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ATDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE

A SUBCOMMITTEE OF

THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

ISSUES REGARDING A PEDIATRIC DRUG-DEVELOPMENT PROGRAM FOR THE TREATMENT OF INSOMNIA

DAY II

Tuesday, November 16, 1999

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at

Holiday Inn Silver Spring
Kennedy Grand Ballroom
8777 Georgia Avenue
Silver Spring, Maryland

at

PARTICIPANTS

P. Joan Chesney, M.D., Chairperson
Jayne E. Peterson, R.Ph., J.D., Executive Secretary

MEMBERS

Judith O'Fallon, Ph.D.
Keith Rodvold, Pharm.D.

VOTING SGE CONSULTANTS

David Danford, M.D.
Kathryn Edwards, M.D.
Robert Fink, M.D.
Mark Hudak, M.D.
Richard Gorman, M.D., FAAP
Naomi Luban, M.D.
Robert Nelson, M.D., Ph.D.
Victor Santana, M.D.
Stanley Szefler, M.D.

NON-VOTING CONSULTANTS

Ralph Kauffman, M.D. (AAP)
Stephen Spielberg, M.D., Ph.D. (PhRMA)

GUESTS AND GUEST SPEAKERS

Leslie Clapp, M.D.
Richard Ferber, M.D.
Richard Malone, M.D.
Mark Riddle, M.D.
Robert Ward, M.D., FAAP, FCP
Alan Zametkin, M.D.

FDA

Thomas Laughren, M.D.
Dianne Murphy, M.D.
Rosemary Roberts, M.D.
Russell Katz, M.D.

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P R O C E E D I N G S

Call to Order and Introductions

DR. CHESNEY: Good morning and welcome to this session on issues regarding a pediatric drug-development program for the treatment of insomnia. We would also like to welcome again Dr. Julia Dunn from the Medicines Control Agency in the United Kingdom.

I think, today, our microphones are working so we can start with introductions. Maybe we can start down at this end of the table. Again, if you could just give your name and where you are from, your affiliation, please.

DR. MALONE: I am Richard Malone. I am a child psychiatrist from the MCP Hahneman University.

DR. RIDDLE: Mark Riddle. I am a child psychiatrist at Johns Hopkins University.

DR. CLAPP: Leslie Clapp, general pediatrician, Buffalo, New York, at Main Pediatrics.

DR. ZAMETKIN: Alan Zametkin, child psychiatrist, Intramural Research Program, National Institute of Mental Health.

DR. O'FALLON: Judith O'Fallon, biostatistician,

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Mayo Clinic.

DR. WARD: Bob Ward, neonatologist and pediatric pharmacologist, University of Utah.

DR. RODVOLD: Keith Rodvold, University of Illinois Colleges of Pharmacy and Medicine.

DR. LUBAN: Naomi Luban, Children's Hospital National Medical Center and George Washington University. I am a pediatric hematologist/oncologist.

DR. SZEFLER: Stan Szefler, University of Colorado and also National Jewish Medical and Research Center, Director of Clinical Pharmacology.

DR. EDWARDS: Kathy Edwards, pediatrician, Vanderbilt University, Nashville, Tennessee.

DR. FINK: Bob Fink, a pediatric pulmonologist at Children's Hospital in Washington, D.C. and George Washington University.

DR. SANTANA: Victor Santana, pediatric hematologist/oncologist, St. Jude's Children's Research Hospital, Memphis, Tennessee.

MS. PETERSON: I am Jayne Peterson. I am with the Advisors and Consultants staff with the FDA and am an executive secretary with that staff.

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DR. CHESNEY: Joan Chesney, the University of Tennessee, Memphis.

DR. DANFORD: Dave Danford, pediatric cardiologist, University of Nebraska Medical Center, Omaha.

DR. GORMAN: Richard Gorman, pediatrician in private practice in a Baltimore suburb.

DR. NELSON: Robert Nelson, pediatric intensive care. I am at the Medical College of Wisconsin and Children's Hospital of Wisconsin in Milwaukee.

DR. HUDAK: Mark Hudak, neonatologist at the University of Florida at Jacksonville.

DR. SPIELBERG: Stephen Speilberg, Head of Pediatric Drug Development at Janssen Research Foundation, Johnson & Johnson, representing PhRMA.

DR. FERBER: Richard Ferber, pediatrician. I run the Sleep Disorders Program at Children's Hospital in Boston.

DR. ROBERTS: Rosemary Roberts, Pediatrics Team.

DR. MURPHY: Dianne Murphy, Associate Director for Pediatrics, CDER, FDA.

DR. LAUGHREN: Tom Laughren, Team Leader for

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Psychopharmacology in the Neuro Pharm Division.

DR. KATZ: Russ Katz, Director, Division of Neuropharmacological Drug Products, FDA.

DR. CHESNEY: Jayne Peterson will read the conflict of interest statement.

Conflict of Interest Statement

MS. PETERSON: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Since the Subcommittee's discussions will not have a unique impact on any particular firm or product but, rather, may have widespread implications with respect to an entire class of products, in accordance with 18 USC, Section 208, general-matters waivers have been granted to each member and consultant participating in the subcommittee's discussions.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, room 12A30, of the Parklawn Building. In the event that the discussions involve any products or firms for which an FDA

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participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous involvement with any firm whose products they may wish to comment upon.

DR. CHESNEY: I just wanted to introduce, for those of you who do not know Dr. Murphy or who have just talked to her on the telephone, she is the Associate Director of Pediatrics for the Center for Drug Evaluation Research. She is wearing red today and she is not from a Baltimore suburb.

Our first speaker this morning is Dr. Tom Laughren who is the Acting Deputy Director of the Neuropharmacological Drug Products Division of the Center for Drug Evaluation and Research. He will be providing us with an overview of the issues.

FDA Introduction/Overview of Issues

DR. LAUGHREN: Good morning and thank you.

[Slide.]

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The topic for today is insomnia and, possibly, other sleep disorders in children and adolescents and the question of whether or not FDA should be encouraging sponsors of hypnotic products to expand those develop programs into this younger population.

I have given you a copy of my overheads. It is the blue document so you don't need to try and take notes on this.

[Slide.]

What I am going to try and do in these next ten minutes or so is to try and give you some background information that I hope will be helpful in facilitating the discussion. There are four issues that I wanted to deal with. I wanted to give a very brief overview of some of the FDA pediatric initiatives in recent years that are, really, the context for this discussion as well as the new law, the 1997 FDAMA law, which also has an important role in the current level of activity.

I want to give you a couple of examples of currently active pediatric programs in psychopharmacology just to give you a sense of what kind of additional work is being done to expand claims in other areas into this

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population.

Then I want to talk about the current status of adult programs for insomnia and, finally, end up, again, going over the specific issues and questions that we would like to have you address with regard to insomnia in the pediatric population.

[Slide.]

First, a little background on the FDA initiatives. Actually, there are three pediatric rules over the past twenty years that address pediatric use. The first one was in 1979 which, basically, established the pediatric-use section of labeling. The hope was that it would stimulate interest in doing research in children. It didn't really have that effect but it did establish, at least, that section of labeling.

Then there was a rule in 1994 and one in 1998 and then, finally, the Modernization Act.

[Slide.]

The 1994 Pediatric Rule focussed on marketed products. It basically required sponsors to review existing data and submit labeling supplements if appropriate. In other words, if their review of the

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existing data for their product revealed some information that would be helpful to put in labeling, they were required to submit a supplement.

But there was no requirement that they actually do studies as part of that rule.

The other feature of this '94 rule was to emphasize the possibility of extrapolating data from adult studies into children, if feasible. Of course, in psychopharmacology, that is generally not a terribly useful strategy for most indications.

[Slide.]

The most recent rule, the '93 Pediatric Rule, actually goes beyond asking for a review of data. It actually gives us the authority to require pediatric studies. This is focussed on both new and marketed products, but the focus is on the specific indication that is being reviewed or being considered for submission under two circumstances.

One would be if there is a meaningful therapeutic benefit that might be expected as a result of doing those studies. Basically, what is meant by a meaningful therapeutic benefit is either there are no

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existing products for the indication or the existing therapies are not particularly effective.

So there would have to be an expectation that those studies might result in a meaningful therapeutic benefit or the other possibility would be if there is already substantial use of that product in the pediatric population and where lack of labeling information about that use would pose a risk.

So those are the two conditions that would kick in a requirement for pediatric studies under the '98 rule.

[Slide.]

There are alternatives to actually conducting the studies. I am not going to go into a lot of details, but a company could get a waiver--in other words, a delay of doing the study, say, to post-approval under certain circumstances or there could be a deferral of doing the studies.

[Slide.]

Now I want to say a little bit about the '97 law, FDAMA, the FDA Modernization Act. This also applies to both new and marketed products. As opposed to

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requiring, this encourages the conduct of pediatric studies when it is determined that information from these studies may produce health benefits.

This is slightly different than the meaningful therapeutic benefit under the Pediatric Rule, but similar. One other difference from the Pediatric Rule is that this is not limited to approved indications. In other words, FDA could, theoretically, encourage the development for an indication that is not already approved in adults or is not the focus of an existing application.

Again, these studies would be voluntary. They apply, basically, to drugs that have additional patent protection because there is a financial incentive in this law that basically gives companies additional patent protection for six months beyond their existing date of the patent. So there is a financial incentive included under this law.

[Slide.]

This is fairly complicated, even for us at FDA. Basically, what I want to do is to summarize the bottom line in this slide and that is that FDA wants and can

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require, under certain circumstances, pediatric studies for certain indications where this is a need.

Sponsors now have a financial incentive under FDAMA to conduct pediatric studies and so it behooves us to try and identify those indications that would benefit from pediatric development programs. In addition, we need to work out the details of those programs so that we know what kind of additional work would need to be done.

[Slide.]

In this slide, I want to give you a couple of examples of other areas where pediatric programs are either already under way or have been encouraged by us. Those are in major depression, in obsessive-compulsive disorder, generalized anxiety disorder, more recently social anxiety disorder and mania. So these are all areas where programs are already started or FDA has encouraged companies to expand these programs into pediatric populations.

[Slide.]

Just to give you an example of the kind of additional work that would be required under one of these programs. This is an example of what was required to

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expand the major depression claim into the pediatric population.

What has been required is two randomized, double-blind, parallel-group, placebo-controlled, short-term trials very similar in design to the kinds of studies that are done in adults to be done both in children and in adolescents with major depressive disorder.

In addition to that, we are asking for pharmacokinetic data in those populations and, finally, safety data, again, from both subgroups of that placebo, both short-term and some long-term data.

[Slide.]

Now, I want to switch to the current status of drug-development programs for insomnia in adults. I want to deal with two issues; first of all, what claims are currently approved for hypnotics in adults and, secondly, what are the features of a typical adult program for developing a hypnotic.

[Slide.]

This is an example from the most recently approved hypnotic. Sonata was approved last summer.

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From the indications section, this is the exact language. It says, "Sonata is indicated for the short-term treatment of insomnia." It then refers to the clinical trials section for the details.

If you look to the clinical trials section, you will see that there are basically two claims for insomnia in adults. First of all, there is the claim for something called transient insomnia. This is generally meant to refer to a very short-term problem, either getting to sleep or staying asleep.

The claim is ordinarily established using a model of transient insomnia that involves putting normals in a sleep lab and you look at the first night in the sleep lab as the model of transient insomnia.

The second claim is for chronic insomnia. I will talk about that later.

[Slide.]

These are the features of a typical adult program to get a claim for insomnia in adults. Again, for chronic insomnia--generally, and I will talk about this later, the population that is recruited are patients who meet DSM-IV criteria for what is called primary

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insomnia. I will define that later on.

We generally ask for outpatient studies, usually up to four weeks, sleep-lab studies up to two weeks. For transient insomnia, again, the usual model is this first night in a sleep lab involving normal subjects. Sometimes, we will get a patient study involving, for example, the first night in a hospital for patients who are in for some routine procedure.

In addition to that, for a hypnotic, we generally get quite a lot of exposure, 3,000 to 4,000 patients exposed, including some longer-term data meeting ICH criteria. For almost any hypnotic, we also get some special studies to look at things like respiratory effects, effects on memory, next-day residual effects, various kinds of withdrawal phenomena, same-night anxiety, next-day anxiety, rebound insomnia, tolerance and dependence. So that is standard for almost any hypnotic.

[Slide.]

This is the DSM-IV categorization of the various sleep disorders. It is divided into the primary sleep

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disorders and what are basically secondary sleep disorders, disorders that are secondary to another psychiatric disorder or to a general medical condition or substance abuse.

For the primary sleep disorders, it is divided into the dyssomnias and the parasomnias, the parasomnias being various troublesome behaviors that emerge during sleep. Of the dyssomnias, again, the one that is generally the target of an adult program is what is called primary insomnia.

But, in addition to that, if you will notice on this list, there is narcolepsy. Now, narcolepsy is another sleep disorder for which there are approved drugs. These drugs are generally very different pharmacologically from the kinds of drugs that are used in treating primary insomnia.

The only other disorder on this list that I think is of some interest is what is called Circadian-rhythm sleep disorder for which there are no approved claims in adults at present. But that might be a topic that I think would benefit from some discussion here this morning.

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[Slide.]

So, again, in terms of the kinds of claims that are currently approved for hypnotics in adults, you have chronic insomnia which, again, is equivalent to DSM-IV primary insomnia and you have transient insomnia for which there is no DSM-IV equivalent.

[Slide.]

These are the DSM-IV criteria for primary insomnia. You can read through the list. Let me just basically talk you through it. These are patients who have difficulty either initiating sleep or maintaining sleep for at least a month. They have some level of functional impairment as a result of that sleep problem and the sleep problem cannot be explained on the basis of any other primary disorder, whether it is a psychiatric disorder, another sleep disorder, a medical disorder or substance abuse.

So it is basically unexplained insomnia that is chronic and that results in functional impairment.

[Slide.]

Finally, these are the questions that we would like you consider today. This is a little bit of a

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reworking of the questions that you have in your package.

Basically, the first question is are there equivalent disorders in the pediatric population for which hypnotics are approved in adults. Again, in adults, hypnotics are approved for both primary insomnia and transient insomnia. So, do those conditions exist in children, in adolescents.

If the answer to that is yes, then should hypnotic development programs be required, as we could under the Pediatric Rule, or encouraged as we could under FDAMA, in pediatric patients to study those disorders. If so, what kinds of studies would be needed, what ages should be studied, what durations; in other words, a little bit about the details of the specific kinds of studies that might be needed to support the expansion of those claims.

From the standpoint of safety, are there safety concerns associated with the use of hypnotic drugs in pediatric patients that would be unique, in some sense, to that population. Again, as I pointed out, in adult programs for hypnotics, we always look at things like respiratory effects, memory, next-day residual effects,

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withdrawal effects, dependence, and so forth.

Are there other specific safety concerns with using those drugs in pediatric patients and, if so, what kinds of studies would be needed to evaluate those concerns?

Finally, are there other sleep disorders in the pediatric population that may benefit from the use of hypnotic drugs? Again, under FDAMA, it would be possible for FDA to encourage companies to look at other sleep disorders, even disorders that are not currently approved in adults.

The one example that comes to mind is the Circadian-rhythm sleep disorder. I know there is a lot of interest in that disorder or something like it in adolescents, so that is a question for discussion, whether or not that is an entity that would benefit from a development program using hypnotics.

So, again, if there other disorders, what kinds of studies would be needed to explore the benefits of hypnotic drugs in those populations.

Thank you.

DR. CHESNEY: Thank you very much.

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I think maybe we could take one or two questions if anybody has questions for Dr. Laughren.

DR. SANTANA: I am not a specialist in this area so you are going to have to help me understand some of this. A lot of issues of insomnia are self-reporting, so how would you get around that in a pediatric population where, in essence, their reporting would be done by parents or secondary people observing the insomnia or the behavior.

Then the second question is are these studies so specialized that they can only be conducted in controlled environment like sleep labs and, if so, are there enough facilities that one could do those pediatric studies?

DR. LAUGHREN: I will answer the second question first. Typically, the two kinds of studies that are done are sleep-lab studies. That does require a fairly special kind of environment but those are already well established. To expand those kinds of studies into children, I wouldn't think, would be any great difficult.

The other kinds of studies are outpatient studies. That sort of gets at your first question of how do you diagnose and assess insomnia in a pediatric

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population. I would see the problem more one in looking at children with insomnia than adolescents who probably are, clearly, better able to report the problems.

That is a good point for discussion. Obviously, you would have to be relying more on parents' reports. It is something that needs to be fleshed out. I don't know the answer to that.

DR. FERBER: May I just make one quick comment. There are actographic studies that are done frequently that get away from the sleep lab but still study long-term sleep in the home situation. That can be quite applicable in this setting.

DR. EDWARDS: Is there any data to suggest that parents that use hypnotics tend to report that their children need them also? Is there a link between those two issues?

DR. LAUGHREN: Good question. I don't know the answer to it.

DR. FERBER: It is the parents that are awake at night, not the parents that are asleep at night that are the problem.

DR. GORMAN: Looking at the diagnostic criteria

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from DSM-IV, a lot of these would become increasingly difficult as you move down the pediatric age range to establish or disestablish. At least in your primary view of this, have any of the sponsors or the FDA thought about how they are going to look for manic-depressive disorders in five- and six-year olds or generalized-anxiety disorders?

Again, going back to the reporting issue, who is going to decide that it is nonrestorative sleep.

DR. LAUGHREN: Your first question is asking about disorders other than insomnia?

DR. GORMAN: More to the point of the diagnostic criteria in DSM-IV. How are you going to establish this as an exclusionary diagnosis, because it sounds like this is an exclusionary diagnosis, after you have ruled out a lot of other things? Ruling out a lot of those things becomes increasingly difficult as you move down the age ranges.

DR. LAUGHREN: You are looking at the criteria for primary insomnia?

DR. GORMAN: Correct.

DR. LAUGHREN: The question is how do you rule

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out other psychiatric disorders that might be the basis for the sleep problem?

DR. GORMAN: In terms of designing the study, going forward, if we decide this is an important area, they would become increasingly difficult to rule out as you move down the age continuum.

DR. LAUGHREN: Again, I don't have any specific comment. I agree with it. I think that it is always a problem when you are dealing with children and you have to rely on sources other than the child to make the diagnosis and to rule out these other conditions.

I agree that it is a major additional challenge that has to be built into any program. I disagree with your view on that.

DR. SZEFLER: Just one more question. How did this come to kind of hit the radar screen? Is this something you picked up on and saw as a problem with more companies coming in and want to organize a program or did somebody approach you from, say, the Academy of Pediatrics and say this is an emerging issue?

DR. LAUGHREN: There have been a couple of companies who have expressed interest in expanding their

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programs into younger populations under FDAMA. Again, of course, there is a financial incentive for companies to do that. But there also is the clinical question; as you will hear later, there is a lot of use of various kinds of drugs for treating insomnia in pediatric populations so it raises the question of whether or not there is an entity that needs to be treated and needs to be explored.

So there are both of those issues.

DR. CHESNEY: Thank you for clarifying that.

Our next speaker is Dr. Leslie Clapp who is, as she said, a pediatrician in Buffalo. She is going to give us the perspective of sleep disorders from the general pediatrician's point of view.

General Pediatrician's Point of View

DR. CLAPP: Thank you, Dr. Chesney, and well as Dr. Rosemary Roberts, Dr. Monica Roberts who is not here and members of the Pediatric Advisory Subcommittee for the opportunity to participate in this dialogue in pediatric insomnia.

As a primary pediatrician for over fifteen years, I have worked in several settings, initially precepting medical studies and residents in training,

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then as a staff pediatrician in a staff model HMO as well as a disability review pediatrician for the State of New York.

Over the last eleven years, I established a private practice, initially a solo practice that evolved to, currently, a small group practice where I, along with another pediatrician and two nurse practitioners, attend to the healthcare needs of approximately 6,000 patients from birth to twenty-one years of age.

Please bear with me, recognizing that as a result of serving in the trenches as a general pediatrician, I am recovering from a cold complicated by laryngitis, no doubt an occupational hazard acquired from one of my 6,000 patients. So thank you for your patience as you tolerate my gravelly voice today and the need for me to adjust the microphone accordingly.

It is from this vantage point, as the first in line to become aware of the sleep disorder that I offer my perspectives on the presentation of insomnia and the pediatric and adolescent patient as well as the management of insomnia from a generalist point of view.

The definition of insomnia no doubt has been

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discussed exhaustively by this panel but, from a practical point of view, I would like to note that, oftentimes, the patient in pediatrics does not, himself, present insomnia as the chief complaint or in the review of systems.

As we all know, because of the breadth of the age ranges and developmental stages we serve in pediatrics, the complaints of insomnia may come from a parent, not always a child. Older teens may actually describe the inability to sleep at night while babies may be described as not sleeping through the night.

I am sure that we all agree that insomnia is a symptom describing a disturbance of sleep that results from an inability to obtain the quality and/or quantity of sleep a person needs to feel rested, refreshed, restored and maintaining optimal alertness during waking hours.

Insomnia, as the chief compliant or problem mentioned in passing while eliciting data at well visits, is described and perceived differently by the parent and the child. The history is the most crucial part of the evaluation and workup of insomnia.

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As was taught in medical school, 85 percent of the diagnosis can be made on the basis of a good history. Initially, when a parent or a patient complains of insomnia, they are more likely to describe the phenomenon as trouble sleeping or being sleepy throughout the day or not sleeping well at night.

A very detailed night and daytime history is the first step in understanding the phenomenon the patient is experiencing. Questions posed include what time does a child get in bed at night? When does she actually fall asleep? When does she awaken in the morning? Does she get up during the night? When? What for and for how long? Does she get back in her bed or yours?

Does she share her bed or bedroom with anyone? What is day like after a relatively sleepless night? Are there any troubles at school noted by teachers? Does she take a nap during the day? At what times and for how long? What does the nighttime routine include in the two or three hours preceding bedtime?

As one can see, many of these questions will vary according to the age of the child. The answers are crucial in getting to the root cause of insomnia. As

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much as possible, the child, herself, is encouraged to answer the questions and describe the routines during the day and night.

Often, the child will provide the most revealing answers and actually serve to solve the mystery as to the cause of insomnia.

Next, a dietary history is elicited from parents and children. Children will oftentimes reveal what parents are reluctant to admit, so focussing on the child when obtaining this as well as other aspects of the history can be particularly revealing

What are their favorite beverages? Are they drinking soda pop that includes caffeine like cola drinks, Surge, Sunkist Orange, Mountain Dew? Parents and patients alike are surprised to know that non-cola drinks like Mountain Dew and Sunkist have caffeine in them.

Do they drink hot or iced-tea regularly? Are the adolescents part of the Starbucks craze and enjoying a cafe latte before and/or after school? Is dinner immediately preceding sleep? Are night wakers given snacks when they wake up after a few hours of sleep because they claim to be hungry?

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The role of stress has long been established as a factor weighing in heavily in sleep disturbances. Change is not always a good thing, particularly to children and adolescents and can lead to insomnia. Changes such as transitioning an infant from a crib to a toddler bed, while seemingly innocuous, can be major disruptors to the child.

Other recognizable stressors that represent change and, therefore, may induce insomnia in the pediatric patient include depression or mental illness in the parent, a new baby in the family, step-siblings or additional extended family members joining the nuclear family, or disintegration of the family unit by estrangement of parents or by death.

Parents' financial pressures sometimes have a ripple effect and children sense the after shocks as well. Clearly, a move to a new environment, be it a new city, a new home, new school, can lead to sleep disturbances including insomnia in children.

Not to be forgotten is that insomnia is often the precursor of psychiatric illness in the child or adolescent. After ascertaining the psychosocial factors

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impacting on the life of the child with insomnia, an update of the current health status is crucial to determining the etiology as well.

For starters, how is the patient doing. Does she have a good appetite? Is she active, fairly energetic? Has she had any signs of illness like fever or general malaise? Is there any shortness of breath with exertion? Does she cough at night while sleeping? Does she sniff loudly or frequently rub or itch her eyes or nose? Is there snoring at night or does it seem as if she is snoring while awake?

Are there bouts of breath holding between snores?

A review of prescription and nonprescription medications used must be made as well. Is the child tasking any medications for chronic diseases? Certainly oral steroids and bronchodilators may cause insomnia. Is the child on Ritalin, Adderal or Cylert for AD/HD?

Is the parent medicating the child with Sudafed or even an antihistamine resulting in paradoxial hyperalertness or insomnia? Is the teenage girl taking ephedrine or lose weight or a high-school student popping No-Doz to cram for projects or reports?

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All this historical data must be gleaned in hopes of being able to provide the family with a plan to combat insomnia, yet, although the diagnosis frequently can be made on the basis of a history, a physical must complete the picture.

One is on the lookout for physical findings that corroborate historical leads pointing to a physical malady. A mouth-breathing child with adenoid facies may have obstructive apnea. An allergic crease, allergic shiners and pale engorged nasal turbinates help to focus attention to allergic disease as an etiology of insomnia.

A faint wheeze or diminished peak-flow reading with a history of night cough puts reactive-airway disease or nocturnal asthma as a possible explanation for insomnia.

An emaciated teenage girl with a prepubertal body habitus could have an eating disorder possibly accentuated by diet-pill abuse. Illicit drug use including alcohol, amphetamine, marijuana abuse as well as the use of nicotine can also factor in in insomnia.

To illustrate how variable the presentation of insomnia can be in general office practice, I will give

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you a few real examples of patients I have seen who either themselves complained or whose parents complained of their children having insomnia.

Amanda is an eleven-month old whose mother says never sleeps. Her frazzled mother described Amanda seeming as if she actually doesn't need sleep. Amanda went to sleep at about 2:00 a.m. every night only to awaken at 6:30 to get ready for the babysitters. Her mom dropped her off by 7:30 or so at the grandmom's house whereupon Amanda received a warm bottle, cereal, lots of hugs and was promptly back to sleep by 8:30 or 9 o'clock at the latest.

She slept until 1:30 p.m. then awoke to get a diaper change, lunch, play with grandmom and later have a snack until her mother's arrival at about 5:30 in the afternoon. On the car ride home, Amanda slept and remained asleep until about 8:00 p.m. Her mother then gave her dinner and Amanda was up and ready to play until the wee hours of the morning. Then the cycle repeated itself.

Kevin always seemed to be a peaceful child and a quiet boy who was really good at self-soothing

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pacification. By two years of age, he seemed excessively quiet and his parents insisted that he actually lost behavioral milestones. Now he seemed to spend more time rocking and playing with his hands.

In fact, he didn't sleep well preferring to sit up in bed and make repetitive drumming motions for hours prior to sleeping. His parents were most concerned about his lack of sleep but Kevin clearly displayed the social distance and repetitive movements characteristic of autism.

Tyler is a massive child who, at almost four years old, is morbidly obese weighing in at 132 pounds. I just saw him last week. His guilt-ridden mother was unable to avoid office visits any longer after he had an asthma attack that wound him up in the hospital.

Tyler, whose weight is clearly a time bomb for this poor child, snores audibly while awake. His mom confirmed loud nocturnal snoring as well and multiple night wakenings. She said his day-care provider says he is always sleepy and seems sluggish throughout the day. This pickwickian child has central and obstructive apnea confirmed by sleep studies.

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Jennifer's mother complains that her eight-year old is always sleepy during the day even though she is in bed at 8:30. Jennifer is so tired that she takes a nap for two to three hours after coming home from school every day. Her parents are in bed by 10:00 p.m.

Jennifer, who has a t.v. in her bedroom revealed that, after her parents sleep, she makes a bathroom visit and then turns on the t.v. and watches the Cartoon Network until about 2 a.m. Then Jenny makes a second bathroom visit and turns off the t.v. Her mother was shocked by this revelation.

A pretty girl, Marie had become discouraged by her thick thighs as compared to her mates on the cheerleading squad. Her mom was concerned because Marie just can't sleep at night. On questioning, Marie described rigorous late-night workouts on the treadmill and a big exercise routine before bed.

After lots of gentle prodding, she divulged that she had gotten generic Metabolife diet suppressants from the drug store and was taking several daily. In addition, she drank two or three Starbucks cold capuccinos every day. This athletic girl's heartbeat was

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racing at 120.

Darrell came to my office with an appointment last week. At twenty, he was just returning from an unsuccessful second attempt at college. His major complaint was an inability to sleep. He got no more than five hours at night and it usually started at about 4:00 a.m.

Darryl would lie in bed for hours feeling tired but sleep just wouldn't come. He told me of his unhappiness at returning home as well as sensing rejection by his parents. On further questioning, he acknowledged having no appetite, feeling uninteresting in having fun or finding old friends and generally feeling worthless. Darryl was entering into a major depression.

A retrospective of my experiences with insomnia led me to several conclusions. Most interesting is my realization that primary insomnia is an entity that I have yet to run across in my practice. Insomnia has been coupled with other physical or psychological findings and is often multifactorial.

As far as insomnia is concerned, well, I really couldn't think of any patients having isolated primary

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insomnia. Those that can't be sorted out through the history and physical exam by alterations in schedules or life styles or by attending to the underlying medical condition causing the insomnia require referral to a subspecialist.

Among the disciplines that are of particular help to me in the treatment of insomnia are psychiatry, psychology, neurology for sleep studies and otolaryngology for curative surgical intervention.

I have not prescribed hypnotics for insomnia. I have prescribed medicines that induce sleep for reasons other than insomnia, primarily for allergies. I do explain to the parents that their child may actually become drowsy when taking that Benadryl or Dimatabb or Zyrtec or Claratin. You should see the twinkle in parents' eyes as they anticipate with glee the secondary gain they may potentially be having in treating Johnny's allergies.

Yet, the very fact that antihistamine effects often linger on through the next day causing diminished alertness in children makes me use them sparingly opting for less sedating antihistamines first as well as

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increasing the use of nasal cromolyn or nasal steroids among compliant families combatting seasonal allergies.

My impression is that if a child truly has chronic intractable insomnia and that his general pediatrician is really unable to make a positive impact on the problem by recommending alterations in sleeping habits, daytime schedules, nighttime routines or by dietary modifications, stress reductions or appropriate management of medical and/or psychiatric illness, this patient needs a referral to an appropriate specialist rather than a prescription from his general pediatrician for a hypnotic agent.

Thank you very much for your attention.

DR. CHESNEY: Thank you very much, Dr. Clapp. That was superb.

Any questions?

DR. KAUFFMAN: Could you please comment on what you consider the normal developmental variation in the normal sleep patterns that you would expect. It seems to me, as we consider this, we need to really be very cognizant of, within variation, what is considered normal at different developmental stages. Could you comment on

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that, please.

DR. CLAPP: I would like to because, in my practice, I have become aware of a fact that is well-known by the NIH and others that we are a sleep-deprived nation. So many of us parents are living on the edge with regard to sleep and we are encouraging our children to do likewise. I run into a lot of tired children who are just exhausted by our rigorous activity schedule for them and the school requirements and lots of homework.

So sleep is oftentimes an issue brought up at my office. I find that, certainly for the toddler or the infant, a baby can sleep anywhere from twelve to sixteen hours a day and that is perfectly normal. Unfortunately for the parent, it is usually not in one stretch.

The younger child, maybe the ages of four to six, would appreciate and benefit twelve to ten hours of sleep a night. As children get older, that is when we see that they require more sleep but actually are not receiving it. They are very busy with their social agendas these days and, unfortunately, sleep deprivation is a frequent complaint that my patients come in with.

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I think that we would benefit our children by having them receive at least ten hours and a minimum of eight hours of sleep, the older children and teenagers. But I oftentimes see children who come in with eight solid hours of sleep who are very exhausted and I think they need more.

I really should defer this question to Dr. Ferber who could certainly answer far better than I.

DR. CHESNEY: Any other questions?

DR. DANFORD: Although you don't prescribe hypnotics for your patients in your primary practice, do a substantial number or any of them at all return from their psychiatry consultations with such drugs prescribed?

DR. CLAPP: I can remember, in my experience, one child that I sent to a neurologist who actually has a congenital disorder. She has hypomelanosis of Ito and she is mentally retarded. She was having some behavioral problems in school. She is not profoundly but significantly mentally retarded.

I sent her to the neurologist. Sleep was an issue but, in my mind, it wasn't the primary issue.

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Behavior was the issue. She came back from the neurologist with the suggestion of Benadryl only, not Valium. After a couple of weeks of trying, it really revved her up and so that was the end of Benadryl.

This young lady who is now--I think, at that time, she was about eight and she is eighteen now--it was a transient time in her life and, in my impression, whatever social stressors triggered her insomnia changed and it wasn't an issue for her. So I haven't had any come back with hypnotics.

DR. GORMAN: While not prescribing any hypnotics, have you had an experience with clonidine as a sleep aid for patients on stimulants with ADD?

DR. CLAPP: Interestingly, I haven't had any patients on stimulants for ADD who have had sleep disorders. Of my patients, it seems like they are very exhausted by the end of the day because they are hyper and busy. I will take that back. The only time that I can think of someone was a child who required three dosages and, at dinnertime, his mother was giving him, like, five or ten milligrams in the evening because he couldn't focus on homework. He was really, really far

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out.

Actually, rather than add clonidine what I did was send him to the neuropharmacology unit in Buffalo where they adjusted his medication and put him on another stimulant medicine.

DR. CHESNEY: Thank you again, Dr. Clapp.

Dr. Richard Malone from the Eastern Pennsylvania Psychiatric Institute will speak next on the perspective of the child psychiatrist with respect to sleep disorders.

Child Psychiatrist Perspective

DR. MALONE: Good morning.

[Slide.]

I would like to thank the committee today for the opportunity to speak about the possible use of hypnotic medications in pediatric populations. What I am going to do today is emphasize sleep as a possible symptom in psychiatric disorders in children and I am really not going to speak about primary sleep disorders.

I am a child and adolescent psychiatrist from an academic center and I treat a lot of children with serious psychopathology. In addition, I am involved in

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research in the pharmacologic treatment of childhood disorders.

[Slide.]

The FDA rules have been talked about already so I am not going to say anything.

[Slide.]

I would like to say that, both from my own experience and from many discussions that have occurred in national meetings for child psychiatry, it is evident that many children are treated with medications for which the safety and efficacy has really never been thoroughly investigated.

Most of the data, for instance in psychiatry, for medications comes from adult populations. There is evidence that the use of drugs in treating child psychopathology is increasing. Here I present a slide from an article we published about the use of antipsychotics in children and adolescents.

This is not about sleep disorders but just to say that I know that medication use is increasing. Dr. Julie Zito who had a large Midwestern Medicaid dataset looked at the use of antipsychotics in children.

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Although the overall use is low, which is, I guess, good, you can see that, between 1990 and 1996, there was a 63 percent increase in the use of antipsychotics in children in this population.

Actually, most of the increase began after 1993 when a new class of antipsychotics was introduced into the market. I think what this slide shows is that practitioners are actually willing to prescribe new drugs in children whether or not they have been tested in that population.

[Slide.]

What I would like to do now is emphasize that sleep disturbance is a part of psychiatric disorders in children. What I did is I looked at the DSM-IV which is the official American Psychiatric Association classification system.

You can divide most disorders into three types: those in which sleep disturbance is a diagnostic criteria for the disorder; secondly, those in which sleep disturbance is an associated symptom of the disorder although not one of the criteria; and then, thirdly, the other disorders where actually sleep disturbance is not

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mentioned in the official DSM-IV but, if you review the literature, many of these disorders also include sleep problems.

[Slide.]

The disorders in which sleep disturbance is a diagnostic criteria mainly come under the anxiety disorders and the mood disorders. I have listed a few of the relevant ones here. In the anxiety disorders, I am going to review a little bit about separation anxiety and then mood disorders, depressive episodes and mania. Having a manic episode is the main feature of bipolar disorder.

What I would like to say about separation anxiety disorder is that it occurs with some degree of frequency in children. The main feature is a an excessive distress regarding separation from the attachment figures who are usually the guardians. This distress can lead to--I have them with asterisks here--a persistent reluctance to sleep without the figure nearby and, actually, repeated nightmares of separation from the figure.

The other thing I would like to point out that

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is not so clear in this slide is that this occurs in up to 4Êpercent of children which makes it fairly common.

[Slide.]

These are the criteria for major depressive episode which mainly includes a two-week period of depressed mood or loss of interest or pleasure which is called anhedonia. Actually, in children, you can have irritability instead of depressed mood, as it says here.

What I would like to point out is that both insomnia and hypersomnia are key features of the disorder.

[Slide.]

This is mania. There have been questions. Mania, actually, is not that common particularly in younger children. It might have more of an increase once you get into adolescence. It is mainly an adult disorder. It has a distinct period of abnormal behavior that includes mood problems such as elated or expansive mood or irritable mood. They say that it lasts at least one week, but, really, if someone has a manic episode, it lasts longer than a week.

The thing that often happens is that the manic

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episode starts out with a decreased need for sleep and, actually, some of these people can stay awake for days on end and not really seem to require sleep.

[Slide.]

Before I go on, what I would like to say is that in the case of anxiety disorders and mood disorders, sleep improves when the disorder, itself, is treated. Actually, it would be a mistake just to target the sleep problem alone for treatment.

This is the second class of disorders in which sleep is an associated symptom in the DSM. This includes things like delirium which can occur for a number of reasons including serious medical conditions and fever. In fact, many infants and young children have delirium when they have fever.

Then there are things like substance abuse. Sleep disturbance can occur both as a direct result of taking substances or as a result of withdrawing from substances. This would be a thing to look at particular in adolescence. Then there are other serious psychiatric disorders such as pervasive developmental disorder, one of the main forms of which is commonly called autism.

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These children also have, often, a very deceased need for sleep. Schizophrenia, which can occur in children and, to some degree, more in adolescence although, really, it occurs more in adults, often has serious problems.

Again, in these disorders, if you treat the underlying disorder, the sleep problem generally is improved so the main purpose of showing them is to indicate that you should treat the disorder and not just the sleep.

[Slide.]

These are a group of disorders that occur in children for which the DSM-IV, at least, does not really talk much about sleep. But if you look at the literature, the literature often describes sleep problems in these disorders. In fact, the tic disorders include Tourett's disorder and the sleep literature, really early on, started talking about sleep problems in Tourett's disorder.

As well, there are what are called the disruptive disorders like attention deficit/hyperactivity disorder and conduct disorder which commonly have sleep

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disturbance, at least reported by the parents as part of the disorder although, again, I guess it is true that children don't often really complain about sleep problems.

Other things like the learning disorders often have accompanying sleep problems.

[Slide.]

This is the diagnostic criteria for attention deficit/hyperactivity disorder. Mainly you have at least six months of three kinds of symptoms; inattentiveness, hyperactivity or impulsivity. The onset is before the age of seven. So, actually, the onset is often a way to figure out what the child has.

The thing I would like to point out is that it, too, is a fairly common disorder occurring in 3 to 5Êpercent of school-age children.

[Slide.]

These are the criteria for conduct disorder. Conduct disorder is a disorder mainly in which the children and adolescents break social rules. This would include things like lying, stealing, and, actually, many of the items of the disorder are because of aggressive

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behavior.

This is also a fairly common disorder occurring in 6 to 16 percent of male children, and less in female children, 2 to 9 percent of female children. Females are usually less aggressive. If you are aggressive, it is easier to meet the criteria for conduct disorder. But, again, it is a fairly common disorder.

[Slide.]

This really is related somewhat to attention deficit/hyperactive disorder. This is a slide that shows part of what is in the PDR. As you know, the use of stimulant medication is one of the main treatments for attention deficit disorder. Ritalin is one of the name brands.

It is true that stimulants can cause sleep problems, but what I want to point out is that, in the PDR, there is labeling that Ritalin is indicated as an integral part of a total treatment program which typically includes--and it goes on to describe things.

This is a unique kind of labeling in the PDR. I put it up so that I might suggest that if we would ever get to the point of labeling hypnotics for use in

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children that there would be some sort of addition like this, both in labeling and advertising, that the main treatment for sleep disorders in children is not medication but other behavioral treatments and that sleep problems can be caused by a number of other treatable conditions.

[Slide.]

I looked through the literature to try to find out how much medication is used in treating sleep problems in children. There are probably more studies than this but I found two. One was by Mindell et al., published in 1994 in Pediatrics. In both of these studies, they used Mindell's survey and they surveyed various people.

Mindell surveyed pediatricians. She had a number of findings. One of the findings was that, in pediatric residencies, the mode number of hours devoted towards sleep disorders was 0. She did find that they commonly used behavioral techniques for treating sleep disorders, but she was alarmed, somewhat, in finding that 14.8 percent of them would prescribe pharmacologic treatments additional for sleep disturbance.

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[Slide.]

Now this is a slide about a European study using very similar methodology in which Oliviero surveyed pediatricians and child psychiatrists. He found that, in this European population, 58 percent of pediatricians used pharmacologic treatments for sleep disturbance and 61Êpercent of child psychiatrists used pharmacologic methods.

Mostly, it was antihistamines that was used. I don't know how well this speaks about child psychiatry, but, in 22 percent of the cases, they were willing to use benzodiazepines which was significantly more than pediatricians who used benzodiazepines 4.6 percent of the time.

That is the end of the slides but I would also like to add that, in a recent editorial in JAMA, Dr. Rennie gave caution about drug studies. The caution was that drug studies that are published emphasize the benefits of drugs. This is mainly for three reasons. Firstly, it is the positive results that are more quickly and easily published in the literature and the negative or neutral findings are not published, giving an unbiased

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opinion that drugs are very beneficial.

Secondly, what they actually found was that the same data is often published multiple times, sometimes different author sets with the same data, which also gives a false impression about the benefit of drugs. It gives you more studies to show.

Thirdly, many drug studies are designed in a way to stack the results that the drug of interest is better than the standard treatments, again, sometimes giving false results, actually. They had talked about--I am not really familiar with the use of antibiotics, but they talked about the fluconazole study which was really stacked against amphotericin and nystatin.

Fourthly, one of the problems that I think we have is that most of the drug studies are really done by industry and, at least in psychiatry, very few other studies are done in children that are not really--very few studies are done in children so, in the end, you end up with datasets that really might have an economic slant towards them more than the best interest of the child.

So, in summary, what I would like to say that it is important to do studies in children because we do need

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data on safety and efficacy but we should be careful about the way we are going to label and advertise for hypnotic use in children.

Thank you.

DR. CHESNEY: Thank you very much for your perceptive comments and words of caution.

Any questions?

DR. SZEFLER: It has been interesting listening to these three talks. What was the major topic coming into that room was sleep, and I would wonder if a pharmaceutical firm came to your office, in terms of a research-development person, and said, "Dr. Malone, I want to study this drug for sleep," would you design a study for sleep and, first of all, how would you approach inclusion and exclusion, or would you convince that person to try to study a disorder in children, like one of those that was listed?

It seems like, from both talks, it would be hard to design a study that was primarily oriented at sleep without having to do an extensive differential to remove what were the other problems and then approach those in different ways.

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DR. MALONE: My main area is not sleep studies but I agree that there would be a big differential. I guess if I were to design a good study for drug study and sleep problems in children, you would have a number of exclusion criteria. Something I forgot to mention, for instance, is that in the DSM-IV field trials looking at insomnia, the most common reason for insomnia was insomnia related to a psychiatric disorder.

The second most common reason was primary sleep problems, but it was 44 percent of the time that it was a psychiatric disorder and only 20-some percent of the time that it was a primary sleep problem.

So I think you would have to have a lot of exclusion criteria including psychiatric disorder and that you might even want to have a run-in in which certain behavioral techniques or ways of adjusting the environment at home were used to assure that you were dealing with a sleep problem--

DR. SZEFLER: It would seem, kind of from what you are both saying, that sleep is a worthwhile thing to look at but it is more of a secondary variable than it is a primary variable.

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DR. MALONE: It can be a primary variable in some disorders, but sleep disorder is not my main area of expertise. I think Dr. Ferber might talk more about primary sleep disorders.

DR. GORMAN: I think you have been very cautious, appropriately cautious, to say that it is maybe not the primary disorder in a lot of things that you look at. The FDA is interested in having us look at hypnotics. In your experience, is that the only class of drugs that is used as sleep aids or is that the one most widely used by the psychiatric community at this time?

DR. MALONE: I would guess in psychiatry it would be one of the least-used agents. For instance, in the slide I had, I would have to guess, but I would guess that it would be antihistamines. People have mentioned clonidine. But it is not very commonly the hypnotics that are used in child psychiatry, that I see, or that I read about in the literature.

DR. WARD: Dr. Malone, once you have treated the primary psychiatric disorder, how often would you use a hypnotic or some treatment, pharmacologic treatment, for sleep in addition to that?

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DR. MALONE: I think that, often when you treat the primary disorder, you don't really end up with sleep problems. However, I did mention there are a number of psychiatric disorders in which sleep disturbance is associated so I would guess that, in some percent of times, you would end up having a child who is treated for the disorder yet may have remaining sleep problems.

That doesn't mean, though, that they would need drug treatment for that problem. It has been brought up that, often, sleep problem is not the complaint of the child but the complaint of someone else. However, I am not sure that these sleep problems are always appropriately treated in the community so that people may end up using medications even though there are better methods they don't know about or don't have time to discuss or some other reason out there.

I wanted to comment also about attention deficit disorder with stimulant use in sleep problems. I have found that one of the problems that occurs is that people never ask about sleep problems before they give the stimulant so, on the first visit, they say, "So how is the child sleeping?" And they never did sleep well. So

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it is not even always that apparent what the stimulant is doing to the sleep unless you get a good history beforehand.

DR. CHESNEY: Any other questions for Dr. Malone? Thank you again.

Dr. Ferber is at Children's Hospital in Boston and, I understand, runs a sleep-disorder program. He will speak to us about sleep disorders from the perspective of an expert.

Expert Perspective

DR. FERBER: Thank you very much.

[Slide.]

We have been running a center for sleep disorders in Boston for over twenty years now and have seen many thousands of youngsters, both in our clinical setting and in our laboratory. The vast majority of youngsters that we see in the clinical setting come in with complaints, usually from the family, that the child is not sleeping well and, as has been pointed out, the term "insomnia" usually is not applied at least to the young children, and so that may explain some of the numbers that may be presented in terms of the frequency

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of insomnia.

But, if you add on sleeplessness as a label, I think you find that it is very common.

Before I try to run through some of the settings in which we see a child who is not sleeping well, and it will be similar, in some extent, to what has already been presented, I would like to make a few lead-in comments.

First of all, like Dr. Clapp said, we very rarely resort to hypnotics in the treatment of these youngsters, although there are some situations in which we do require hypnotics. The question of do we see primary insomnia in children is a actually very complicated one and raises a question as to what is primary insomnia and does it even exist and does it exist in adults.

I would like to point out, like Dr. Laughren showed, the indication for Sonata. If you look up other hypnotics in the PDR, zolpidem, triazolam, temazepam, for instance, they all say the same thing, "indicated for the short-term treatment of insomnia."

Under "indications," it does not say, "indicated for the short-term treatment of primary insomnia." I

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think that, in practice, most people are not trying to make that distinction when they are using these agents. Although most studies, in fact, have selected groups of subjects more or less listed in that category, there are studies that have been done on hypnotics and other groups such as, particularly, depression, arthritis and so on.

The DSM-IV is not the only nosology in the world. The International Classification of Sleep Disorders--I am sorry I don't have a slide from this, but I will read it--has a category called idiopathic insomnia which is, I think, from what primary insomnia comes.

I would like to read the definition because you will see the overlap between what this disorder is and what many of us would be calling "other disorders." It says, "For idiopathic insomnia, synonyms are childhood onset, lifelong insomnia, insomnia associated with problems of the sleep-wake system, excessive arousal, inadequately developed sleep system."

And it says, "The disorder may be due to a neurochemical imbalance of either the arousal system or the many sleep-inducing and maintaining systems. Some patients with idiopathic insomnia may merely fall toward

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the extremely wakeful end of a normal distribution curve." I think that sentence may be the way many of us are thinking of primary insomnia.

But it goes on to say, "In others, actual dysfunctions or lesions may exist within the sleep-wake system, be they neuroanatomical, neurophysiological or neurochemical. Theoretically, either hyperactivity within the arousal system or hypoactivity within the sleep system may cause idiopathic insomnia."

In other words, even in this category of idiopathic, it doesn't mean that there is not a cause. It may mean that, in the individual patient, it may be difficult to identify that cause directly.

What I would like to do, then, is continue to emphasize the fact that the vast majority of youngsters we do see who are not sleeping well have problems that we have put another label on. Most of them are treatable without medication. In fact, I feel that, in most of them, medication is not indicated. But there are some situations where we want to consider it.

Most studies show huge numbers of youngsters are up at night. This is within the first year and you can

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see, in the second half of the first year, about half of the youngsters are still up at night at least occasionally, which is an extraordinary number.

As you move on into the toddler years, it is not quite so high but we still get complaints, in most studies, of about a quarter of children having at least occasional problems at night, quite extraordinary numbers.

[Slide.]

Some of the common situations that we see, and some you have already heard about. Dr. Clapp described some of the history leading up to some of these diagnoses. I am not going to talk a lot here about the treatment except to emphasize that it is usually behavioral. One of the more common that we see is a child who technically could sleep well, has normal wakings at night but, each time they fall asleep, they do it in a certain way that involves some type of habitual behavior, usually habitual parental interaction. If that is there, they go right back to sleep. If it is not, they don't. Rocking, patting, pacifiers, are some of the more common.

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Feedings at night beyond the age at which feedings are required on a nutritional basis can cause an extraordinary sleep problem particularly in young children. The feedings may be viewed as a way to get the child back to sleep. It may be viewed as responding to hunger which is there because the child learns to be hungry in the middle of the night.

This causes a cascade of effects including wetting, hunger at night and markedly disrupted Circadian patterns. This causes one of the worst problems that one sees in practice and, yet, certainly, the treatment is by decreasing or eliminating the feedings and not by putting a pharmacologic agent in this otherwise normal youngster.

[Slide.]

Limit setting. This is a problem in the older toddler or middle-aged child, in particular; refusal, stalling, demands, extra--"I want another drink of water." "I need another story." "I need to go to the bathroom again."

Basically, this is a youngster who could sleep perfectly fine if the family could keep the youngster in bed or in the bedroom. The problem is one of limit

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setting. Limit setting, itself, is a very complicated disorder or problem--I shouldn't say disorder. In terms of dealing with it, the family may not understand that limit setting is important. They may not know how to set limits. They may have trouble setting limits because of guilt, perhaps because of a child's illness.

There may be secondary gains to the child being up, for instance, keeping the parents from fighting with each other. Limit setting is very difficult in a psychosocial setting. But, still, dealing with all of these things can be done and can be done fairly successfully.

[Slide.]

Into the schedule part of sleep disorders, this is of enormous importance and, I think, very often, the area in which people know the least, both patients and the practitioners.

Schlafbereitschaft means sleep readiness. That is when the Circadian phase switches from wake to sleep, in which it becomes from hard to fall sleep to hard to stay awake. The forbidden zone is the hours preceding that. Many people do not realize that, in the couple of

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hours before the onset of sleep, everybody, actually, not just children, go through an increased period of wakefulness where it is the hardest time of the whole day to fall asleep.

Very often, that explains much of the problem. The child is put to bed in a phase when they simply have not chance in the world of falling asleep. That is a timing issue. It is not a dysfunction of the underlying sleep system at all.

We have heard about the AD/HD group, for instance. Most studies of that group show normal sleep. One of the problems with that group is that they may be so difficult to manage during the day that people are anxious to get them to sleep at night and they may go with an earlier bedtime than is actually appropriate.

[Slide.]

Another problem with schedule is similar to what I just said, when the parents, in their mind, believe that the child should get more sleep than is physiologically possible. This would be very much like the youngster that Dr. Clapp described who was in bed at night and awake and who slept all day.

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If a child is in bed for twelve hours and had a ten-hour sleep requirement, you are going to have two hours of waking. It is as simple as that, although it may not be seen that way. It can happen in the early morning. It can happen at bedtime or, particularly, in the child who still naps. It can happen in the middle of the night.

People do all kinds of things so I will see youngsters who are not sleeping at bedtime for two hours and come in on hypnotics, but the child is sleeping perfectly normally and getting a completely normal amount of sleep.

Like the case Dr. Clapp described, not only can it be redistributed in the night, of course it can be redistributed throughout the day and that will just pull itself from the nighttime. Children, in general, are very good sleepers and they are going to get pretty much the sleep they need, especially young children.

If they don't get it in one place, they are going to get it in another place. So it tends to redistribute and, by controlling the schedule, by not allowing sleep in one place, it will then fill in in

at another place.

[Slide.]

Delayed sleep phase is where the child's timing, their Circadian clock, has shifted later and they are ready to fall asleep later and ready to wake later. That is the natural direction our sleep phase wants to shift. This would, then, lead to bedtime struggles or inability to sleep or insomnia at the desired bedtime and then difficulty waking or late sleeping in the morning.

This is an extremely common problem at all ages, actually even from infancy. Throughout childhood, though, it is very easy to control. As long as you get parental cooperation, as long as the morning waking is enforced on a regular basis, including the weekends, and excessive sleep not allowed during the day, the child will gradually be able to move the sleep phase earlier and correct and fall asleep earlier.

It becomes an enormous problem in adolescence where the drive to a later sleep phase seems to be biologic anyway and the social factors interfering with this shift become enormous. We just had a meeting a few weeks ago at the National Academy of Science down here,

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mostly on this problem, and everyone felt the frustration.

They knew, technically, how to correct this problem but you cannot get a sixteen-year olds to go to bed at 8 o'clock. It is just not even worth discussing in our society. This is such a problem because it leaves these adolescents chronically sleep deprived. There may be a place to consider medication, at least until we can get society, school systems, to flip around and take a different view of this what I consider an enormous problem.

Whether the problem is technically in the hypnotic range, there are more and more reports of medication like melatonin to be used as phase shifters. I think this has to be one area that we, unfortunately, do have to think about this type of intervention.

[Slide.]

Anxiety you have heard a lot about. Most of the anxiety that we see actually can be treated with various types of support. As far as I am concerned, if putting a parent in the bedroom temporarily will get a youngster to sleep, I would rather do that than go the medication.

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But there are definitely situations where we have global, chronic anxiety. If the youngster is terrified at night, then they may not be able to sleep because of that fear.

It is the anxiety syndrome that should be treated but, as part of that, it is conceivable that one would need to have some extra help at night. It may be the same type of medication, if medication is being used.

There are certainly other psychological conditions; obsessive-compulsive worrying at night. You just heard, mania is not a very common problem in childhood but can certainly cause sleep loss. Depression is a well-known cause of poor sleep in adults. It is much less likely to cause the same type of sleep problem in children, although it can. It may even cause hypersomnolence rather than insomnia.

Psychosis, of course, is another issue. Again, the main thrust is usually treating the underlying syndrome, but there may be a place for treating the sleep component separately.

[Slide.]

Medical problems; here, again, there are a number of medical conditions that can interfere with

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sleep. More than the ones that I have listed here for this discussion, I think the ones that are most important are conditions that cause pain. That is certainly going to interrupt sleep. If the pain cannot be adequately treated medically, then there may be a place for treating the attendant sleep disorder.

Spasticity, spasms at night, disorders such as that can lead to a sleep problem and the underlying conditions are not always satisfactorily treated.

[Slide.]

You can't really see that, but that is a mouthful of tonsils. You already heard about that. If breathing is interrupted, whether on an upper airway basis like this, with chronic snoring and, perhaps, full sleep apnea or, on a lower airway basis, with reactive airway disease, you will have sleep disruption although, in both of these cases, I think the treatment is rarely the sleep problem directly. It is almost always the underlying condition.

[Slide.]

We have heard about bit about treating other conditions. The treatment of the other conditions may,

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in fact, cause an attendant sleep disorder. We have heard about the treatment of asthma. The SSRIs that are used in the treatment of depression may actually lead to a worsening sleep. The stimulants, and so on.

Clonidine; I certainly have seen clonidine used in a number of youngsters, particularly in those in which the AD/HD is more complicated, where there is underlying dysfunction on a deeper level. But if you have a child who is on medication that they have to be on and there is a secondary sleep disorder, it is not a situation we very often have used medication, to, then, treat the side effects.

But you have youngsters who are treated with multiple drugs for cancer, for asthma, and so on. There may be a place to at least think about it in this condition where you cannot withdraw the medication they are on and the child is not sleeping well. It is actually a very complicated area and, for study, extremely complicated but probably should be considered.

[Slide.]

Finally, to me, one of the most important areas, or at least one that we come to medications most

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commonly, is that in which there is underlying central damage. These are usually youngsters with marked neurologic damage, whether syndromic or related to injury, in which total sleep time is definitely reduced and the ability to sleep appears to be damaged.

Again, in the crossover between primary insomnia, very often, we don't know exactly what the injury is that is causing the sleep problem but this may be part of global injury. But this is a pretty wide spectrum. If you have youngsters who are completely blind, for instance, the ability to control their Circadian schedule may be lost.

There are more and more reports about the treatment of blind individuals, again usually with medication, if I can call it medication, such as melatonin. But there is an area in which we have very little other choice right now and the need is certainly there.

PDD or autism was mentioned. Here we have a presumed dysfunction of these systems. The sleep disorder that may go with PDD is sometimes extraordinary and behavior intervention may simply not be able to solve

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that. These problems for the families can be quite marked and is an area in which I think a lot of thought needs to be given.

So, in summary, I would like to emphasize that insomnia, or at least sleeplessness in children is extremely common, that the vast majority of problems such as these are treatable by behavioral intervention or by schedule adjustment without the need for any medication.

Some of these problems resolve by treating the underlying medical or psychiatric conditions. However, like adults, there are conditions in which further treatment may be necessary and these include damage to neurologic systems controlling sleep, arousal and Circadian function such as caused by perinatal injury, syndromic conditions, malignancies and the like.

There may be presumed damage to these systems, as we assume is the case, in disorders such as PDD. There may be altered function of these systems as may occur in global anxiety, psychosis and other psychiatric conditions. The function of these systems may be interrupted by various medical conditions, particularly those causing pain or spasm.

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There are situational conditions where these systems cannot function well, short-term, following a scary event around the time surgery, before neurophysiologic testing, for example. And then we have a delayed-sleep phase, particularly in certain adolescents where we know the problem but, for various reasons, it cannot be corrected and we cannot get the system functioning as it should be.

Again, I want to overlap that, in this description, I think there is quite a bit of overlap between the various causes of sleeplessness that I have described here at the end and what might be meant by primary insomnia which I think is a questionable diagnosis at best.

Thank you very much.

DR. CHESNEY: Thank you, Dr. Ferber.

Questions?

DR. NELSON: I was wondering if you could comment on whether there would be an area of use of medications in transient insomnia or in insomnia related to issues such as hospitalization, disruption of day-night cycling based on, for example, ICU admission

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and the like.

DR. FERBER: Right. That is what I mentioned at the end. I think that is a fairly obvious one. That is an area in which hypnotics are certainly used today and they are going to be used, whether they are formally approved or not, for children. But people don't have a lot of guidelines in that group.

But you have a youngster in the hospital, presurgery, very frightened, it seems to me a place one could make a good argument for the use of hypnotics and post-surgery, particularly if the pain cannot be controlled. It is certainly used before studies such as MRI or EEGs. Again, one is going back, often, to just medications that have been used for fifty years.

We don't have a lot of guidance in these areas and I think it could be useful there.

DR. SZEFLER: Dr. Ferber, I was wondering if you could make a gross estimate of the percentage of kids who go through your sleep-disorders clinic who end up on hypnotics for the so-called primary insomnia program. When you rule out all these myriad of psychiatric conditions, structural problems, et cetera, et cetera,

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where, in the final analysis, you are convinced that there is a significant enough problem to try a trial of hypnotics.

It is obviously going to be a very small number, but how small is it?

DR. FERBER: We don't use the term "primary insomnia." We generally will attach a cause but I think, in some of these, you could say idiopathic in the sense that we can't put our hand right on it because there is no way to measure that.

It is probably less than 5 percent in our group, and, remember, we get the referrals, often, of the worst of the worst. Even if the youngster comes in with retardation, perinatal hypoxia, and so forth, we don't start, generally, with medication. We look for all kinds of other causes first because even that youngster can develop many kinds of behavioral or schedule issues.

We fix those first, but there are groups that, at the end of that, I am convinced their sleep systems simply don't work right.

DR. SZEFLER: As a quick follow-up question, we certainly know that self-report in adults of sleep can be

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highly flawed. I think that is a fairly well-established phenomenon that some adults report they have terrible sleep and you study them.

I guess the question becomes is it common to see that same dynamic where we generally don't rely on self-report from children but where, in fact, there may be kids who sleep pretty well but their parents, for whatever psychiatric reason, are over reporting sleep dysfunction. Does that ever occur?

DR. FERBER: It occurs quite frequently. If I had a dollar for every parent who has told me that their child has always been a poor sleeper or that their child has never slept more than two hours straight in their life, I would be rich.

One of the ways to go about that is simply by charting. As is true in adult insomniacs, as has been pointed out by others, people have memory, basically, for two days. They remember last night and they remember the worst night. That is usually what they want to tell you about.

"Well, last night, he slept--" "What about usual?" "Well, he could be up as much as--" If your

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sleep is disrupted twice during the night, it may feel that you have never slept. On the other hand, if you have to put it down on paper, people will frequently come back and be very surprised.

If that is not enough, there are actographic measures that can be done to try to correlate and corroborate the reports. But, you are absolutely right; you have to take the history very cautiously or you might well be assuming a much bigger problem.

DR. GORMAN: Dr. Ferber, as the parent of three sleep-deprived adolescents which occasionally causes sleep deprivation in their pediatrician father waiting up for them to come home, could you outline a set of diagnostic criteria you would use to initiate hypnotic therapy in adolescents, because I think we heard from the FDA that it is a proposed indication for hypnotics in Circadian rhythm disorders which I think approaches this adolescent delayed sleep.

So is there a set of criteria you would have in your mind before you would initiate these agents in that group of individuals?

DR. FERBER: Yes. At first, we would try to

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identify what the sleep phase is and take a look at what time they have to get up in order to get to school and what time they would, then, have to be asleep by if they were to get enough sleep on that schedule and then what their social life is like and what they are willing to do and is it at all possible.

We have youngsters, for instance, who have to be up by 5 o'clock in order to get ready and to catch the bus. That means they would have to be asleep by 8 o'clock to get nine hours of sleep. To get sixteen-year olds asleep by 8Êo'clock is simply out of the question.

So we have a real dilemma here. Exactly what is the best way to sleep--they are going to go to sleep later than that. They are going to be sleep-deprived which means, if you get them up at the same time on the weekends, which they won't do--but, if you did, they would just simply be chronically sleep deprived.

So you have to let them sleep later to make up some of that sleep, but that affects that Circadian rhythm and then comes the weekday, can you get them to sleep any earlier. I am not sure of the answer to this because it is just a very difficult question.

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I think, ultimately, the answer is societal. There is legislation sitting there about changing school starting time. There have been encouraging results when that has been done. I think, ultimately, the solutions are going to come from there plus education.

People talk about who would have believed that smoking could change in so many people. Who might believe that kids would start to think it is important to go to sleep earlier. But you have a youngster who is chronically sleep deprived who is working at it somewhat but we can never get them enough sleep and they are willing--this is the crucial part--they are willing to go to bed earlier during the week, they just simply cannot fall asleep because of where their sleep phase is.

That is the youngster I would consider it in, but it is probably not an every-night thing. One study, for instance, showed using, in this case it was melatonin, again, on Sunday nights to try to advance them so they could go to sleep early enough during the week.

We just don't know the answer to that but that is the situation.

DR. WARD: On your slides, the only

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pharmacologic agent I saw you listed was chloral hydrate, one that most of us have sort of discouraged for chronic treatment. Of the drug classes available for hypnotics, which ones would you think are most appropriate to study and to have labeling for children?

DR. FERBER: Again, it depends on the situation. But you are asking me to give the answer before we do the study. That is part of the problem. In the youngsters that are severely neurologically compromised, I can give you some anecdotal experience which is I have not had great luck using the usual hypnotics that are used in adults, such as the benzodiazepines.

I have been able to get almost any youngster to sleep with a drug like chloral hydrate if I am willing to go to a high enough dosage which, sometimes, is a fairly large dosage. And I do find that the effect persists, but I would be much happier using a less toxic agent in these youngsters. I don't have a lot of choices in that group.

Again, I am really not trying to push melatonin, but there are so few data out there. There are few reports of melatonin in that group, but it is not even

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carefully diagnosing these youngsters into separate categories. It is just sort of anybody who is subnormal function and this one medicine is thrown at them reporting some good results.

I think that just emphasizes not what drug should be studied but we don't know. We simply don't know in these settings.

DR. SZEFLER: Just to follow up on Dr. Ward's question, is there a gap to be filled. It sounds like, from all the speakers, there has been a description of a problem and maybe not a concentrated effort to look at a problem. There is, potentially, a drug being proposed for that problem. It is a significant enough problem to look at to concentrate some effort.

It sounds like you have the patients. You don't have the answers. There may be a drug. We don't know enough about the drug but does it sound like this is an effort worth going after.

DR. FERBER: I am not sure I completely followed that, but if you are saying--

DR. SZEFLER: I think it is just like what Bob was asking. You have a problem out there. You want to

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use medications. You have listed the medications and it sounded like you were unsatisfied about them except for melatonin, if this is an answer.

DR. FERBER: I wouldn't say I am satisfied with melatonin. I am just saying that is an area in which there have been studies. It is one area in which there have been studies and more and more studies recently and some encouraging data in certain settings.

I am trying to make a distinction here. I am very worried about people applying medication to the vast majority of youngsters who are really normal function and whose sleep problem is quite soluble without going to a pill. I think that going to a pill, in that setting, is very dangerous for many, many reasons, not the least of which gives a message to the parents that their child is somehow abnormal and that the solution comes from the medicine cabinet when it really is interactive.

But if we get down below that, that are plenty of youngsters who have medical neurologic dysfunction or psychiatric dysfunction where sleep is a significant problem. Some of these youngsters, for example--I mean, it gets complicated. You may have a youngster who is

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sleeping five hours a night.

The youngster couldn't care less. And there may not even be obvious dysfunction carrying over into the daytime. Does this youngster get treated? On the one hand, no. But, on the other hand, if the youngster gets five hours of sleep and is wild and needs management the rest of the time, you cannot ask a family to take care of this youngster on only five hours of sleep.

So, getting this youngster to sleep may be the difference between keeping this youngster at home or have him go out into placement. So I think yes, there are definite indications to consider.

DR. SZEFLER: I am kind of seeing the wisdom in the questions that they asked here. The other question you could ask is that some of these problems that you are seeing secondary to sleep deprivation. Of course, on a medication like--

DR. FERBER: Sometimes. Dr. Clapp presented one case--obviously, she just gave a snippet--but where I would have a youngster who was lying awake until 4 o'clock, getting up during the day after four or five hours of sleep and is acting depressed during the day,

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this youngster may have a primary depressive syndrome but I would have trouble making that diagnosis until we got this youngster enough sleep and then saw if the psychological symptoms persisted.

You can certainly get an overlap of a sleep-deprived child and one who is depressed in terms of appearance. That is absolutely correct.

DR. CHESNEY: Just one more question. Dr. Fink

DR. FINK: Could you comment on the use of the sleep lab, particularly polysomnography, in looking at percent sleep efficiency and REM time to actually separate out the organic from the sleep-hygiene problems? Do you feel that if you do polysomnography, would you, looking at sleep efficiency and REM time, be able to separate the majority of truly organic sleep disorders in these neurologically impaired children from just sleep deprivation?

DR. FERBER: I am sure you could. But, in most of the youngsters who I am calling normal, that is hardly necessary. If you did it, you would certainly find normal sleep, if not the first night, as they adapted to the laboratory. I think what is striking in this other

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group is the fact that you can confirm in the laboratory, if necessary, the poor sleep patterns reported at home.

DR. CHESNEY: Thank you, again, Dr. Ferber.

We would like next to hear from Dr. Riddle who, I believe, will give us the perspective of the American Academy of Child and Adolescent Psychiatry. Following Dr. Riddle's presentation, we will take a fifteen-minute break and then return for the next presentation.

American Academy of Child and Adolescent Psychiatry

DR. RIDDLE: I am grateful to the advisory subcommittee for this opportunity to speak this morning. I am here representing the American Academy of Child and Adolescent Psychiatry. This is a national professional organization of over 7,000 child and adolescent psychiatrists.

I am a member of the Council of the Academy which is the fifteen-member governing body and also a member of the research committee. The Academy is already on record in support of safety and efficacy research that may lead to indications for medications used in children with psychiatric disorders. However, the Academy, at this point, has not official position regarding insomnia

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in drug development so, unofficially, I am going to offer four suggestions on behalf of the Academy.

Let me say that virtually everything I am going to talk about has been presented already by Drs. Clapp, Malone or Ferber so I will try to be brief because I think you have heard most of this.

The first suggestion would be to target what we have called primary insomnia but, perhaps, we should call it intractable or otherwise untreatable or I am not sure what the term would be. But let's say otherwise untreatable insomnia for studies and for labeling.

Then, specifically, consider excluding insomnia associated with other disorders that can be treated with other drugs and therapies; anxiety disorders, mood disorders, et cetera. Exclude insomnia that is an adverse event of another drug unless that drug is an absolute requirement for treatment.

Exclude insomnia that is secondary to substance use or abuse including caffeine. And, finally, exclude children whose insomnia resolves in response to parent and child training in sleep hygiene management. The second suggestion would be that if there is labeling,

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please indicate that the medication would be part of a total treatment program.

The third suggestion, for studies and labeling, consider separate studies for each developmental stage, adolescence, school-age children, toddlers, infants. Finally, the fourth suggestion, if there is labeling, consider limiting the length of treatment with an hypnotic agent unless a qualified sleep expert has diagnosed a chronic otherwise untreatable insomnia.

Thank you.

DR. CHESNEY: Thank you, Dr. Riddle. Any questions?

DR. KAUFFMAN: Mark, do you think there is any role at all for labeling these as an adjunct to the otherwise treatable conditions that have been discussed in addition to the so-called primary or untreatable?

DR. RIDDLE: As has been said earlier this morning, I think that is a complex question. There may be situations where having a specific medication targeted at sleep would be helpful although we haven't heard the profession kind of crying out for that.

DR. FINK: If you took your first suggestion,

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could you give us an estimate of how many children that would leave that would potentially require medication or benefit from medication treatment?

DR. RIDDLE: I think that that is a very important question. I don't know of data that will speak to that. I think we are going to hear, in the next talk, about what is known epidemiologically. In my practice, that would be virtually no youngsters, but I see kids with psychiatric disorders. So I think that that is a very, very biased sample.

I don't know of data right now that would give us a good answer to that question.

DR. SZEFLER: Mark, I know you are aware of this as a problem but I think the panel, in general, needs to appreciate that stimulants certainly are being used in combination with hypnotics quite regularly. The hypnotic that I have read mostly about is, of course, clonidine which I, personally, have concerns about its side effects, carryover to the next day, et cetera, et cetera.

There are actually two or three or four papers. This is more of a comment rather than a question for you, so I would be interested in your thoughts. But the point

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is that the child and adolescent psychiatrists have not been the most critical of the use of off-label compounds for the treatment of sleep, for the treatment of rebound of stimulants.

Given the tremendous increase in the number of children now entering adolescence and now entering adulthood who will have the ongoing definite need for stimulant pharmacotherapy and, given a certain percentage of them will have difficulty initiating sleep because of that classic and well-described side effect. Obviously, certain cases can be handled by giving the stimulants earlier in the day, alternative forms of stimulants, but it remains a common practice in this country for child psychiatrists to try to add on some sort of hypnotic therapy to settle these kids because the stimulants really can't be used later in the day.

I just wondered if you had any suggestions for the panel about how to address this kind of somewhat unusual need for a safe and effective method of helping kids sleep.

DR. RIDDLE: This is, obviously, a very important issue, Alan. I think that there are

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differences of opinion about this within the field and also within the Academy that I am here representing. I would go back to the suggestion, although I am sure this is helpful enough, and that would be to exclude youngsters with insomnia that is an adverse event of another drug unless that drug is needed to treat the disorder, for example, the stimulants with AD/HD.

I do believe that, whether it is stimulants for AD/HD or some of the medicines we use to treat other disorders, there are times when it is very hard to adequately treat the child without having some negative impact on sleep.

I don't know how large that number is and I believe that experts would vary as to how rare or common they would say that problem is.

DR. SZEFLER: Just to put some closure on this, it is very clear in the adult psychiatrist literature that once we effectively treat depression or anxiety disorders with, say, serotonin reuptake inhibitors, there still will be a certain percentage of adults whose depression will be totally treated but which will still require a short-acting benzodiazepine in addition to

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really restore them to normative functioning.

I wouldn't be surprised that there are certain adolescents who, once the depression is effectively treated, still could benefit if we had some safety data on standard hypnotics.

DR. RIDDLE: Again, I would agree. I think that goes back to the first suggestion excluding youngsters that have other disorders that can be fully treated with the other drugs, and that isn't always the case.

I think one needs to be careful, and it can be a slippery slope, to begin to use a second medicine to treat a side effect potentially of a first medicine--and when I say side effect, I think sometimes what may appear to be an untreated part of the primary or component of the primary disorder is, in fact, a side effect of the medication.

DR. SZEFLER: I agree that, very commonly, the problem with getting AD/HD kids to bed is not rebound and insomnia but it is just the primary disorder that we have trouble treating between the hours of 7:00 and 10:00 at night. So I totally agree on that.

DR. RIDDLE: In terms of the point also you

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mentioned about adolescents, again I think the profession is not in complete agreement about this but very simple things that have been mentioned like encouraging parents to allow teenagers to sleep in late on the weekends, reducing stimulation late at night, encouraging exercise.

I have a sixteen-year-old daughter. I don't think any of the members of her field-hockey team had too much trouble getting to sleep at night during the season, for example. I know that is anecdotal, but I do think there are things that can be done that won't cure a Circadian rhythm problem--there is no question about that. I think Dr. Ferber is right--but can help considerably.

DR. NELSON: This question might be appropriate for everyone to address at some point in the discussion but it occurred to me what your opinion would be in terms of primary or transient insomnia for those two indications, whether one could extrapolate efficacy data from the adult setting given the similarity or not and whether what we would need is predominantly dosing and safety information to extend that.

DR. RIDDLE: I am not an insomnia expert. When

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you mention transient, I am not even sure what I am going to say meets the exact definition or criteria, but there has been some discussion of pain and pain syndromes in children. Also, major procedures, surgical procedures. Kids being treated for various types of cancer go through a lot of procedures that can be quite painful and distressing. I do believe that they can experience transient insomnia that can be quite problematic.

I think those would be situations where we should definitely consider medications for treating the sleep. Again, I would want to check in with Dr. Ferber about whether or not I have defined transient insomnia correctly.

DR. FERBER: In specific response to your question, I don't think it is simply a matter of dosage. I think, particularly as you get down into the preadolescent group, efficacy is a major question. We don't know for sure how these drugs are going to work, whether it is going to make them sleep better, make them sleep worse, whether that is the ideal choice of medication for them in that setting.

I don't think we know that.

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DR. CHESNEY: Thank you, again, Dr. Riddle.

Why don't we take a fifteen-minute break and by back here by twenty-five after 10:00.

[Break.]

DR. CHESNEY: Our next speakers are Drs. Carolyn McClosky and Amaryllis Vega who are going to speak to us about the epidemiologic issues from the Office of Postmarketing Drug Risk Assessment.

Epidemiologic Issues: OPDRA Assessment

DR. McCLOSKY: Good morning.

[Slide.]

I am Carolyn McClosky. Amaryllis Vega and I worked together on this presentation on insomnia in pediatrics. We are going to cover some information on prevalence from the literature review and then from some data on office-based information, we are going to cover diagnoses and drug use.

[Slide.]

Basically, we are going to describe, for the pediatric population, the prevalence of insomnia. That is the literature review. We are going to describe the types of sleep problem diagnoses and drug use for these

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sleep problems.

[Slide.]

In reviewing the literature, at least in terms of finding a prevalence in insomnia, we found there were several points that we needed to cover that will affect this. One of the things is that the definition of insomnia or sleep problems was basically all across the board. This could be anything from waking or sleep disturbance type of diagnoses to parasomnias such as nightmares or enuresis. I think most of you have heard a lot about that this morning.

Also the methodology of data collection. The information we are going to cover today came from questionnaire information, parent and child information, but also you can have direct measures in sleep laps such as polysomnography.

We need to cover the confounding factors which I think most of you are probably aware of and have covered a lot today. But regarding the child, there is the difference in age and development. There might be different bedtime routines. They might have medical conditions or allergies.

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The family confounding factors, some of them, are the parental habits, the parental expectations, and others. Environmental confounding factors such as noise and light can also affect this.

[Slide.]

This next slide is a busy slide, but what I am trying to do is to give you an overall view of what is out there in the literature for pediatrics. The first column covers the sleep problems. As you can see, there is a large degree of definitions or descriptions. The second column, you might have different ages and different ranges of ages that are covered in the article.

The prevalence varies and then, of course, the last column is whether or not medication was used for this particular sleep problem. The first line there is chronic poor sleepers. Those are defined as those who have a wakefulness once at night for at least 30 minutes at least three times a week or wake once a night three or four times a week or have a greater than 40-minute latency in falling asleep.

The next line is described as poor sleepers. Those were described as having a sleep latency greater

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than 30 minutes plus at least one complete awakening per night at least two nights per week.

The next line is sleeping poorly. By the way, I should point out to you that these are different authors except the sleeping poorly and, below, that the sleep difficulties are the same author. The sleep difficulties were the poor sleepers described in the third line plus parasomnias such as night fears, talking or walking in their sleep and enuresis.

The last one, the sleep disturbance, was described as difficulties falling asleep, staying asleep, need for more sleep, early awakenings and chronic sleeping-pill intake. So, as you can see, these are going to describe a lot of different things.

Now, the first two, the age ranges were twelve to eighteen and fifteen to twenty. Those are self-report and the prevalence for those two different groups were 12Êpercent overall and then the second line, 13 percent for males and 17 percent for females.

The third line in a group of eight to ten-year olds, that was parental report. The prevalence for that group of sleeping-poorly children was 14 percent. The

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medication use--now, remember, this is self-report or parental report, was between 4 and 10 percent. It did not describe the exact kind of medications but at least they said that there was some sort of medication used for facilitating sleep.

Below the line is a different category, different group, it seemed. This is my breakdown, but if you want to try and break it down between above the line, below the line, it seems that above the line, they either had more frequent sleep problems or more severe sleep problems or, at least in the parents' mind more severe sleep problems.

Below the line, they might not have been as severe or as frequent, but the chronicity was there. As you can see, the younger group, the eight to ten-year olds, that was parent report, 43 percent reported that they had a child that had some sort of sleep difficulty. The high-schooler self report had 41 percent of those describing a sleep disturbance.

These cover different areas of the world. The first line is Canadian, the second French. The sleeping poorly and sleep difficulties are from Belgium and the

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last one is from France.

So I covered a lot, but keep in mind, this is parent and child self report.

[Slide.]

We are going to another article. This is in five to twelve-year-old children. These are New York children. This is just to give you an idea of the different types of sleep difficulties and their prevalence, a range from bedtime resistance of 27 percent through all these different things, morning wake-up problems, fatigue, sleep onset delays, night waking of 6.5 percent. These were U.S. children.

[Slide.]

This is from a group of English and Scottish children. We had a larger number with this article. The top line describes sleep problems which are basically overall sleep problems in these children. This is parents' report. The point here is that the younger children, the parents tended to think they had more sleep problems than the older children, like 20 percent in the five-year olds and 6 percent in the eleven-year olds.

When we looked down at the disturbed sleep

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greater than once a week--in other words, a little bit more frequent, more severe, situation, 4 percent of the five-year olds had that problem and it dropped down as the children got older to 1 percent in the nine-year olds.

Of note, in this article, they described that less than 25 percent of these children were seen by a physician. So, with that in mind, we are going to switch corners here and we are going to look at IMS Health National Disease and Therapeutic Index where we are looking at office-based surveys. About 3,000 physician offices in the Continental U.S. are surveyed.

This is a systematic stratified sample of physicians and their work days and this information provides demographic diagnostic and drug-use data. It is a representative sample of the physician's specialty and geographic region.

[Slide.]

I need to point out that here we are talking about office-based information and so they used ICD9 codes to code the different diagnoses and NDTI--let's back up. ICD9 codes; there were two major ones that had

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sleep problems. One was specific disorders of sleep of non-organic origin. The other one was sleep disturbances which excluded the non-organic ones.

But NDTI, underneath each of those larger subheadings, had an insomnia subgroup that was specific for insomnia. So what we had to do was, in order to find the office diagnoses, we had to lump those two together. I will tell you right up front, we had very small numbers so you are going to see all of these sleep disorders lumped together under what I have termed sleep problems.

So that is going to be your overall group. Within that sleep problem group, we are going to look at insomnias and another subgroup.

[Slide.]

I have already mentioned that these were small numbers. In order to give you folks an idea of what we are talking about, the sleep problem, this first line, all types, the sample that we studied in six years--that is 1993 to 1998, so we are talking six full years of sampling--only 177 office visits had a diagnosis of sleep problem.

Now, this is out of the total pediatric office

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visits of 312,000 samples. These are extrapolated to the United States and so the extrapolated number that we are going to use for the rest of the slides is the 745,000 sleep-visit problems for the pediatrics.

As you can see, that is out of 1 trillion, et cetera, et cetera, total pediatric office visits.

[Slide.]

Follow me. Here we are. We are still talking about six years of data but, in this slide, we are showing you the age range of zero to sixteen. This is just to show you that the sleep problem visits in the zero to six-year-old group is much more frequent than the sleep problem visits in the seven to sixteen-year-old group.

[Slide.]

This is in the preschoolers, the zero to six-year-old age range. That total number is that first column we saw on the first slide, but this is broken down into sleep disturbances not otherwise specified, other sleep problems where we lumped them all together, and insomnia.

We are going to be looking at the disturbances

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of sleep not otherwise specified and insomnia subgroup a little bit more closely, but in this preschool group, it is this disturbances of sleep subgroup that stands out.

[Slide.]

This, again, is the six-year, 93 to 98, range but the age range is seven to sixteen years of age. Here the insomnia subgroup takes up a larger portion of their total sleep problem visits followed by disturbances of sleep not otherwise specified.

So, in summary, it is the preschoolers that had disturbances of sleep, NOS, and the school-age children, insomnia.

[Slide.]

So, to look at some numbers, of all the sleep-problem visits in NDTI, 0.05 percent or 5 in 10,000 of all the pediatric visits had a code for a sleep problem. Now, these ranged in severity from mild to severe with most of them being mild or moderate, about a third of them unspecified in severity, and 7 percent severe.

Underneath this larger group, the disturbances of sleep, 3 in 10,000 visits had a diagnosis of

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disturbance of sleep not otherwise specified. Of those visits, 70 percent are single diagnosis. The insomnia subgroup, we had 1 in 10,000 of all pediatric visits but only 30 percent of those visits had a single diagnosis. The other 70 percent had a concomitant diagnosis such as fatigue or headache.

[Slide.]

Of these sleep problems, we looked at how many of these visits had what we call a drug mentioned; in other words, the physician made a diagnosis of some sort of sleep problem and had some sort of drug mentioned, either prescribed a drug, gave a drug sample, suggested that the drug be bought over the counter, whatever.

So, in 42 percent of these sleep-problem visits, a drug was mentioned. Under disturbances of sleep, 32 percent of all those visits had a drug mentioned and the most frequent of those were diphenhydramine and hydroxyzine. Of the insomnia subgroup, 73 percent of these visits had a drug mentioned and the most frequent drugs were imipramine and temazepam.

Now, remember, this is 73 percent of the insomnia visits had a drug mentioned which is different

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than the 70Êpercent that were insomnia mentioned alone.

[Slide.]

This is an overall slide again, because we had such small numbers. We are again looking at six years, the whole pediatric age range, zero to sixteen, and just gives an overall view of the types of drugs used in this sleep-problem pediatric group.

Most of the drugs used are the psychotherapeutics followed by the sedatives followed by the systemic antihistamines and then it drops off with the cardiovasculars, antinauseantes, et cetera.

[Slide.]

This one just looks at the individual drugs in the whole pediatric group, zero to sixteen, again, for the six years, 93 to 98 again. Diphenhydramine is at the top with 20 percent followed by chloral hydrate, imipramine, et cetera.

[Slide.]

So, overall, I want to repeat that for the NDTI summary, the numbers are small. Remember, this is office-based information. These are diagnosis visits and the drugs mentioned for these office-based visits, not

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parent or child questionnaire responses. The most frequently reported sleep problems were disturbances of sleep which were often a single diagnosis and mostly in children under six.

The other subgroup is insomnia which was most frequently reported with another diagnosis. Of all the drugs used for all the sleep problems, the most frequent drug used was diphenhydramine.

So now I have taken you really quickly through a literature prevalence review and NDTI office-based review. I can entertain questions, if you have any.

DR. CHESNEY: Thank you very much.

DR. NELSON: From this data, is there any way you can estimate number of patients as opposed to number of visits?

DR. McCLOSKY: That is really difficult, especially with the numbers being so small that we just used the one big number, made a gross assumption that we are going to call these visits but knowing that we are going to have repeat visits of the same child in there.

DR. LAUGHREN: In looking at drug mentions for the visits, I am looking at numbers like 42 percent or, I

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guess, 73 percent of visits where insomnia was the diagnosis. That may lead one to what I think is an erroneous conclusion. I just want to get this point clarified.

It would appear from that there is a high percentage of prescribing when there is a diagnosis of a sleep problem but what I am wondering is whether or not there is a diagnosis made may depend, in part, on whether or not there is a prescription.

DR. McCLOSKY: I am glad you brought that up. Thank you. That is very important. These are diagnosis visits and so we are counting what the sleep-problem diagnosis might have been, but there are other diagnoses. Then we are just looking at the same visit. We don't know whether the diagnosis was the indication for the drug or a concomitant diagnosis.

Thank you very much, because that is a very important point. So, yes; you are right. These could be prescribed for one of other concomitant diagnoses.

DR. LAUGHREN: My point is, in part, that the diagnosis may have been mentioned in the record to correlate with the prescription. It would give the

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impression--do you see what I am saying? It seems discordant with the other discussion that we have had earlier suggesting that a relatively small proportion of kids who have some kind of a diagnosis of a sleep problem end up with a hypnotic or other drug treatment for that problem.

Here, it may be perhaps to support payment, or whatever. The diagnosis is put in the record when it might not be otherwise.

DR. McCLOSKY: All I can say is that this is what we found. I want to reiterate that this is not necessarily that a prescription was written. This could just be that the doctor suggested it to the parent. It could be that the parent was to buy it over the counter or the doctor only gave a sample without a prescription.

So you are right. This might not be that the child received the actual medication. This is just a drug mentioned at that visit.

DR. LAUGHREN: It just seems discordant with what we heard earlier about a relatively small proportion of kids who have some kind of a sleep problem for whom a prescription is given or recommended.

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DR. VEGA: My name is Amaryllis Vega. You are absolutely right, when you look at the percentages that we are describing here. But if we go one step before the use of the drug, we need to remember that percentage of patients with the diagnosis is very small, so this 72 or 70 percent and 40 percent come from a very already small number of patients. So we need to keep the background number of patient which we are using to make these estimates because the precision is very, very--it is inaccurate because of the size of the numbers.

DR. RIDDLE: To follow up on Dr. Laughren's point, could a child that had a severe ear infection get a diagnosis of ear infection, get an antibiotic, have it mentioned in the note that this child was having trouble falling asleep and the parent was told, "If the child continues to have trouble falling asleep, you might want to give an antihistamine." Would that have counted?

DR. McCLOSKY: That is highly possible.

DR. FINK: With the ICD coding, do you have any breakdown from the NDTI data? Were all of these reported sleep disturbances codes used by psychiatrists? These codes are very difficult to find and the ICD coding is

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really obtuse. I have just gone through revising our billing sheets for the sleep lab and was looking for ventilator dependency. It is a psychiatrist code under "dependency, ventilator."

I am not sure that the average pediatrician would ever have access to these ICD codes.

DR. McCLOSKY: You are right. Most of the ICD9 coding is for claims data instead of actual--30? We cut this talk down, but we did have a slide prepared, fortunately.

[Slide.]

This shows you the ICD9 coding of 307.4, specific disorders of sleep, and 780.5, sleep disturbances. ICD9 coding did not have a specific subgroup of insomnia. They had various others that were lumped together. The NDTI data gave us these subgroups. As you can see, insomnia is the first one up here, 401, and the second one over there, subgroup 502.

DR. EDWARDS: I think the extrapolations that we are making, given the very small sample size, are distressing. Are there other databases such as Group Health or Kaiser or something that you could probe for

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these questions, not simply in a mental-health database? Are there other ways that you could look at this or options?

DR. McCLOSKY: Yes, ma'am. There are. We didn't have the time to go through that and it is costly, but you have got a good point.

DR. FERBER: I think in studies that take a look at the complaint rather than the diagnosis, you see a much higher incidence of sleep complaints. There is no, obviously, control here in interviewing parents after they leave the office. So this requires a parent to, first of all, even mention it. Generally, people only mention it if they think they may get some help for it.

So, in many settings, they don't feel there is help, they don't even mention it. Secondly, even if it is mentioned, it may not be thought of as a specific diagnosis as much as a problem so I think if you look at the coding as a disorder, it almost certainly is going to significantly underrepresent the problem.

DR. McCLOSKY: I think you have a good point there, too. As you noticed, the literature review had a different prevalence versus the NDTI data. The NDTI data

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do no make a distinction between whether it is a complaint coming in or if it is the final diagnosis. It is just if it is mentioned in the chart, it gets into the NDTI code.

DR. GORMAN: I would like to pursue this coding problem one more time. I am sure Dr. Clapp will substantiate this from her set of trenches to mine is that we all have cheat sheets when we are sending up the patients to our billing office where I am sure sleep disturbances are not listed on mine and, therefore, are not listed in, I suspect, the vast majority.

Sleep is often a secondary diagnosis. Sleep disturbance is a secondary diagnosis to be made with a well-child exam or other exams. It is not the primary complaint and it is much easier to circle one diagnostic code than two for both us and the billing office.

DR. DANFORD: Recognizing all the methodologic weaknesses in the numbers, I wonder if you would be willing to guess in sort of orders of magnitude whether the use of sleep drugs in children represents the substantial-use criterion described in the 1998 Pediatric Rule of 50,000 patients using this drug.

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Do you think that is well in excess of that? Do you think that is well below that, or do you think you can't tell?

DR. McCLOSKY: Well, we kind of guessed on this one. Could you give me slide 25?

DR. CHESNEY: What other questions would you like us to ask?

[Slide.]

DR. McCLOSKY: I am going out on a limb on this one because, like Amaryllis Vega said, these are small numbers. Please remember that. Your confidence intervals, if you think in those terms, are huge. In other words, you cannot really have a lot of confidence or precision in these numbers.

Based on that, we were thinking, "Well, we shouldn't present this at all." But you need to know something and this is information. So we decided, since they are rough and dirty numbers, we will take rough and dirty denominators and went to the Web for the census information, took the same six years, 93 to 98, different age range because that is how the census website had it lumped, 0 to 17, so we are including one extra year.

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And we took the NDTI data, 93 to 98, 0 to 16. Here are the prevalence numbers, rough, very rough, very imprecise, that we came up with of about 18 per 10,000 children for all sleep disorders, going to an office and having that as a diagnosis. Disturbance of sleep not otherwise specified, 10 per 10,000 children. Insomnia, 5 per 10,000.

Now, these numbers and ranges next to the diagnoses are from the NDTI data so, for the six years, the range for, like, all sleep disorders was 52,000 to 183,000 extrapolated office visits. That, remember, is extrapolated from that sample of 177 visits.

Does that help? And then, of course, taking into consideration that we had much higher percentages of drug mentions than what other people have mentioned before that they felt were being prescribed.

DR. FINK: Looking at this slide, are these six-year figures so that the actual number per year would be about 35,000 if you took your average?

DR. McCLOSKY: I'm sorry; where are you getting that?

DR. FINK: I am just dividing all your sort of

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guesstimates of the median by 6 and coming up with 35,000 patients per year, roughly.

DR. McCLOSKY: Oh; I see. Right.

DR. FINK: Okay; so that is the correct interpretation. It would be 35,000 per year.

DR. McCLOSKY: For all sleep problems, you are talking about.

DR. FINK: Right; adding those three together.

DR. McCLOSKY: Right.

DR. HUDAK: I have a question about the methodology. When you talked about visits and getting this from visits, did this data take into account the fact that the same patient may have multiple visits? Did you correct for that?

DR. McCLOSKY: The same patient may have multiple visits; yes, sir.

DR. HUDAK: So we are looking at--when you said you extrapolated this information from visits, for instance, out of 177 visits, they may have represented 60 patients.

DR. McCLOSKY: Right.

DR. HUDAK: Was that able to be factored into

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the--

DR. McCLOSKY: We did not do that. The numbers are so, so small that we couldn't do it.

DR. HUDAK: So it would be some smaller number than this, in terms of actual patients.

DR. McCLOSKY: Right. May I go back to the previous comment? All sleep disorders, 123,000 is the average. The range is 52 to 183,000. So I'm sorry; don't divide the 123 by 6. Forgive me. So disturbances of sleep, the average is 66,000 and insomnia is 32,000 per year. Sorry.

DR. NELSON: I just want the remind her, in terms of the Pediatric Rule, isn't it an either/or? So it is either meaningful therapeutic benefit or substantial use? It is not an "and."

DR. FERBER: The data on enuresis is probably the best data that is out there on sleep disorders. The incidence in enuresis, alone, is much higher than those numbers, way above that. So for all sleep disorders, I assume enuresis is included.

DR. McCLOSKY: Slide 30.

[Slide.]

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This was our NDTI breakdown. Enuresis would have been included as the concomitant diagnosis but it was not one of the subgroups for these specific disorders in NDTI data.

DR. FERBER: But it would have been listed under "all sleep disorders," or just those?

DR. McCLOSKY: The NDTI coders are supposed to get as specific as they can. So we are making and assumption that they coded on the smallest subgroup possible. We think that enuresis is a totally separate NDTI code, if you are looking for that specifically.

DR. FERBER: So it is not included in the category of all sleep disorders.

DR. McCLOSKY: Not specifically unless it is a concomitant.

Any other questions?

DR. CHESNEY: Thank you very much.

Our last formal presentation is by Dr. Spielberg who will give us the perspective of the pharmaceutical industry.

Pharmaceutical Industry Perspective

DR. SPIELBERG: Thanks, Dr. Chesney.

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[Slide.]

This is, obviously, not one of my areas of expertise so I am really going to come at it from a general drug-development point of view and strategy. It strikes me that the discussions today are very different from many of the discussions yesterday where we had pretty clear definitions of an area of therapeutic need, various drugs to meet that therapeutic need and a general agreement the those drugs should be used in those conditions and that they are being widely used in the pediatric population, and that lack of information about those medicines in labeling is a real detriment to both pediatricians and patients and to parents.

This is, obviously, much more confused. We have a condition and we think there is a therapeutic need for dealing with it but the role of drugs is much less clear and the role of specific medications even is much less clear. Those are the kinds of things that we are going to have to deal with.

So, insomnia in pediatrics. Just to review the rule and the issues of FDAMA again, because I don't want us to lose sight of several things and the real reason

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that we are all in this which is really trying to get information about medication into labeling for children.

Clearly, for the '98 rule, we are talking about specific to the adult label indication or indications. I think we struggled with that a little bit this morning in terms of definitions of insomnia, whether insomnia was thought of in the labeling for adults is the same as insomnia as thought of in the labeling for children.

We talked a little bit about meaningful therapeutic benefit and that really comes down to the need for specific medications or for the evaluation of those medications in kids that is going to give us an idea of whether or not those things worked.

We talked about the issue of substantial use and the 50,000 prescription issues. Again, we talked a lot in the last few minutes about the difficulties of some of the diagnostic databases. It is worse in the utilization databases. One of the reason that often the IMS databases are particularly bad for children and medications is when there is not a pediatric formulation and a pediatric pharmacist comes up with an extemporaneous formulation for a lot of these meds. For

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younger kids, there is no code for that and, therefore, they don't code it.

A lot of use of extemporaneous formulations never ends up included in the IMS database and, therefore, we really get very little information on that for younger children. This is a major problem the pediatric pharmacists have pointed up for years but I think is not generally appreciated.

So, in fact, the data on use of specific medicines really is a problem, both with databases and, obviously, the diagnostic codes. One of the things that I rail about in adverse-reaction reporting in children is any chest pain in kids ends up being coded as angina so that companies get reports of angina in children associated with different medications and immediately cardiovascular flags go off.

We have some real language problems in English.

[Slide.]

FDAMA; the reason that we struggled so hard to get this legislation through is not only, however, to deal with labeled indications. It is also to deal with those other indications in children where we really need

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information. For example, if there is a use of Viagra in primary pulmonary hypertension in the newborn, obviously rather different than its adult use--if that turned out to be an important use of that medicine, we should get information about it.

So issues here, even if diagnoses are not necessarily comparable, the whole idea behind FDAMA was to provide an incentive for going after those relatively rare conditions where the market, indeed, is very small, could never justify drug development in and of itself but where an incentive, in fact, could be the jump start to it.

So it can be for other potential pediatric uses and therapeutic needs. We heard a little bit today about special patient populations. I don't know. I don't really understand from the discussions this morning whether those are valid targets, but certain children with autism or mental retardation, children with altered biologic-clock functions and insomnia, could these be potential targets where a sponsor, getting together with the academic community to define the therapeutic need could come to the agency and say, "We have a proposal for

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studies of our medication in this particular aspect of sleep disturbance. For this specific group of patients, this is our proposal," and then end up having a written request based on that, or some hospitalized patients, under unique and, again, controlled circumstances where a medicine that might help with sleep would be useful.

Could this be a basis for a written request? I would posit that probably the process under which this should really be occurring is sponsors with these particular medicines engaging in dialogue with sleep experts, with experts in pediatric psychiatry to define those conditions and those situations under which these drugs might have a useful benefit and then come forth with a proposal to the agency under FDAMA to see if, in fact, that really does reach the level of therapeutic need in kids and whether those studies functionally can be done in the number of children available with the number of experts out there.

It is pretty easy doing studies in infectious disease, now, in pediatrics. It would be very difficult, both defining the patient population and having investigators who can do it.

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[Slide.]

This is a good summer read. It is a little bit of a divergence, Time, Love and Memory by Jonathan Weiner. He wrote The Beak of the Finch, a wonderful discussion of Darwin and of evolution. He is a molecular biologist and writer in residence at Princeton. He writes wonderfully, so it is not a good book for insomnia. You will stay up all night reading it.

Time, Love and Memory, however, is the biologic genetic basis of behavior in drosophila. It is really a biography of Seymour Benzer, the Cal Tech drosophilogist, if you will. Benzer has been particularly interested in the molecular biology of behavior in drosophila and looking at the underlying genetic basis of biologic clocks and drosophila who don't sleep, and drosophila who end up with biologic clocks sufficient to influence their sexual behavior so that they can't mate with drosophila who have different biologic clocks because their rhythm--part of the way drosophila get together is rhythm and beating of wings and things. If their rhythm is different from the rhythm of the mates, it doesn't work.

The reason I bring this up is not because of

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drosophila--it is a wonderful book. I really recommend it. It is a lyrical reads--but that the bottom line is these kinds of genetic studies of underlying causes of behavior on a molecular basis begin to get us at trying to understand the biologic basis of the things we are talking about today.

We are talking about vague diagnoses that we make without the aid of being able to separate out, often, the underlying bases. I was fascinated by the discussion, was it primary depression that led to sleep disturbance or was it sleep disturbance that leads to depressed behavior.

We often don't know. I would posit that, in the next few years, the horizons that are going to get us out from under this conundrum are going to come heavily from the human genome project and being able to get molecular links to some of these diagnostic categories that we have and, in turn, that will lead, hopefully, to rational drug development in the future for many psychiatric conditions and for many other conditions as well. Hypertension ain't just hypertension; it is a whole series of molecular things that lead to hypertension, different in

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different populations, different in different individuals, that lead to different therapeutic choices, ultimately.

I think the same thing is going to happen here. The issue, too, though, is that, although often there are genetic underpinnings, there are also phenocopies, things that look like the same genetic disease, the way we used to confuse marfans and homocystinuria because they sort of look kind of the same. But they are really not, obviously. They have very different molecular bases.

So we have to be very careful and this suggests to us, particularly in psychiatry, that we are going to have to much more specific with our diagnoses and, in turn, put those diagnoses to the rigor of genetic testing that may, then, ultimately suggest to us which drugs we really should be looking at in different conditions and different kids.

I bet--I mean, look; sleep is controlled by biologic systems in the brain. There have to be underlying disorders that either occur on a genetic basis or secondary to brain injury or to other phenomena that lead to disrupted biologic clocks that really,

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ultimately, are going to be our true insomnia targets.

[Slide.]

What would the content of request letters be like? The first issue is age ranges. I am not sure we have defined that. Obviously, there are big differences in three-month-olds who are not sleeping and teenagers who are not sleeping. But we really have to define age ranges before we talk about therapeutic need.

That is particularly important because if age ranges are different and if age ranges include younger kids, then, up front, we need to talk about formulation. One of the things that we have been pushing and, really, one of the critical rationales for this whole initiative is to get formulation sufficient to give kids accurate dosing with palatable formulations that they will, indeed, take, from a compliance point of view.

Anything short of that really isn't serving our patients. All this extemporaneous sticking it in applesauce and in custard and everything. Unfortunately, there is one class of request letters in hypertension that even suggests that can be done. I think that is wrong.

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The issue is to get good formulations in kids to allow accurate dosing by age and, if the requests in this particular area are going to include younger children, remembering that most seven-year-olds can't swallow pills. A lot of eleven-year-olds can't swallow pills. A lot of adults can't swallow pills.

But by the time you get to seven or so, greater than 50 percent of children are going to have difficulty, particularly with large pills. We are going to need formulation so you have got to consider age ranges here before you think about anything else.

PK studies to define dose; modeling on adult pharmacokinetics, most likely, here, performed in patient populations. I think many of us would have some real difficulties with psychoactive drugs being examined in entirely normal kids. But that argument was discussed yesterday and others have different opinions.

The bottom line is it is most likely to be done in the patient population. From what Dr. Ferber has told us, PK/PD relationships may not necessarily be the same in kids and adults. So we may have to do some clinical studies.

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Study-design endpoints here are going to be very important. Do we have adequate endpoints either in the laboratory setting or in the home-diary setting that are validated and not just validated to publish an article on three patients in J. Peds but validated from a regulatory point of view to actually get something into labeling, a very different issue. You have to think about whether or not we have those.

I would also like to suggest the two well-controlled study hurdle. We have been talking about this a long time. The whole rationale behind the 1994 rule was recognizing the two well-controlled studies in children was really one of the major impediments to not getting labeling in the first place for a lot of drugs in kids.

I think we seriously, seriously, have to think about what is needed, as we talked about yesterday, doing the minimum number of studies consistent with good study design to get the data we want and not to set up new hurdles.

If we start setting up new hurdles, it ain't going to be done. What we need to do is be very creative

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in thinking about PK/PD studies, short-term studies, other kinds of markers, that are going to get us where we need to be as pediatricians without the assumption the kids are a different species and, therefore, require replication of all the studies in adults.

But we sure want to look at specific safety issues in the context of our patients. Indeed, with psychoactive drugs, there is loads of literature on how children behave differently and have different outcomes and their lifestyles and the consequences of their lifestyles on learning and cognitive development, school performance, performance with peers. All of those things are terribly important when we are dealing with psychiatric drugs or any drug that is going to influence behavior, positively or negatively.

Therefore, to me, the emphasis on any request that should go out should be focussed heavily on PK, trying to come up with PK/PD relationships and endpoints that obviate hurdles that are going to make this impossible, either from a patient number point of view or from a study design point of view and focus heavily on pediatric-specific safety issues.

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[Slide.]

So, therapeutic need; what drugs? I am not sure yet. I am not sure I heard this morning any specifics. I heard several drugs mentioned. Melatonin, sadly, is not going to be studied in this context in this country, given its current status and availability, which is too bad but that could still be done on an academic basis, certainly.

Again, I would suggest that, probably, any sponsor who has such compound should be coming forward, talking to the experts in the academic community, in the practice community, who are likely to prescribe these medicines, come forth with a proposal to agency and have the agency evaluate that proposal from a regulatory standpoint.

For what conditions? I would say exactly the same thing.

One final comment; the need for positive labeling and the need for negative labeling. Positive labeling obviously says that this drug is indicated for such and such. The questions that have been bandied out around the room are some of these drugs really indicated

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for such and such or are they, in fact, not indicated for a given thing. Or, in fact, is the risk/benefit of the drug sufficiently bad that the drug really should not be used in pediatrics.

Our current labeling, remember, are disclaimers, not for use in children, because there are not data. That is not really helpful to a pediatrician. Certain drugs probably shouldn't be used in children in an active sense. For many of us, part of the rationale of FDAMA was if you do a study and come up with a negative result, that negative result is as important as a positive result.

You don't have to get a positive study to get FDAMA benefits. What you have to do is demonstrate how that drug performs in kids in a positive or negative sense. If the side-effect profile is unacceptable in children, that really can be included in labeling and probably should be included in labeling.

On the other hand, the cautionary note is that labeling does not define medical practice. That is not the intention of labeling in the first place. It is not the intention of the Food and Drug Administration or the

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Pure Food and Drug Act. It can't really define medical practice and there are going to still need to be other places where such information is going to be present, whether it be USPDI or other sources, that are going to provide definitive information as authoritative as can be on practice issues.

So those things are going to have to be defined. But I think we really should think both about positive and negative labeling that could result from studies in children where either a drug is found not to be efficacious or the side-effect profile to be such that even though it works, really, there are other things, behavioral or other pharmacologic modalities that really should be used in preference.

So I will close with that. In honesty, I really don't know how we should go forward except in the context of sponsors with specific medicines, talking to the experts, coming to the agency with a proposal and then having the agency look at that proposal, both from the vantage point of the 1998 rule and even more from the vantage point of FDAMA.

Thanks very much.

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DR. CHESNEY: Thank you, Dr. Spielberg, for your vision and inspiration.

Any questions?

DR. KAUFFMAN: Steve, several things have struck me this morning. One is that I haven't heard an outcry from either the community of psychiatrists or practicing pediatricians for drugs for insomnia in kids. Secondly, we have heard that the population, at least in the office data, is very, very small. Thirdly, if you look at what office practitioners are apparently using, they are predominantly using old grandfather drugs.

How would you sell the idea to your company that they should even think about getting involved in this?

DR. SPIELBERG: I think the issue, really, in honesty, the driver has to come from the community who is going to be prescribing these medicines. Both the pediatric community and the psychiatric community is going to have to say there really is a therapeutic need.

If, in fact, a company comes to a bunch of pediatric, psychiatric experts and the consensus is this medicine really doesn't have a place, that should be pretty much the end of it. That is life. There are

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medicines that are not going to qualify under FDAMA because they don't meet the criteria of really providing a meaningful therapeutic benefit to kids.

That is okay. On the other hand--and I am still uncertain from the discussion today--if there is a subpopulation of children really in need, and if there is that subpopulation out there, for heaven's sake, let's define it and then figure out in discussion with sponsors of various different alternative medications which of those really make sense to go forward.

If a sponsor does want to go forward, despite the fact that the marketplace is 3,000 patients a year because they get FDAMA benefit, those 3,000 children will benefit. That's fine. That's okay.

DR. KAUFFMAN: I see this unfolding in two very different ways under FDAMA versus the '98 pediatric rule. For example, if we would conclude that there was a very small population for whom these drugs, hypnotics, were indicated, under the '98 rule, that could be the basis for applying for a waiver.

On the other hand, under FDAMA, with the incentive of FDAMA, we could end up with a situation

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where a company gets a letter of request, there is no real need in the pediatric community but we end up studying it in kids because the company needs the exclusivity extension for their adult marketplace which would have totally the opposite effect.

So I think we have to think about what the implications of what we come up with today, how that is going to play out under these two different provisions.

DR. SPIELBERG: I agree completely with you. I think that is exactly right. The two approaches, indeed, if it looks like the marketplace itself wants to go for a waiver--I think this is why, particularly in this circumstance where we are really having difficult defining therapeutic need, this is going to have to be a joint venture between companies and real experts and the FDA and, ultimately, the FDA making the judgment about whether those studies are of sufficient value to the patient population that we are talking about to warrant participation in FDAMA.

Obviously, what we don't want are studies done where there really is going to be no benefit, just for the sake of exclusivity. That is not the rationale

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behind the legislation.

DR. LAUGHREN: Dr. Spielberg, you made a very valid point about FDAMA, that under FDAMA, FDA can encourage the development for indications in pediatric populations for which there are no approved indications in adults. But then you went on to say, or to argue against, the need for two adequate and well-controlled trials. That seems to me contradictory.

DR. SPIELBERG: It depends on how you look at the Pure Food and Drug Act and all the regs. I think there are circumstances where, indeed, even on the adult side, we are beginning to question whether every indication does, indeed, require two well-controlled studies in adults.

In children, we have all recognized that this can be a burden, both in terms of patient numbers, in terms of study design, that simply can't be done, both over the periods of time in which one would like to do the studies. It would take, for example, years and years and years to accrue enough patients.

That doesn't mean we can let down our guard in terms of what ends up in labeling with respect to the

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quality of data and the acceptability of that data to meet the therapeutic need. I think we are going probably have to come up with some creative ways around that for some compounds.

DR. LAUGHREN: But, surely, you wouldn't argue for a common condition.

DR. SPIELBERG: No.

DR. LAUGHREN: For example, if a company wanted to pursue something like delayed sleep-phase syndrome in pediatric patients for which there is not an approved indication in adults, there you wouldn't argue that two adequate and well-controlled trials would be a reasonable request.

DR. SPIELBERG: I am not sure. I am not sure. I think still, in the pediatric population, there are going to be real problems in overcoming that hurdle of two well-controlled studies. This gets us into the issue, again, of what information can be included in the label, whether it is a formal indication, whether it is a formal indication, whether it is a statement in the pediatric section of the label and such.

This is a real problem. It is a real conundrum

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that I think we are going to face with many indications in pediatrics for which there are small patient populations. It is unlikely that two well-controlled studies will be able to be done in our lifetime.

We will want that information in labeling but with the kind of data that we can all trust. I think we are going to have to work on that one.

DR. MURPHY: But, Steve, I think the other point that we are trying to make here is that, clearly, the '94 rule tried to carve out an area where the disease and the effect of therapy are sufficiently similar that it might be permissible to make that extrapolation.

I think we need to be very careful because there are situations here that you are correct, it may be difficult, numberwise, but we do have situations where we either think the diseases are not sufficiently similar or we actually know, because of a controlled trial in children, that the response isn't the same.

We are going to need efficacy trials. The numbers situation is a problem but the worst thing to do in that situation would be to not do efficacy trials.

DR. SPIELBERG: Oh; absolutely.

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DR. MURPHY: Because you may be treating kids with a therapy they don't need or won't work.

DR. SPIELBERG: There is no question about that. In our ICH document, I think we clearly enunciate that efficacy trials are, indeed, going to be required under some circumstances. What I am saying is that every opportunity we can take, however, to use some of the intermediate things that we also discussed in ICH such as bridging PK/PD studies that increase the confidence of extrapolation where we think we can extrapolate but we really aren't sure.

So we do need some kind of bridging studies, surrogate markers, other study design in children that enhance our ability to understand the efficacy of the compound short of two well-controlled studies. In other words, two well-controlled studies may be what we need to do for certain drugs under certain circumstances. Absolutely. But, also recognizing that there are many circumstances--and it is even being discussed in the adult situation where two studies are not going to be required.

One study may be adequate for certain types of

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studies. If we can use PK/PD to increase our confidence that, for example, depression in children and adults is behaving relatively similarly, fine. If the PK/PD studies suggest it doesn't work, then we are back to the old modality and no one is going to argue that.

But, in every circumstance, given both the difficulties of the studies, the number of patients available, the number of investigators available, I think we have to try, to the extent we possibly can, to also be very practical about it but guided by the data, no question.

DR. MURPHY: I think what Steve is getting at is that one of the things that is happening in pediatric drug development is this concept of bridging studies where you think the disease is similar, you have evidence maybe of different endpoints that--I don't want to use the word "validation."

I think this arena of the neuropsych drugs, though, is an area where we are not dealing with that situation. We have evidence that, in depression, we are going to need efficacy trials.

So I think that we just need to be careful in

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how we are applying some of these statements.

DR. NELSON: The one area of my concern in practice, working in an intensive-care unit, is what is currently happening, an assumption of efficacy on many of these drugs that have been mentioned in the outpatient and chronic setting, but in the absence of any clear dosing guidelines or any clear knowledge of the extensive drug-drug interactions that take place with all of the other medications that we are using in that environment.

So the question I am asking myself is whether or not, from the transient insomnia data of using first-night in the hospital or sleep labs, it would be appropriate to infer efficacy in that acute setting, say, two or three weeks into an ICU course after having had an injury from a car accident and one is off the ventilator, et cetera, but trying to sort out those issues, but then try to develop dosing guidelines in drug-drug interaction information using, like, the PPRU network or some other network to generate that kind of data.

I would feel, as a clinician, that that would be valuable information. I am not sure if I am appropriate in inferring efficacy-based, but that is what is, in

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fact, happening from a regulatory point of view.

Whether that would be a population that could be focussed--I would think that would be a meaningful therapeutic benefit. I don't know if it would reach the 50,000 use threshold, but I would be interested--I know there are some neonatologists in the crowd--how they would feel in that younger population.

DR. HUDAK: I would like to echo that. I think one of the things that seems clear to me in all this discussion is that trying to do primary studies of efficacy in the outpatient population is pretty clearly impossible given the fact that Dr. Clapp, with her 6,000 patients, has maybe one that might have been a candidate for the study and the data that was presented on the outpatient visitations shows that even lower diagnostic incidence there than the numbers suggest, I think.

But I think, certainly, in the ICU, certain babies in the intensive-care nursery--maybe Bob wants to comment--who are sort of chronic babies who we sort of throw up our hands and say, "How do we manage these babies? How do we make them comfortable? How do we get them to maybe come off their ventilators? How do we make

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the parents happier? How do we make the nurses happier?"

Those babies get a lot of drugs in the nursery and we have very little information on any of those drugs. This seems like, between the ICU, the intensive-care nurseries and even some patients who come in for procedures where the length of stay can be anticipated to be several days, that secondary endpoints such as even length of stay and things like that could be used.

The primary, important things for those would be issues of PK/PD and safety as well some efficacy endpoints. But I think that that population is a fairly large population that is currently getting drugs like this or similar to this that would could do better for.

DR. WARD: I would just like to respond to that. When you talk about, especially, procedural sedation, the hypnotics are very widely used literally every year in thousands of patients. We do have some efficacy data based on how long they stay asleep.

We have some data about apnea. But there is a marked paucity of labeling. When you move to the newborn ICU setting and the diverse population we deal with,

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there is no labeling that is developmental over that range of developmental changes in liver metabolism, for example.

DR. CHESNEY: Any other questions for Dr. Spielberg?

DR. FERBER: I just want to clarify one point. In the FDAMA ruling for a drug company to get a patent extension, that requires doing studies on children but it does not specify the age; is that correct? So if the study is done into adolescence only, that would still qualify; is that correct?

So there is a huge difference there in terms of generalizing. One can generalize, often, fairly well in terms of safety and efficacy, I think, down into the adolescent range but that is totally different if you want to talk about getting down into toddlers and infants.

DR. SPIELBERG: The age ranges are something that are negotiated between the investigators, the company and the agency, the agency ultimately setting the age ranges based on therapeutic need. So, for example, if the drug is likely to be used and is going to be

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important in children from, I don't know, six and up, that will be the age range that the request letter will go out for.

If the compound is going to be used throughout the pediatric population, the whole pediatric population would be--if it is going to be used in adolescents, it would be for adolescents. So the decision making is based, really, on therapeutic need at different ages.

DR. FERBER: Because there are many drugs that are approved for age 12 and up and something like that. Then, in practice, one is faced with the same problems about using it off-label which is the way it is used.

DR. MURPHY: I just want to emphasize that, for FDAMA, the way the exclusivity is obtained, is that the studies must be responsive to what is requested by the agency so that, as Steve said, we would look at where we thought the need was. So they could just bring in what they thought was the need.

DR. CHESNEY: Thank you very much, Dr. Spielberg.

Advisory Subcommittee Discussion of Questions

DR. CHESNEY: I think maybe we had a false sense

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of complacency or security that there were only two questions and it wouldn't take very long to answer those.

If we could see the first question; is there a public-health need for the FDA to encourage, through written requests, or require, as described in the Final Rule, that hypnotic medications be considered a therapeutic option to treat insomnia in the pediatric population.

Let's deal with that question first. If I may be presumptuous, I would like to reword the question or to re-ask the people at the table, is there anybody that would disagree that there is a public-health need for the FDA to encourage, et cetera? If you disagree, would you please put up your hand and tell us your reasons.

DR. KATZ: I don't disagree. It says, now, "insomnia." I wonder if it shouldn't be amended to ask if there is any sleep disorder that we should require studies in and then, maybe we could have subsequent discussions about which sleep disorders the committee thinks should be evaluated and then we can go from there.

Insomnia--we have already heard that there are so many things out there that people call insomnia, I

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wonder if we should just consider that the broad placeholder for any sleep disorder.

DR. CHESNEY: I think that is key, and I was afraid you were going to ask that.

DR. LAUGHREN: Can I just amplify the question a little bit because it is a little bit different whether we are looking at the Pediatric Rule or FDAMA. Under the Pediatric Rule, at least as I understand it, we would be limited to approved indications in adults. Again, as I pointed out earlier, the two indications that are approved for hypnotics in adults are transient insomnia and this thing called primary insomnia.

Under FDAMA, it could be broadened. We could look at any of the sleep disorders that might benefit from studies in a pediatric population if there was an expectation of substantial benefit.

DR. CHESNEY: I think everybody has agreed that we need to do the studies. From what you have just said, I think probably the best option would be to go by the FDAMA legislation. Let me ask people if they could define something--the conditions in place of insomnia where they feel the need exists.

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DR. GORMAN: I think the two places that the ambulatory pediatricians would be interested in is separation-anxiety disorder and ADD, or AD/HD for sleep augmentation for both the patients and their parents.

DR. NELSON: I would just, again, put on the table my comments about what we would call day/night cycling disturbances in the intensive-care unit and, in particular, at least offer the possibility that that be based on dosing and safety issues and whether the efficacy data in transient insomnia could be extrapolated.

But I mention that as a lay person without knowing what the proper interpretation of that might be.

DR. WARD: I think that mention of the children with neurologic disabilities and the neurosensory problems of vision disturbance is a terribly important segment of the population that needs to be served as well

DR. LUBAN: You could also probably add the hospitalized, chronically hospitalized, child who might be treated for a hematologic or oncologic disease.

DR. FERBER: Similar in that regard are the pain syndromes or spasticity where there is interference with

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sleep. If it is open to all sleep disorders, then you are opening the door to the parasomnias where hypnotics have been used quite successfully with certain indications. I don't know if you meant to do that or not, but sleepwalking, sleep terrors, have been treated with benzodiazepines quite well when needed.

DR. CHESNEY: I think we should include that.

DR. SZEFLER: What about the sleep disturbances associated with psychiatric disorders. We spent the presentation on that. It is a component. Can it be looked at in terms of a phenomenon.

DR. FERBER: You mentioned separation anxiety, but I think you could open that up to generalized anxiety. I don't know that it needs to be specifically separation.

DR. CHESNEY: Generalized anxiety disorder.

DR. FINK: I am a little concerned, as we broaden this list of indications for drugs, that I think, as great a need as there is for labeling of the drugs, there is also a tremendous need for physician education about the whole issue of sleep disorders, how to define them, what they are, how to diagnose them, how to treat

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them and what should be treated as sleep hygiene versus a sleep disorder.

Somehow that needs to be worked into this because I am a little concerned we are going to get all these drugs out there for a variety of conditions that the average pediatrician doesn't even know they exist or how to define them.

DR. WARD: The problem of drug-induced problems was alluded to earlier. Certainly, everyone that uses diuretics on the chronic basis has to deal with the induced electrolyte disturbances with the stimulants. It sounds like it is a very real problem at bedtime for some children. I think it is a legitimate area to be studied.

I think the education component that you allude is very important in this whole issue. I was intrigued with Dr. Clapp's reflection that she wouldn't treat these primarily but, yet, would refer to them someone else. I think a lot of physicians would launch and maybe not appropriately.

DR. CHESNEY: I would like to add the hypnotic use and procedural disorders. I don't know how much information we have about pharmacokinetics and efficacy

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and so on.

Others?

DR. SPIELBERG: I think we are beginning to kind of define many of the areas. Just a cautionary note, and it is something, again, that we have to engage in dialogue with the agency. Given the realities of these conditions which, I assume, we are not going to be able to consider extrapolation and the need for clinical efficacy trials, if a request went out listing fifteen conditions and you have to do each of those to get your exclusivity, no one is going to do them.

It is just not going to be doable. It is going to be extraordinarily difficult even to mount two trials for a single condition. So, in the practicality of it, in trying to figure out how to get the maximum benefit to the maximum number of children in doing it, we may have to prioritize a bit for agency.

If we list all of these conditions with equal importance, the requests will go out with each of those listed. Given that each of them probably does, indeed, differ from the adult conditions would require clinical studies, would take several of our lifetimes to get them

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done.

DR. CHESNEY: Could the company not select which ones they wanted to address? Would they have to address all of them?

DR. KATZ: It is hard to know, but the way I have had the pediatric-request process explained to me and the way we have invoked it, it is the agency's opportunity to ask the sponsors for everything we want to know about pediatrics. There is a big benefit to be gained by the companies if they go through with this which is that they get six months of exclusivity.

So we feel that is a pretty big benefit and the quid pro quo is that we get everything we want in pediatrics with that request. So I think Dr. Spielberg raises an interesting point which is that if the committee thinks that this is everything we should want, presumably, the requests would ask for fifteen different indications.

So, perhaps the data you would need to satisfy a given one would be different from another one. One may need two trials. One may need one trial. One may not need any trials. I don't know.

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So, as I understand the process, we would have to ask for every--that is our one opportunity to ask for everything we want.

DR. SPIELBERG: Reality check. To ask for that, you will get nothing. That is why we really need to think about this is a very serious way.

DR. KATZ: I agree. Just before you raised the point, I was discussing the exact same point with Tom. My personal view is that an even more important bit of advice we could get from the folks here relates to the Pediatric Rule requirement.

Under the Pediatric Rule--that doesn't mean you have to stop talking about FDAMA, but I would just be interested in that aspect of things because, under the Pediatric Rule, you have to understand we are required to require sponsors--that they submit pediatric data for the already approved adult indications. They have to do that, unless there is some compelling reason why that requirement should be waived.

But, other than that, they have to. So I would be very interested to hear whether or not the committee thinks that we should require evidence of safety and

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efficacy in pediatrics for the already approved indications under the Rule, the '98 Rule, because that is something we have to do as an agency.

DR. NELSON: A couple of comments in response to that. As I was listening to all this information and not being versed in this area extensively, my first impression was there weren't any patients to study, as I am listening to the first several presentations.

And then we come up with the Christmas wish list of things that we want to study, which I used to do all the time when my folks would ask me what I would want for Christmas, independent of the resources available to do it. So I think there needs to be some prioritization based on a recognition of resources of the patient populations, not necessarily the resources of the companies relative to what they may stand to gain as a practicality.

One suggestion would be for those disorders where there are clear behavioral and other environmental interventions that could be made to where a drug intervention would be, clearly, an adjunct, even if used at all, of a low priority regardless of the prevalence of

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that particular indication.

Those items that may be less frequent but yet where there is not other behavioral approaches that could be used would be higher on the priority. In the issue of the FDAMA versus the Pediatric Rule, it is unclear to me that, of the indications that we have mentioned, any of them would fit into the transient or the primary category so it is unclear to me that you could use the Rule.

DR. KATZ: That is fine but, I think, again, for my purposes, for our purposes, as regards these issues, it is very important for us to hear what the committee hears about what should be required under the Rule. That is actually the easy part of this, I think.

Either at committee thinks there are enough patients or that primary insomnia or transient insomnia don't exist in the pediatric population--if that is the view, that there are so few patients that it is impossible to require a company to study it, if that is the view, it is very important for us to hear that.

So, again, my personal view is that maybe we ought to discuss that first because that is possibly more easily dispensed with. At least we can get out of the

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way what it is that we should require of companies because you have got to remember, under FDAMA, nothing is required. The companies want to do certain things because they get a big benefit and what they need to do is going to be difficult.

We have already seen the beginnings of that. But if we could just focus on the Rule and what we ought to require vis-a-vis the already approved indications in adults, that, at least, will get us some concrete answers to something we need to know.

DR. CHESNEY: Can I just make one comment. Again, we all thought, in the beginning of the morning, I think, that there weren't enough patients to be studied. But, as I look down our list, there are many, many--there are thousands of patients--millions--with the things we have talked about AD/HD, generalized anxiety disorder. We have always done very poorly, I felt, by children, young children, particularly, with psychiatric disorders. Neurologic disorders; there are many of those patients out there.

Chronically hospitalized, pain syndromes, procedure hypnotics; it looks very complex and if you

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require companies to do this, it may look overwhelming but, really, there are plenty of these patients out there to be studied.

Maybe one of the purposes of the whole FDAMA issue is to make them study these because we don't have answers.

DR. MURPHY: Joan, I think we are not disagreeing but we are asking in a way--when Dr. Laughren presented, he put a different set of questions. I think what Dr. Katz and Dr. Laughren are saying is could we address this question which we just put up there, which is No. 3, are there equivalent disorders in the pediatric population for which hypnotics are approved in adults, primary insomnia and transient insomnia. Could we address that one first?

Then, what you are saying is the FDAMA issue might--do I have this correct? Okay.

DR. SPIELBERG: The other cautionary note in any clinical trial is Lasagna's law; as soon as you define a condition to study, the patients disappear. Many of these ideas may be entirely valid for small numbers of patients and the question is, if you had a formulation

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and adequate PK and adequate safety information, would those small numbers of patients be benefitted by having that information if the drug is currently being used without that information in those same patients.

Those, again, are judgment calls and balance calls and the practical aspects of benefitting the maximum number of children in the process.

DR. CHESNEY: Let me just read the question we are being asked again; are there equivalent disorders in the pediatric population for which hypnotics are approved in adults; i.e., primary insomnia and transient insomnia. Let's answer that first.

Does anybody feel that there are equivalent disorders in the pediatric population and, if so, please raise your hand and let us know.

DR. SZEFLER: I think what we have heard is that primary insomnia is not a condition. What I don't know is how is transient insomnia defined in adults and what are those situations and if those situations parallel what we see in pediatrics.

DR. LAUGHREN: Unfortunately, it is very loosely defined in adults. As I pointed out, it is not even a

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diagnosis in DSM-IV. So there is no equivalent as there is for primary insomnia. So it is defined, really, in terms of the models that are used to study it.

DR. SZEFLER: The models being--

DR. LAUGHREN: The general model, the usual model, is first night in the sleep lab in normals. Occasionally, companies will study an actual patient population and the usual population would be, for example, adults who are put into the hospital for a routine procedure and the difficulties they have sleeping that first night.

That is the typical patient model for defining transient insomnia.

DR. SZEFLER: So that helps identify what we said in terms of yes, we have the same kind of patients.

DR. LAUGHREN: So there would be a potential benefit, then, from expanding those studies into a younger population looking at a similar population, a population in children or adolescents.

DR. SZEFLER: From the model that you described, if that is what the approval was based on was that kind of a model, then the answer is yes.

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DR. FINK: It would seem to me that, along with the hospitalized child who would qualify as a transient insomnia that the AD/HD children, since they do represent a large number, would qualify as a primary insomnia if we assume that their drug is necessary for their functioning and that that is a significant number of patients and a significant pediatric need.

DR. LAUGHREN: That is not what is meant by primary insomnia in adults. Again, I don't know if there is an equivalent entity in pediatric patients but, again, the diagnosis of primary insomnia in adults is almost by exclusion. You exclude every other possible reason for the patient having difficulty sleeping, including psychiatric, other primary sleep disorders, other medical conditions, drug or substance abuse, any other possible explanation.

Once you have run out of everything else, you still have a patient who is having difficulty sleeping and is functionally impaired and it is a chronic condition, then you make that diagnosis.

DR. FINK: How would you handle the adult issue of an adult who requires a psychiatric drug for

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functioning that interferes with sleep and their ability to lead a normal life. Would you call that a primary insomnia? It is not a transient insomnia.

DR. LAUGHREN: Say that again?

DR. FINK: If you have an adult whose drug therapy that was required for functioning significantly interfered with sleep and it was clear that it was a drug-related problem, would you classify that as a non-insomnia or--

DR. LAUGHREN: There is no approved claim for that kind of insomnia. The hypnotics are not approved. I am sure they are used for that, but there is no approved indication for that type of insomnia.

DR. SPIELBERG: Do we want these medicines labeled for something that is vaguely defined in adults. If fewer than 1 in 6,000 children in a practice who have sleep disturbance would be defined by their pediatrician as in need of this medicine for these indications, are we encouraging its use? I don't know, but we have to think about that. Do we want it labeled for that indication?

DR. CHESNEY: One other issue is we may be missing it because we don't have anything that we know is

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available.

DR. CLAPP: I think I would consider the term "idiopathic insomnia" being one that we can all agree on better. Primary insomnia in children, as I mentioned, I am not sure that I am convinced that there is a such an entity. But, if we have an indication for a drug defining primary insomnia in children, I have an uncomfortable feeling that we will have an increase in the diagnosis being made as well as drugs being utilized for that purpose.

It is kind of a quick and dirty way of many people dealing with a problem by prescription rather than by history and appropriate referrals. I was impressed by the data that someone showed on an Italian study where there were something like 53 percent of children with sleep disorders being treated by their pediatricians with benzodiazepines.

I was concerned and distraught by that practice. We know that cultural influences do impact on modes of practice, but, certainly, such a statistic wouldn't be tolerated in the United States. Is that because they have a huge incidence of primary insomnia in Italy, or is

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it rather that they have a prescription pattern that is conducive to writing prescriptions to make children sleep.

I am pretty convinced that the indications that were discussed today seem important to consider for children who are impaired. Certainly, Dr. Ferber made a strong case for those who have neurologic disorders of a very extreme sort, perhaps, and psychiatric disorders of an extreme sort, could benefit from agents helping with sleep.

The interesting question is aren't those children currently being helped somehow with agents for sleep but, perhaps, have no FDA indication for that, the old guys like you mentioned, choral hydrate, which is kind of scary, or Benadryl.

Currently these problems are not being ignored, but they are not addressed in a formal way. I think it is appropriate to explore that but whether or not there is a compelling need to develop a drug line for these indices is kind of questionable to me.

DR. CHESNEY: You make excellent points. I thought Dr. Spielberg made one very good point which

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always bothers me and that is that we shouldn't let labeling determine physician practice. It ends up doing that, and we often make judgments based on that, but we probably shouldn't do that.

DR. MALONE: I had the slide on the Italian practice. It wasn't that they were using benzodiazepines that often. It was any drug. The benzodiazepine use was less. Actually, I tried to talk to someone to see what were the labeling practices in Europe and Italy, whether they were the same ones we use. I couldn't figure that out.

One of the things I was wondering about was do they label them for that usage. I actually wrote to the guy who did the paper and he said that they were labeled for that use. But I am not sure if he understood my question.

So it could be that labeling does change usage.

The second thing I wanted to say, though, is everyone keeps talking about the psychiatric disorders. I did try to emphasize that they were common by pointing out their prevalence rates.

The other thing that I was trying to emphasize,

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though, is that if you treat the disorder, often, in many circumstances, the sleep problem also decreases. It improves. But, thirdly, if it didn't improve, that does not automatically mean that the next step would be medication. It could, rather, be some scheduling or behavior intervention that wasn't being done.

Actually, in ADH kids, you often get very disorganized families and very disorganized schedules.

DR. KATZ: I would like to, if I could, focus the discussion on this question again because I think we are starting to get off the point a little bit. It is very important for us, given the regs, to get an answer to this question first and foremost, in my mind. And the first part of the question says; do these disorders exist.

Now, we can talk about idiopathic versus primary. That is not an important difference to me. The first point is to find out whether or not the committee, in a consensus sort of way, thinks they exist. We are not asking the question, yet, are there too few of them to study or is there a good reason not to indicate for this even if it does exist because it is going to be used

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off-label in everybody who has got a sleep disturbance and that is a bad outcome--that is the second part of this question.

But the first part, we need to hear, which is do you think these things exist. And then, if they do exist, we can talk about should we require companies to develop drugs for them in the pediatric population.

But we would really like to answer to the first part.

DR. CHESNEY: Thank you for focussing us. Let me ask the voting members of the committee, does anybody disagree that disorders of transient insomnia exist in children? Does anybody agree that primary insomnia exists in children?

Is that a good enough answer?

DR. SZEFLER: Maybe I could help you with approaching this because I think you are asking some excellent questions. Maybe the best perspective is to look at the drug. Again, we had a lot of "depends" yesterday because we didn't know the drug and today we don't either. But maybe the best thing to do, if this is a patent drug, is to look at its present application.

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There are two things you can do. One is to see if it is being used in pediatrics and, if so, where, and if it is being used in adults, if it is being used in some of these situations that it was intended to be used for by the indications and do those situations occur in children, because what happens is we kind of look to our adult colleagues where they are using their things and we look for these medications and then potential applications in children.

This is how the non-approved uses happen is because we look at adults and how the medications are being used. So I guess I would have to turn to what is the present use of the drug and are these situations existing in children.

DR. FERBER: I would like to respond to that. In terms of whether it is the same situation exists in children, the indications on the labels to not say primary insomnia. They only say insomnia. Again, I don't think you would find a lot of people who feel they are treating primary insomnia.

I think if we ask the same question, how many people feel that primary insomnia exists in adults, I

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think you would find the exact same problem. If you, again, come back to the definition, it talks about disorders of the sleep or arousal system. It is basically disorders that you can't identify which means, if you can't identify, then you can treat them with hypnotics.

Once you get the neurochemical basis of it, now you understand the disorder, you suddenly cannot treat them because now you have a cause. I think we are just talking about how good a grasp we have on the cause.

I think most people who study insomnia feel that if somebody is not sleeping well, there is a reason that they are not sleeping well. It is just our sophistication at this level and date how well we can identify that particular problem in that particular individual.

Again, I think primary insomnia is not in the sleep nosology. That showed up in the DSM-IV nosology, I believe, which there was a lot of debate about what nosology got transferred over and what fit with their coding criteria. But, just because it showed up there does not fit with how people are making diagnoses in the

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specialty and it certainly doesn't fit with the indications, as listed by label, and it does not fit with prescribing practices.

So I think if we try to do that, we are going around in circles.

DR. CHESNEY: Let me just take two more comments and then we will vote on the second question, there.

DR. LAUGHREN: I wish we had a member of the adult sleep community here to respond to this because I think we would get a different response. These studies that support the labeling for hypnotics in adults are almost always done recruiting patients who meet DSM-IV criteria for primary insomnia. They seem to have no difficulty getting candidates who meet those criteria.

You seem to be raising the question of whether or not this entity exists in adults. Again, in terms of the studies that we see that come in as part of NDAs, there seems to be an abundance of such patients who have met those criteria. So I am a little bit puzzled.

DR. FERBER: Part of the definition requires that it start in childhood and persist into adults. So, by definition, it can't exist in childhood. It has to be

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a chronic disorder, lifelong--

DR. LAUGHREN: Where does it say "lifelong" in DSM-IV criteria?

DR. FERBER: I don't think we should be hung up on DSM-IV criteria.

DR. LAUGHREN: What criteria are you referring to here?

DR. FERBER: I was looking at the International Classification of Sleep Disorders Diagnostic and Coding Manual.

DR. LAUGHREN: Again, in the adult programs that we have looked at, they almost always rely on DSM-IV criteria. I am just saying that the entity, primary insomnia, is felt to be a real entity and a rather abundant entity among adult experts in sleep problems.

DR. SPIELBERG: There is a bit of a double-edged sword to labeling, folks, particularly when the diagnosis is a little bit vague. The question came up about utilization. If you are labeled, you can promote. If you are not labeled, you can't promote. Pediatricians use medications off-label all the time for subgroups of patients.

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If a drug is labeled for pediatric use for insomnia, that means a manufacturer can promote it for whatever vague insomnia means. That still worries me a little bit. When we go after studies of specific pediatric indications where we define the circumstances where those drugs are really needed, and get those studies done in conditions where the drugs really are going to be needed, it can only be promoted for that indication if that indication makes the label.

If it is labeled for whatever insomnia is, and I am getting very confused what insomnia is and I bet practitioners out there are going to be confused about what insomnia is, it can be promoted for insomnia.

DR. CHESNEY: I think we need another break. I am just kidding.

DR. NELSON: I would like to speak towards my own interpretation of the one subpart of that question. I think we can operationalize transient insomnia in pediatrics but I don't think it would help me to basically have a labeling indication knowing that kids fell asleep a little faster in a sleep lab on their first night or fell a little faster sleep in the hospital on

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their first night for the kind of settings within which these drugs would be used that we have been talking about.

So, unless, for some reason, I shouldn't be confident about efficacy, that wouldn't help me. So I don't think, in requiring a study directed towards transient insomnia, it would get at the issues that we have talked about in the chronically hospitalized patient where there is no underlying psychiatric or other diagnosis, we really would need dosing and the PK/PD kind of data in that setting.

It would be my understanding, the only way you could get that would be to request it under FDAMA. So, yes; transient insomnia could exist because we can operationalize it. But whether it is of any clinical significance to do that, I would argue no.

DR. CHESNEY: Dr. Spielberg, can I just ask you, are you implying that we should not say yes to the transient insomnia but ask that it be defined in more specific terms?

DR. SPIELBERG: It sort of sounds like, whatever it is, sort of probably maybe exists. But then the issue

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comes down to, under the '98 Rule, is there a meaningful therapeutic need for these compounds in those conditions? Does it mean the criteria of either numbers or of therapeutic need where lack of labeling is placing patients at risk because it is being used heavily in that situation and, therefore, labeling is needed?

It is really the meaningful therapeutic benefit. If we think it exists but that is not really where the meaningful therapeutic benefit is, I would argue we try to define where that meaningful therapeutic benefit is and get those studies done and get that in the label which, then, rather more defines what can be promoted.

That doesn't mean pediatricians can't still use it for other off-label indications, but pick those things where having it in the label and being promoted, everybody is going to be comfortable about it and think it really is going to contribute to kids.

Having that PK information and safety information and formulation in the label and on the marketplace, thereby is going to make treatment of the rarer conditions safer and better.

DR. CHESNEY: I guess I was assuming that many

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of the things that we talked about would fall into the bailiwick of transient insomnia and that when the companies were asked to do studies or came in, that they would specifically address certain of these issues, not the issue of transient insomnia. That may have been a wrong assumption.

DR. KATZ: If the committee believes that there does exist an entity called transient insomnia in the pediatric population and that we should require sponsors to study that, to get evidence of safety and effectiveness for that specific indication, you can discuss what sorts of studies that ought to be.

Maybe the somewhat artificial model that we use in adults where they bring someone into the sleep lab and look at it there on the first night, maybe that is not an appropriate model for the pediatric population. Maybe looking at kids who are chronically hospitalized, if you want to call that transient insomnia--we would be willing to entertain what the appropriate model to be studied ought to be in kids with so-called transient insomnia.

DR. GORMAN: Would the agency be willing to say if there are any other indications for sleep promoters

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that are presently labeled, once again recognizing this two-edged sword of labeling? Is insomnia the only indication for sleep promotion of all the pharmaceutical agents in present labeling?

DR. KATZ: I don't know about sleep promotion. There are approved treatments for narcolepsy, which is a sleep disorder. I don't know what other sleep disorders have approved--what other sleep-related indications there are, if that is the question you are asking.

DR. GORMAN: That is the question. I am trying to get away from the definition of insomnia as our only possible choice for labeling. If the only other choice is narcolepsy, I don't think that is a big advantage to us.

DR. SPIELBERG: If the disease that we are talking about in adults and kids, if we really believe it is the same, we should be able to argue that we don't need efficacy studies. I think we are really talking about different diseases. If we are talking about different diseases, then it really doesn't fit under the rule, as such, because the indication, I think, that we are talking about really is different.

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An adult going into the hospital may say, "Gee; I need sleeping pill tonight." A five-year-old is not going to say that. What we do is provide an environment to help that child feel comfortable in the hospital or maybe admit him in the morning rather than sleeping over the night before surgery.

These are very different things and that is what worries me about invoking similarity under the rule here and then getting this sort of broad thing out of it.

DR. O'FALLON: I am really worried because that question said "equivalent." To me, that means something--we have gone to 4, but we can go back to 3. That things says are there equivalent disorders.

I am not a physician but what you guys have been saying doesn't--you have not convinced me that we are talking about what is insomnia in adults is anything like what you are interested in using it in children. They are different things and so I couldn't answer yes to that.

DR. LAUGHREN: As I understood the vote earlier, it was unanimous against primary insomnia being a disorder that one can consider in children. So the only

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question is whether or not something called transient insomnia--and I am getting the impression that, even there, where the clinical need is not at all equivalent to what is usually considered transient insomnia in adults. That is the impression that I am getting.

DR. CHESNEY: I think that is fair. I may have misled, but my assumption was that we would include all of these very different diagnoses in children under the category of transient insomnia. So that was, obviously, an incorrect assumption.

So maybe we should ask the question again. Of the voting members, does anybody feel that there are equivalent syndromes in children to primary insomnia and transient insomnia in adults. Let me rephrase that--well, no; that's right. Does anybody feel that there are equivalent diseases in children?

DR. KATZ: Again, I want to sort of clarify because I think people are sort of probably thinking together is it worth treating these in kids, are there other ways that we should better treat these in kids.

It hard to imagine that, when an adult comes into a hospital and can't all asleep the first night,

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that a ten-year old in the same situation wouldn't also have problems falling asleep at night.

So it is hard for me to understand how it is that there could not be an equivalent thing. It is a separate question as to what sort of data we would need to approve it for that in kids, but the existence of the problem, transient insomnia, as it is defined in adults, it seems to me, not being an expert in this area, there must be some pediatric age group that has the same thing.

Remember that the pediatric population is defined as people under the ages of sixteen. If a fourteen-year-old comes into the hospital, it is hard to imagine that they are going to have a different response.

DR. CHESNEY: I think that is fair. I think our problem is that we are reluctant to use the term "insomnia," or we are reluctant to group all of these disorders that we listed into a broader category because we feel like they are all very different disorders.

DR. LAUGHREN: Actually, this gets at a very complicated problem that we are trying to deal with right now, making a transition from sort of an older style of labeling to a newer style of labeling. It is a difficult

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transition because there are lots of things that are established by precedent.

But if you look at psychotropic labeling over the past ten years or so, you will see a gradual shifting from these fairly broad indications like anxiety or depression or psychosis to more specific entities.

In recent years, we have been targeting specific entities, certainly in the anxiety disorders. Drugs are now approved for panic disorder or socialized-anxiety disorder and so forth, generalized-anxiety disorder, rather than the broad term "anxiety."

That term, anxiety or depression or psychosis or insomnia, should be thought of more as an umbrella category whereas the actual entities studies are the ones that we allow promotion for.

So, for example, if you look at the antidepressants, it is true that there is this language in labeling suggesting that a drug is for the treatment of depression. But it immediately goes on to define the population that was studied to support that claim.

If a company tried to promote beyond the entity that they actually studied, they would not be allowed to

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do that. Then cannot promote a drug--for example, there are other subtypes of depression other than the kinds that are studied.

Major depressive disorder, up to now, was the only depressive subtype that is targeted in development programs. A company cannot promote its drug for dysthymic disorder, for example, because they have not studied that population. I think you ought to think about insomnia similarly.

I think, at some point in the future, we probably will move to change the labeling to focus more on specific entities like primary insomnia or transient insomnia or whatever other category seems to make sense and the community can agree on.

So I think it is very appropriate to target as specific entities as you can.

DR. CHESNEY: Thank you. That was very helpful. I think that is what this group is saying is that we would want the indication specifically targeted for pain syndromes or procedural hypnotics--more specifically than just transient insomnia.

DR. SZEFLER: I think we have kind of gone in

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circles. First we were presented with primary insomnia and then our expert said it doesn't exist, and we said it does exist. Then we haven't heard a definition of transient insomnia and we have listed ten situations of what we think is transient insomnia.

So, it sounds like, in order to get the drug approved, you had a certain model, that the company has had to take the steps and do the model and then come back with the studies. What we are trying to do is develop a scenario where it was have clinical applications which you say you are striving for but would a company have to apply your model to children in order to get their drug approved for that indication?

DR. LAUGHREN: Not at all. It has to make sense. It has to be consistent with what the academic and clinical community sees as the need. If you define it a different way--

DR. SZEFLER: Then you have to be willing to say, if we say there is a model in pediatrics like procedures, you have to be willing to say to the company that, if they do that study, then they will get the approval or otherwise somebody else might come along and

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say, "You didn't follow our dotted lines; therefore, you can't get approved."

DR. LAUGHREN: That is where we look to you for advice. You have to tell us what the appropriate clinical entities are, what models should be used to develop those entities, what those development programs should look like in order to get that claim.

DR. SZEFLER: It sounds like we are moving in two different directions.

DR. LAUGHREN: It doesn't have to be transient insomnia. It can be whatever makes the most sense.

DR. SZEFLER: Let me put it this way. If we knew the definitions of primary insomnia, which we haven't seen, and the definitions of transient insomnia, then we could say whether they exist or not.

DR. LAUGHREN: You have a definition of primary insomnia. That is included in this blue sheet. It is the DSM-IV criteria.

DR. SZEFLER: I don't know the DSM-IV criteria.

DR. LAUGHREN: I am saying that is the way it is defined. It is in this sheet.

DR. SZEFLER: But, in order for us to respond,

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we have to see that definition and then say, do we have situations. Did we see that? Maybe I missed it. Maybe I fell asleep.

DR. CHESNEY: I think what we are asking is to redefine insomnia in children.

DR. RIDDLE: I was about to suggest that it would be helpful to have the definition of primary insomnia and transient insomnia up there. But, after hearing what Dr. Laughren just said, maybe it doesn't matter. I am totally confused.

DR. O'FALLON: Look; I think it is irrelevant what the definition is. What this committee has identified is a whole class of conditions in which we would be interested in having effective medication. The real question is have there been any agents approved for those indications in adults. We have got to go the other way around, not try to fit our conditions into the adult approvals.

They have got to figure out whether they have got an approval that fits the needs of the peds population.

DR. LAUGHREN: I think I have already heard the

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committee express the view that what is defined as primary insomnia in adults may be such a rare entity in pediatric patients that it is not worth pursuing that. Perhaps, similarly, what is considered transient insomnia in adults may not be the entity where there is a clinical need.

I encourage you to move beyond that. But then I think what we are doing is moving beyond any requirements under the '98 Product Rule and moving into FDAMA territory. That is fine. But tell us what the clinical conditions are in the pediatric population that need study.

What are those conditions that would benefit from studies of an hypnotic because, again, this discussion today is focussed on the class of hypnotics. Would there be any expectation of a health benefit from studying hypnotics in children or adolescents with various sleep disorders and what are the disorders and what are the kinds of studies that would be needed to support those claims?

DR. CHESNEY: Thank you. I think this is one of the most wonderful things about the fact that we are

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focussing on pediatrics is that there are some entities in pediatrics that don't exist in adults and vice versa. I think that is where we are coming from.

I think that we have actually come up with a very, to me, excellent list of disorders that do need to be studied in children that may not comfortably fit into transient insomnia or primary insomnia. To set up a model for each one, I don't think we could do today. I think that is going to take a group of experts getting together to work out the models for each individual one.

DR. FERBER: I think if you look carefully, if that is the diagnosis you are using, which is trouble sleeping which is not caused by one of a few other things, that leaves a huge list of things that could cause it. If you are going to define it like that, you may, then, be argue that it does exist because insomnia caused by a tumor would fit into that because it is not ruled out by anything else or medication.

I think that is why it was so easy to fill patients into that study is because it is such a wide-open category. I think that, again, DSM-IV--I don't know if that is the best direction to go because it is

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coming from a completely different viewpoint. It certainly doesn't fit the type of definition we use in sleep.

DR. LAUGHREN: Let me press you a little bit on this. You mentioned a tumor as one possibility that would not be excluded. But this definition does exclude any other general medical condition that is causing the insomnia. Wouldn't that be excluded on those grounds, if you look under the last bullet?

DR. FERBER: Okay; a tumor would be from that. That's right.

DR. LAUGHREN: So what conditions would be included in the pediatric population? You are excluding all other primary sleep disorders, all psychiatrist disorders, all general medical conditions and drug abuse or other--

DR. FERBER: It may not be a general medical condition, but if you have a disorder of a neurotransmitter, for example, which is--the hypothesis behind what causes this anyway, I don't know if you would stick it into that category or not. It is basically a general identifiable medical or neurological condition.

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If you can't identify it, it doesn't show up there.

That is why you can pull people into that. You have people who can't sleep and you can't get a handle on exactly why because you can't blame it on their arthritis and you can't blame it on their heart condition and so on, so you can stick them in.

We have chosen not to go that route in pediatrics. Do we have children for whom we don't understand why they are not sleeping well? Yes; I think we could say that. But we don't generally tend to think about that.

In terms of transient, I think that actually is easier to come up with the definition. I don't know if you have the definition there. Our definition is it represents a sleep disturbance temporally related to acute stress, conflict or environmental change causing emotional arousal. It gives as its first example, I think, a child before the first day of school or before exams.

We certainly don't want to put out a request for sleeping pills for children before their exams, but there are obviously other situations as mentioned where it is

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quite analogous in adults.

DR. NELSON: Whenever I get into complex discussions in the world of ethics, I always like to ask myself what are the practical consequences of the decisions that we make. The diagnostic classification of psychiatric disorders, I think, is a very complex issue.

The practical consequences is whether or not you can use the pediatric rule to enforce a requirement to do studies. I would like to at least express my view and I think I have heard this sort of emerging as a consensus view is that the use of the Pediatric Rule in this arena would be inappropriate given the difficulties in classifying pediatric disorders into either primary or transient and that, regardless of the complexities of getting your hands around those classification, that, because of that difficulty, it would be more appropriate to do it under the FDAMA regulations which could then be focussed precisely to the eight or nine specific areas that we outlined that needed further clarification and then we would get useful information.

So that, to me, are the practical consequences of what is, otherwise, a very complex issue. I think at

at least what I heard was pretty much of an agreement that, from a practical point of view, we think it would be more appropriate in FDAMA than under the Pediatric Rule.

So, independent of what I admit are complex definitional issues, that still exists. I guess I would like to see if that is where we are to wrap up a little on this.

DR. CHESNEY: Thank you for articulating that so well.

DR. WARD: I would like to respond to that. I think we need to balance what you just said Bob, or Skip with what Steve said as well, and to agree with what Dr. Katz said, and that is if we make a laundry list of nine situations, clinical situations, in which we think these drugs have to be studied in every one of them, we probably won't get that data we need.

DR. NELSON: But FDAMA would be voluntary. I think what we could do is prioritize the list that we just outlined, would be one approach.

DR. WARD: We could, but I think under FDAMA, what the FDA defines as the studies that are needed to satisfy our information deficit, if we make that list too

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comprehensive, it may impeded the process.

DR. NELSON: Can we prioritize this list now, do you think?

DR. MURPHY: I was going to say, the message that we just got is that, under the Rule, it is your opinion, expert opinion, at this point that the indications that are approved for adults are not the same in children, that there is an area in which we think hypnotics maybe need to be studied.

You have heard Dr. Katz say that our approach is that, because FDAMA does include an incentive which can be quite large, we want to make sure that we ask for the studies that are needed.

Now, I think we would like you not to decide what we should ask for exactly in the written request. What we would like to hear is your discussion of the most important to the least important of those studies which we really do need. And then we can decide where that health-benefit cut is because that is under FDAMA. That is the definition.

We would need to hear what is on your list of where you think the product is being used and where we

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may have a health benefit by obtaining information and, as asked, I think it would be helpful to hear the most important one and then we will have to look at where the numbers and all those sorts of things are. But we do get the message now that we are onto FDAMA.

DR. CHESNEY: Can I just read through the list and then we can ask for priorities, the list as I have it and then please correct me; generalized anxiety disorder, AD/HD, intensive-care unit, day/night cycling disorders, neurological disorders with possibly neurologic abnormalities of rhythm, the chronically hospitalized child, pain syndromes, the parasomnias to include sleep walking and sleep terrors and so on, psychiatric disorders, drug-induced insomnia and hypnotics as used for procedures.

DR. RIDDLE: I would like to suggest a couple of modifications. Under the psychiatric disorders, I think we would suggest psychiatric disorders where insomnia remained after the psychiatric disorder was treated. I think I would say the same thing--well; then, if that were the case, I am not sure that I would have a separate category for separation-anxiety disorder. I would

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include it within that group. I am not sure I would have a separate one for AD/HD. I would include that either within the psychiatric group or the neurologic group.

But if we get into specific psychiatric disorders, I think we could quickly come up with twenty or so.

DR. CHESNEY: I think we took out separation and made it generalized-anxiety disorder, but I hear what you are saying.

DR. RIDDLE: I would take that out, also. Again, if we start to make a list of disorders, we would want to have major depressive disorder, dysthymia, generalized-anxiety disorder, separation anxiety, panic disorder, on and on and on. So I would either make a long, long list or, preferably, no list.

DR. CHESNEY: We will put that into the psychiatric disorder where insomnia remains after the disorder had been treated. Let me ask; AD/HD, do people want to put that into the psychiatric disorder or keep that as a separate category?

DR. RIDDLE: I was saying you could either consider that in the psychiatric list or in the

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neurologic list depending on how you want to think about it.

DR. CHESNEY: Would people like to put it in the psychiatric list or the neurologic list or keep it separate?

DR. CLAPP: I think if it is separate, we run the risk of my concern of general pediatricians overmedication and, rather than trying to find alternative therapies, if you are stuck on Ritalin, you will just add whatever the new medicine will be because you think you ar up on things. It is a dangerous trend. Parents are more interested in children sleeping when, as Dr. Ferber mentioned, perhaps they really have no underlying sleep disorder. We really haven't evaluated for that so anything to kind of keep these drugs limited to the hands of specialists I think would be particularly helpful.

But, as generalists, we often treat AD/HD without referral.

DR. CHESNEY: Thank you for your comment. I guess I am reluctant to put it back in the neurologic category after it took us so long to get us out.

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DR. MALONE: I would actually recommend against having the psychiatric disorders--I mean, treating the sleep part of a psychiatric disorder as one of the things to study, actually. As we have discussed, if you treat the psychiatric disorder, the sleep disorder often improves. So I don't know how you are ever going to decide that you have treated the psychiatric disorder correctly to the point that now you should look at the sleep disorder separately.

Actually, for instance, in ADH, I think the main thing that ever gets discussed is the side effect of other medications, like stimulants. I don't know how you would be doing these studies such that you would want to study being awake from Ritalin by--the effect of hypnotics on sleep problems caused by Ritalin. I just don't know how you would study these things clearly.

Then, when you get concerned about pediatricians overusing medicine, I would be very concerned about having medicine in any way labeled for ADH, a hypnotic, because then I would be concerned about psychiatrists overusing the medication, or using it inappropriately in ADH.

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DR. CHESNEY: Thank you. I think those are very good points.

Could I just risk something here and ask if anybody would disagree that the use of hypnotics for procedures would not be at the top of our list?

DR. KAUFFMAN: Can I comment on that? I think it is a mistake to include that in this discussion at all. It is a totally different indication, a different use, different purpose. There are already drugs approved for kids for that purpose. I think it is irrelevant to this discussion, frankly.

DR. CHESNEY: Are there hypnotics approved and they have all the kinetics and everything--

DR. KAUFFMAN: Last year, midazolam was approved for young children orally and IV for procedure sedation, and fentanyl, of course, down to two years.

DR. CHESNEY: So we have enough information--

DR. KAUFFMAN: For those age groups and for those drugs we do, yes. At least the FDA approved them.

DR. CHESNEY: Take that off the list.

DR. KAUFFMAN: We have a lot more there than we do for most other drugs.

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DR. LAUGHREN: That is a very good point. We wouldn't even be entertaining that kind of a claim in this division. It is a totally different division that handles the use of sedatives for sedating patients during procedures.

DR. CHESNEY: Any other modifications to the list before we try to choose our highest priority?

DR. NELSON: I think, from a practical standpoint, you could probably lump together the issues surrounding chronic hospitalization, NICU, PICU and bone-marrow-transplant oncology. Now, from a study-design perspective, you may want to separate those out but I think, from a priority point of view, if the oncology and bone-marrow-transplant people found out they could use something successfully up there, I would feel a little more comfortable if I have got dosing and drug-drug interaction to use it in the ICU.

DR. KAUFFMAN: Skip, would you be willing to make it generalized to hospitalization? I see a lot of sedatives in our hospital being written for, maybe not appropriately, but for kids that are not in chronically.

DR. NELSON: That is a separate issue, whether

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it is appropriate. But, from my standpoint, defining a patient population that has been messed up in the hospital sufficient enough to where we need to intervene to unmess them up roughly, in defining that population, I see that as sort of two weeks into a course and not it is the third day and mom can't sleep because the kid is up at night, kind of similar to one of the case examples that were given earlier.

That is very different. I wouldn't want to do that. I see the chronically hospitalized patient and define that more closely.

DR. FERBER: I am still uncomfortable with AD/HD being on that list. There have been lots of studies of sleep in youngsters with AD/HD and almost of those studies in youngsters who are otherwise normal function show normal sleep. So I don't think there is good evidence for that.

The situations in which you see AD/HD and poor sleep is often when there is another problem and the AD/HD is reflecting the underlying dysfunction and it is really the other problem that is at fault.

DR. CHESNEY: So you would take it off the list

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totally or incorporate it into drug-induced? In other words, the child is not sleeping because of the Ritalin?

DR. FERBER: We didn't discuss that much, but probably the first thing that should be done in that setting is modify the stimulants before one adds another drug. I just don't see that as the real driving force here.

DR. CHESNEY: Dr. Gorman, did you have a question?

DR. GORMAN: I have a comment. I think I would like to fall back to the model suggested by our psychiatric colleagues of if the initial disease is treated appropriately, then, if sleep is still needed, it be treated as an adjunct. I have a lot of trouble reducing or eliminating ADD from our discussion because that is the only condition that I see routinely in my practice that people are on sleep aids. It is not a hypnotic. It is a cardiovascular, but it is being used extensively in the community that surrounds Baltimore.

DR. MALONE: I would suggest that is a reason to study the cardiovascular drug if you are concerned about it. But I still am reluctant to keep ADH on the list for

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all the reasons that Dr. Ferber said. I think often the sleep problem is related to--if it is the stimulant, you can change the dose, but often it is related to the home situation or the way the parents are getting the child to go to bed. So I still would rather take it off the list.

DR. LAUGHREN: This is a very interesting discussion from an academic and the clinical standpoint. I have grave reservations about the applicability of this discussion and this list to the FDAMA process for a couple of reasons. One reason is that none of these entities that are now being entertained, there is no precedent for approving drugs for any of these.

That is a very daunting task to try and establish an indication for the first time. There are a number on this list. There are seven or eight or nine or ten. There isn't even agreement among those here about these entities, about whether or not they even belong on the list.

I guess the difficulty for me is imagining how we are going to go from here to writing a written request. Ordinarily, FDAMA works well when you have a well-defined, accepted clinical entity where everyone

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agrees on what it is, agrees that there is a need for it. You can, then, move very quickly to a written request.

Our experience with written requests in the psychopharm group has been entirely with entities that are already accepted; depression, social-anxiety disorder, other disorders that are already established in adults and accepted--obsessive-compulsive disorder--accepted disorders where there is no question about what the diagnostic criteria are.

Here, we are moving into very new territory and, although, as I say, very interesting and probably very clinically important and relevant, it is hard for me to imagine how we are going to be able to move very quickly from this kind of discussion and list to written requests.

DR. CHESNEY: I hear what you are saying and I had thoughts about that but let me ask other people for theirs.

DR. FINK: The issue I see that we may be overlooking is not defining this but looking at what is current practice and what should be done there. In that respect, would hypnotics be superior to chloral hydrate,

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diphenhydramine. But drugs which are widely used have significant known clinical problems and maybe the question we should be asking is would a hypnotic be preferable to those drugs, however they are used.

I am not sure I can define it better than that but I think that is really the clinical issue. We are using drugs we know are bad for conditions we can't easily define.

DR. LAUGHREN: But none of the drugs have approved indications.

DR. SZEFLER: But you just reversed what I asked you ten minutes ago because I asked you specifically, are you willing to relinquish the model that you have requested for adult studies for pediatrics, and you said, "Yes; give me some models."

We have given you some models and now you say you are not willing to relinquish the old standards.

DR. LAUGHREN: No; I am quite willing to give up on the application of the Pediatric Rule which would have to focus on the current approved entities in adults. I am perfectly happy to do that and I hear that coming from the committee that you don't think that it would make

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sense to try and expand those claims into the pediatric population.

I am not questioning the clinical importance of the entities that you are discussing. The problem is there are no drugs that are approved for the entities on this list.

DR. SZEFLER: You asked us to do that. I am kind of saying which way do you want it? Do you want to take the standards that you have applied for adult indications, move them down to pediatrics--

DR. LAUGHREN: No. I don't have any bias one way or the other. We are in a situation where we have to decide two things; number one, is there any reason for invoking the Pediatric Rule and requiring companies to do studies in pediatric population for the currently approved claims in adults for hypnotics.

The clear answer I am getting from the committee is no. So then the question is should FDA be encouraging companies to explore other indications in the pediatric population. There are some indications that are well defined. The parasomnias, for one, are well defined. There are diagnostic criteria. I am not sure if those

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are or are not on the list.

I guess they are. But the other disorders that you are talking about, sleep problems resulting from a needed medication or sleep problems that are residual from a psychiatric disorder that has been mostly treated but still has some sleep difficulties, those are not well defined. There are no drugs approved for those.

So that is a daunting task to get an indication established and get a drug approved for it for the first time. I am just cautioning you that, while totally clinically relevant, this is a daunting task and it is not something that is going to be easy to translate into a written request.

DR. NELSON: I would like to at least offer the possibility that the hospitalized patient that we talked about in terms of the chronic hospitalization might be an exception to that. I think that patient population could be defined. You could define endpoints. Whether you would require an efficacy study or not I think is an open question in my mind versus the safety in the PK/PD studies.

Now, whether that is sufficient to give someone

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an extra six months of marketing--as an intensivist, I would value that information. So I think it would. I think you could define that. The endpoints could be defined.

DR. SPIELBERG: The other possible way, again trying to think of the greater good and what the goals are, if some of the parasomnias fit comfortably within definitions for which studies can be written--remember, the bottom line is to get something labeled.

You have to have a study that fits diagnostic categories and for which you have endpoints so you can validate everything else. If the parasomnias would do it, and you also ask for formulation development because some of these disorders in little kids, sleepwalking, go down in little kids, you end up with formulation, you end up with pharmacokinetics, you end up with acute and chronic safety information and you end up with at least one pediatric indication.

The first three of those, the safety, the pharmacokinetics and the formulation, is what we need as pediatricians anyway most of the time in order to use these drugs in our patients. The drug-drug interaction

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stuff, Skip, is really dependent on mostly adult drug-drug interaction and specificity of p450s and everything.

I think we can get that information for you. If we have a chronic-use situation, we get the safety in chronic use, at least in that patient population. It is not perfect, but if it works within the FDA's definitions on the efficacy side and you do the efficacy trial in the population, and you get formulation, PK and safety, that advances us way down the pike.

DR. KAUFFMAN: I think I have been thinking along the same way that Steve just articulated and I don't know if it will fit for you folks regulatorywise under FDAMA or not, but the question is to get this done, could we make a list of possible indications, albeit new indications, and have the letter of request say, "You pursue at least one of these indications plus all the things that Steve mentioned. If you do that, you can get exclusivity."

Is that possible for you regulatorywise under FDAMA?

DR. LAUGHREN: Let me comment first and then I

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will ask Dr. Murphy to respond to it. I think our obligation, under FDAMA, is to require companies to study all the entities for which there would be a clinical benefit in the pediatric population. So I don't see us sending a very broad request letter and saying that you can pick and choose among those on the list.

I think we would have to decide in advance which were the conditions for which there would be an expected health benefit from doing those studies and limit it to that list.

DR. MURPHY: One of the cuts here is that we need to ask for those things which provide a health benefit and where it gets dicey is that often there is information we might want to know from a scientific point of view that--it does not extend to you can ask for everything you ever wanted to know. So I think that that is where the cut has to come.

I think the difficulty we are having here is that we don't have clear indications that we would know how to--and this is not uncommon. In pediatrics, we have different presentations that sometimes are the same disease, sometimes are not. We have different endpoints.

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That is why we are having this difficulty right now in defining.

What is being said, though, is that if there is an indication that we know occurs in adults and that we think occurs in kids but hasn't been labeled, it is an indication that we know is being used, for which this product is being used, could we define that.

But it sounds like we are not able to do that at this point. The parasomnias are the only thing which we have come up with that would be--the other area that you talked about was the neurologically impaired but, again, that is a subpopulation. It is not an indication.

DR. SPIELBERG: If that is the case, the issue is how do you get to the goal. If all the other indications that all of us want to use the drugs for that would fit under the things that you might like to ask you tell us you can't ask because you don't know what they are.

Let's pick one thing that we all can agree on as a diagnosis, include that as the outcome variable from a labeling point of view, and get the formulation and get

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the PK and get the safety. Then you know full well that the reality of life is things are going to be used off-label. But if they are used off-label, at least with the right formulation, with a lot of safety information and a lot of PK, they are going to be used, by definition, more safely.

DR. HUDAK: Dianne, I think that the hospitalized patients, although it presents some challenges in terms of precisely defining the population and some of the endpoints, really presents practically the best population to study. I am not sure how many parasomniacs there are, for instance. I have not met one yet.

But, certainly, I deal with hospitalized patients all the time. I think the patients are different in the NICU and in the PICU by class as to whether they are post-op or have chronic diseases and so forth. So you would have to define the endpoints differently.

But I think that you could fairly readily come up with some good efficacy studies that provide important clinical information and that would improve care, no

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matter how you slice it. I think the other information that Steve was talking about would come out of that very easily in terms of formulations which are going to be different across the age ranges against the PK/PD data.

I think, if there is one thing that you could request that would easiest to do, the companies could do and would be willing to do, I think that would be the group to go after.

DR. MURPHY: Help me with what are we going to call this? I am asking. We can't just write a label for chronically hospitalized children.

DR. HUDAK: I think it would take several more hours to sort of come up with that.

DR. MURPHY: Yes. I am just trying to demonstrate the problem.

DR. SPIELBERG: But it is soluble. The issue is if we get the experts together with companies, together with you, to find one critical area of therapeutic need where we believe we have valid endpoints--it may turn out studying four parasomnias is going to be it, or studying this population, whatever it is, to get the safety information, to get the PK information, to get all of

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that together, that then provides the meaningful therapeutic benefit that we want out of it with one entity that we can all define, then it will be worth putting in that effort.

DR. CHESNEY: I would like to concur with that and, also, when you look at our list, you could, by extension, include neurologic disorders because, frequently, those children are hospitalized for intercurrent infections, for example, and the pain syndromes, because a lot of those children are going to be hospitalized for a variety of problems.

So if we use the hospitalized child, whether it is chronically, NICU, PICU, neurologic disorder, pain syndrome, I think we would pick up a large group. Dianne is shaking here head. I am being rejected already.

DR. FERBER: I think the problem we are having defining the patient group is relevant and it explains why the adult studies have been done on the so-called primary insomniacs because it is not that the same syndromes don't exist in adults, that they face the same problem defining the patient groups as well.

So, to get away from what medicines are they on,

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how long have they been in the hospital and what surgical procedure have they had and what psychiatric condition, they tried to go to the cleanest group they could possible go to which is where you didn't have any other identifiable variables.

The problem is, in pediatrics, we are stuck going in the opposite direction. We can't take that group because we don't feel that most of these children require medication anyway. So we are forced to go to the group that is more impaired. There is no way, if we do that, we can get a perfectly clean group in the sense of everybody having the same history, the same treatment, the same diagnosis.

But I was very impressed in what I heard you say is that, even if we do that, even if it is not perfectly clean, we can get the missing information about safety, dosage and then one can begin to generalizing from that, but at least do it with some data that completely is nonexistent right now.

DR. CHESNEY: I know Dr. Gorman wanted to raise one other totally separate issue before we finish, but let me ask Dr. Laughren and Dr. Murphy, do you still want

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us to address these specific questions or do you need any more information from us at this point in time?

DR. LAUGHREN: I think we have ultimately gotten to most of the questions on the list, if not directly, so I am satisfied. But I still have one concern about what this entity is that is being proposed. Not that I want to discourage you, but from a regulatory standpoint, we have to have a very clear idea of what that entity is in order for us to, first of all, write a written request and then, ultimately, deal with the whole issue of reviewing the data, writing labeling for it, instructing clinicians on how to use the drug for whatever that condition is.

It has to be something that is well enough defined that we can tell clinicians how to use the drug.

DR. SANTANA: But, if I heard correctly, what we are trying to tell you is that we, as a group, do not feel, collectively, we have that expertise that we can define that for you today and so you are going to have to go to the experts, you are going to have to go to the drug companies and find out that information.

DR. HUDAK: Do you have to have this as a DSM-IV

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diagnosis?

DR. LAUGHREN: No; it doesn't have to be. There is nothing sacred about DSM-IV.

DR. HUDAK: It would be more descriptive about it.

DR. LAUGHREN: As long as it is something that is well enough defined that we can ultimately write labeling and instruct clinicians on how to use the product.

DR. HUDAK: For the NICU, that would be very easy. We could get that done in fifteen minutes. For the PICU, I think that would be more difficult but, again, if you are descriptive, it could be done. As long as it was descriptive and not a DSM-IV. Otherwise, we are forced into, what is the term, "situational insomnia" sort of trademarks which we don't want to do.

DR. CHESNEY: I wonder if there wouldn't be role for the American Academy of Pediatrics here. They have a lot of expert groups that--I know it might take a little bit longer, but to have all of their buy-in and their recommendations, whether it is the Committee on Drugs along with the Committee on Psychiatric Problems and the

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general practitioners. I think maybe that would be helpful.

DR. LAUGHREN: I think any of those are possibilities. We would welcome help from any groups on this. Again, FDA, in this instance, I don't think is going to be able to take the initiative. It is going to have to come from the outside.

DR. CHESNEY: I agree with Dr. Santana. We are strongly voicing that we don't have the expertise. But I think the Academy might be extremely helpful in this realm.

DR. FERBER: You might include the American Academy of Sleep Medicine as well. They have a guidelines standards of practice group that works on defining these issues.

DR. CHESNEY: Include the AASM as well.

Dr. Gorman, do you want to raise your outside comment and then we will be finished?

DR. GORMAN: I am going to start with the punch line and then give the lead-in. I would like the FDA to consider adopting, either as a guideline or as regulatory language, subpart D of the special protected populations,

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the vulnerable populations.

Reflecting upon yesterday's discussion, there was a lot of assumption that every IRB, which we were asked to function as yesterday, operates under DHHS's rules and regulations, that hospitals all have MPAs and, therefore, need to invoke these extra protections for children.

Dr. Wilson at his lunchtime comment mentioned a small subgroup of IRBs that he felt might not be operating under those rules, but the vast majority of IRBs in this country operated without multiple project assurances and, therefore, do not fall under DHHS regulations.

I have heard an estimation that there are approximately 5,000 IRBs in the United States associated with hospitals. While this room represents, and yesterday especially even more so represented, some of the best and brightest of those IRBs and IRB constituents.

It struck me that children throughout the country, both in children's hospitals and in community hospitals and being serviced by central IRBs should all

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have the added protection of section D of those regulations.

Being a complete neophyte and incredibly and determinantly ignorant about the process about how that would happen, it seems to me that there should be some mechanism in which FDA can use its influence, either as a guideline or regulation or some other mechanism to provide that protection to the children as we move forward under FDAMA and the Pediatric Rule because the number of studies, as we have heard, is increasing.

We have documented that dramatically. I think that is a small incremental protection for the children as we go forward in clinical studies.

Thank you.

DR. CHESNEY: Dr. Spielberg, did you want to add to that?

DR. SPIELBERG: Just very strong support from PhRMA for that and I know talking to Bob Ward very strong support from the American Academy of Pediatrics Committee on Drugs as well. I think we really all are concerned about this. We want to assure that all IRBs and all pediatric studies are being done under the same ethical

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bases and that the DHHS guidelines really provide that.

Obviously, there are some interpretative issues and there are always going to be differences of opinion among IRBs of good will. That is okay but we want to make sure that those same basic guidelines and protections are present for all children in all studies.

DR. NELSON: As an addition to that, I think that if FDA goes down that route, which I support 100 percent, is that there has to be a major educational effort because these things are not easily interpreted, as we figured out yesterday when we did the case discussions, so that requirements also should be tied into educational efforts by FDA or other agencies to make sure that there is an environment where the regulations can be interpreted correctly.

DR. RIDDLE: The American Academy of Child and Adolescent Psychiatry I also believe would be fully in support of this.

DR. NELSON: Let me just add another voice in support and also point out that, in terms of educational efforts, I know, for example, Arena has formed a group to look at certification of IRB administrators where they

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hope to have an examination based on knowledge and content a year from December.

So there are various opportunities for educational efforts that will look at making sure there is at least a base of knowledge about the regulations. So, from that standpoint, I know the Committee on Bioethics of the Academy would likely support that as well.

DR. CHESNEY: Let me thank our guests and consultants for a very, very interesting and stimulating discussion. From my point of view, I look forward to seeing everybody again in X months.

Dr. Murphy, do you have concluding remarks?

DR. MURPHY: I just want to thank everybody because you are grappling with the difficulties that come into opening up a new field, almost. That is what is going on. As I said yesterday, as we begin to study children more intensively, we are finding out what we don't know.

Sometimes, we do get a little--how should I say--depressed; is that the word--in that it seems that it is difficult to carve out exactly what we are going to

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do or how we are going to do it. But I think that the fact that people will continue to work on this and will work to--I highly encourage that if a group of people want to get together and develop an indication for chronically hospitalized children who have sleep disorders or, again, I am not trying to make up a diagnosis but get to the situation with insomnia, that they should do so and present that.

I think what Dr. Laughren is saying is that we will certainly evaluate that and try to come up with a study design that we think is appropriate but we don't think we should be just creating these new indications as proposals come in.

We really do need this expert advice to help us define if there is an area that we don't have defined thus far. Thank you for putting your minds to this new and evolving field. We will continue to look at the ethical issues.

The recommendations that were made here today, I can certainly say that we will not have regs passed that incorporate subpart D before we meet again. So we might wish to really look at those recommendations that you

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just made and think about how you wish to frame them at our next meeting because it is somewhat difficult to take the end part of this transcript and put it onto the end of yesterday's transcript on ethics, but we will appreciate your continued thought and recommendations in that area.

Rosemary, did you want to thank anybody in particular today?

DR. ROBERTS: I certainly want to thank all the help that we got from the Division of Neuropharmacological Drugs, Dr. Laughren, Dr. Katz, and most especially Dr. Roberta Glass who is a member of the Pediatric Subcommittee and is also in that division and really worked with getting all the speakers, invited speakers for today. I certainly appreciate her help. Thank you. Also our folks from Epidemiology and the work they did. Thank you.

DR. CHESNEY: We are adjourned.

[Whereupon, at 1:03 p.m., the meeting was adjourned.]

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