is delivered may be improper. So you have calculations of how difficult it is to do calculations of Epinephrine. So you may find some surprising ways of looking at that, which is implying what you are talking about the emergency drugs, for example.

To do an Epinephrine infusion takes four or five people to take their calculators out to do it, and side effects follow.

DR. WARD: Yes.

DR. SACHS: Actually, I just wanted to say

something that I found very powerful and helpful. I mean, several of the drugs that came up on superficial glance, I can say that I looked at them and said, "Well, gosh, there is adequate information in the label. It is labeled all the way down to this age or that age," not necessarily understanding that in practice the duration of treatment is different, or the dose that is being recommended is outdated.

I think that is information that has been very, very powerful. I am not 100 percent sure that we would get that feedback otherwise.

I mean, I just, for one, want to thank everyone for the very good quality of the presentations. I mean, I guess you guys aren't called experts for nothing.

[Laughter.]

DR. ZAOUTIS: Two comments; one small one regarding the scoring system. One of the things I heard from people was regarding the safety of the drug for this indication versus the safety of the drug in general. I think for safety specifically, the drug has been used in X-number of patients and studies of the safety may be less of an issue to break out by indication, or have an

additional score for general safety across all indications. For efficacy, it is much more important for that indication.

The other is, there are threads of this, and Tami got up there and mentioned this. Although the mission, from what I understand, was to look at these drugs, I think it provides an opportunity to study diseases in children where we do not know how to manage them appropriately.

It was obvious in the discussion about influenza and thinking about the design of a study comparing Amantadine and Rimantadine. Now, those were the drugs that were the triggers here, but there were other drug options. This may be the time that we can address bigger questions about diseases and what is the best way to manage a disease.

The same thing was obvious in the finding about the over-the-counter Hydrocortisone, how that has not been studied long-term in the treatment of eczema.

So I think a conceptual framework that starts with the disease should be considered.

DR. WARD: Would you respond?

This seems to be one of the real conflicts having to do with labeling. We begin with a drug and then what its indication is, as opposed to starting with an indication and let's talk about all the drugs.

DR. MATHIS: Right. I actually think that that is a very good approach because one of the other things it does is it helps us address the needs in the pediatric treating community if we start with the indication.

The other thing is, too, that frequently, like you said, drugs are used off-label. We saw that with Amantadine. There might be bigger uses for a drug other than the current labeling.

Now, frequently we know that and we can give that feedback. When we talked about Clonidine, we certainly didn't talk about it for hypertension because we knew it was being used off-label for TIC disorders and ADHD.

However, approaching this process by looking at most frequent diseases or diseases that are in most need of therapies would allow us, I think, to survey the users much more efficiently. What drugs are you using for this indication at this time that you don't think have

labeling for it.

DR. ZAOUTIS: You will eventually get to the data about the specific drugs.

DR. MATHIS: That's right, that's right.

Just to take the opportunity to comment about safety in relation to the indication, you're right, frequently we can say this drug has been used at this dose for another indication so we know the safety profile. Frequently, as we are looking at approving a drug, we have to look at the risks in light of the benefits, which is the difference between if you are treating cancer versus acne -- excuse me, Dr. Epps.

I mean, there certainly is, really, a different benefit profile that you have to weigh the risk profile against.

So I think that is probably where that came from, but you're right, frequently we can look at the risk profile from another indication where the dosage is the same.

DR. ZAOUTIS: I'm just saying, maybe in reviewing, adding a score for a lot of data in another indication.

DR. MATHIS: Yes, definitely.

DR. MATTISON: Just a follow-up, you heard Tami describe her interest in collecting data on conditions. The fact that Congress put together the NIH and the FDA suggests that they intended to improve the label information that is available to practitioners caring for patients, but they also understand that the NIH has a different mandate from the FDA. So we have looked at that as an opportunity to think critically about conditions that occur in pediatric populations.

The comments, for example, about why are kids admitted to hospitals with burns, I think, points out some of the kinds of information that we are going to sort of begin to probe and ask questions that are sort of outside of our own venues a little bit.

DR. WARD: I think that is excellent.

One other point I would make, though, is that with respect to the safety, in specific patient populations and disorders, the safety margin and the effects may vary. There may be more adverse effects that show up in a particular disorder.

So I would be careful with that extrapolation.

It is complex.

Debi.

DR. AVANT: I think it is a great idea to start with the indication, but we also need to remember the patent status of the drugs.

PARTICIPANT: We have been caught on that, haven't we?

[Laughter.]

DR. LASKY: We will try.

PARTICIPANT: There is nothing to say we couldn't look at the indications, list the drugs that we need studied, and then screen out those that are still on-patent.

DR. LASKY: Debi, you have to not let these off-patent drugs go on-patent again.

DR. AVANT: I'm going to work on it.

[Laughter.]

DR. WARD: Again, this may be why this comparative process that we have talked about may be helpful so we could take the off-patent and on-patent and do some comparison studies.

DR. LAWLESS: Just out of curiosity, is there a

listing for each of the drugs, an electronic list, and the different organizations that actually say, these are the on-label uses? We can't have a listing of off-label uses, but on-label uses of these drugs?

DR. WARD: No.

[Laughter.]

DR. WARD: I asked for that in '97. I said, "Where is your database about labeling?" Each division keeps it, and each in a different database.

They have made some progress toward reconciling those variations. The newer things, I think, are being entered into a common database.

DR. SACHS: There is a "Drugs at FDA" website now. Just go to the FDA link. I think it is "Drugs At FDA." You just punch that in. If there is a current label available, it is available.

The problem is, with some of these old drugs that are off-patent and there are a lot of generics, the labels are a little harder to come by, but that is something we are actively working on.

DR. LAWLESS: Because if you are talking about the electronic part of it and you have that, that is the

thing that links it. Are you using it for these on-label things? No, I'm using it for something else. It would help that way.

DR. LASKY: Yes. We have been wishing for a while.

DR. WARD: John.

DR. ALEXANDER: Just a couple of things. I mean, realizing that we are talking about drugs that are now off-patent, I think that one of the things that we need to think about is exactly how and what process are we going to be using to sort of decide on whether something needs to be studied or not.

Under the law, when FDA is looking at those drugs that are new that are just released and are on-patent, we sort of have to assess those drugs, and it is fairly easy because the only things that those drugs have really been studied or proven for are actually the indications that they are seeking for those new drugs.

So it is easy for us to sort of go into the process and just say, okay, so which of these diseases that we are dealing with are important for pediatric patients; which ones do we need information on younger

age groups, down to how young; and whether we can actually extrapolate information from adults down to pediatrics.

With this process, the off-patent process, part of the difficulty is that we are dealing with drugs that have been out there for ages, and in some cases where we are sort of looking at drugs that practitioners feel they have adequate information on and are using it already, or in some cases, they don't have adequate information on it and are using it anyway.

So that is sort of what makes it difficult to try and assess this by the same sort of disease-based process. A lot of times there are new drugs that have come along that are still on-patent, and those are the ones that we really ought to be referring to, like the discussion that we had earlier on, Cyclosporine versus Tacrolimus and Sarolimus and the others.

Then, in other cases, the thing that is really generating something ending up being on the list is specific safety questions that come out for a particular drug. Those studies are usually hard to do because, if it was a common safety problem, you wouldn't be using the

drug. It is usually an uncommon safety problem, the example being Erythromycin and pyloric stenosis, that are then difficult to go in and do studies on unless you are talking about large trials.

DR. ZITO: I just want to say, we don't have to only talk about large trials. That is our bias in the United States, there is no question about it, but the safety research could be addressed from different designs, particularly for a drug that has already been out there for 50 years. You would have more confidence then that the unique things or the big flag things would have shown up through MedWatch. So now you are really going for more nuanced understanding of chronic exposure.

For example, we studied Pemoline as an example of a safety issue. Pemoline was out there as a treatment for ADHD. It came to the United States somewhere in the '80s for the elderly for wake-up-your-brain stuff. It didn't work very well for them, so they said, well, let's try it in the kiddies.

You need more than one drug in a class, so people adopted it. It was never really a big world-beater, but it was there as an alternative.

It has taken 26 years to discover that it produces liver transplants or death in children. So the hepatotoxicity is a real thing. I mean, I don't know if you want to randomize kids to a trial to convince yourself of that, but it is off the market in Canada, it is off the market in the U.K., but we don't take it off the market in the United States because we don't want to deprive the handful of people that are left out there that are in treatment.

So we really have some problems about attitude around safety stuff. I think this is a great opportunity with the off-label to think about some creative ideas for answering that question about safety.

DR. ALEXANDER: Understood, but at the same time, I think that Erythromycin points out an example of where that sort of system and that sort of looking at drugs from what we are stuck with, which in the past has mostly been a passive reporting system, didn't really give us the answer 50 years into its use.

DR. ZITO: So something between MedWatch, ideally.

DR. LASKY: I was going to say, in between

passive reporting and randomized clinical trials. There are a whole range of study designs. Some of the best for adverse events are the case control studies, but there are other study designs as well that can be used to collect very convincing data and sound scientific data to test a hypothesis of the relationship between a drug exposure and an adverse event.

So we don't have to go from one extreme to the other. We can find the middle ground.

Something else to throw out which I hadn't put on the slides, but people have approached me with data from Europe, particularly from England. I think at CHOP you have the British --

DR. WIEDERMAN: The GPRD database.

DR. LASKY: Right. I think we need experts to help us understand when we can use European or Asian data and when we can't use it. What are the limits. We don't have to redo everything, and some things are done in Europe or in Asia, but some things do have to be done in the United States. So that input would be very valuable.

DR. WARD: The Erythromycin experience, I think, is actually instructive. I find lots of

historical things of constructive value.

There was the signal that came out in the six cases in the Carolinas that Peggy Honine [ph] reported. It has been confirmed by going back to the Tennessee Medicaid database and looking at exposure to Erythromycin and then the diagnosis of pyloric stenosis.

So we have done both, but you have to have that signal. Nobody went to the Tennessee database and found this at the beginning, so we need the astute clinicians. We need the observers.

DR. ZITO: I would suggest, when you have one Medicaid Tennessee database and you are looking at a drug like Erythromycin, you are in better shape than when you are looking at a much smaller exposure.

We have 50 states of Medicaid with that capacity that sits at CMS every year where, if we were funding a research initiative that would look for those small exposures, we could examine some questions on a regular basis.

DR. WARD: We had the transplant population where they receive a minimum of five or six drugs a day and we try to sort something out.

DR. ZITO: That is very tough.

DR. WARD: That is the complexity.

DR. STILES: There are two other things you probably ought to consider, and I sort of shudder to bring both up.

One has to do with cost, because clearly, we have some medications out there that are astronomically expensive and are being used not as labeled and really push the cost of care, particularly where we have such a large group of children with chronic disease that fall in the Medicaid population.

So I don't know how to factor that in. I do know that there are a number of those there that we struggle with every year in our state when we try and figure out how to set up the listing of what we are going to pay for and not pay for.

The second thing is that because all hospitals are being driven toward outcomes reporting, we will have an opportunity to see where there are things that have wide variation and outcome to help us consider whether there are things we ought to be looking at within that.

Now, I have no clue how to approach that. I'm

just bringing it up as an issue, but places where there are variability are likely also to be places where we are going to find issues that relate back to these medications.

DR. WARD: I think you are probably very right. The more complex the disorder, it seems the greater the number of medications undertaken or used.

DR. MATHIS: I would like to somewhat reassure the group that the FDA is working on more active surveillance of adverse events. We are trying to figure out the best way to do that.

Dr. Solomon Iyasu, who was here earlier -- he is not here now -- is with the Division of Pediatric Drug Development. Of course, as always, pedes is in the forefront of trying to pull together a lot of safety, but he has been working very closely with many of the review divisions as well as with the Office of Drug Safety to try and figure out where that middle surveillance program is. That way, it is not completely passive.

Obviously, we can't do a completely active one without violating everybody's privacy. However, there is something in between, and he has really been working on

that hard. We do see that as a very important issue that the FDA needs to address.

DR. WARD: Yes.

DR. GRAYLOR: A few comments related to a couple things that were just said.

Tami, first, in your bullets about getting better data from the European and Asian countries, there have been a lot of efforts and coordination of some activities related to large databases in Europe and Asia. We have had some frequent recent discussions about them, and perhaps we could explore to see if they made sense for you later.

One of the other issues that you just talked about was basically related to FDA's activities in some of the broader areas. It relates also to some of the activities related to the electronic medical record before.

Back when I was at the FDA, we were very much involved with some of these standards activities and seeing how the agency could be more actively involved in the standards community so that we could have better access to the information and use it more effectively.

When I retired from the FDA, Randy Levin took over my role in the HHS Data Council, and he has been the one who really was active from the early days in terms of the FDA interaction with HL7. So I think he would be a good person to talk to.

To look further to the future, David Raylor [ph], who is the Health Information Technology lead for the department now, is very much interested in pharmaceutical issues. I talked with him a few weeks ago at a meeting we were both at, and I think in terms of development of the future infrastructure and one of the key issues we talked about really is the really rotten infrastructure we have to many extents. Well, let's say it is not perfect.

I think there are some opportunities in giving him some opportunity to really think through providing input on some real applications that he would find very interesting to build into what the department will support in the future as a real possibility.

The last thing I will mention is in terms of the best practices issues we have talked about. Clearly, in terms of having an impact sometimes, another group I

think would be also very interested in hearing what has taken place here and what is likely to be thought about for the future is the Joint Commission on Accreditation of Health Organizations.

We have talked to them in the past about some of these related issues, and I know they are very interested in being at the table for some of these things.

DR. WARD: They are a double-edged sword, though. They can make some very profound efforts and can be very misguided at times.

DR. GRAYLOR: You can help them see the right way.

DR. WARD: My favorite is just the evaluation of pain in the newborn. It has been, sort of, mandated. Nobody knows how to do it right, but by golly, we are out there doing it, because we have to.

Anyhow, there is my platform. I want to thank every one of you for excellent participation and contributions. This has been a very, very thorough process. I think the discussions have been illuminating. I think they have made the outcomes better. I just

appreciate everybody taking the time and the effort you have put into it.

Thanks so much.

[Whereupon, at 3:00 p.m., the proceedings were concluded.]

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**CERTIFICATION**

This is to certify that the attached proceedings

BEFORE THE: NICHD Best Pharmaceuticals for Children Act (BPCA)

HELD: October 26, 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