DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Joint Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) and the Psychopharmacologic Drugs Advisory Committee (PDAC)

Thursday, July 10, 2008

8:00 a.m.

Sheraton College Park Hotel
4095 Powder Mill Road
Beltsville, Maryland

PAPER MILL REPORTING
(301) 495-5831

C O N T E N T S

C O N T E N T S

(Continued)

P A R T I C I P A N T S

Larry B. Goldstein, M.D.,
Chair

Yvette Waples, Pharm.D.
Designated Federal Official

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Britt Anderson, M.D., Ph.D.
Lily K.F. Jung, M.D., M.M.M. (Consumer Representative)
Ying Lu, Ph.D.
Matthew Rizzo, M.D.
Stacy Ann Rudnicki, M.D.

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBERS (Non-Voting)

Roy E. Twyman, M.D.

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Jorge Armenteros, M.D.
Rochelle Caplan, M.D.
Gail Griffith, M.L.S
Susan L. Schultz, M.D.
Robert F. Woolson, Ph.D.

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Non-Voting)

William Z. Potter, M.D., Ph.D.

TEMPORARY VOTING MEMBERS

Ruth S. Day, Ph.D.
Sid Gilman, M.D. FRCP
Wayne Goodman, M.D.
Andrew Leon, Ph.D.
Richard Malone, M.D.
Daniel S. Pine, M.D.
Delbert G. Robinson, M.D.
Andrew Winokur, M.D., Ph.D.

P A R T I C I P A N T S (CONTINUED)

DRUG SAFETY AND RISK MANAGEMENT VOTING MEMBERS

Sean Hennessy, Ph.D.

PEDIATRIC ADVISORY COMMITTEE VOTING MEMBERS

Melissa Hudson, M.D.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH PARTICIPANTS (Non-Voting)

Robert Temple, M.D.
Russell Katz, M.D.
Tom Laughren, M.D.
Alice Hughes, M.D.
Evelyn Mentari, M.D., M.S.
Mark Levenson, Ph.D.

DR. LEVENSON: I don't have much more to add than what I said earlier today. When you look at the forest plots of the individual drugs, topiramate is not really an outlier, it does have a lot of patients, but in terms of odds ratio, it is kind of right among the drugs.

DR. GOLDSTEIN: Dr. Rizzo

DR. RIZZO: I just want to make sure that I understand one point. Is there any evidence one way or another if the increased risk of suicidality, after stopping the medication, persists or stops? In other words, is it possible that a person would be having increased suicidality for weeks or years after taking the drug, and could you say anything one way or another?

DR. KATZ: Well, we excluded trials or events that occurred anytime later than one after the trial ended, so we have no information about what happens over time after drug is discontinued. We just didn't look for that. We didn't ask for that data, and we didn't look at it.

DR. GOLDSTEIN: Dr. Armenteros.

DR. ARMENTEROS: I was wondering, were the trials excluding patients that had suicidality on baseline, and if so, that is good, if not. Is the data available to

compare, not only the incidence of this event, but whether there is a difference between baseline data and then the occurrence.

In other words, if we have some events, you know, suicidality thinking at baseline, is there any way of measuring maybe the disappearance of such during the trial?

DR. MENTARI: Regarding your question on whether suicidality or suicidal thoughts existed at baseline, it is contained in my review. I don't have the data in front of me, but I can say that the exclusion criteria related to baseline psychiatric illness and suicidal thoughts really varied from drug to drug, but it is contained in the briefing packet if you want to refer to that.

DR. GOLDSTEIN: Dr. Pine.

DR. PINE: I want to come back to the issue that Ms. Griffith and Dr. Hennessy raised, which I thought did nicely summarize some of the issues about black boxes and their potential unintended consequences, and maybe ask the FDA to talk a little bit more about the points that were raised by both people in terms of what have you learned from the black box experience with the antidepressants in terms of intended or unintended consequences that we should

consider and think about when we evaluate what the most appropriate action would be in the current situation.

DR. GOLDSTEIN: As an addendum to that, could there be a more nuanced approach rather than a black box, but just a warning or alert of possible concern rather than black box?

DR. KATZ: Let me just answer the second part, because that is easier. Of course, there could be--we are coming to you asking your advice on whether or not you think a black box is warranted, and if it is what should we say, and if it is not, where should we put it and what should we say.

My only view about putting something in labeling, even if the something is a bad thing like suicidality and a serious thing, is we have to be pretty sure we think the drug did it before we put it in labeling. Then, we can figure out where to put it in labeling. I mean that is the first thought of question, but certainly how we say it, where we put it, it is up for discussion, sure.

DR. TEMPLE: Before Tom tells us what our experience is, there is one other thing to think about, and that is, how much to say about the data. In the depression

one, we give the conclusions, but we don't give a lot of forest plots or anything like that.

One possibility here that the previous conversation has made me think about is that we might sort of have a section that describes the data with its infirmities. I mean it would be a big step to do drug by drug and say, oh, well, it doesn't look like this one did, but there is still things you could say about it and caveats, and even explaining the difference between risk ratio and actual numbers needed to harm or actual risk.

Those things seem like matters that the Committee was quite interested in, and those things are all on the table from our point of view. We don't have a rigid way.

It is our inclination, though, that if something is important, it gets noticed better if you put a box around it, and it doesn't mean--and Tom is going to emphasize this I know--it doesn't mean don't use this drug. It means pay attention, think about it, if the person gets funny, note that it might be the drug doing it.

But you are right, there can be unintended consequences, but I have interrupted Tom long enough.

DR. LAUGHREN: Clearly, when we were thinking

about what to do with the antidepressants, we worried a lot about unintended consequences. The Committees on both occasions are worried about that.

In terms of what the impact has been, we have some early results, but it is probably something we are not going to learn for some time. Actually, Andy Leon, in a nice editorial about this referred to that regulatory action as sort of a public health experiment.

I think what we have learned is that prescribing in pediatric patients of antidepressants has declined somewhat since the introduction of the black box. But the other part of that, you know, what has happened with suicides is less clear.

There was a lot of concern at the time that we had the Advisory Committee in December 2006 about a possible increase in adolescent suicides because the preliminary data from CDC had just come out, but now the numbers--that was for 2004--the 2005 numbers are down somewhat. They are not down to where they were in 2003, but they are down from where they were in 2004.

Actually, the change in antidepressant prescribing didn't occur until 2005, so I think the only thing we can

say at this point, it is not clear. It is not clear whether or not the black box has had any impact on the thing that you care most about, which is suicide.

You do know that prescribing is down somewhat. That could be a good thing, it could be a bad thing.

DR. PINE: Well, I guess on that point, that is from again an FDA perspective in particular, and again going back to where we were when the black box first came out, you know, were you surprised by that, did you expect that down turn and if yes or if no, how does that influence what we would think about now.

Given that it happened once, you know, should we be thinking that if we put a black box here. Maybe there is going to be a similar down tick in prescriptions of antiepileptics, and maybe that should be part of the equation what we discuss here.

DR. LAUGHREN: First of all, let me go back to what is actually in the box. As Bob Temple pointed out, it doesn't tell clinicians not to use the drug. It says that if you are going to use it, do basically a risk-benefit analysis, consider the risks, consider the benefits.

In terms of, you know, we didn't know really what

to expect in terms of prescribing. It is always hard to predict what the impact is going to be. It is something you worry about, but it is hard to know.

What has happened, I think everyone is in agreement that there has been a slight decline in prescribing in adolescents. There has not been an epidemic of suicides, but it is too early to tell. We will know over the next three to four to five years I suppose.

DR. PINE: Let me make one last comment and then I won't say anything more about this. I mean obviously, from my line of questions, I have a certain point view, and to be explicit, I voted against the black box both times, and I think that there was real concern at that time that there was going to be a decrease in prescribing, and I think a lot of people weren't that surprised when it happened.

I realize that you guys say that it doesn't say not to prescribe in the black box, and that you really do not--you want only people who need the medicine to get prescribed the medicine, you want physicians to think very carefully about that. But, given what happened in the past, I think it at least has to be on the table as a possibility that the actions here will influence the likelihood with

which medications will be prescribed.

DR. KATZ: Look, we have to acknowledge that even though we don't say don't use them, you put a box warning on, it affects people's prescribing or is likely to anyway. But again, it depends upon what the indication is.

I think we would assume--and this is obviously something for the Committee to discuss--but I think we would assume, for example, in epilepsy, if every drug approved to treat epilepsy has this language, it is very unlikely that people are going to stop treating people who have epilepsy. There is no alternative to turn to that is approved that doesn't have that in its label as well or assuming this comes to reality.

I don't think we would expect--but again there is lots of off label use. There are other things that are approved for that are perhaps not as serious as epilepsy, so as Tom points out, the decrease in prescriptions for antidepressants might be a good thing, it might be a bad thing. It may be that people who shouldn't have gotten them in the first place aren't getting them anymore, while physicians who don't really know how to wisely prescribe them aren't prescribing them anymore.

So, it's hard to predict, but yeah, we certainly acknowledge that just because we don't say don't use them, we know the box has an effect or expect it would.

DR. TEMPLE: The other thing, of course, is you can emphasize something at the expense of other things. The box for antidepressants now says the major reason for committing suicide is being depressed, so it says that. That was an addition.

Of course, one of the things that was at least somewhat distressing to me about the whole antidepressant thing is that we were looking at studies of acute depression, which is where this emerged, and if you think about what the likely benefit of an antidepressant is, it is preventing recurrence over the long term or at least that is my impression. I am not the shrink here.

Of course, there were no studies of that at all, so we are very conscious of trying to present a balanced picture and call for your help in doing that. But I think what Rusty says is surely right, nobody is going to stop treating epilepsy. That is hard to imagine.

DR. GOLDSTEIN: Dr. Potter.

DR. POTTER: I actually want to follow up on

something Dr. Leon was saying and perhaps ask him or the Committee about some implications. I think he drew very clearly the number needed to harm and, if you run the numbers over large numbers of people, you clearly have a public health problem potentially, which you want to alert people.

At the same time, given the statistical arguments, the conclusion of the statisticians is you can see no difference between drugs, but--and this is more than a mind game--but if you really believe that multiplied out, there is a significant health problem in the relative risk of a suicidal behavior, then, I would assume it would be very important to know if there are true differences between drugs and if the relative risk difference is shown in the FDA analysis from 5.4 to minus 4.16 on carbamazepine, just to take two numbers, if there is any reality in that, is that important to know, and are you losing that information or how does one follow up on that potential information?

It is interesting. I mean I understand from a risk point of view you emphasize the risk, but embedded in here is another question, are there real differences between drugs, and it seems very difficult to address that issue or

even talk about what one might do to address that issue.

I mean it is a point and obviously from society and a drug development point of view, it is extremely important for us to know how to go about this. But, frankly, one's concern is if the standards for saying that drugs are different and you lump them together with data like this, are so difficult to exceed, then, the likelihood that we, as a society, will invest what you need to do to show that one drug is different from another. It is something we all need to deal with, that is all I am going to say.

DR. TEMPLE: Can I just comment on that? Bill has identified what we I think said at the beginning, or Rusty said at the beginning, is one of the major fundamental problems here.

Our initial conclusion as you heard is that the sorts of differences that we have seen are expected with relatively small numbers, so they don't prove to somebody's satisfaction anyway that there was a difference.

But it is a profoundly good question and one of the issues I think is how much one should say in any box or other warning that you give about the variability and how

much you should dismiss it and how much you should emphasize it, and all kinds of things like that, and you are right.

Once you have a, quote, "class effect," the kind of evidence you would need to make it go away is daunting to even think about.

DR. GOLDSTEIN: Dr. Caplan.

DR. CAPLAN: I would like to address the issue of the unanticipated effects of putting a black box. Parents of children with epilepsy are really very concerned about adverse cognitive and behavioral effects on their kids. And the neurologists might continue their prescription patterns, but the parents make the decision if the children are going to get the medication or not.

We really don't want parents to withhold medication from their kids because of their concerns of these adverse effects, and seeing suicidal ideation I am sure would make parents very concerned.

The issue about withholding these meds from the kids, we also know that withholding meds have significant adverse cognitive, linguistic, academic, and other effects, so this really is a serious issue.

The other thing is in terms of adolescents and