DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# PSYCHOPHARMACOLOGICAL DRUGS

# ADVISORY COMMITTEE

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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

**Call to Order**

DR. TAMMINGA: We will start this meeting now, the Psychopharmacology Drug Advisory Committee. The topic for today is the regulatory issues in the development of drug treatments for psychiatric and behavioral disturbances associated with dementia.

My name is Carol Tamminga, and I am from the University of Maryland and the chair of this committee. What I would like to do is ask people to just to go around the table and identify themselves, and, Dilip, I think we will start with you.

DR. JESTE: I am Dilip Jeste, from University of California San Diego.

DR. TARIOT: Pierre Tariot, University of Rochester, in New York.

DR. SCHNEIDER: Lon Schneider, University of Souther California.

DR. COHEN-MANSFELD: Jiska Cohen-Mansfeld, Research Institute of the Hebrew Home of Greater Washington and George Washington University.

DR. CAINE: Eric Caine, University of Rochester in Rochester, New York.

DR. LEBOWITZ: Barry Lebowitz, National Institute of Mental Health, Bethesda.

DR. REISBERG: Barry Reisberg, New York University School of Medicine.

DR. WHITEHOUSE: Peter Whitehouse, Case Western Reserve University.

DR. TITUS: Sandy Titus, FDA. I am the Executive Secretary of the committee.

DR. GRUNDMAN: Michael Grundman, University of California, San Diego.

DR. CUMMINGS: Jeff Cummings, UCLA School of Medicine, Los Angeles.

DR. DOMINGUEZ: Roberto Dominguez, University of Miami School of Medicine.

DR. HAMER: I am Robert Hamer. I am from Robert Wood Johnson Medical School.

DR. BANISTER: Guardia Banister, Providence Hospital, Washington, DC.

DR. WINOKUR: Andy Winokur, University of Connecticut Health Center.

DR. LAUGHREN: Tom Laughren, Team Leader for Psychopharm. at FDA.

DR. KATZ: Russ Katz, Division Director in Neuropharm. Drugs, FDA.

**Conflict of Interest Statement**

DR. TITUS: I am going to read the conflict of interest statement into the record for this meeting. 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.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions: Since the issues to be discussed by the committee at this meeting 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 208(b), each participant has been granted a waiver which permits them to participate in today's discussions.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office which is located in Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA 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 financial involvement with any firm whose product they may wish to comment upon.

DR. TAMMINGA: The topic of today is a very interesting and rich topic, and an opportunity for the FDA to get input and perspective from people in the field in order to form their decisions. I think the field has responded in a very rich way, and we will have a very interesting day. Next, I think we will hear from Dr. Katz.

**Welcome**

DR. KATZ: Thanks. I really just wanted to say welcome back to the committee, and a particular welcome and thanks to our invited consultants and experts who have willingly given their time to come and share their views on this topic.

We recognize that we are putting to you, the committee members, a particularly difficult task. Unlike the typical task where we bring to you a particular application and ask for your views, this is a much larger task, and we recognize that an attempt to bring some order and possibly some consensus in an area where there is not unanimity and where we are breaking new ground is always difficult. So, I wanted to thank you for your thoughts. We

will be listening very carefully, and I want to welcome you again. I particularly want to thank Tom Laughren who has done a tremendous amount of work in making this meeting a reality. So, welcome. Thanks very much. And, I think I will turn it over to Tom at this point.

**FDA Overview of Issues**

DR. LAUGHREN: Good morning, and I would also like to welcome everyone and thank you all for coming.

[Slide]

The topic today is discussion of regulatory issues in the development of drug treatments for various psychiatric and behavioral disturbances in dementia. In particular, what we would like to focus on is the problem of how to identify and define those specific clinical entities under this broad category for drug development. This is a very important topic and we hope to have a full discussion of all aspects of it today.

At the end of the day, it would be nice to be able to reach consensus on some issues. That may not be possible on all. At the very least, we would like to be able to identify those issues and areas that need further work.

[Slide]

I think there has been some concern that FDA has not paid enough attention to this aspect of dementia, and I want to just clarify in this slide that we do think this is

very important. Obviously, there is an increasing prevalence of various dementias, in particular Alzheimer's disease. The clinical spectrum includes not only the cognitive impairment but also various psychiatric and behavioral disturbances, and we recognize fully that both aspects are important and represent a burden for patients, families and the community.

In terms of drug development, I think the primary emphasis in the past has been on treatments for the cognitive impairment. Obviously, there is also a need to look at treatments for the psychiatric and behavioral disturbances. This is an important target.

[Slide]

We think that an important obstacle in drug development programs for the psychiatric and behavioral disturbances has been this difficulty in identifying, defining and naming the different clinical entities that fall under this rather broad umbrella.

[Slide]

Now, how does this translate into a regulatory problem? In order for FDA to approve an NDA there are a number of requirements, but among the clinical requirements is a need to show efficacy for some indication, to show safety, reasonable safety for that same indication, and to have acceptable labeling.

[Slide]

Now I am going to give you some language that comes right out of the Food, Drug and Cosmetic Act under which we operate and that lays out the labeling requirements. An NDA must have labeling proposed to be used for such a drug, and that would include language describing the indication. The Secretary may refuse to approve an application if, based on a fair evaluation of all material facts, such labeling is false or misleading in any particular. In this context, we would argue that a poorly defined indication is potentially misleading since, in that situation, it would not be possible to inform prescribers about how to use the drug if we can't define what the indication is.

[Slide]

Traditionally what kinds of clinical entities are considered for indications? There are basically two. Most drugs are approved for either specific diseases or syndromes. Examples of that would be an entity like congestive heart failure or something like rheumatoid arthritis. That is the usual approach to getting an indication.

An alternative approach is, rather than focus on a specific disease, to focus on some non-specific sign or symptom, in other words, something that is not unique to a

specific disease, something that cuts across diseases. Examples of that would be something like pain or fever.

[Slide]

In either case, whether you are looking at a disease, syndrome or a non-specific sign or symptom, the next question is what is required for a particular clinical entity to be considered an acceptable indication? We think there are at least these three things: In the first place, it has to be an entity that is reasonably accepted in the clinical and academic community that is involved. Secondly, it should be operationally definable. Third, it should identify a reasonably homogeneous patient group. Again, this all relates back to the issue of labeling. We have to be able to describe the indication in labeling.

[Slide]

In the next few slides what I am going to try and do is to clarify what I think is a misunderstanding about psychotropic labeling. This is a bit of an aside, but I think it is important for this discussion. I think it is directly relevant to what we will be talking about later.

The misunderstanding is that psychotropic claims appear to be broader than they are in fact. This has to do with somewhat dated language that gets carried forward by precedent, and the reason it gets carried forward is that it is very difficult to change this language because of the

effect it has on other drugs in the class. And, this is something that we are working on trying to fix, but it is hard to change these kinds of precedents but it does lead to a misunderstanding.

[Slide]

Some examples of that are the claims for depression, for psychosis and anxiety. The standard antidepressant claim is that drug X is indicated for the management of depression. For anxiety -- and this is old language now, drug X is indicated for the management of anxiety disorders or the short-term relief of the symptoms of anxiety. Finally, for psychosis, drug X is indicated for the management of the manifestations of psychotic disorders.

[Slide]

For those three broad categories, the actual claim is the disorder that was studied in getting that claim. That is specified after that general claim is given in labeling. In fact, promotion in those areas is limited to that specific entity, not the broad category and the actual claims, in fact, in those three areas are for depression, major depressive disorder, because for all currently approved anti-depressants that is the entity that was, in fact, studied. The older drugs that have that general anti-anxiety claim, by and large, what we consider to have been studied is the entity generalized by anxiety disorder. So

that, in fact, is the claim. For psychosis, in all cases thus far, what has been studied is schizophrenia. So, in fact, schizophrenia is the actual claim.

[Slide]

So, what is the correct interpretation of the broad categories that are used in psychotropic labeling? I would argue that it should be the same interpretation as is applied to other broad categories of drugs, like antiepiletics, antibiotics, antirheumatics, antineoplastics. In all cases, drugs that are approved in those cases are not approved for every subtype within that category; they are approved for specific diseases under that broad umbrella.

[Slide]

In one way I think we have successfully transitioned into this current way of thinking, and that is the area of anxiety disorders. We now have drugs that are specifically approved for obsessive-compulsive disorder, panic disorder, social anxiety disorder, post-traumatic stress disorder and generalized anxiety disorder. These are all categories in DSM that fall under the general category disorders. We now have drugs that are specifically approved for those specific diseases. We are no longer approving drugs using that old language for anxiolytics.

[Slide]

In general, our intention from this point forward

is to approve drugs for specific indications, in other words, the subtype not the broad category. We will no longer be using the previous language that I gave earlier for anxiolytics, antidepressants and antipsychotics.

[Slide]

Earlier on I laid out the two possible ways of getting an indication, either for a specific disease or syndrome or a non-specific symptom or sign. The question is, is there a basis for targeting non-specific psychiatric signs and systems as an indication? What I am laying out here is what I think are the ideal criteria that one would have met in order to support that kind of a non-specific claim.

Ideally, that entity would have a universal definition wherever it happens to appear, in other words, with whatever specific disease symptom it is associated it would be universally defined. There would be commonly accepted approaches to assessment and measurement. Again ideally, you would have some understanding of the pathophysiology of that symptom. You would hope that it would be equally responsive to treatments regardless of the disease with which it is associated. And, you would hope that you would be able to establish that claim in several disease models.

[Slide]

Now I want to turn back to the topic for today, which is psychiatric and behavioral disturbances with dementia. This is a list of some of the kinds of specific signs and symptoms that are seen in this population: delusions, hallucinations, paranoia, depression, mania, anxiety, anger, aggression, labile mood, sleep disorders, eating disorders and a variety of other behaviors -- wandering, pacing and so forth. This is not a comprehensive list, but it gives the flavor that this is a broad array of findings that occur in this population.

[Slide]

Up until now what are the approaches that have been proposed for looking at this? Now what I am talking about is what we, at the agency, have been confronted with in our discussions with industry. Again, this is not a complete list but these are the two major approaches that we have seen in recent years. Probably three to four years ago, when we began having conversations with companies about this problem, there was a focus on the broad category. First it was behavioral disturbances; more recently it has shifted to this BPSD, the comprehensive term to identify a patient having dementia and having any of this wide variety of psychiatric signs and symptoms. In the last couple of years the focus has shifted to specific entities. In particular, companies developing antipsychotic drugs have

focused on something called psychosis associated with Alzheimer's disease.

[Slide]

First I want to talk about the concept of BPSD, and first of all make the point that we do think this is a useful concept in the sense that it focuses attention on this important aspect of dementia. Secondly, it identifies dementia as a population with possibly unique psychiatric disturbances, most of which remain to be defined. So, we think it is a useful concept. However, we are not so convinced that it is a useful indication. The reason that we don't think it is a useful target is that it, again, is too broad. It refers to multiple clinical entities. Again getting back to my earlier point, this could lead to labeling which is potentially misleading because it is unclear which of those many entities is responsive to treatment.

[Slide]

The other approach for looking at psychosis in dementia, from our standpoint, makes more sense. In a sense, it is attempting to borrow somewhat from the claim in schizophrenia, however, there is still the same regulatory concern. The concern is that you have to adequately define that population. You have to say what you mean by psychosis in dementia and get some agreement on that, otherwise the

claim is still potentially misleading if you can't tell prescribers what you mean.

[Slide]

The two approaches -- again, this gets back to the earlier standard approach for indications -- the two approaches we think are reasonable are, first of all, to try and define whatever unique psychiatric behavioral syndromes might exist in this population, and a unique psychosis would be one example of that. The second possibility is, again, to try and discover whether or not there is some non-specific sign or symptoms that might exist in this population and might be teased out as an indication. I am just proposing agitation as one possibility. I am not promoting that as a possibility, but it seems to me that it is one thing that might be discussed as a non-specific symptom.

[Slide]

The focus of this meeting, again, is on trying to discover what entities to focus on in drug development programs. But I did want to have at least one slide raising the concern about safety from a regulatory standpoint but we have not looked at a lot of data. I realize a lot of studies have been done. Our focus has been fairly limited but I can say that from what we have seen, it seems clear to us that the tolerability profile of these drugs in this

fairly elderly and frail population is not as good as in younger populations, and not even as good in older populations with other illnesses. So, that is a concern. In our mind, it raises the concern of having some kind of a uniform policy for evaluating risk as we move into a lot more studies in this population and deciding exactly what it is that you want to look at in terms of risk in this population. I hope there will be some time for discussion of this issue later on.

[Slide]

Finally, this is the agenda for today's meeting. My comments will be followed by comments from our invited guest speakers. We will then have a very extended open public session. Most of the afternoon will be taken up with discussion and, hopefully, at the end of the day there will be time for some summary comments. Thank you.

[Applause]

DR. TAMMINGA: Thank you, Dr. Laughren for a lucid presentation of the FDA position and certainly clarification of the questions that the committee and the committee guests need to address today. This is a particularly exciting topic, a topic that is certainly important to dementia but even important more broadly to other psychiatric syndromes in psychotropic development.

The committee is fortunate today to have a group

of guests that are experts in the area. Each of these experts will present a particular position. We have a number of experts so I am going to ask that each of the people making presentations will take care to stay within their ten-minute time period. Because these presentations may stimulate some questions from the committee, we will have a short period of time directly after each presentation to address questions to the particular person but then, remember, for any more general questions or integrative kind of comments we certainly have the afternoon to pull all that together.

So, I think we will start now with Dr. Dilip Jeste from the University of San Diego. Dr. Jeste will talk about the psychosis of Alzheimer's disease: a distinct syndrome. All the speakers will notice that there is a timing box right on the podium, and the audience can see the timing box as much as you can.

**Presentations by Consultants**

**Psychosis of Alzheimer's Disease: A Distinct Syndrome**

DR. JESTE: Thank you, Carol, and good morning.

[Slide]

First of all, I want to thank the FDA for giving me the opportunity to participate in this very important meeting. I am going to address the question whether psychosis of Alzheimer's disease is a distinct syndrome.

[Slide]

This question can really be subdivided into three sub-questions: One, is there public health importace to this entity?

Two, is this really a distinct entity? Now, how do we know it is a distinct entity? We need to show that patients who have Alzheimer's disease and psychosis are different from Alzheimer's patients without psychosis, and also they are different from non-Alzheimer's patients with psychosis. The best prototypical psychosis for this purpose is schizophrenia.

Lastly, if it is a distinct entity we need to have diagnostic criteria, and we need to see if there is some neurobiological basis and whether there are measurement tools that can assist in a reliable fashion. So, I will go through these three one by one.

[Slide]

The first aspect is public health importance. In this slide I will show the incidence of psychosis of Alzheimer's disease. Secondly, studies by the Columbia and Pittsburgh groups have shown that the psychosis of Alzheimer's is not a very short-lasting or transient syndrome, but it is chronic or recurrent. Thirdly, there is excellent evidence showing that psychosis of Alzheimer's produces functional disruption and requires ongoing

treatment. I will come back to that a little later.

[Slide]

There have been studies on prevalence of Alzheimer's psychosis. This is a study that we just completed that looked at the cumulative incidence of psychosis in patients with Alzheimer's. These are the studies done at UCSD Alzheimer's Disease Research Center. It is in press in Neurology.

We found that patients who presented at the Alzheimer's Disease Research Center for the first time had an average Mini-Mental score between 20 and 21. We followed these patients longitudinally and we found that 20 percent developed psychosis within one year; 36 percent within two years; 50 percent within three years; and after that the incidence seemed to plateau. So, it looks like the cumulative incidence of psychosis of Alzheimer's over a three-year period is about 50 percent.

[Slide]

It is estimated that there are about four million people with Alzheimer's disease in the U.S.A. today, and if that figure of 50 percent were accurate, one would assume that there would be about two million people with Alzheimer's plus psychosis -- two million people with Alzheimer's or psychosis at some point in the course of their illness.

Going to the question of whether psychosis of Alzheimer's is a unique syndrome, do Alzheimer's patients with psychosis differ from Alzheimer's patients without psychosis? May studies done by people in this room have shown that Alzheimer's psychosis patients have significantly more agitation and aggression. A number of studies have shown there is more rapid cognitive decline in this group. There is greater caregiver distress which leads to earlier institutionalization. That is why there is greater cost of care. And, last but not least, there are different treatment considerations. I will talk about that shortly.

[Slide]

The second part of the question about this being a distinct syndrome is whether psychosis of Alzheimer's is different from psychoses that occur in patients without dementia. The best prototypical example for primary psychiatric disorder is schizophrenia. There are a number of differences between psychosis of Alzheimer's and schizophrenia in the elderly population. The prevalence in most of the reported studies of psychosis of Alzheimer's if 30-50 percent, whereas the prevalence of schizophrenia in the elderly is less than one percent. Bizarre delusions that have no realistic basis or complex systematized delusions are common in schizophrenia, very rare in Alzheimer's patients. The typical delusions in Alzheimer's

patients are simple delusions such as somebody stealing things; hiding things; the caregiver is an impostor, and so on. Usually hallucinations are much more common in Alzheimer's patients with psychosis, whereas schizophrenic patients tend to have auditory hallucinations.

[Slide]

Symptoms such as voices talking or voices commenting on the patient's actions are frequent in schizophrenia, very rare in Alzheimer's patients. Alzheimer's psychosis patients may wish that they were dead, but active suicidality is extremely rare. In contrast, 50 percent of patients with schizophrenia attempt suicide and 10 percent die from suicide. Past history of psychosis is quite rare in Alzheimer's patients, whereas most of the elderly schizophrenic patients have had many episodes of psychosis in the past.

[Slide]

Schizophrenia in most cases is a life-long illness, whereas psychosis of Alzheimer's tends to remit as the senility of dementia increases. It is not clear whether it is a true remission. It is possible that some neuronal entity is necessary to have delusions/hallucinations and when it is no longer there the patients cannot have psychosis. It is also possible that the remission is not true remission but, as patients become more severely

demented and aphasic, they will not be able to articulate their delusions and hallucinations. Nonetheless, the point remains that whereas patients with schizophrenia need treatment for years and years, and sometimes for their entire life, Alzheimer's patients with psychosis need treatment for a much more defined time period.

Also, the average dose of neuroleptics required for Alzheimer's psychosis patients is significantly lower than that in patients with schizophrenia. In addition, even when we use lower dosages there are different treatment considerations. We have found that the cumulative incidence of tardive dyskinesia in Alzheimer's psychosis patients who are starting treatment with conventional neuroleptics is 25-30 percent, whereas in a schizophrenic patient who is in the very early stages of treatment -- these are mostly young schizophrenics, the incidence of tardive dyskinesia is about 5 percent per year. So, there is a high risk of tardive dyskinesia with conventional neuroleptics even at very low dosages.

[Slide]

Is this a distinct syndrome and can we define it? Sandy Finkel and I published criteria for Alzheimer's psychosis which are modeled after DSM-IV criteria for schizophrenia. At the outset, I should say that these are not perfect criteria. I don't think we have perfect

criteria for any psychiatric disorder. Even after a hundred years we are still struggling with the right criteria for schizophrenia. So, we will continue to make some modifications in those criteria.

Nonetheless, one can say that psychosis of Alzheimer's patients should have delusions or visual or auditory hallucinations. Obviously, the primary diagnosis has to be Alzheimer's. One should show, in terms of chronology, that the onset of symptoms of dementia preceded the onset of symptoms of psychosis. The duration should be at least a month, although the symptoms may be intermittent. The severity should be such that it should cause functional disruption. Obviously, one has to exclude other causes of psychosis, such as schizophrenia, delusional disorder and other primary psychiatric disorders. Delirium is an important exclusion although delirium and psychosis of dementia can coexist for a period of time; and other causes of psychosis such as different types of encephalopathies also need to be excluded.

[Slide]

There are some important associations. These include agitation, negative symptoms and depression, and each of these has its own therapeutic concentrations.

[Slide]

Is there evidence for a neuropathological basis?

At the outset I should say that the evidence is not well established, but again I want to say that even after a hundred years of work on schizophrenia we still do not know the exact neuropathology of schizophrenia. So, our expectations in that regard have to be lower than for some other aspects of the disease. However, there are a number of studies looking at neurobehavioral, neuropsychological, brain imaging, EEG and postmortem aspects that have suggested that there is a frontal temporal involvement in the psychosis of dementia. By frontal temporal I also include prefrontal and hippocampal regions.

[Slide]

There is some suggestion, more indirect than direct but some suggestion that dopamine, norepinephrine, serotonin and acetyl choline are involved in psychosis of dementia.

[Slide]

There are excellent measurement tools, however, they are broad -- and Barry Reisberg will talk about behavior and Jeff Cummings will talk about NPI -- some ideas like BPRS to look at a number of items, however specific items from those scales can be used for measuring psychosis of Alzheimer's.

[Slide]

This is my last slide. I think there is good

enough evidence to suggest that psychosis of Alzheimer's is a unique syndrome, accepted by much of the relevant clinical-academic community. I thought it was quite gratifying that the three major geriatric psychiatry organizations have all endorsed these criteria. It is operationally definable. It identifies that there is a homogeneous patient group, and it has major public health significance. Thank you.

[Applause]

DR. TAMMINGA: Thank you, Dr. Jeste. Are there any specific questions by the committee or its guests for Dr. Jeste? Dr. Caine?

DR. CAINE: Dilip, why did you pick the dementia before psychosis criterion in your set? What was your thinking behind that?

DR. JESTE: The thinking behind that was to exclude patients with primary psychotic disorders who may then go on to develop dementia. For example, patients with schizophrenia in the later stages may have what looks like dementia and be excluded. I see your point, which is that sometimes Alzheimer's patients may present with psychotic symptoms before they have cognitive impairment.

DR. CAINE: Sure.

DR. JESTE: That is possible, however, that is in general quite uncommon. Psychosis is usually more likely to

occur not in the very early stages of dementia but more in the middle or more severe stages. So, I agree with you that this may exclude a few patients, however, I think from the point --

DR. CAINE: So, as I understand, you are using it as a safeguard convention as opposed to something based on huge data sets.

DR. JESTE: I guess the only point in terms of data sets is that most Alzheimer's psychosis patients have dementia first and then psychosis.

DR. CAINE: That is because they were selected with the dementia first at the beginning of the study.

DR. JESTE: I haven't seen, I must say, too many reports of patients who first presented with psychosis.

DR. CAINE: I am just bringing it up because if you look at the literature, it is a skewed literature because people get into the Alzheimer trials, natural history studies, etc., on the basis of not of having had a psychosis with the emergence of a dementia but, rather, having a dementia with the emergence of a psychosis. So, I think it is really important, and we can come back to that later but I think it is an important point.

DR. JESTE: Sure, it is an important point.

DR. TAMMINGA: This may be a good topic for some general discussion in the afternoon. Are there any other

specific questions? If not, we will move on. Thank you very much, Dr. Jeste.

DR. JESTE: Thank you.

DR. TAMMINGA: The next person to make a contribution is Dr. Pierre Tariot from the Monroe Community Hospital in Rochester, New York. The concept of secondary mania in dementia. Dr. Tariot?

**The Concept of Secondary Mania in Dementia**

DR. TARIOT: Thank you, and I want to thank the FDA for focusing so thoughtfully on a matter of great public health significance, and I want to thank Dr. Laughren and Dr. Tamminga for the invitation to speak.

If I understood the disclosure request properly, I should indicate that I have received honoraria and consultant fees from manufacturers of several mood stabilizing agents and, in particular in my discussion today that will be true of Novartis and Abbott Laboratories.

[Slide]

I am going to make a couple of comments about DSM, the application of DSM criteria to patients with dementia, especially but not exclusively in Alzheimer's disease; talk about some phenomenology and treatment data and wrap up.

[Slide]

You will note that, in my manic preparation phase for this talk, I prepared more slides for your handout than

I am going to present on the screen. DSM gives us clear-cut guidelines for the definition of a manic episode, basically a period of persistently abnormal mood associated with several other features. Note that the mood can include irritable mood. Note that some of the features include sleep disturbance, talkativeness and psychomotor agitation -- features that are very common in dementia.

[Slide]

Although mania is most frequently or classically associated with bipolar disorder, we can see it in association with other general medical conditions, and DSM allows us to have ways of describing that.

[Slide]

In the spirit of what Dr. Jeste just talked about, can we make a case that the secondary manias somehow characterize a distinct population? The answer may be partially yes. These folks with secondary mania tend to have a later age of onset; are less likely to have a family or personal psychiatric history; don't respond nearly as well to lithium as young patients with bipolar disorder; and very frequently have neurologic diseases. Probably up to half of older people with secondary mania have some kind of brain injury, particularly in key brain areas. However, this connection that has been partially mapped out in traumatic brain injury is not so clear in dementia.

[Slide]

This is really the point that I just made, so can I go on to the next slide?

[Slide]

So, if you apply rigorous syndromal criteria to patients with Alzheimer's disease what do you see? Dr. Lyketsos is here, one of the investigators who has addressed this question. Basically, what you see is a prevalence of syndromal mania in patients with Alzheimer's disease that is roughly what you see in the general population. The numbers range from 2-5 percent. The 5 percent, however, is from a skewed sample of psychiatric inpatients in a hospital.

This is the paper of Holm, et al. Holm also generalized the discussion a little bit, I think, in a way that is useful for me rhetorically by saying, well, 5 percent met DSM-IV criteria for a manic syndrome but nearly 20 percent had features of bipolar disorder. So, what I want to talk about now is what those features might be.

[Slide]

As is often the case, they may be in the eyes of the beholder or at least influenced by the scale that is used, for instance, Dr. Reisberg's well-known BEHAVE-AD -- this is from his first publication; he has done many others. If you look at some of the items that are frequently endorsed in outpatients with Alzheimer's disease, you see

features that are reminiscent of the kinds of features you can see in patients with mania.

[Slide]

I could go through lists of other scales and make the similar point, but let me go on to data that Marshall Folstein has allowed me to present. These are unpublished data. He has carried the argument, I think, further than anybody by applying a uniform behavior rating scale, the Psychogeriatric Dependency Rating Scale, to three populations, all older folks, with mania, Alzheimer's disease and depression.

[Slide]

The essential finding is that when one looks at behaviors that are frequently abnormal in patients with mania, the profile in patients with mania is remarkably similar in many cases to the patients with Alzheimer's disease, whereas both appear to be different from the patients with depression.

So, these are unpublished data, not peer-reviewed, but they are probably the best case that the phenomenology of Alzheimer's disease overlaps with the phenomenology of syndromal mania.

[Slide]

So, by way of summary of that portion of the literature, I think these are the specific features that one

sees in mania that one can see in dementia.

[Slide]

Of course, there are features that are lacking in dementia. If Dr. Folstein were here, I think he would say the common indifference to cognitive deficits might be construed as grandiosity in some cases, but most of us I think would accept that these are not found in patients with dementia.

[Slide]

What about treatment? This slide makes the point that therapies that are used to treat mania, namely anticonvulsants, are actually used by clinicians in the field. I won't go through the details here. It is just that simple point. It doesn't prove anything about specificity.

[Slide]

What about trials that are published? There are controlled and uncontrolled studies with the anticonvulsant carbamazepine in patients with agitation and, of course, that is different from syndromal mania. In the aggregate, I would argue that the data suggest but don't prove that agitation can be relieved by carbamazepine, and the level of evidence is probably not sufficient to dictate clinical practice.

[Slide]

Valproate, divalproex sodium is approved for treatment of acute mania associated with bipolar disorder in the U.S., and its congeners have been looked at in agitated patients with dementia in uncontrolled studies. We have unpublished data from one controlled study indicating a good effect on agitation. Abbott Laboratories has conducted, but not presented, a very interesting study looking at patients who were selected for having manic features. Those data have not been presented publicly yet and I can't comment on them.

[Slide]

I can say something about a meta-analysis of our own anticonvulsant studies in these agitated patients, what symptoms responded, and you see them here. Again, there is a partial overlap with the features of a manic syndrome but what is lurking in my comments is that the notion of specificity here is suspect so far.

[Slide]

On the other hand, there are symptoms that we see in these agitated patients that don't seem to respond very well to anticonvulsants in our hands in placebo-controlled studies, and perhaps notable on this list is irritability, one of the key features of the definition of a manic syndrome.

[Slide]

So, in an effort to wrap-up on time, here are two last slides giving how I make sense of this literature and this phenomenon. Is there a distinct idiopathology of mania in Alzheimer's disease or in other dementias? I would have to say, as far as I see the literature right now, the answer is we don't know; it is not very compelling.

Are the clinical features of mania in dementia -- let's say Alzheimer's disease is the paradigm -- well defined? I think it is fair to say yes for the rarely occurring full-blown manic syndrome, but not so well for this more heterogeneous group of manic features.

Do these features identify a homogeneous patient group? Yes, for the rare full-blown manic syndrome but not for the more diffuse features.

Are there appropriate instruments that the academic community has agreed on to assess these clinical features? Not particularly. I don't think this is an insurmountable barrier but we are not there yet. For instance, the application of well-known mania rating scales has just been attempted in this population and the results are still open for discussion.

Are antimanic drugs specifically effective for these clinical features? The answer is not known yet. The Abbott results will be interesting in this regard, however, one could make the case that whether the answer is yes or no

that doesn't cinch the argument. Of course, safety is a major consideration. Are these drugs proven to be safe?

[Slide]

So in final summary, I would say that a full-fledged manic syndrome is rare in Alzheimer's disease and other dementias but that these appealing manic features certainly overlap with a manic syndrome and the features of agitation that we see. But, at this point, we don't have sufficient evidence to achieve a broad consensus that there is syndromal significance of these manic features in dementia. Thank you.

[Applause]

DR. TAMMINGA: Thank you, Dr. Tariot. Dr. Katz?

DR. KATZ: Yes, if I remember one of your earlier slides, I think you said that the incidence of perhaps full-blown mania in this population was about the background rate in the general population. But then you said, I think it was 17.6 percent, or something along those lines, had these manic features.

DR. TARIOT: Right.

DR. KATZ: Does anybody have any information about what the background rate in the general population would be for these manic features?

DR. TARIOT: Dr. Lyketsos will address that later on in his talk. If we use the Folstein data from his

Horizon sample as any indicator, that would be a much lower level. Also, the Alzheimer's Disease Cooperative Study has published results with behavior rating scales in older normal subjects and they are far lower, almost an order of magnitude lower in terms of the hit rates for these behavioral items.

DR. TAMMINGA: Any other questions or comments for Dr. Tariot?

[No response]

Thank you very much, Dr. Tariot.

DR. TARIOT: Thank you.

DR. TAMMINGA: Next we will hear from Dr. Cohen-Mansfeld from George Washington University. Her presentation will be on the conceptualization of behavioral and psychological symptoms associated with dementia: issues related to the development of pharmacologic interventions. Dr. Cohen-Mansfeld?

**The Conceptualization of Behavioral and Psychological Symptoms Associated with Dementia: Issues Related to the Development of Pharmacologic Interventions**

DR. COHEN-MANSFELD: Thank you very much for inviting me here.

[Slide]

I addressed myself more directly to the questions in the original concept paper, and probably addressed too

many questions but I will try to skip through it.

[Slide]

In relation to the position paper of the FDA, I tried to address whether BPSD is one entity; whether it is part of the diagnosis of dementia; or whether there are symptoms that cut across diagnoses, etc. We will quickly go through these one by one.

[Slide]

Is it one entity? My answer is quickly no. Different behaviors that were listed before, some of them occur in some of the people who have Alzheimer's disease but most of the time most of the people don't have most of these syndromes, and even though there are some correlations I believe those are too low to be considered one entity.

[Slide]

When we look at the relationship of these different syndromes or behaviors in Alzheimer's disease patients we find that they relate differently to the different stages of dementia. Here I am citing four independent studies that all have similar results.

[Slide]

This relates to three syndromes of agitation -- physically non-aggressive behaviors which can also be called motor restlessness; physically aggressive behaviors and verbal vocal agitation and their relationship to stages of

dementia. So, we see that motor restlessness increases linearly with stages of dementia. Physically aggressive behaviors occur at late stages; and verbal vocal behaviors occur more in the middle to late stages and then decrease, and that was found in a number of different studies.

[Slide]

Is BPSD part of the diagnosis of dementia? As I said before, I believe most people don't have most of these symptoms most of the time, so I would not call it an essential part of the diagnosis even though many of those symptoms obviously are in dementia.

[Slide]

Are these symptoms which cut across diagnoses? This was partly addressed in the two previous presentations.

[Slide]

If we look at the agitated behaviors, as I mentioned before, some of them occur some of the time in normal people and there are quite a few diagnoses if you look at DSM-IV where people have motor hyperactivity, aggression, repetitive movements. However, are these the same in terms of their underlying causes, either behaviorally or neurologically? We really don't know.

[Slide]

We already heard about how delusions in Alzheimer's disease are different. But I would like to say

an additional word about this. They are different in all the features that we heard about before by Dr. Jeste but the content of these delusions is different. If we notice what are these delusions, many of them are "someone is stealing from me." That is frequently related to memory impairment, not being able to find the object. Another common one is that their relative is an impostor. That may be related to not being able to recognize your regular caregiver, the hired help or even your relative and, again, may be related to cognitive problems.

[Slide]

Hallucinations have been related to visual impairments, and I will get to that later.

[Slide]

Sleep problems also appear in either DSM-IV diagnoses and their relationship to sleep problems in dementia would take a whole other presentation but, again, we don't know.

[Slide]

As I said before, delusions are an interpretation of the memory problem. As someone said, the experience of having a severe memory problem can affect people more than we give it credit and, therefore, delusions when you can't find something and you attribute it to stealing may be more similar to confabulation or to misinterpretation than to

delusions. Again, there are many studies that show hallucinations to be related to visual sensory deprivation and that has to be taken into account when we speak about hallucination. Other types of hallucinations are when people talk to loved ones who have been gone for a long time. Is that wishful thinking? Is that a memory problem? I am not sure but it is not exactly the hallucinations that we are used to in schizophrenia.

[Slide]

Which syndromes have been reliably identified in BPSD? Again, that is a longer presentation than I have time for but I will show some.

[Slide]

These are a number of studies in different populations, Dutch, Chinese, Japanese and United States, all of which found the same syndromes of agitation, these three syndromes I mentioned before -- aggressive behaviors, motor restlessness and verbal behaviors.

[Slide]

So, I believe they are pretty reliable three syndromes. There are also over 40 assessments that can assess those syndromes of agitation. In terms of psychotic symptoms, again, we have consistent results, however, I believe those consistent results are based on our definition. If we call a person who says people are

stealing from them delusions, we have consistent results and we have assessment instruments that give those reliable results but what this means is a different issue.

In terms of depression, in our findings we found that the affect is unrelated, not correlated necessarily to appetite or sleep problems and I believe those have to be looked at separately.

[Slide]

Should drugs be developed for BPSD? I said we have some reliable syndromes that we can assess pretty well but what does that mean? What I would like to say is that some behaviors do not have to be treated at all. When a person is talking to their loved one, even though that loved has died years ago, and that is some kind of a hallucination, who cares? Some behaviors seem to be related to loneliness, physical pain, boredom and other causes and, indeed, these etiologies have been shown in different treatment studies to respond to non-pharmacological therapies. These are examples of four studies that have a reasonable success rate in reducing different agitated behaviors.

[Slide]

I just want to go into some more detail as to what these results may mean and how we might go about this. This is an going study. It is a small N but it is just to show

the thinking about it. In this ongoing non-pharmacologic study we started with 12 residents. We identified needs of the kind that I mentioned before in 9 of them. We had full success so that anybody can clearly see that these people are doing better. With 5 we had partial success. Then we had failures. We had 3 failures. One had terrible tardive dyskinesia and akinesia that interfered with everything they did. One had severe infection so that we couldn't do any treatment. The third is where I think possibly a pharmacologic study can be used. It is important to know most of these are the people with severe dementia who are usually excluded from such studies.

[Slide]

There are two issues that I just want to quickly mention that need to be addressed. One is sample representativeness. In one pharmacologic study that we were involved in, we pre-screened 400 people and got 4 in. We lose most of the important population. Most people who I think are really the aggressive and the more demented are lost in the real trials. Just as important is looking at the impact on non-target symptoms. Even if we can decrease the negative behaviors, we might decrease all functioning and that has to be looked at. Thank you.

[Applause]

DR. TAMMINGA: Thank you, Dr. Cohen-Mansfeld. Are

there any questions?

DR. WHITEHOUSE: Jiska, your scale, the Cohen-Mansfeld Agitation Inventory, has been used in a variety of studies and it is fair to say we have some consistency of use and some consistency of understanding agitation in dementia. But, I guess, in terms of this being a non-specific symptom that we might look for treating in other conditions, and you listed them on your slide -- pediatric and adult conditions, has your scale been used in other conditions, or are there other scales to assess agitation in some of these other conditions that are accepted in those fields? Does the structure of agitation look similar in these other conditions? I mean, how much do we know about this non-specific syndrome in other areas besides dementia?

DR. COHEN-MANSFELD: I don't know of any in children besides my kid suggesting that it would be appropriate for assessing him. I have no idea.

DR. TAMMINGA: Yes, Dr. Schneider, go ahead.

DR. SCHNEIDER: Jiska, on one of your early slides it looked like it was with Brief Cognitive Rating Scale data showing aggression increasing with severity of dementia. For clarity, those were cross-sectional data or were those longitudinal data?

DR. COHEN-MANSFELD: Well, three of these studies were cross-sectional and, actually, two had also

longitudinal data in them. Those support it. Now, I don't think these are necessarily the final word but the fact that these different studies that were conducted by different groups have similar results makes me believe that it is probably correct phenomena. The aggression starts towards the end of dementia and that is where the increase occurs.

DR. SCHNEIDER: Yes, I think my question is really going to your definition of syndrome. A little bit later you showed syndromes of agitation or psychosis based on factor analysis, and my general questions are whether, when you identify aggression or physical aggression, there is a natural history to it in particular patients where it is maintained over a period of time, or whether what is described in the cross-sectional data is just an increase in prevalence of, for instance, aggressive behaviors with severity of illness.

DR. COHEN-MANSFELD: Well, the research is sort of divided. That means there are a couple of studies that suggest that people who develop aggression in dementia were somewhat more likely to have had aggressive episodes or more aggressive personality before. These are not very strong data but they do exist. In addition, we think that the prevalence of aggression increases in late stages of dementia.

Again, what I really wanted to say is that we need

a more thoughtful process here because even in aggression a lot of the issue has to do with our communication with the person who has dementia, with misunderstanding -- let's say, a lot of aggression occurs in ADLs. The person who has dementia does not understand the person is coming to help them; they are scared, and that is the process that is going on. So, it is not always necessarily a drug study that is needed but it has to do actually with the decreased cognitive ability.

DR. TAMMINGA: A last question from Dr. Cummings.

DR. CUMMINGS: Jiska, you raised a very important issue of the interplay between the cognitive deficit and particularly the psychotic disorder, and you are willing to attribute some of the delusions to the memory impairment. Now, memory impairment is ubiquitous and often severe across the population whereas psychosis occurs in 25 percent and perhaps as many as 50 percent. We have done one study where we could not find a difference in the severity of memory impairment between psychotic and non-psychotic patients. I am wondering what the evidence is linking memory impairment and delusions.

DR. COHEN-MANSFELD: Well, I think Barry has some data on this, and I have basically the same data from a different study. I hope I am quoting you correctly, but I think it is your stage 5 or so, which is very interesting

because those are the stages when you are really very cognitively impaired so you might not understand what is going on, or you might misinterpret it, but you can still communicate that you think they are stealing. Later on, at stage 7 of Barry's scale we don't know what a person with dementia is thinking. So, actually the staging does fit this but also we were just analyzing a study and there was a delusion of an impostor and I asked, well, what is actually going on with this person, and in this case it was in the morning, when the nurse comes to dress the resident -- this was in a nursing home, they don't recognize her; they think that she is coming to harm them. Well, is that a delusion or not? Even more than that, is it helpful to use the term delusion in this context, or is the label misguiding us in terms of treatment? Those are things that I think we need to think about.

DR. TAMMINGA: Dr. Hamer, one more comment?

DR. HAMER: I am going to play the role of the pedantic statistician. In the transparency you showed that had three plots on it, first of all, the vertical axis wasn't labeled at all. I have no earthly idea what those three plots mean. Second of all, the curves on them were smooth. It would be an amazing coincidence if those were actually data as opposed to some sort of idealized or fitted curve. So, I am not sure just what I learned from them.

DR. COHEN-MANSFELD: Okay, these are fitted curves and they fit data from the different studies, and I will be glad to show you the studies and the detail. Because I only had ten minutes I didn't have really time to get into much of the data.

DR. HAMER: But you could have labeled the vertical axis.

DR. COHEN-MANSFELD: The vertical axis was the actual behavior, the physical aggressive behaviors, the verbal behavior and the motor restlessness. The horizontal axis was the stage of dementia.

DR. HAMER: And, in your discussion of factor analyses you had one slide in which you presented factor analyses and then the next slide talked about syndromes. I just want to make sure that we understand that merely because you can group items into factors doesn't necessarily imply at all that you can group people based on those factors into clusters. Simply the presence of factors does not imply clusters of people with specific characteristics.

DR. TAMMINGA: Thank you for your comments, Dr. Hamer. I think that will carry on with discussion more this afternoon since there are a lot of additional things here to address. Thank you, Dr. Cohen-Mansfeld. I appreciate your contribution.

DR. COHEN-MANSFELD: Thank you.

DR. TAMMINGA: We will next hear from Dr. Eric Caine from the University of Rochester. Dr. Caine will discuss classifying the manifestations of Alzheimer's disease in DSM-IV-TR.

**Classifying the Manifestations of Alzheimer's Disease in DSM-IV-TR**

DR. CAINE: Thank you for the opportunity to speak here today. I do want to mention that over the years I have provided consultative services to a number of companies that are representing themselves here today.

[Slide]

DSM-IV-TR, the first thing I will say is that TR stands for text revision and that, indeed, the rules of this game were that I wasn't allowed to change criteria, nor was anyone else, albeit as you will see, I sort of stretched the rules a bit without changing any criteria.

Whenever you do psychiatric classification -- and I have been thinking about psychopathology in the context of neurodegenerative diseases for about twenty-five years -- whenever you do this kind of classification you are sort of in a middle position. How do you communicate effectively? How do you understand what is in the field? How do you not push the field too far but, at the same time, how do you try to make the language and the common knowledge a bit clearer and more useful?

So, part of what you are seeing is a transitional process going back to DSM-I, II, III and trying to undo some of what we might call the institutional inertia and, remember, inertia is not only sitting still; sometimes it is moving -- directionless perhaps but moving, and how to change that direction such that it begins to communicate what we know about disease processes and make clear what we understand is the underpinning of those?

[Slide]

Now, if we think about a disease process, you know, we talk about fundamental pathobiology; we can talk about pathomolecular or biochemical processes. In the language of people outside of psychiatry, the primary manifestations of disease are not used as they are in the DSM but, rather, as the fundamental histopathological kinds of things that they looked at in the 1850s. Psychiatry may one day catch up with what they were looking at in the 1850s but, nevertheless, outside of my editorial comments you will see that the secondary manifestations are what we call symptoms and signs.

[Slide]

Indeed, we can look at something like Huntington's disease which used to be called Huntington's chorea. Of course, in 1872 George Huntington described the choreiform movement disorder and then, lo and behold, some of us

started to look at it and say, gee, the neuropsychological impairment is as prominent and disabling, if not more disabling at times than the choreiform movement disorder. The psychopathology may precede the choreiform movement disorder, but for terms of convention before there was an understanding of the molecular biology, and it is still an incomplete understanding of the molecular biology but, indeed, the convention said until the movement disorder shows we will not diagnose Huntington's disease even though you have a variety of psychiatric and cognitive impairments, and even though you have a positive family history.

Indeed, now we have a molecular mechanism. It is not fully understood yet. We understand that there are nuclear inclusions in the neostriatum in the cortex of protein-protein aggregations that probably lead to premature cell death. We are actually, I think it is fair to say, paying less attention to the clinical symptoms and more attention to the pathobiologic mechanisms. We don't wait for the motor signs anymore to say it is Huntington's disease. What we say is, ah, here's a person who is at risk on the basis of their genetic predispositions. Then we see the disease manifest itself in a variety of ways, all of which we might call co-equal manifestations, albeit the psychopathology is much more variably present than the motor pathology; that the neuropsychology is present usually

before the motor pathology; that the neuropsychology or cognitive impairment has one kind of course and the motor signs and symptoms another kind of course. They are dynamic. They are changing over the course of the disease.

[Slide]

So, Alzheimer's disease -- well, we know that it has multiple unknown molecular mechanisms. It does have a characteristic primary presentation which we would call its primary histopathology, and it has a variety of cognitive -- we call them dementia, but cognitive and psychiatric symptoms and signs. So, as we started to think about how to modernize the DSM, we certainly decided to change the way we used to do it and to move ahead toward a more common language, understanding that future psychiatric classifications have to grapple with the notion that there are going to be fundamental mechanisms, physical manifestations, as well as psychiatric behavioral and cognitive manifestations.

[Slide]

The past DSM classification had dementia of the Alzheimer's type focused on the dementia as the cardinal feature. It had early and late onset, and then it had issues of subtypes. There were a number of problems with this. It turned out, of course, that the subtypes didn't include all the manifestations of Alzheimer's disease.

There were no rules of when to use one subtype versus another. A subtype with delirium -- in fact, if you look at the literature carefully, it is not clear that Alzheimer's disease causes delirium at all. And, it wasn't clear when you used the subtype versus when you used a secondary mental disorder due to diagnosis, secondary meaning that it is a disorder due to a specific etiology. So, in reworking the DSM we basically said get rid of this. So, I stretched the rules there a bit.

[Slide]

The transitional coding, and I say transitional, in DSM-IV-TR is dementia due to Alzheimer's disease. Of course, you can also have dementia due to Parkinson's disease, dementia due to Huntington's disease, dementia due to HIV, dementia due to severe head trauma. So, there are, or will be, two subtypes.

Now, this coincides with the coding that will be in ICD-9-CM which is the official classification used by the U.S. government and all record departments and Medicare and anyone else that really counts, like people who pay the bills, and it will be without behavioral disturbance and with behavioral disturbance, fundamentally recognizing that there are people with dementia who become agitated, or wandering, or other kinds of behavioral problems -- and I am using the word behavior, not just emotional or psychiatric

but behavior as in manifest behaviors -- behavioral problems that are going to be a lot more difficult to take care of than people without those complications.

[Slide]

There will be a variety of mental disorders due to Alzheimer's disease. Dilip Jeste, in his previous discussion, actually captured many of the features that are right there in the DSM chapter saying how you decide that something is due to something else. Quite frankly, this has been in the medical literature, and in the environmental medicine literature, the toxicology literature, or other literatures for 30 to 40 years and is really well described. You know, if you want to go to Feinstein's book on clinical epidemiology, these kinds of things are not new. They may be new to psychiatry but they are not new to the rest of medicine.

So, there are a number of things and Dilip captured them quite well -- prevalence, phenomenology, the company it keeps, treatment responsiveness, course, characteristics and the like. So, the DSM will have already present in DSM-IV, except cleaned up, mental disorders due to psychotic disorder, mood disorder, anxiety, personality and sleep disorders. Sleep includes, of course, the diurnal rhythm disturbances.

[Slide]

Coming down the road towards ICD-10-CM -- CM stands for clinical modification. It is the U.S. version of the ICD-10 -- will be dementia due to Alzheimer's disease using a "G" code which is for neurological or brain-based degenerations, and not an "F" code which is mental disorders. Of course, if we look out over the horizon we know that a number of currently called psychiatric disorders are going to end up in "G" codes. Of course, as psychiatrists, neurologists and neuropsychiatrists we are going to continue to treat their behavioral disturbance. So, we are talking about dementia due to Alzheimer's disease with early onset or late onset, with and without behavioral disturbance. Behavioral disturbance can be present when someone does not have a specific psychosis due to Alzheimer's disease or mood disorder due to Alzheimer's disease. It may also be present when someone does have psychosis or mood, or the like. It is a non-specific subtype, very clearly defined that way; very clearly intended that way.

There is no data to suggest that the agitation in Huntington's disease is different than the agitation in Alzheimer's disease, or late stage Parkinson's disease or other kinds of things, except that Parkinsonian patients can't act on it as much when they are frozen.

So, indeed, what we are trying to do is move the

field ahead; improve the language and the communicative abilities; make things clearer. Clearly, issues such as time of onset for purposes of FDA type studies for something like psychosis or depression due to Alzheimer's disease, by convention we may say, oh, it has to be after the onset of dementia in the same way that once upon a time by convention the onset of chorea was a useful marker. But we understand that that is a conventional use, not necessarily scientifically based on any preordained emergence of signs or symptoms.

So, this is where we are going. I would be glad to answer questions now or this afternoon.

[Applause]

DR. TAMMINGA: Thank you, Dr. Caine. Dr. Lebowitz?

DR. LEBOWITZ: I am trying to understand how you made the transition from the slide on the expression of disease, where you make the point that the primary expression of disease is histopathologic and all clinical signs and symptoms are secondary --

DR. CAINE: Right.

DR. LEBOWITZ: -- going from that to then talking about dementia due to Alzheimer's disease as the condition of interest, where then behavioral disturbance is either accompanying or not accompanying the dementia due to

Alzheimer's disease. Would it not be consistent to have the Alzheimer's classification be Alzheimer's disease with or without dementia, with or without behavioral disturbance?

DR. CAINE: You are jumping ahead to DSM-V because basically you have certain limitations in terms of -- how shall I say? -- the politics in power of the National Center for Health Statistics and what we can negotiate with them or what we can't. Clearly, some day there will be Alzheimer's disease, 331 or a "G" code in the future. Sone of those Alzheimer patients won't have any signs or symptoms that we can detect as manifest. They will simply have this gene or pathobiology or multiple genes. They may already be expressing themselves at a neuronal level but not yet manifest. We know that in order to manifest Parkinson's disease you probably have to lose 80 percent of your neurons before they manifest as a disease process. Clearly, if you have the kinds of tests that are sensitive to that you may treat that pre-symptomatically.

The issue, as we saw it, Barry, was that right now there are people with dementia as in a clinical presentation, some of whom have behavioral disturbances such as agitation that grow out of that dementia process, not as a separate entity, such as Dr. Cohen-Mansfeld was saying when a person doesn't understand something and is, in fact, suspicious transiently, irregularly, and they haven't risen

to the level of disorder. Remember, the other things are disorders and disorders have to rise to a threshold of symptomatic severity such that they can stand on their own as a disorder. So, dementia is one disorder; mood disorder when it arises to a level of severity; psychosis when it arises to a level of severity -- these are all disorders due to Alzheimer's disease.

DR. LEBOWITZ: Yes, but that is not where the criteria is.

DR. CAINE: Actually, the criteria says that. What we are saying at this point is that behavioral disturbance can be a subtype of some people with dementia. Down the road behavioral disturbance will be freed up. I can't fee it up now.

DR. TAMMINGA: Dr. Caine, I have a question for you about the term behavioral disturbance. While behavioral disturbance may be a useful clinical concept and may be useful for clinical diagnosis and categorization, it may not be specific enough for labeling according to the criteria and in the way of thinking that Dr. Laughren presented this morning. I know we will discuss more about that this afternoon.

DR. CAINE: I think that is true, and I think it is very clear that behavioral disturbance is a generic, broad thing for the DSM which could include wandering,

agitation, and those types of on-the-unit type of behavioral disturbance that get people in trouble. That is quite different from what we see as mood disorder, psychosis, or sleep disorder which we see as much more explicit, discrete and definable, as Dilip talked about it. Within the cluster of behavioral disturbances I think certainly one could then carve out something such as agitation, define it, shape it, make it specific enough to be measured, and then study it. But this is clearly a transitional issue, which I said at the beginning. Barry would like me to transition faster but I can't outrun the National Center for Health Statistics.

DR. SCHNEIDER: Eric, one quick question. I probably don't understand ICD-10-CM, but it looks as though in order to diagnose psychosis associated with Alzheimer's disease first you would be diagnosing something like dementia due to Alzheimer's disease with behavioral disturbances and somewhere else you would have to specify psychosis. Is that correct?

DR. CAINE: In the DSM-IV that has existed for much of this decade --

DR. SCHNEIDER: Right.

DR. CAINE: -- we have always had the ability to diagnose dementia and psychosis "due to." It hasn't been used, and that has been part of the confusion. Clearly, there is one axis, two diagnoses. So, all you are saying

is, look, someone has a dementia diagnosis as we are talking about it -- dementia due to Alzheimer's disease. By convention, we say clinically that Alzheimer's disease isn't present unless dementia is there. We know that is a convention. The second would be psychosis due to Alzheimer's disease -- second axis, one diagnosis. I don't know if I am being clear with you or not.

DR. SCHNEIDER: ICD-10-CM --

DR. CAINE: It will be the same way until such time as we can get rid of certain things.

DR. SCHNEIDER: Could you have psychosis due to Alzheimer's on the one hand, and dementia due to Alzheimer's without behavioral disturbance on the other?

DR. CAINE: Yes.

DR. SCHNEIDER: It seems that your description of behavioral disturbance, as you are representing it in ICD-10-CM, is something other than psychosis or depression.

DR. CAINE: Clearly, this is both a technical and a conceptual problem that both you and Barry are hitting on, and I certainly don't disagree with it. What we tried to do in the writing of DSM-IV in the late '80s and in the early '90s was begin to capture those people who had behavioral disturbances which were sucking up extra time and attention and were clinically significant in treatment settings. These could be things that don't fit into any neat psychosis

or other cluster. When someone is agitated it can be quite non-specific. When someone is wandering it can be quite non-specific.

The issue you are saying is can someone have psychosis and not be behaviorally disturbed? That gets to the point of can someone have quiet significant hallucinations and delusions but be tractable clinically, manageable clinically and not be the subject of treatment for those things? And, the answer is sure. That is not a big deal. It is just that right now we are moving through the stage of language inadequacy to capture clinical reality.

DR. TAMMINGA: Dr. Laughren has a question.

DR. LAUGHREN: Yes, I have a couple of questions. Actually, I share the concerns that have been raised about the non-specificity of the behavioral disturbance qualifier. Again, from a regulatory standpoint that would be difficult to grapple with.

I think it is very useful to come up with the names for the different possible syndromes that you have identified -- psychotic syndrome with dementia, affective, and so forth. Is there a plan at some point to come up with fairly distinct diagnostic criteria because again, from a regulatory standpoint, that is what we rely on, I mean, the same kinds of criteria you have for other syndromes like

schizophrenia and major depressive order, and so forth?

DR. CAINE: Sure. I think it is quite clear that that is the next evolutionary step but, given that there was a ban on criteria, then there are no criteria. It is very clear that the kinds of things that Dilip laid out this morning are just the sorts of things that one would look for because they deal with the common parameters of how you establish due to a fundamental disease process relative to prevalence, to phenomenology, to course, to treatment responsiveness, to what company it keeps in terms of other manifestations of the same pathobiologic process. So that very much follows exactly where we want to go to. I wouldn't have some of the subtypes because that gets confused with subtypes again. Certainly, one could get into a discussion of how one sets time of onset. We would probably go with what I might call a peri-onset, you know, within a zone -- 2 years before or 18 months before. Again, those are by convention at this point. But, clearly, that is exactly where the field should go but, clearly, we are also limited by what you can do with the text revision and what you can do relative to the regulatory agencies that classifiers deal with, which is called the National Center for Health Statistics.

DR. LAUGHREN: Yes, and I think this can all be discussed this afternoon, but I think what people are very

interested in knowing is what sort of a time frame we are looking at for evolving all of this.

DR. CAINE: I don't think DSM-V is going to emerge very quickly. So what I think is going to happen, quite clearly at least in terms of my own way of thinking, is that once we have this structure in IV-TR, then we fill in, in the academic field, what is already being filled in. To me, in terms of the kind of data that exist, I would certainly use psychosis as a good exemplar of, hey, this is a good standard for the kinds of things we can then compare mood, sleep, diurnal and other things to in the sense that there has been data presented about prevalence, about responsiveness, about natural history. You know, there are data out of the U.K. as well as the U.S. about these things. So, I think this is something that can fall into place quite neatly.

DR. TAMMINGA: Thank you, Dr. Caine. Next we will hear from Dr. Jeffrey Cummings from UCLA. He will present a talk titled criteria for psychiatric symptoms in Alzheimer's disease clinical trials.

**Criteria for Psychiatric Symptoms in Alzheimer's Disease Clinical trials**

DR. CUMMINGS: Thank you very much, Carol, and thanks to the FDA for inviting me to be part of this panel.

[Slide]

I would also like to disclose a relationship to several companies that have a financial interest in these criteria and the development of drugs relevant to psychiatric symptoms in Alzheimer's disease.

[Slide]

I think it is reasonable to start by acknowledging what we do not know. this is kind of a Cartesian slide of getting down to basic doubt. We do not know the pathophysiology of the psychiatric symptoms of Alzheimer's disease. This, of course, does not distinguish this condition from our lack of knowledge of the pathophysiology of the psychiatric symptoms of schizophrenia, depression or any other major mental illness.

We do not know whether there is a similarity to the pathophysiology of the psychosis of Alzheimer's disease and that of schizophrenia and I think there is substantial reason to doubt a similarity. That is, the cerebral environments differ and these could affect the response to therapy. In Alzheimer's disease we have plaques, tangles and a marked cholinergic deficit that may create a hostile environment for the usual conventional psychotropic medications.

[Slide]

For these reasons, I believe that separate trials are required for the treatment of symptoms or syndromes in

each disorder, that is, schizophrenia versus Alzheimer's disease. It is reasonable to try established agents as first approach to therapy. That is, since we know that antipsychotics work for the psychosis of schizophrenia, it is reasonable that we would test antipsychotics for the psychosis of Alzheimer's disease but it is not necessary to limit our considerations to that class of drugs. For example, there is evidence that cholinergic agents may have a benefit to psychiatric symptoms in Alzheimer's disease or we would not expect these agents to be useful in other neurobehavioral and neuropsychiatric syndromes such as schizophrenia. So, while it is reasonable to start with the established drugs, it is important that we not limit our thinking to those established drugs when we cross disease categories.

[Slide]

We need specific criteria for each target symptom, and I think there is a consensus on that point. The behavioral and psychological symptoms of dementia, the BPSD concept, recognize the common occurrence in Alzheimer's disease and are useful in that regard but are not sufficiently precise to guide clinical trials or diagnostic considerations.

[Slide]

Dilip and Sandy I think have brought us to a new

point in this discussion, and I think it is an important advance in terms of crystallizing the criteria for psychosis in Alzheimer's disease.

I have two additional recommendations for these draft criteria. One is that I think psychosis must be operationalized. In the Jeste and Finkel criteria psychosis is defined as the presence of delusions and hallucinations. That is essentially to define psychosis as a presence of psychotic symptoms, and I think we must go beyond that in order to allow clinicians to be able to select patients specifically for clinical trials.

The other part of the criteria that I would revise and recommend revision on is that distress to others is in the criteria a sufficient indication for treatment. I think that opens up the possibility of abuse. That is, a staff member in a nursing home who is distressed by a behavior would be sufficient to allow treatment of that patient, and I think that that needs to be narrowed.

[Slide]

Therefore, I would propose more operationalized definitions, such as psychosis manifested by delusions, and I would define delusions as false beliefs not directly attributable to memory or cognitive abnormalities such as disorientation, such as delusions of theft, delusions of infidelity, phantom borders and active misinterpretations.

Let me comment on several of these. Jiska has already raised the problem of the interface between the cognitive deficit and the psychosis. Now, if you say to a patient what year is it and the patient says it is 1963, he holds a false belief which is resistant to evidence to the contrary and, therefore, meets broad criteria for delusion. We clearly want to avoid including that patient in this kind of classification. So, what I would say is that we need false beliefs that are not directly attributable to memory and cognitive abnormalities. For example, if the patient experiences misplacement and interprets that as theft, that is already an active misinterpretation because I would suggest that everybody in this room has at one time experienced enough of a memory abnormality to misplace something and, yet, you have not assumed that somebody stole it from you so you did not have the active misinterpretation that is required for the presence of a psychotic syndrome. So, I would move towards these kinds of delusions as required for the presence of a delusional disorder.

Note that I have excluded the misinterpretation syndromes here. The misidentification syndromes, and Barry's paper addresses this very directly, because they are too ambiguous for inclusion at this point in the diagnosis of a delusional disorder.

[Slide]

I would also include hallucinations as part of the definition of psychosis and, again, I would operationalize the hallucinations as, for example, talking with individuals unseen by the observer, or responding to voices and sounds not heard by the observer. Again, a report that I saw my mother this morning would not be adequate because that can be a memory abnormality, but the active discussion with a non-seen person is sufficient. It also implies that the individual endorses that hallucination as real, meaning that psychosis is present not just a benign hallucination such as might occur in migraine or visual impairment.

[Slide]

Then I would go on basically to mimic Dilip and Sandy's criteria -- onset of psychosis after onset of dementia. You would exclude only a very few patients by that criterion -- no other Axis I diagnosis, disabling or distressing to the patient. I would not go on to the patient or someone else; and not present exclusively during a delirium. It could be defined with agitation, with irritability, etc.

[Slide]

I believe that agitation should be seen as a separate identifiable syndrome in Alzheimer's disease. For example, it does not always occur with another type of psychopathology. We have now done a series of studies in

which we matched groups of patients for delusions, hallucinations, irritability, anxiety, depression, euphoria -- all of the elements of the Neuropsychiatric Inventory, but one group had high agitation and one group had low agitation. So, we controlled for all of the other psychopathology and could still see two groups of patients, one with agitation and without. We then showed that they have SPEC scans and that they have contrasting brain pathology in terms of the neurofibrillary tangle burden of the frontal lobes.

So, I think that this is in some cases a separate syndrome and should be a separate target for drug development. In addition, I am worried that the agitation of Parkinson's disease may well be different from the agitation of Alzheimer's disease. One with a dopaminergic deficit, one with a cholinergic deficit may differ from the agitation of schizophrenia, and I believe that agitation will have to be studied separately in each disorder to be assured that it will have a replicable drug response. These are criteria that I would suggest, modeled after Jiska's criteria as she has been very influential in this area.

[Slide]

Finally, I would use the same kind of model for depression in which we would need to define specifically the kind of depression that one sees in Alzheimer's disease,

depression manifested by tearfulness attributable to sadness. Why do I say that? Because in neurological illnesses one may see tearfulness without sadness in a form of pseudobulbar palsy. So, you must make these criteria definitely mappable to neurological disease. Statements reflecting sadness, hopelessness, worthlessness, helplessness; statements of burden; statements concerning death -- I agree with Jiska completely that the neurovegetative signs can occur in dementia without depression and, therefore, should not be part of these criteria. Also, apathy occurs frequently in dementia without depression and should not be part of the criteria for depression.

[Slide]

So, I would suggest that the general approach that we are moving towards is that, first, we would diagnose a patient with Alzheimer's disease. We would then use criteria for a specific syndrome such as those suggested by Dilip and Sandy, maybe with some modifications for psychosis, or agitation, or depression. We would decide whether those are sufficiently severe to require treatment on the basis of the distress to the patient. We would then use a rating scale to decide on the severity of the symptoms since it is very rare for a drug to eliminate the syndrome. So, you must have a quantification so that you can see

whether it has been reduced but not eliminated. You would then have treatment and an outcome assessment. Thank you.

[Applause]

DR. TAMMINGA: Thank you, Dr. Cummings. Comments or questions? Dr. Jeste?

DR. JESTE: This is more a comment than a question. I agree with the suggestion that you made, Jeff. However, I want to distinguish between criteria for a clinical diagnosis and the criteria for a clinical trial. The criteria for a clinical diagnosis is step one and then step two is criteria for a clinical trial. For example, if somebody meets criteria for schizophrenia, he may have residual schizophrenia and may not be appropriate for a drug study. So, then we have to have a criterion of a certain BPRS cut-off score on something.

The same thing applies to tardive dyskinesia. They may have minimal dyskinesia which is sufficient to warrant a clinical diagnosis but they may need to meet Schooler Ken criteria in order to participate in a study.

So, I think the modifications you are proposing are a step two. Once they meet the criteria for psychosis or Alzheimer's or psychosis due to Alzheimer's, then they need to have certain amount of severity to be eligible for a clinical trial.

DR. TAMMINGA: Dr. Schneider?

DR. SCHNEIDER: Jeff, I do think we are now turning the discussion to criteria for clinical trials and I wanted to just endorse Dilip's comment. But moving on to your comments about agitation, it seems everything depends on definition, and the slide that you put up defined agitation on two components. One was threatening vocal behaviors and the other was threatening physical behaviors. To me, you could also call that aggression and distinguish at least those components from overall agitation and, hence, be more specific. So, I am interested in your comments on that. Essentially, it seems there is a distinction here between aggression and agitation.

DR. CUMMINGS: I think that is a great idea, Lon. I think anything we can do to narrow the definition of agitation to specific target symptoms will advance our cause, and aggression is the set of behaviors that is of greatest concern in terms of managing these patients. So, I think that would be a very reasonable kind of relabeling of this area.

DR. TAMMINGA: Dr. Winokur?

DR. WINOKUR: With regard to your discussion of depression in the context of dementia, would there be any qualification with regard to chronology that we talked about with psychosis or past history?

DR. CUMMINGS: That is a very difficult issue and

I am not the best one to talk about that. Barry will be addressing depression next. Certainly, patients at greatest risk for depression in Alzheimer's disease are those who have had depression before. So, I think you would not want to have as an exclusion criterion, for example, the previous occurrence of depression. So, I think we will be looking for criteria that are pretty much independent of a chronological relationship to the disease itself.

DR. TAMMINGA: Dr. Cummings, would you comment on the relationship of your criteria for agitation in Alzheimer's disease to what Dr. Tariot presented as secondary mania?

DR. CUMMINGS: Yes, I think Pierre was really defining mania as overlapping substantially with the symptoms of agitation as we see them in Alzheimer's disease, and I think there is no difference between how I define dementia and how Pierre was discussing mania this morning. I would not, myself, be comfortable using the term mania in this setting.

DR. TAMMINGA: Thank you, Dr. Cummings. If there aren't any more questions I think we will move on to our last presentation before the break, Dr. Barry Reisberg, from NYU, will speak about BPSD and the psychosis of Alzheimer's disease treatment possibilities. Dr. Reisberg?

**BPSD and the Alzheimer's Disease Treatment Possibilities**

DR. REISBERG: Thank you very much, Dr. Tamminga.

[Slide]

I would like to begin by thanking the organizers for inviting me to speak to these issues. I also should mention that I have consulted with various companies with respect to these issues.

Let me say I am not speaking about depression. The title of my talk is, indeed, BPSD and the psychosis of AD treatment possibilities.

[Slide]

Alzheimer's disease is the major form of dementing disorder and it is also the best understood. Therefore, in addressing the question can we identify appropriate clinical entities or targets for drug development in this area, it is useful to focus on Alzheimer's disease.

[Slide]

Alzheimer's disease has long been known to be accompanied by behavioral and psychological symptoms. For example, Alois Alzheimer noted these symptoms very prominently in his classic case description.

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Frequently BPSD and AD are disturbing to family members or other caregivers and/or are dangerous or distressful to the Alzheimer's disease patient. In these cases, physicians often endeavor to treat these symptoms

with psychotropic medications. This has been true for decades, and psychotropic medications are among the most frequently prescribed medications for Alzheimer's disease and other dementing disorders.

The kinds of psychotropics prescribed for disturbing, distressful or dangerous BPSD symptoms are very diverse. Doctors prescribe antipsychotic medications. They prescribe antidepressants. They prescribe anxiolytics. They prescribe various medications for mood disorders. They prescribe sedative medications. They prescribe other medications and combinations of these substances.

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However, in the absence of appropriate studies, doctors have had little information to guide them as to which BPSD symptoms respond to pharmacologic intervention; what medications should be prescribed for these symptoms; and what are the side effects of treatment of these symptoms in Alzheimer's disease in the context of this specific disease entity or other dementias.

[Slide]

What BPSD symptoms respond to pharmacologic intervention? Initial studies nearly fifteen years ago indicated that seven broad categories of BPSD which appear to be responsive to intervention with antipsychotic medication, and specifically the medication studied was

thioridazine, could be identified. These categories of BPSD which are potentially responsive to antipsychotic medications are paranoid and delusional ideation, hallucinations, also activity disturbances, aggressivity, sleep rhythm disturbances, certain kinds of affective disturbances and certain kinds of anxieties and phobias.

Studies also indicate that the nature of these psychotic BPSD symptoms in Alzheimer's disease is very different from the nature of these symptoms in other mental disorders. Consequently, although the categories of psychotic symptoms in dementia are superficially very similar to the categories of symptoms in, for example, the psychosis of schizophrenia or the depression of major affective disorder, the specific nature of these symptoms in Alzheimer's disease and related dementias is in all cases different.

[Slide]

These unique features of the psychosis of Alzheimer's disease appear to be the result of two primary interacting factors, which we already heard about. These are the special psychological factors operating in Alzheimer's disease and also the special neurochemical milieu as we heard from both Jiska and Jeff with respect to the importance of these issues.

These unique psychological and neurochemical

features would naturally be expected to produce a unique phenomenology. Studies have indicated that this is, indeed, the case. It should be noted that BPSD is a broad category which includes many symptoms which do not fall within the psychosis of AD syndrome. When symptoms do fall within the psychosis of AD, the extent to which the symptoms are disturbing, distressful and/or dangerous is related to the need for treatment and the magnitude of symptomatology. So for example, as we have already heard, if a patient mistakes their spouse for their mother but accepts their spouse as their spouse when corrected, then this misidentification is not a psychosis of AD symptom. However, if the patient insists that their spouse is not their spouse, then this is a psychosis of AD symptom.

[Slide]

In 1987 we developed a rating instrument, the BEHAVE-AD, which measures the 7 categories of symptoms in the psychosis of AD and measures 25 generally characteristic symptoms in these 7 categories and rates each of these symptoms. Initial studies, as already noted, indicate that the BEHAVE-AD symptoms and symptom categories were responsive to neuroleptic intervention, and also were important in AD.

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A recently published multi-center, randomized,

controlled trial has supported the results of the original thioridazine trial. In this trial, the best dose of an antipsychotic medication produced a decrease in total BEHAVE-AD scores of approximately 40 percent, in the last column. Differences between the placebo treatment group and the neuroleptic treatment group in BEHAVE-AD total scores were statistically significant. Categories of BEHAVE-AD symptoms which differed between the placebo and the neuroleptic treatment groups at endpoint by greater than 10 percent included not only paranoid and delusional ideation, but also activity disturbances, aggressivity and sleep rhythm disturbances. All these differences were in favor of the neuroleptic intervention. Importantly, all these symptomatic changes on placebo and neuroleptic treatment in the BEHAVE-AD scores appeared to occur independently of cognitive and functional effects of the intervention.

In summary, a psychosis of AD syndrome is identifiable. This syndrome appears to have both psychologic and neurochemical origins. Accordingly, the syndrome seems to respond to both psychologic and neurochemical intervention. Rating scales can be developed which can measure this syndrome reliably and sensitively on clinically meaningful parameters. It is important to note that the psychotic syndrome is more than simply delusions, hallucinations and aggressivity or even dementia-specific

delusions, hallucinations and aggressivity.

[Slide]

Just as the BPRS used to assess the efficacy of antipsychotic medications for schizophrenia includes various associated symptoms, including somatic concerns, anxiety, emotional withdrawal, etc., in addition to suspiciousness, hallucinations and uncooperativeness, and, just as the Hamilton Rating Scale includes somatic anxiety, somatic GI symptoms, genital symptoms, hypochondriasis, weight loss, etc., in addition to depressed mood, feelings of guilt and suicidal ideation, similarly the scales used to measure the psychosis of AD should include associated symptomatology.

[Slide]

In the interest of accurate assessment, the psychosis of AD should be assessed independently of the cognitive and functional symptoms of dementia. Because the idiopathogenesis, the phenomenologic manifestation and the symptomatic background of the psychosis of AD are all very different from the psychosis of schizophrenia, and because treatment and side effect issues are different, it is important to focus on the psychosis of AD independently. Appropriate methodologies are available for the investigation of these issues and the psychosis of AD would appear to be an appropriate area for drug development and regulation at the present time. Thank you.

[Applause]

DR. TAMMINGA: Thank you, Dr. Reisberg. Are there questions or comments from the committee? Dr. Laughren?

DR. LAUGHREN: I have a question about you drawing a parallel between the BEHAVE-AD and its use and the BPRS in schizophrenia and the HAM-D in major depression. It seems to me that the difference is when one is doing trials, say, in schizophrenia one captures patients using independent diagnostic criteria and then uses a cross-sectional instrument, like the BPRS, to measure change. Similarly, in depression we use usually DSM criteria for capturing patients with major depression and only then do you use the HAM-D to measure change in those patients. What is unclear with your approach is that there don't seem to be any independent diagnostic criteria that you are using for capturing patients. You seem to be using the BEHAVE-AD as a diagnostic tool.

DR. REISBERG: Thank you for clarifying that. I do advocate using independent criteria such as the criteria developed by Dilip Jeste and Sandy Finkel which are excellent in this regard. I would strongly advocate that. I would advocate doing trials really in the same fashion, using independent criteria but also in assessing treatment I would advocate not being narrowly focused. In all other entities we are not narrowly focused. We are looking at the

wider entity and, in assessing treatment, I would advocate looking at the wider entity here as well.

DR. LAUGHREN: I appreciate that clarification because it wasn't so clear that you weren't proposing BPSD as an entity. Clearly, you are not.

DR. REISBERG: No, clearly not. Also, let me take the opportunity to point out that I think BPSD is a broader entity. I think that the psychosis of AD is a narrower entity within BPSD, but I do think that the psychosis of AD has various associated symptoms apart from just delusions and hallucinations for example.

DR. TAMMINGA: Dr. Hamer?

DR. HAMER: In the slide you showed that had the series of comparative bar charts of placebo and Risperal 1 mg, I noticed that all of the hypothesis tests are hypothesis tests within each group of baseline versus endpoint. Was there any particular reason you did that rather than test to see if the groups, in fact, differed from one another, if the treatments had an effect that was different?

DR. REISBERG: First of all, I didn't mention any particular medication that I am aware of.

DR. HAMER: In our charts in the handout it says Risperal 1 mg.

DR. REISBERG: I see. I was simply illustrating

some of the results from this trial by way of making the general point with respect to treatment possibilities. I was simply trying to use the data, such as it is, not with respect to showing efficacy for any particular medication but by way of showing that the symptoms which respond to pharmacologic treatment are not only paranoid and delusional ideation in particular but also a more general syndrome which is responsive to pharmacologic intervention. Also, I am very interested in the data with respect to the efficacy of not only pharmacologic intervention but also psychological intervention. So, to me, one of the major observations from the chart is that the symptoms are responding to psychological intervention and they are also responding to pharmacologic intervention. Of course, the question with respect to approval agents is whether there is a differential pharmacologic responsivity and whether that differential in terms of side effects and therapeutic effects is a worthy differential in terms of approval.

DR. HAMER: So, by psychological intervention you meant placebo?

DR. REISBERG: In fact, the minimal psychological intervention of putting a patient in a trial and keeping him in a trial seems to be associated with a marked relief, probably in terms of the interaction of the family members and the caregivers with the patient, as well as on the part

of the patients themselves, which seems to be reflective in decrements in scores which I think is very interesting and very important.

DR. TAMMINGA: Dr. Schneider?

DR. SCHNEIDER: Barry, following on the risperidone data because that is what you put up, you were saying, unless I misheard you, that this was an example of the efficacy of an antipsychotic in the psychosis of Alzheimer's disease. You also had said, and maybe this is redundant with Dr. Hamer's comments, that this was an example of where an antipsychotic can treat any of a number of sets of symptoms. I just need to comment that one of the difficulties with these antipsychotic trials, no matter what the typical antipsychotic, is that patients were not chosen because they had psychosis. They were chosen, for instance in this case, because they had a certain score on a test. Then, what you are showing is group changes in different sub-scales of the BEHAVE-AD and you are showing mean changes between within drug and within placebo. So, even though the publication might be showing mean changes in aggression, that aggression symptoms seem to have decreased overall in patients on risperidone, what we are not getting out of this data is the proportion of patients who clearly did have clinically significant aggression, and what proportion of those patients actually improved. Lastly, again, when you

inspect this chart it looks as though in many cases medication was not more effective than placebo. So, I just wanted to make those comments.

DR. REISBERG: Well, I would agree and once again use the opportunity to mention that I just wanted to introduce what I thought was some useful data with respect to the general question of the treatment of these issues.

Let me just, if I may, say one or two things. I think all of us, as clinicians, when treating schizophrenia find one of the earliest signs of a patient becoming schizophrenic, acutely psychotic in the context of schizophrenia is that they have sleep disturbance. We recognize that and presumably we try to treat that with medication. I think the schizophrenia analogy is very useful. Certainly all of us recognize that the first manifestation of psychosis could be that the patient on the ward is hitting people, and we recognize that as very much a part of the syndrome. Similarly, in terms of classical schizophrenia, we all recognize that anxiety could be the earliest sign and we endeavor to treat that.

So, I am just trying to call attention to the wider picture here. I do agree, and I think a number of the speakers have made this point, Jiska and Jeff and others, that there are psychological factors which are very important in Alzheimer's which relate to the cognitive

disturbance and that is one of the ways in which this syndrome is unique. Of course, another way is in terms of the specific nature of the symptoms as well.

DR. TAMMINGA: Dr. Caine?

DR. CAINE: If we go back to psychiatric classification in general and we think of clusters like schizophrenia -- for my statistician across the table, I am using the word cluster in a generic sense --

[Laughter]

-- syndromes, whatever -- groupings, categories, we know that there is a lot of overlap between these categories. We make certain challenges to them. Kendall talks about points of rarity between one and another. And, we know that in some of the major psychiatric clusters or categories we can't show points of rarity.

Nonetheless, I think your point is well taken and also off target. I think it is well taken to say that we know that people with psychosis due to Alzheimer's disease have a lot of other signs and symptoms that are there. That doesn't make it psychosis due to Alzheimer's disease or not psychosis due to Alzheimer's disease. I think the question before us is can we define a group of people in a category who have explicit entry criteria and explicit exclusion criteria? Can this be done in a reliable way, and are there some, ideally in the long run, ways of validating it? Maybe

that is in the future in terms of external measures like genes and other things. And, can this be a useful target for therapeutic intervention? Now, I hear you saying yes, but don't forget all the other symptoms that may be worth measuring as well. Am I hearing you correctly or am I mishearing you?

DR. REISBERG: No, I think that is precisely correct. I endorse everything that you said and, once again, I would endorse the criteria that are before us, the Jeste and Finkel criteria. I would endorse those strongly. The title of my talk was treatment possibilities, and in looking at treatment possibilities I think we have to go a little bit beyond the criteria to understand what we are trying to do for treatments.

I also would like to mention that in terms of treatment possibilities I think we need to understand also that it is not necessarily only antipsychotic medications. In looking at other illnesses, for example major depression, we recognize that so-called classical antidepressants play a role, but I think we also recognize that neuroleptics can play a role and other substances as well. So, by no means is this meant to preclude those wider issues either.

DR. TAMMINGA: Thank you very much, Dr. Reisberg. I would like to thank all the speakers of this morning for being highly informative and for being timely in addition.

It is time for us to take a break. We will take a break for exactly thirty minutes and come back because we still have an open public hearing part of the session where we will gather additional data before we start discussions this afternoon. Thirty minutes from now. Thank you.

DR. TITUS: I need to touch base with one of the speakers from Johns Hopkins and also the American Association of Geriatric Psychiatry.

[Brief recess]

DR. TAMMINGA: The first part of the morning was presentations by the consultants to the psychopharm. committee. The second half of the morning will be the open public hearing for speakers that have requested a chance to speak. Since we have quite a number of people, I will request that the public speakers also limit your remarks to ten minutes. I would like it if you would just kind of come up to the podium, just like the morning speakers did, because the timer is right here. So, you will actually be able to pace yourself to keep yourself within ten minutes.

We will start for our first open public speaker with Christopher Colenda. Dr. Colenda is from the American Psychiatric Association, and has prepared some remarks for us to consider. Dr. Colenda?

**Open Public Hearing**

**American Psychiatric Association**

DR. COLENDA: Good morning.

[Slide]

On behalf of the American Psychiatric Association, we are delighted to present testimony to the Psychopharmacological Drug Advisory Committee. My colleague, Dr. Jacobo Mintzer, who is chair of the Ethnic Minority Committee of the Council on Aging, and I are delighted to be here. Both Dr. Mintzer and I do have consulting relationships with companies who have a financial interest in these proceedings.

[Slide]

We would like to remind the audience and the committee that Alzheimer's patients with psychiatric symptoms experience enormous suffering, and as physicians who are obligated to alleviate suffering, having the ability to define and have targeted treatments will greatly relieve patient suffering, improve caregiver morale and, hopefully, reduce excess disability.

[Slide]

We believe that the central question for the committee is whether there is sufficient scientific evidence that specific psychiatric symptoms are fundamental manifestations of Alzheimer's disease and, thus, warrant drug development or indication.

[Slide]

Echoing Dr. Caine's remarks, we believe that approaching this from a conceptual model of disease allows us some degree of ability to try to answer these questions in a more specific manner. With Alzheimer's disease, obviously there is a long latency period in which the initiation of the etiologic process begins which brings forth pathological processes. For most of us who are clinicians, we look at the issue from the clinical detection of disease and onset of signs and symptoms. So, we are already at the third major box. And, it is at this point that we have concern for developing drug indications, but it is the signs and symptoms that have some impact on the outcomes of the disease.

[Slide]

In order to help articulate our thinking, we looked at some standard ways of looking at causality in which we look at various criteria. The seven criteria that are generally accepted in most of the rest of medicine include the strength of association; dose response effect; lack of temporal ambiguity; consistency of findings; biological plausibility; coherence of evidence; specificity of association.

Now, with Alzheimer's disease and with the psychiatric symptoms of Alzheimer's disease we will probably never be able to have all seven criteria met. But I think

that we would like to point out a couple of syndromes in which we think that there is a preponderance of evidence that does require our thinking about justification for developing new indications for psychopharmacologic agents.

[Slide]

For example, we have heard a lot today about the psychosis of Alzheimer's disease. I would like to take another angle on this and briefly discuss the circadian rhythm disturbances or sleep-wake cycle disturbances of Alzheimer's disease, which are major problems both in home as well as in nursing home settings and cause a great deal of consternation for patients as well as their caregivers.

If we look at our seven criteria by which we measure evidence to support a causal relationship -- let's first look at strength of association. The evidence suggests that between 20-40 percent of Alzheimer's patients have significant sleep disturbances sometime during the course of their illness, some of which may be related to classic circadian rhythm disturbances that are found in other entities.

Is there a dose response effect? Well, from sleep studies, the sleep-wake cycle does tend to degenerate in more advanced disease, demonstrating rhythmic and polyphasic patterns but this is not necessarily with aging-related changes and sleep patterns. There are also some changes

that may have some degree of overlap here.

Is there a lack of temporal ambiguity? This is obviously difficult to determine.

Is there consistency of findings? Several groups have found that disturbed sleep findings are a consistent pattern in Alzheimer's patients.

Is there biological plausibility? If you look at postmortem samples of Alzheimer's patients there is degeneration of the suprachiasmatic nucleus of the hypothalamus and this is the area of the brain that is associated with circadian rhythms.

Is there coherence of evidence? We believe that there is increasing evidence that this can be answered in the affirmative but, obviously, we cannot say in this particular case that there is specificity of association.

Dr. Mintzer is going to be talking about using the same model to talk about psychosis in Alzheimer's disease, and provide some conclusions.

**American Psychiatric Association Council on Aging**

DR. MINTZER: Good morning.

[Slide]

When we, in the discussions in the Council, wanted to move towards what was discussed by Dr. Colenda before, we found, without surprise, that the six of the seven criteria again were met. I want to bring attention to the dose-

response effect. That means that in the infectious disease model the more exposure to the agent or to the disorder, the more likely is this symptom to appear in a higher group of patients, and we observed the same, as was discussed this morning by Dr. Jeste in his accumulative prevalence study where you see that as the disease increases, you see an increase of accumulative prevalence as the disorder compares different areas of the brain and specifically arrives to a plateau.

[Slide]

But I would like to also take a minute to say that the Council is composed of clinicians, and those clinicians observed an article presented by Jeste and Finkel and feel very strongly that these criteria were reflecting their clinical experience. Therefore, the Council is strongly endorsing those criteria.

As per Dr. Cummings' comments, the Council, in their discussions, reflected similar comments to what Dr. Cummings discussed and, indeed, environment -- there was a feeling that those changes or these concerns can be addressed as specific clarifications to the criteria, to be especially emphasized in the context of a specific clinical trial.

Finally, I would not like us to forget that psychoactive medications are widely used in Alzheimer's

patients. The Council discussed the issue that off-label treatments exposed patients to severe side effects without any real knowledge about which level of expectations or benefit the patient will have. Specifically, the off-label use of these compounds is not allowing us, as was said before, an appropriate risk-benefit assessment to the clinician that in each individual case will have to make that decision, even the clinical severity of the symptoms that are observed. Labeling will provide information that a clinician can use then safely in making a decision on which compound, targeted with which syndrome, with benefit which patient.

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But also with establishing specific labeling, we share the concerns that Dr. Cohen-Mansfeld discussed and which were discussed today earlier by the FDA, it will provide a strong incentive to the pharmaceutical industry and the research community to develop safer and more effective compounds. It is very difficult to develop safe and effective compounds if the syndrome is not appropriately established.

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In conclusion, the Council on Aging feels that there is very strong evidence evaluating that psychiatric symptoms are a part of the core manifestation of Alzheimer's

disease. We believe that there is enough scientific evidence to support the labeling of psychosis, alteration in circadian rhythm and -- it was not discussed today but it is in the document that was given, the data for depression as valid targets for pharmacological intervention. We also think that this process is important because it may allow other disorders to come to the forefront of syndrome as the scientific evidence becomes available. Thank you for your time.

[Applause]

DR. TAMMINGA: Thank you very much, Drs. Colenda and Mintzer. Are there any comments or questions? Dr. Caine?

DR. CAINE: Just a couple of points of clarification. Austin Bradford-Hill was an environment medicine individual so it is important for people to realize that his interest in temporal association related to was a toxic agent or an environmental irritant present prior to the development of the syndrome. It isn't easily applicable to some of the kinds of things that we were talking about here. Clearly, the dose-response also was related to that.

But also to clarify that these were the criteria that were used as a basis for discussion in DSM-IV in the mental disorders "due to" section talking about what are the issues and how do you define associated clinical symptoms

and signs which will be a reflection of an etiologic process. In fact, the ones that you cite are, albeit a bit modified for DSM-IV -- I think there is a special writing group that takes common English and turns it into gibberish when they write these books but, nonetheless, those criteria were the ones that were used for that book.

DR. COLENDA: You have to understand I was an epidemiologist so I tend to look at these from an epidemiologic --

DR. CAINE: So do I.

DR. MINTZER: Just to clarify, it was important for us to take it in a different context and see if the syndrome would still rise in a very different context to the same level.

DR. CAINE: I agree. I am just saying it for more general understanding of the origins of those.

DR. TAMMINGA: Dr. Schneider, do you have a comment?

DR. SCHNEIDER: Yes, I was surprised, even though you mentioned it at the end, Jacob, that much of your written document deals with depression in Alzheimer's disease and you chose not to mention it and, instead, to focus on psychosis and sleep disorder.

DR. MINTZER: I would be happy to comment on that. We are here reflecting the discussions and the deliberations

of the Council. In the discussions and deliberations there was a clear consensus that there was evidence on depression as much as psychosis and circadian rhythm, and also that we were encouraged to present the data on both psychosis and circadian rhythm and that is why we did that.

DR. SCHNEIDER: So, why did the Council not encourage you to present depression.

DR. MINTZER: We just had ten minutes and you have to make choices.

DR. TAMMINGA: Well, thank you for sticking to ten minutes and thank you for the presentation from the APA. Our next public presentation will be from Dr. Constantine Lyketsos, from Johns Hopkins Medical Institution, who will present some data from an epidemiologic sample, I believe. Dr. Lyketsos?

**Johns Hopkins Medical Institution**

DR. LYKETSOS: Good morning. Thank you for inviting me, Dr. Tamminga.

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I will be speaking on behalf of two other individuals who could not come here today, Peter Rabins and John Breitner, primarily talking about some of our recent research. I do wish to disclose consult honoraria and research support from several pharmaceutical companies that have some interest in the discussion today.

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As Dr. Mintzer just made clear, in ten minutes one has to make choices as to what to present. So, I will say a few things with a clear focus. Much of what we have said and what our view is, is in the original letter that we sent to the advisory committee.

There are three points that we wish to emphasize. The first is that the psychiatric and other behavioral disturbances being associated with dementia and Alzheimer's is not a new idea. It is not an idea that has come up specifically because there might be new treatments available. I think that historical part needs to be emphasized. I will be talking a little bit more about frequency, and particularly give you some evidence of the population frequency of these disturbances, and that is relevant to one of the questions that was asked earlier on the part of the committee.

The second point is that these disturbances can be identified reliably and can be distinguished quite well from age-related or geriatric psychiatric disturbances. That point has been made to a great extent this morning so I won't dwell on it too much.

I will spend most of my time in talking about research findings from recent population studies of people with dementia and Alzheimer's disease that indicate that the

disturbances in question cluster into two broad groups, one looking primarily like a psychotic disturbance and one looking primarily like an affective disturbance. In case of you have any recollection of Krepelin's work, there is some recollection of the distinction of manic depression and schizophrenia in that.

I am not going to define terms in great depth. Suffice it to say it is important to distinguish whether we are talking about Alzheimer's or any other dementia, and that will become somewhat evident in what I say. I do want to introduce you to the Cache County study very briefly. This is a population study, funding by the National Institute of Aging, which was led by John Breitner and which is a study of the entire elderly population of Cache County, Utah, which is about an hour and a half north of Salt Lake City.

In that study, the entire population aged 65 and older was screened for dementia. Those who screened positive and a probability sample of those who screened negative were evaluated carefully in a detailed neuropsychiatric exam. There were about a thousand people ascertained that way. The Neuropsychiatric Inventory that was developed by Dr. Cummings and his group was used to evaluate all those 1000 participants. So this is, as far as we can tell, the first U.S. population study of the

neuropsychiatric disturbances of dementia and Alzheimer's disease. So, I will be showing you a few findings on that.

Cache County does have a second wave. So, in a few months we expect to have the follow up, so a second rating on the NPI in the entire population, and we expect later this year to have a replication of Cache County in a different population of the Cardiovascular Health Study which now has a dementia component. Yesterday, very preliminarily, I heard, in a meeting in Pittsburgh, that the numbers I am going to give you in terms of prevalences are showing up exactly or very close to the same in the Cardiovascular Health Study sites as far as prevalences of NPI disturbances.

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Peter Rabins, in the early '80s -- if you notice the reference at the bottom of this slide, this was published in '82 -- in a clinical sample identified that hallucinations and delusions were reported frequently in people with dementia and a serious disturbance in a large proportion as well.

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In the Cache County study we have the findings that appear on this table. These results are currently in press in The American Journal of Psychiatry, and they should be coming out in May of this year, as best as we can tell.