What you have in these two columns is a comparison in folks who had a clinical diagnosis of dementia as compared to those who did not have it. You have the N's over there in terms of point prevalences of individual NPI disturbances. In the left column you can see how frequent they are in dementia, and you can see that 61 percent had any one disturbance in this population panel.

You can also see the background rates of some of the points that Dr. Tariot was raising this morning. So, for example, the background rate of irritability is about 4 percent in the population; elation, 0.3 and so forth. So, we now have some estimate of the background rates and, clearly, the background rates of these perhaps manic symptoms are higher than the population in the dementia patients.

Two points that are not on the slide -- we compared frequencies in individuals with vascular dementia of Alzheimer's disease based on clinical diagnosis. Delusions were significantly more frequent in Alzheimer's disease. Depression was significantly more frequent in vascular dementia than in Alzheimer's disease -- for those of you who recall the pathophysiology that goes along with the regions that are believed to be associated with the two diseases.

The second point in terms of disease severity,

there is an instrument called the Clinical Dementia Rating, which is a functional cognitive rating of severity which we used to compare stages of dementia in relationship to frequency of disturbances. Only some of these disturbances were more frequent in advanced stages. I am not going to show you those numbers but you will have to take my word for it. It was agitation and aberrant motor behavior which were the most frequent. These numbers will be out in press and in about a month you can see them there.

We did not have in this study sleep or appetite ratings on the NPI because we had an earlier version of the NPI. So, we will find that out in the Cardiovascular Health Study.

[Slide]

Moving on to this slide, my second point is that these disturbances can be identified reliably. Our belief is that the first step to reliable identification is a structured psychiatric examination. We believe that the present state exam and its current version, called the Schedules for Clinical Assessment in Neuropsychiatry, is probably the most suited instrument for this purpose because it takes a broad approach to developing syndromes rather than having a priori criteria, such as in the DSM, that are checked for their presence or absence.

The other point I want to make has not been made

earlier but should be made. The test-retest reliability and inter-observer reliability of delusions and psychosis, if one looks at the NPI or the BEHAVE-AD for the psychosis side specifically, they are very high. The internal consistency ratings are higher. The percent agreement from some of the published data in many cases approximate 100 percent.

So, the inter-observer reliability of ascertaining these types of symptoms is very, very high and the relationship between the two major scales, the BEHAVE-AD and the Neuropsychiatric Inventory that are commonly used. If you look at the relationships between their psychosis items, what is published suggests that the correlations are very high.

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Further, it is possible to distinguish these disturbances in the context of dementia from the other common disturbances in the elderly that are psychiatric, particularly with regard to psychotic symptoms. They might occur in the context of delirium, schizophrenia, psychotic disorders, and so forth. It is possible to distinguish them from cognitive disorders.

[Slide]

This slide is an analysis done by Jackson, Rabins and others of the National Medical Expenditure Survey. The second column shows what the major predictors in a logistic

regression are of delusions and hallucinations. Now, these are independent predictors. So, cognitive impairment is one; schizophrenia is the second; and other psychosis is the third.

So, in this large nursing home sample the presence of delusions or hallucinations can be independently found to be related to all those three conditions, and can be separated out as being due to one or the other.

[Slide]

Let me move on to talk about the third point that I am making, which is the clustering of these symptoms. From the Cache County study we looked at how the individual symptoms on the NPI overlap.

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This slide is a very busy slide which really makes a simple point. You have on both axes here individual NPI symptoms if you cross-tabulate them against each other, and in the bottom lower left of this graph you can discover what the odds ratios are for one symptom occurring if a second symptom is present. If you look at this cross-tabulation, the bolded boxes which seem a little darker will suggest where you have statistically significant associations. You find that almost all the boxes are bold. It is very uncommon for individual symptoms to occur without others. If you look specifically at agitation, there is only one box

which is not bolded and that is hallucinations.

[Slide]

So, in that context it is hard to talk about individual symptoms but, rather, we took a different approach, called the latent-class analysis which is a statistical technique we applied to this population to see whether our group -- and now we are talking about grouping individuals as opposed to grouping symptoms -- to see whether our group can be distinguished into subgroups based on their profiles of behavior disturbance.

I am going to run over time a little bit, Dr. Tamminga but I will try to get this point in quickly. This is an iterative approach where you see whether your whole population clusters out into one, two, three, four, five or whatever numbers of subgroups you want. So, we tested models that had two, three, four, five subgroups with regard to behavior disturbance and we found that the most coherent statistical model was for the three subgrops.

The three subgroups are one which we called Class A which is minimally symptomatic, which was 60 percent of the sample. These were individuals who, for the most part, had no individual disturbances or, at most, had one or two, and most of those disturbances were milder.

Class B was what we called the affective group, which was about 27 percent. All of this group had either

depression, anxiety or irritability. They tended to have a larger mean number of symptoms and a broader range.

The third group, which is what we called the psychotic group, all had either delusions or hallucinations, and in this group they also had a wide range of other symptoms.

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The final slide that I have really lays out the behavior symptom profile of these three groups in a little bit more detail. Unfortunately, the printing has not shown very well the individual disturbances -- hallucinations, delusions, irritability, and so forth. On the Y axis is percent within each class who had a given symptom. You can see at the bottom that below 10 is Class A. Individuals have minimal symptoms but even some of those individuals have NPI-defined delusions, which is an interesting finding. Then we have Class B, which is the dotted line, which are the affective individuals. Then we have the straight line, which are the psychotic individuals.

So, the point that this makes more than anything is that delusions and hallucinations can occur in the context of what appears to be a primarily affective disturbance, but also affective symptoms occur in the presence of what appears to be a primarily psychotic disturbance. So, we maybe want to discuss these later on.

I appreciate that I ran out of time. So, I am going to wrap up at this point, and thank you very much.

[Applause]

DR. TAMMINGA: Thank you, Dr. Lyketsos. Any comments or questions?

DR. SCHNEIDER: A quick question and then a comment. What did you use as the cut-off for the presence of an NPI symptom? A score of 1?

DR. LYKETSOS: We used a score of 1 or 2 or 4, and it didn't make a difference.

DR. SCHNEIDER: And the data you are showing us is with a cut-off score of --?

DR. LYKETSOS: Score of 1, 1 or none.

DR. SCHNEIDER: One thing that does make a difference is that a score of 1 is arguably or probably not clinically significant certainly in terms of severity.

The comment is this is, of course, cross-sectional data and what you don't know is duration of symptoms or duration in which individual people stay within their class.

DR. LYKETSOS: Correct, and we hope to know that in the follow-up study. The point that you raise is important about the presence/absence but you really get the same clusters, the three same groups, if your threshold for cut-off is 2 or 4. So, even if you raise it to the clinically significant level it doesn't change the final

model in terms of how the classes lay out.

DR. TAMMINGA: Dr. Reisberg?

DR. REISBERG: I very much enjoyed the presentation and the data. One very interesting aspect of the data was your findings with regard to elation. You showed that in the dementia patient group, with over 300 subjects, you only found elation in 1 percent of subjects, which I think is very interesting also in light of some of the other things we heard today. I wonder if you would care to comment on that.

DR. LYKETSOS: Well, I think you are absolutely correct, that is an important observation. Elation is very rare. On the other hand, irritability is quite common, and to pick up on that comment and to go back to what Dr. Tariot said earlier today, my hunch is that we are all agreeing that there are about two or three subgroups of behavior disturbance or psychiatric disturbance. And, one of these groups that I might perhaps call affective disorder or Dr. Tariot might have alluded to as being a kind of a bipolar or secondary mania and Dr. Cummings called an agitation, I think is the same group and we are all arriving at it from a different direction and using a different method. So, I think the psychotic group is the piece I am most confident about because that is where most of the literature outside our research has gone. Then, the affective group is the

piece that needs a little bit more development.

DR. TAMMINGA: I would like to ask a question about the composition of the group. It was very interesting and useful to see data from an epidemiological sample. Was this entirely a community sample, or do you have people included here who were either hospitalized or in a nursing home?

DR. LYKETSOS: Both. It was driven by HCFA records. So, whoever didn't have a HCFA record was excluded, but if they had a HCFA record with a registered address in the Cache County area, and that address might have been in a nursing home or assisted living, they were included. If they happened to be in the hospital at the time that the study was occurring, they were also included. Their address had to be in Cache County. So, it was a rather broadly defined population.

DR. TAMMINGA: If the committee doesn't have any additional questions, we will thank you for your presentation, Dr. Lyketsos, and ask for the next public speaker, Dr. Devanand, from the American Association of Geriatric Psychiatry, to come and make a presentation. Dr. Devanand?

American Association of Geriatric Psychiatry

DR. DEVANAND: Thank you. First of all, I would like to say I have had consulting relationships with

industry involved in these proceedings.

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In terms of the presentation, I would like to start by talking a little bit about some data and then make some broader points. This is a study funded by the National Institute of Aging which was really looking at the course of patients with Alzheimer's disease, and these patients were all recruited at the stage where they had mild or early disease, at least clinically in terms of high Mini-Mental Status scores, and were followed prospectively every six months indefinitely or until death. There was a total of 236 patients in this group.

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Focusing on the issue of psychosis, we used a scale called the CUSPAD, which was really developed at our site, and the purpose of this scale was not to use it for clinical trials; it was really to establish phenomenology -- what symptoms patients did or did not have.

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So, this bar chart represents point prevalence. On the X axis -- I don't think you can see it from the back -- it says 00.51 all the way up to 3. Patients were seen every 6 months up to 3 years of follow up. On the Y axis is 0-100 percent. The point prevalence of paranoid delusions is around 10-20 percent, and it doesn't change that much at

least during the first 3 years of follow up when patients are going from mild Alzheimer's to, say, moderate to severe, in that zone, by the third year of follow up.

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Using the same instrument, we combined agitation or wandering, and if you separate two agitation is still pretty high; wandering drops off. In terms of clinical experience with these patients, this is actually the biggest problem in terms of management, more than psychotic features, just because it is more common although, as we have discussed here, it is somewhat more difficult to define.

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Next, we looked at the issue of what happens over time, and used a Markov analysis which looks at switches from time point to time point as to whether a person has the symptom or does not have the symptom. Again, we made no effort to quantify severity; it is just whether the symptom is present or not. In these Markov analyses if a patient had the symptom at one point in time, the likelihood that it would persist, which is the far right column, six months later is what is represented. So, for paranoid delusions if somebody had the symptom there is a 45 percent chance that it will still be there six months later. For hallucinations it is around 51 percent.

In terms of incidence, which is the column that says "onset," that is, somebody does not have a symptom, then what is the likelihood that seen 6 months later the patient will have the symptom? It is obviously much less, in the region of 10 percent or so. And, in concordance with the point prevalence data, for agitation the numbers are much higher.

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This study using our instrument, and we have heard today that there are other instruments -- the BEHAVE-AD, the NPI, a bunch of other instruments, but the interesting thing in this slide is that these are data from Clyde Ballard and the group from Newcastle Upon Thyne, and they found that about half of their patients were non-psychotic a year later, using a completely different instrument but, again, looking at the issue of whether or not psychotic features were present. So, these are fairly common in the incidence but they tend to wax and wane over time, and the consistency between different studies is really quite striking even though different instruments are used.

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One of the other issues that has come up is this business of symptom overlap because these patients, as we all know, very rarely have pure psychosis or pure this symptom or that symptom. They often have a bunch of

different symptoms. We looked at the issue of diagnosis in DMS-IV and looked at common situations where patients have more than one psychiatric diagnosis, all within Axis I -- let's leave out Axis II for the sake of this discussion. In making a diagnosis of anxiety disorder in somebody who has major depression, the way DSM-IV does it is to way if the symptoms and criteria for anxiety disorder are met while the patient has major depression you cannot call it an anxiety disorder.

On the other hand, for somebody who has symptoms of major depression in the context of schizophrenia there is no reference in terms of timing whether it is critical or not. I think it is important to recognize that the time course is not really sufficient to define a syndrome and what we really need are phenomenologic criteria. So although these symptoms do change over time, that is not the critical issue. The issue is what are the symptoms by which we can make the diagnosis.

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There is also, obviously, the problem of heterogeneity, whether we are talking about agitation or even psychosis within Alzheimer's disease. We like to think of major depression as a very homogeneous entity. For a variety of reasons that is useful. Heuristically it is useful. But in reality it is pretty heterogeneous and even

after we toss out psychotic depression, melancholia or bereavement and try to focus on non-melancholic major depression we all know these patients are heterogeneous. So, the issue is really, in terms of good diagnosis and treatment or even FDA approval, what degree of heterogeneity is acceptable because we all know that psychosis and dementia is heterogeneous -- if we are talking about agitation, whatever it is, these are all very heterogeneous of you are talking about agitation or whatever it is, these are all very heterogeneous entities.

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The other issue, actually, which has not been discussed at all here today for some reason, is that in patients with dementia, Alzheimer's disease most commonly, beyond the mid-stage of Alzheimer's disease a lot of these symptoms are more reported by observers, caregivers, other observers in nursing homes than actually reported by the patient. This is something which we sort of all try to get around while we are doing these various studies, but I think it is an issue worth discussing.

However, this is not unique to dementia. We do see that in psychotic patients, acutely psychotic schizophrenic patients, manic patients, where the patient will not say yes to a number of items but, in terms of the behavior, it is very obvious that they are having these

symptoms. So, I don't think it is unique but it is something to keep in mind.

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This gets back to the discussion earlier which Dr. Laughren had talked about and with reference to one of the speakers -- I forget who exactly it was -- this issue of separating the syndrome from a list of symptoms or a score on a scale which we would track in a clinical trial, and the DMS system basically focuses on qualitative criteria -- Does the symptom exist or not? I am not sure about all the DSM categories, but for the major ones nobody has to say is this a severe symptom, or a moderate symptom, or a mild symptom. You have it, you get the criteria. If you don't have it, you don't get the criteria. But in clinical trials that is a somewhat separate issue because we have to try and see whether we are treating severity because, as Dr. Cummings pointed out earlier, with the treatments that we have it is very unusual for a symptom to totally disappear because of our treatment. They go from severe to moderate, moderate to mild, that sort of thing.

In terms of defining the syndrome as to who enters a trial versus how you will monitor treatment course during the trial, I think we are left with the situation where we really need two separate ways of looking at it. One is what is the syndrome and second is how do we monitor treatment or

just phenomenologic progression.

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Touching on depression, one of the difficulties I think in depression, in the context of patients with Alzheimer's disease or other types of dementia, is that many of these symptoms just overlap. We don't know if somebody has some insomnia or poor concentration but they have no depressed mood at all, do they really have a depression? What is this? And, in DSM-IV there are two ways in which you have contingent criteria for major depression. One is depressed mood, which is obvious. The second is lack of interest. So, even if you don't have depressed mood but you have lack of interest and then you have some of the other symptoms which accumulate enough to give you the threshold for major depression, you meet the criterion for major depression.

Our thinking at this point is that perhaps this would not be sufficient in the context of Alzheimer's disease because lack of interest is fairly pervasive beyond a certain point in patients with dementia. Depressed mood might be necessary and the alternative criterion of lack of interest by itself may not be sufficient.

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In terms of pharmacotherapy in dementia, we know historically that the use of conventional antipsychotics at

high doses led to considerable neurologic toxicity. There is a bunch of studies since then which have shown that low doses of antipsychotics can be efficacious, do cause some side effects, but clearly it is a lot better using these doses than the 10-20 mg a day of haloperidol or 400-800 mg of chlorpromazine which were used in patients with dementia, say, 15, 10 years ago.

I think it is important to recognize that physicians have altered their clinical practice based on maybe these studies, maybe their own clinical experience, and that the field is sort of moving forward to some extent even independent of the labeling process. Very low doses with a narrow therapeutic window are indicated and because this is the case, as Dr. Jeste pointed out, it does support the uniqueness of psychosis in dementia. This is not like treating schizophrenia.

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So in summary, I mean, there is an aging population. There is a clinical need. Patients are being treated anyway, and will continue to be treated independent of the process of labeling, and I think, as Dr. Mintzer pointed out, it is crucial that physicians have proper guidelines in terms of studies, in terms of what is the best efficacy and side effects, and there is obviously the concern that such efforts will diminish and then we will be

sort of at this stage where we know something but we have a lot more to learn. Thank you.

[Applause]

DR. TAMMINGA: Thank you, Dr. Devanand. Any comments or questions from the committee? Dr. Reisberg?

DR. REISBERG: There was one thing, if not more, that you mentioned that no one else here alluded to and I think it deserves a little bit of amplification. That is, the studies which have been conducted to date, for the most part, have emphasized the extent to which caregivers or others are reporting symptomatology but it is important also to look at the patient directly. Caregivers who are at the end of their rope may over-report, and caregivers who want to show their confidence may under-report symptoms. So it is important to also look at symptoms directly. I wonder if you concur, but I do believe that future trials should incorporate direct observation as well as reporter-based scales.

DR. DEVANAND: Obviously, I would totally agree with that. At least in terms of the data, we know that for depression there is a lot of discrepancy in terms of what caregivers report versus what the clinician observes in the patient. That has been shown in several studies. I am not aware that that has actually been shown looking at psychosis but that is obviously a critical issue, and I would agree

totally.

DR. TAMMINGA: Thank you very much, Dr. Devanand. Next we will hear from Dr. Rick Martinez, from Janssen Pharmaceutica. Dr. Martinez?

Janssen Pharmaceutica

DR. MARTINEZ: Thank you. I am Rick Martinez, and I am a medical director at Janssen Pharmaceutica in Titusville, New Jersey. I have been at Janssen for about two years, and I have been fortunate to be able to continue my interest in Alzheimer's disease, which started as a research fellow at the NIMH, and later as chief of the geriatric psychiatry research program at NIMH. Janssen is proud to be part of this conversation. This is a very important topic, and we look forward to the deliberations this afternoon.

Several weeks ago the agency released its issue paper describing the purpose for today's talk. The agency opened up the possibility for a discussion on agitation and psychosis in Alzheimer's disease. Janssen supports the move towards a consensus on diagnostic criteria that identify psychosis in Alzheimer's disease, believing, as some have already said, that this is a specific clinical entity appropriate for medication development.

Janssen has a long-standing interest in developing treatments for mental disorders and, as a result, has

accumulated a large database in Alzheimer's disease patients. This database allows us to make certain information available regarding the persistence, the prevalence and the incidence of psychosis in Alzheimer's disease. We have performed a data review as a result of today's discussion and we came to the following conclusions:

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In our data review we have identified that psychosis in dementia is distressful and disturbing to patients. Psychosis can be identified. It is common. It is persistent. Across the spectrum of the dementia, the characteristics of delusions and hallucinations are similar.

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This slide describes how we arrived at these conclusions. As I said, Janssen has accumulated a fairly substantial database in Alzheimer's disease with 1603 patients. These databases contain information from two studies, a study of mild to moderate Alzheimer's disease in patients who are mostly community-dwelling and patients with severe dementia who are mostly nursing home residents.

In order to get a more naturalistic view of the course of psychoses, but also the prevalence, the persistence and the incidence of psychoses over time, we reviewed the data or the patient assessments of those individuals randomized to the placebo arms of these two

studies. There were 285 subjects in the placebo arm of the community-based study and there were 162 individuals randomized to the placebo arm of the nursing home study.

We also engaged experts in the field of geriatric mental health and dementia to understand the clinical meaningfulness of the patient assessments performed in these trials, and to correlate their clinical experience with the items on those scales, specifically delusions and hallucinations sub-scales from the Neuropsychiatric Inventory, which was used to assess patients in the community-based sample, and the BEHAVE-AD, which was used to assess patients in the nursing home sample. As I said, we asked these experts to correlate their clinical experience with the items and the scores on these items.

An NPI score of 4 or greater identified patients with delusions or characteristics of patients with delusions and hallucinations that were disabling and distressing to the patient. A score of 2 or greater on the BEHAVE-AD identified characteristics of delusions and hallucinations that were clearly identified by verbal information or physical symptoms of the patient. In fact, a score of 3 on the BEHAVE-AD indicates violence or threats of violence in patients experiencing characteristic symptoms of delusions and hallucinations. So, we believe that these criteria are clinically meaningful based on these experts' experience.

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To give you a picture of these patients, these are the demographics of the patients in the placebo arm of our studies. Of the 285 subjects randomized to the placebo arm of the community-based study with mild to moderate Alzheimer's disease, 62 percent of these individuals were women. The mean age was 77 years. The mean Mini-Mental Status score was 18, and 100 percent of these patients had Alzheimer's disease.

The objective of this trial was to study the efficacy and safety of galantamine. So, all of these patients had Alzheimer's disease. These patients were also mostly independent for their ADL functions, that is bathing and hygiene. Those types of problems did not require much supervision, however, these patients had impairments that may have required supervision for independent activities of daily living, such as dialing a telephone or remembering appointments.

The patients in the placebo arm of the nursing home study with severe dementia entered this trial because they had at baseline a host or range of neuropsychiatric symptoms. This study evaluated the safety and efficacy of risperidone in patients with a range of neuropsychiatric symptoms at baseline. The majority of these patients, 67 percent, were women. The mean age was 83 years. As

indicated by the single digit Mini-Mental score of 7, these were patients who had severe cognitive problems and 84 percent of these patients had Alzheimer's disease.

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This is an overall pictorial that describes the prevalence and incidence of the characteristics of psychoses in these two groups, and 2/10 patients who were community-dwelling with Alzheimer's disease had psychoses during the study. Again, these were patients who were randomized into this trial not because they had behavioral symptoms but because they had mild cognitive impairment. And, 7/10 nursing home residents had psychoses during the study.

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We derived these data from the following frequencies. This is the prevalence, persistence and incidence data from the two trials. Of the 285 subjects, again, in the placebo arm of this community-dwelling study in patients with mild to moderate dementia, 12 percent of these patients had psychoses, clinically significant psychoses at baseline. Two-thirds of these patients had psychoses that persisted for at least one month. One-third had symptoms that persisted for at least five months after entry into the trial. Another 12 percent, over the course of this 5-month trial, developed a psychosis. Again, this is longitudinal data.

In the nursing home sample, of the 162 residents who were randomized to the placebo arm, 64 percent had psychosis at baseline. Again, the objective of this trial was to assess the effects of risperidone in patients with a range of neuropsychiatric symptoms and 64 percent of these patients had psychosis at baseline. Two-thirds had symptoms that persisted for at least two weeks after entry into the trial. Another one-half had symptoms that persisted for as long as one month after entry into the trial. Of those patients who did not have psychosis at baseline, an additional 17 percent developed a psychosis over the course of the three months of this study.

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We believe that these data build upon the consensus opinion that psychosis in Alzheimer's disease is a legitimate or is a specific clinical entity, and that it builds upon the validity criteria described by the FDA, especially the second validity criteria, that they be able to operationally define a sample of patients.

We believe that psychosis and dementia that is distressful, disturbing and disabling in patients can be identified with instruments that are accepted by the field; that these symptoms are common; that they are persistent; and that across the spectrum of the dementia, that is in mild to moderate dementia as well as in severe dementia, the

characteristics of delusions and hallucinations are similar. Thank you for your attention.

[Applause]

DR. TAMMINGA: Thank you, Dr. Martinez. Any questions from the committee? Dr. Jeste?

DR. JESTE: It is possible that you might have underestimated the persistence of psychosis in this population because although they were on placebo, they received all the TLC and excellent evaluation. So, if one were to look at this in a different sample the persistence and development figures will be even higher.

DR. MARTINEZ: You are actually right. As I said, the 12 percent prevalence rate that we reported in the community-based sample was from a study of patients who were entered into a trial to measure the effects of galantamine on cognition. Behavioral symptoms were not inclusion criteria for that trial. So, you are exactly right. That figure may actually be an underestimation.

DR. TAMMINGA: Any additional questions?

DR. DOMINGUEZ: Yes, I am interested to know in the community-based sample in what percentage of patients did their psychosis remit over time, over that five-month period of time?

DR. MARTINEZ: A proportion of patients did have symptoms that lasted the entire duration of the trial. The

assessments were done at one, three and five months. So, I can only give you crude estimates as an answer to that question. Actually, I have to refer you to our document that we submitted to the agency that describes the persistence at one, three and five months to get a perspective of who remitted. But we do see patients changing. I mean, patients who have psychoses may have them for two weeks, may have them for one month, but the rates change over the course of those five months. It is not consistent.

DR. TAMMINGA: Thank you for your comments, Dr. Martinez. We will move on to the next presentation, which will be made by Dr. Sanford Finkel. Dr. Finkel is from the International Psychogeriatric Association.

International Psychogeriatric Association

DR. FINKEL: I would like to thank the FDA for providing the International Psychogeriatric Association an opportunity to address the Division today. Like many others, I have also the opportunity to consult with many pharmaceutical companies.

On a technical note, for those of you in the back, I don't have any slides so if you can't see anything, it doesn't have anything to do with your vision. I am going without them today.

My presentation will be divided into four parts.

First of all, why is an international organization, such as the IPA -- the only international organization here -- why are we here today? What is IPA's interest in today's proceedings?

Secondly, many of the speakers have referred to the term behavioral and psychological symptoms of dementia, a term that nobody had even thought of four years ago but which emanated from a meeting convened by the IPA -- just what is that term about, and how did it evolve?

Third, what are the applications or usefulness of that, and also what are its limitations? Fourth, what does all this have to do with clinical trials, anyway?

The IPA is the largest international organization dedicated to the mental health of the elderly. Obviously, just like in the United States, worldwide there are many people that have Alzheimer's disease and have what has become referred to as behavioral disturbances dementia, and many of them need treatment and deserve treatment. So, we are interested in people in those 62 countries who comprise IPA as well.

IPA includes psychiatrists, neurologists, geriatricians, internists, family practitioners and many others. Now, we got interested in this area for the reasons I explained in 1993 because, first of all, up until that time there was very little activity in clinical drug trials.

Lon Schneider described his meta-analysis of seven studies in the worldwide literature as of 1990, looking at placebo-controlled studies in antipsychotics for demented elderly with what was then called BVD. Yet, in 1993 it was clear that new studies were coming up, that more studies were going to be happening. Industry was interested; NIMH was interested. And, this was an area that, back a few years ago, it became clear was going to grow.

Secondly, in 1985 there were no measurements or scales specifically to look at, again, what was called BVD, none at all. All the scales that were used in clinical trials had to do with scales that were developed for people with schizophrenia or bipolar illness. Yet, by 1995 there were 18 scales that have been developed and, here, five years later between 30 and 40, each scale having somewhat of a different orientation, and we are beginning to feel like there was a bit of a Tower of Babel -- just what was it that we were talking about?

So, in 1996 IPA convened an international consensus conference where there was participation on the part of 60 experts from 16 countries, and the goals were threefold: One, to update where we were in this whole field, which we did. Secondly, to take a look at the nomenclature of what we were talking about and figure out just what it was we were talking about. Third was to set a research

agenda.

The first and third worked out very well. The second was a bit of a problem. We were calling the field behavioral disturbances of dementia. That is what we were referring to, all these diverse symptoms that we saw -- agitation, psychosis, etc., and the field felt, certainly the experts felt that we needed an umbrella term. We needed a term that encompassed all of the diverse symptoms that we had in the field.

Now, if you can imagine 60 experts getting together to come up with a term that would be an umbrella term, that was a real hoot. There were many very good terms that were proposed that had been used in the literature -- non-cognitive symptoms, neuropsychiatric symptoms, behavioral psychopathology of dementia -- and after much debate, it was determined that the consensus term would be behavioral and psychological symptoms of dementia -- actually, at the time behavioral and psychological signs and symptoms of dementia and then shortened to behavioral and psychological systems of dementia, "a term used to describe a heterogeneous range of psychological reactions, psychiatric symptoms and behaviors occurring in people with dementia." Now, this wasn't a unanimously approved term. However, it was a term for which there was a consensus. It was not an IPA-created term; it was an umbrella term created

by the experts in the field.

Now, we knew even at the time that BPSD was not going to be something that was going to be studied as a clear indication for a drug trial. We knew that it was going to be all-inclusive, and what we were interested in doing, and part of the research agenda we set up in 1996, was to try to look at clusters of symptoms to determine whether or not there were specific syndromes that we could identify. Indeed, when we had a second international conference, in 1999, almost a year ago now, indeed, it looked like there were a number of discrete syndromes. Dilip has described the syndrome of psychosis, but other researchers have also looked at the syndromes of Alzheimer's disease psychosis, depression and otherwise -- Tony Hope and his group from Oxford and McShane. So, this idea was absolutely catching up. But it certainly wasn't the intent of IPA to say drug treatment should be specifically for BPSD, but it was the intent to try to look at clusters of symptoms and, indeed, that is what has happened.

So, what is the relevance of all this? Well, we certainly have seen the psychosis of Alzheimer's disease described here, and it has been very exciting this morning to listen to professional groups, industry and individual researchers talk about the fact that it appears that there is a psychosis of Alzheimer's disease that is worthy of

study. Indeed, the IPA supports this strongly, and also is appreciative of Jeff Cummings' comments in elaborating the operational component of the psychosis of Alzheimer's disease.

There are a couple of other aspects of this that IPA wanted me to bring out today. First, as has already been heard, the majority of people with Alzheimer's disease do develop psychosis over the course of the illness, and if you look at psychotic symptoms, perhaps two-thirds or more develop psychotic symptoms over the course of the illness. Yet, without labeling, many of the patients that receive medication receive it on an ad hoc basis. Physicians do not have guidelines on when and when not to prescribe these medications, which ones are associated with greater or fewer risks in this vulnerable population, and what dosing can be expected to be the most effective and safest dose.

In addition to that, other countries have regulatory bodies, regulatory agencies, and are looking at what happens in the United States to facilitate development of their own policies within their own respective countries.

So in conclusion, this has been a very refreshing morning and the FDA is to be congratulated on attempting to move the whole field forward. I am reminded of what Samuel Johnson once wrote, and I quote, nothing will ever be attempted if all possible objections must be first overcome

-- nothing will ever be attempted if all possible objections must first be overcome. We have to begin somewhere, and this feels like it has been a wonderful beginning. Thank you.

[Applause]

DR. TAMMINGA: Thank you, Dr. Finkel. Anybody on the committee have a question or comment for Dr. Finkel?

[No response]

Well, thank you very much for your comments. Our next speaker in the morning will be Dr. Alan Breier. Dr. Breier is from Eli Lilly Company, in Indianapolis. Dr. Breier?

Eli Lilly

DR. BRIER: Thank you, Carol. I too will disclose that I have received financial support from one pharmaceutical company.

[Laughter]

[Slide]

I also just want to commend this group for tackling an extremely important issue, and we are delighted to participate in this very important public discussion.

[Slide]

What I think is very, very important, and where I want to begin, and it is almost stating the obvious but I think it is terribly important that we not lose sight of the

human face of this illness, the impact that this illness is having on our society. You can go through the numbers -- we all know them all. We have heard allusions to them already, but when it comes down to the individual person suffering with these disorders, the impact is very, very significant. I think as we deliberate and think through a course of action keeping this in the foreground becomes very, very important. A very large number of U.S. citizens have Alzheimer's disease, with dramatically rising numbers with the aging population, massive human suffering for both patients and families. It is a very, very expensive disorder, ranking third of all illnesses in the United States with substantial costs for families.

Getting more to the topic of today's presentation is that the psychosis and behavioral disturbances are very common. What is very important about these disturbances is that they are often the precipitants which leads a person residing in the community, perhaps being cared for by their family members, to become institutionalized, such that if we can improve the state of treatment of psychosis and behavioral disturbances, then we will have more patients living in the community. That is going to impact very, very dramatically on the cost of the illness and lead to much higher quality of life. So, again, it is a very, very important mission.

Neuroleptics are commonly used off-label. There is currently insufficient FDA direction to prescribers, which we have noted and, again, I applaud the FDA for bringing this group together to make progress in this area and, as we all know and have heard from the other speakers, there is a high rate of adverse events.

[Slide]

This is the use of antipsychotic drugs in the elderly, defined as 65 years or older, in a year in the U.S. The bottom line is that there 50 million days of therapy of antipsychotic drugs -- a huge number of individuals being treated with antipsychotic drugs, 14.7 million in the dementias alone. So, there is a huge amount of use, and the importance of labeling is to provide guidance to assure safety and efficacy. As we all know, many professionals prescribing these agents are not psychiatrists. They may be primary care physicians. They may be less familiar with antipsychotic drugs, and the label and the direction becomes their guide post in the appropriate use of these agents.

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So, that really brings us to the critical challenge for this group. That is, we have a spirit of urgency, that is, there is an urgent need to establish clear guidelines for drug approval. Pharmaceutical companies like Eli Lilly & Co. need a clear path to registration, and we

need to do that in terms of the public good in the most expedition way as possible. Each month there are 20,000 more cases of Alzheimer's disease with a substantial cost. So, in some ways I would argue that we can't afford to delay; that we can't afford a prolonged suspension in drug development. On the other hand, should we rush forward with criteria or methods that are inappropriate of scientifically unsound? Of course, not. But it is really striking the balance between the appropriate clinical nosology and accelerating drug development to meet this national need.

Just in terms of the drug development piece, if we all agreed on criteria today, if we locked the door and we are not leaving until we have all agreed on the criteria and it was decided that that criteria then became the standard, and we would need to use that criteria from this day forward, we are still talking about a three to four year period in which new registration trials and approval occur, and that is a relatively aggressive time line for all of the steps in developing a protocol, entering subjects, analyzing the data and the review process.

So, what we hope is that there is a way to leverage or use existing clinical trial databases, and there are those, that are under way now, that are available, and is there an attempt or an approach in which we can use nosological criteria that is scientifically sound and apply

them to existing clinical databases which could then accelerate the availability of perhaps promising new treatments.

[Slide]

This area I think is well worn, and it seems like there is unanimous agreement that the psychosis associated with Alzheimer's is, indeed, a distinct clinical entity and warrants its own unique indication. We have supported that in our position paper, and I think that this group will likely come to that conclusion as well based on the other opinion papers and based on the presentations. So, I will not go through that data; it has been done quite elegantly.

[Slide]

However, what I think is the important point is that what we do agree on is that there are essential diagnostic criteria to move forward. We agree that psychosis deserves its own indication. The next challenge is how do you categorize these individuals? How do you diagnose them?

Having gone through this process or a similar process in schizophrenia and trying to develop diagnostic criteria, at one level it looks like should be fairly simple and straightforward but when you actually get down to doing it, it can be a rather laborious process, and there are no optimal criteria at the end of the road. It is an

evolutionary process that changes over time as more data become available. So, as opposed to looking for the absolute, finite, perfect criteria, I suggest that we agree on essential diagnostic criteria and then allow those to be applied to clinical trials data.

Those essential criteria really fall into three groups: that the diagnosis of dementia of Alzheimer's type be present; that there be prominent delusions and/or hallucinations, and that they meet the test of severity and persistence; and that the psychotic symptoms not be due to other medical conditions -- delirium or Axis I disorders. If those criteria are met, then we are probably on the right road to having the kind of diagnostic criteria we need for clinical trials.

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I would suggest that there is an approach available now. Again, if you agree that there is a degree of some urgency to move forward, then I would suggest that DSM-IV offers an approach, a diagnostic approach that could be used now. Is it perfect? No. Would it benefit from more elaboration, more operationalization? Yes, it would. But could it be used as it is now and meet a standard for capturing a diagnosis? I would suggest that that may be the case. When one looks at the DSM-IV criteria patients must meet diagnostic criteria for Alzheimer's; the psychotic

symptoms are not due to other medical conditions; the delusions are prominent; the hallucinations are prominent with coding, again, allowing sort of a generalizability of the findings, something that is familiar to clinicians, and this then could be augmented with validated rating scales which could further flesh out phenomenology, severity, etc. So, the combination of the existing DSM-IV criteria and a validated rating scale could be a combination that could be applied diagnostically. This is, again, not to say that further evolution should not take place, and we hope that it will and that over time this criteria become better and stronger.

So just in conclusion, we support the indication of psychosis. We feel that there is an urgency in moving forward because of the public health need. And, we think there are essential criteria that can be captured and can be utilized now.

[Slide]

Just moving quickly to the area of behavioral disturbances, there are many. This is a short list. There are obviously more that have been talked about. We would suggest that this group as an undifferentiated mass is too broad for an indication; that one must look at each one of these one at a time, and look at them for their own merit and then make decisions based on the data and the qualities

of each one of these behavioral disturbances. We would suggest that one reasonable target for drug development is acute agitation.

[Slide]

Acute agitation is a common feature across a number of disease states. It is a behavioral syndrome that has both verbal and motor components, comprising hostility, tension, uncooperativeness, poor impulse control and excitement. There is reasonable strong face validity and reliability to the concept of acute agitation. Physicians tend to know it when they see it. There are numerous instruments, which have been mentioned, that have been proven metrically to be valid and reliable. Acute agitation causes significant adverse impact on patients, again, a common precipitant which may lead a patient to go from care in their home to an institutional setting, and commonly warrant pharmacological intervention.

[Slide]

We would suggest that acute agitation would stand best as a broad indication; that, in fact, acute agitation is not unique or specific to Alzheimer's disease; that there are core clinical characteristics that are relatively common across disease states, not necessarily precisely but if you use the pain model and you look at pain, pain occurs in different forms, different characteristics, but there is a

similarity to the characteristics of pain and, indeed, acute agitation so that they are somewhat consistent with the pain and fever model. The indication, therefore, should be supported with data from a number of different disease states.

[Slide]

An assessment approach for acute agitation could be as follows, based largely on clinical judgment; that there be abrupt onset of agitation with the key features that we have talked about; that there be sufficient intensity and severity of the agitation so that it requires treatment; and/or results in impairment and distress. Again, which is a very common approach in clinical trials, one can use that clinical judgment, the clinical phenomena, and then enhance or augment the capture of the material through validated rating instruments which are available and that can further characterize severity and phenomenology.

[Slide]

There are, as mentioned, a number of different rating scales. The PANNS excitation component might be one measure that one could use across many different disease states; strong face validity; strong reliability; capturing some of the key components of agitation. It could then be used and compared across a number of disease states. Then, this could be complemented with perhaps other validated

ratings scales for unique populations -- the Cohen-Mansfeld, for example for dementia; the Corrigan which has been used in schizophrenia. So, the package of one, two or perhaps rating scales might be sufficient in terms of our knowledge.

[Slide]

Finally, I will just conclude by summing up and saying, again, an urgent need to develop new therapies for Alzheimer's disease patients with psychoses and behavioral disturbances. The psychosis associated with AD warrants a distinct indication. Diagnostic approaches available now for registration trials of psychosis associated with AD and, lastly, acute agitation is a non-specific behavioral syndrome that warrants a broad indication across many disease states. Thank you very much for your attention.

[Applause]

DR. TAMMINGA: Thank you, Dr. Breier. Anybody from the committee -- yes, Dr. Tariot?

DR. TARIOT: Alan, I liked a lot of what you said. Why the emphasis though with agitation on abrupt onset or acuteness? If I can elaborate on why I am puzzled by that, as I listened to Jiska Cohen-Mansfeld's data and Dr. Devanand's, and I think Jeff Cummings has data that he didn't talk about, it suggests that agitation actually emerges not exactly monotonically over time as dementia progresses but something like that, and Hope and McShane

data suggest that it persists until death once it appears.

DR. BREIER: Yes, I think that is a good point. I think that we wouldn't rule out the value of looking at a chronic or more persistent form of agitation but, again, we are focusing on agitation across a number of different disease states, not just the agitation in Alzheimer's. When one looks across disease states the acute form of agitation is perhaps a little more conservative. I think one might argue that perhaps psychosis is a little bit further along than some of the other behavioral disturbances. So by limiting it that way, acute agitation has some characteristics that perhaps are a little bit more commonly recognizable across schizophrenia, bipolar, dementia, ICUs, etc. So, that would have that broader appeal or recognition across.

Obviously, there is another form of agitation in Alzheimer's disease that is more persistent and chronic, and the data is very compelling. We are not ruling that out. We are just suggesting that acute agitation may be a bit more of a conservative path that one could pursue at this point.

DR. TARIOT: I understand the distinction you are making and I appreciate it. Just as a clinical cautionary note though, I think most of us in geriatric medicine would view the acute onset of agitation as a red flag for delirium

or an environmental stressor and not necessarily first off the object of pharmacotherapy.

DR. BREIER: Fair enough.

DR. TAMMINGA: Dr. Schneider?

DR. SCHNEIDER: Alan, this is a comment I made earlier but it seems that much of the agitation that you are describing actually, it seems to me, to be aggression. I am wondering if you are trying to make a distinction between aggression and agitation when you are arguing for a broader-based claim across disease entities.

DR. BREIER: I think that is a good point and a good debate. I think that aggression can be a component of agitation but agitation exists without aggression. So if you look at the PANNS, for example, hostility implies the aggressive component but there are clear forms of agitation that are not directed in an aggressive way outwardly or inwardly that would constitute agitation. For example, the person who is pulling the IV tubes out of their arm and needs to be pharmacologically controlled, that would not be an aggressive or hostile act but, yet, it would be clearly agitation.

DR. TAMMINGA: Dr. Lebowitz?

DR. LEBOWITZ: Unlike the psychosis issue where there are fragments of data that may or may not contribute to a whole story on a neurobiological substrate, you don't

mention any kind of neurobiology of your agitation recommendation.

DR. BREIER: Yes.

DR. LEBOWITZ: Do you see that as a part of the picture leading toward satisfying your recommendation?

DR. BREIER: We addressed this in our opinion paper for both psychosis and agitation, and I have to kind of humbly admit that the field has probably not progressed far enough where one can talk about distinct or common neurobiological mechanisms. The knowledge has just not evolved to that point. So, it relies really on phenomenology, clinical judgment, the characteristics that one sees, and the characteristics one would see in the clinic to make these distinctions. It would be lovely to have a neurobiological substrate for both psychosis and agitation and it would in some ways make our work a lot easier but the state of knowledge is not there, in our view. So, one then does rely on validated rating scales and psychometric properties.

DR. TAMMINGA: A short last question from Dr. Schneider.

DR. SCHNEIDER: Alan, just as a follow up, would it be fair to say that you or Lilly are asking for a claim for agitation or aggression in, for instance, specifically depression or schizophrenia or other disorders?

DR. BREIER: A broad claim. In other words, we would suggest that agitation, like pain or like fever, is probably best viewed across a number of different disease states and, therefore, the claim should be broad as opposed to specific and only unique to dementia. The characteristics of agitation that we are describing here, particularly acute agitation, we think are relatively similar -- the acute agitation, the symptoms, the presentation are relatively -- not exactly but relatively similar in an acutely agitated manic, in an acutely agitated schizophrenic patient, etc.

Now, where are the limits of that breadth? I think there probably are limits, and one would have to then work with that in the context of labeling, etc., to determine perhaps, just like pain and just like fever, that there can be, in fact, some limits to the breadth. But what we are doing is taking this out of something very unique and specific, dementia of Alzheimer's disease, and saying that psychosis, yes; agitation, probably not.

DR. CUMMINGS: Carol, can I ask a follow-up question to that?

DR. TAMMINGA: Yes, short.

DR. CUMMINGS: This is a question for Tom. It is ambiguous in the White Paper how many disorders are enough to establish the claim for extending to other disorders.

So, if Lilly has studied depression, psychosis and mania and treated agitation, is that enough for them to claim that it also treats agitation in AD?

DR. LAUGHREN: There isn't any absolute rule. Across the agency, if you look at other divisions that have approved these non-specific claims, they generally look at three models.

Just as a little bit of background here, I should explain a little bit about how this notion came up because FDA did have some role in this. It might help in understanding the context. Several years ago several companies expressed an interest in developing intramuscular forms of antipsychotics without any particular intention of doing any kind of efficacy studies with those new formulations, and that is where they ran into a roadblock from us because we are not willing to make the assumption that the time-concentration profile, which is different with an IM formulation, doesn't make a difference. So, we were all struggling with trying to figure out how one would look at efficacy for this new formulation, an intramuscular formulation. It occurred to us, if you think about how these drugs are used, say, in a setting of schizophrenia, they are not really used to treat psychosis per se. They are used early on in managing an agitated person. Then the switch to oral medication is made fairly quickly.

So, that is how we ended up working with companies in trying to focus on something like agitation, and it occurred to us at the time that the non-specific model, sort of the pain model as Alan talked about, perhaps made some sense. That was then. Now, after having all this discussion about agitation in the context of dementia, it is not so clear to us anymore that that is the right way to proceed. And, I hope that this issue gets a lot of discussion this afternoon. It is a very important one. Again, this is all very important because whatever decisions we make, whatever precedents we set at this point, we want them to be ones that we can live with. So, I hope this issue gets a good bit of discussion. But that gives you a little bit of background as to how we arrived at that sort of model of agitation. But, like anything else, it has to be defined. You have to know what it is that you are talking about.

DR. TAMMINGA: Thank you, Dr. Laughren, and thank you, Dr. Breier, for your presentation. It was highly informative. Our next presentation will be from Dr. Judith Saxton, from the University of Pittsburgh Medical Center. Dr. Saxton?

University of Pittsburgh Medical Center

DR. SAXTON: Thank you. Good morning. We can have the lights up. I don't have slides; I am not going to

be presenting data this morning.

I want to thank the committee for inviting me to come and present to you today, and to let you know that I am a neuropsychologist from the Alzheimer's Disease Research Center at the University of Pittsburgh. The only disclosure that I need to make is that I do receive royalties for a cognitive test that we developed at the ADRC to assess severe dementia, which is the topic that I want to address the committee on today.

It is my goal to talk about a related topic, not specifically about the psychiatric and behavioral disturbances but the fact that these disturbances vary not only across disease states but along the disease continuum, as well as across states, and to make the committee aware that if we do not include individuals with more advanced dementia we will not know the full extent of these psychiatric and behavioral disturbances. Indeed, we won't know how these symptoms covary with the cognitive decline of Alzheimer's disease.

I want to pick up on a topic that has been mentioned this morning, and I do agree with Dr. Cummings, I am one of the individuals that does experience memory problems in everyday life. I have lost my keys and I have lost my car in the parking lot. I think that perhaps the reason that I don't jump to the conclusion that somebody has

stolen my keys or my car is that, although I have a memory problem, I hope I still have fairly functional frontal lobes. So, instead of jumping to the immediate conclusion, I start to think of alternative reasons why I might have lost these items. I suspect that patients with Alzheimer's disease have both a memory impairment and an impairment in their frontal ability, their executive abilities so they are unable to consider alternative reasons.

I am not suggesting that these two cognitive deficits explain the disorder of delusions or the false belief, but they may be necessary but not sufficient to explain. But if we don't have the cognitive assessment tools available to look at advanced dementia we won't be able to investigate these areas.

Very early on in the Alzheimer's Disease Research Center when we were bringing patients back for longitudinal evaluation, we identified that the current cognitive tools that are available are insufficient, and we noted that within two years of doing longitudinal follow-up individuals were unable to complete these standardized tests that are available, and we were unable to get good profiles to look at not only overall mental status but to look at these relationships between semantic memory and other types of cognitive disorders because the tools were not there.

We did start to develop an assessment scale, which

is the one that I have discussed with you. I quickly found out, as soon as I put this tool out on the market, that what I called severe dementia in a research setting was not, in fact, what individuals in nursing homes called severe dementia. I found that as I went out to nursing homes and I was talking about individuals with Mini-Mentals of below 10, let's say, but still able to complete the Mini-Mental scale, in nursing homes when people were trying to use my scale they were talking about individuals with Mini-Mentals of 0.

When I started to use the scale more in the nursing home populations, I also realized, what I had known before but now was much more clear to me, that even though individuals can score 0 on some of our tests, it is not to imply that they are without cognition or are untestable. It is simply that our scales are not sensitive enough at the lower end of the range and, in fact, individuals in nursing homes even with Mini-Mentals of 0 can quickly find the fastest way out of a building and over the fence. It is a big problem. They can quickly identify where the restaurant is, where the cafeteria is, where lunch is going to be served. They can also develop relationships with specific aides and seek out that specific aide. Indeed, not only with specific aides but with other residents, which also causes problems sometimes. So, these individuals are able to perform on cognitive tests if we only lower the

sensitivity, lower the range of our cognitive tests down to be more sensitive at that end of the range.

Just to belabor the point a little bit, when we look at most of the research studies, there are a few. And, I think Janssen was wonderful in including the nursing home group in their study but the majority of research studies include only mildly to moderately impaired patients. By mildly impaired patients, we typically mean individuals scoring 20 or higher on the Min-Mental. While we may identify patients with higher than 24 as having Alzheimer's disease on an individual clinical basis, for most research studies we use 24 as a cut-off to ensure that we have individuals who are demented. So, mild dementia often ranges from, say, 19 or 20 on the Mini-Mental to 24. Moderate dementia may range from, let's say, 10 or 11 on the Mini-Mental up to 18 of 19. We know that the decline in the Mini-Mental is typically about three points per year, suggesting that the mild range may last only one or two years and the moderate range may last only two or three years, maybe four years.

We also know that individuals with Alzheimer's disease are now living significantly longer than they used to live, certainly nine, ten years and in many cases the individuals that we have been following over almost twenty years in the University of Pittsburgh, up to twenty years

with the diagnosis of Alzheimer's disease. That means that a great deal of the time that these individuals have Alzheimer's disease will be spent within this stage of severe dementia, and they will be excluded from the majority of research studies.

I am asking the committee today to not only identify and define different disease states or clinical entities, but also to consider defining levels of dementia. By doing so, you will encourage researchers and neuropsychologists to develop adequate scales which we will be able to then use to encourage individuals to incorporate these more advanced cases of dementia within their research and, therefore, for us to be able to look at the relationship between cognitive decline and psychiatric symptoms in this group. Thank you very much.

[Applause]

DR. TAMMINGA: Questions or comments for Dr. Saxton? Yes, Dr. Reisberg?

DR. REISBERG: I want to first of all strongly endorse your major points. I think they are very, very important. I think it is very important to understand the behavioral symptoms, the BPSD symptoms in association with cognition as the disease evolves. There is a paper in press from a multi-center study conducted by the NIA on the SCU units, which is Tracy, Holmes et al., which indicates that

approximately 25 percent of patients in nursing homes -- and there are a million and a half persons in nursing homes so we are speaking of a great number of persons -- have Mini-Mental State scores of 0. So, we are speaking about hundreds of thousands of people with illness. If we think for a moment that there are only about 700,000 people in all hospitals at any given time, hundreds of thousands of people with Mini-Mental State scores of 0 is a very large number.

We, as you know, have also been involved in this area at a somewhat lower range than you have addressed, and we have also tried to develop measures. We have one measure, the MOSPD, the Modified Ordinal Scales of Psychological Development, which can measure cognition for about 6 years after the Mini-Mental is 0. So, I strongly endorse what you are saying.

DR. SAXTON: Thank you. I know that there are a number of people looking at this area, and I am encouraged by that but I think that this is an opportunity to draw awareness to this issue and to include these individuals in research.

DR. TAMMINGA: Thank you, Dr. Saxton.

DR. SAXTON: Thank you.

DR. TAMMINGA: We will go on to our next speaker, Dr. May Sano. Dr. Sano is from Columbia University.

Columbia University

DR. SANO: Thank you. Yes, I am from Columbia University but I am presenting data to you today from the Alzheimer's Disease Cooperative Study.

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The information I will be telling you about was summarized by several members of the ADCS, including, in addition to myself, statistician Julie Berg, Lon Schneider, Paul Aisen, Ruth Mulnard and Leon Thal. The ADCS is an NIA-funded project that has been running clinical trials in Alzheimer's disease for nearly ten years.

What I will present to you is a summary of data collected from clinical trials conducted in well-characterized patients with Alzheimer's disease. The specific position that we believe this data supports is that psychosis, which can be identified in Alzheimer's disease using traditional descriptive terms, has a relatively predictable rate of occurrence; is typically treated pharmacologically, yet continues to persist across a wide range of dementia severities even in relatively healthy patients with Alzheimer's disease.

Now, the nature of this data that I am about to describe to you consists primarily of adverse event reports made throughout clinical trials conducted by the ACDS, specifically three long trials. The first study recruited 341 moderately impaired patients with Alzheimer's disease,

following them for 2 years. The second, 138 mild to moderately impaired patients with Alzheimer's disease, followed for 1 year. The third recruited 120 mild patients, followed for 14 months.

In all cases, inclusion criteria for the studies were designed to select relatively medically stable individuals who were outpatients, living in the community, who had no significant psychopathology that would require medication, and who could be expected to cooperate with the study for the entire length of the study period, one year or greater.

Now, adverse events in these clinical trials are reported through unstructured reports, and they represent significant symptoms noted by caregivers and by clinicians. Unlike assessments of standardized instruments that we have heard about, this technique captures only those events that are perceived as problematic by relevant observers.

The methodological approach that we used was to assess the adverse events which are reported in text fields, using key terms to identify those things that would fall into the category of psychosis. In the particular word of psychosis the key words that were used were delusions, hallucinations, paranoia and psychosis. This method was tested in the first study that I described of 341 patients to ensure that it captured all of those patients who

appeared to have psychosis and did not capture individuals whom we would not want included. These terms were, as I mentioned, validated by such a review.

For each adverse event the clinician rated severity and the date of onset, the day that the event ceased. He also recorded an action taken, including the use of concurrent medications to treat that symptom. The number of patients who ever experienced such an adverse event was recorded. So, if an individual experienced this adverse event repeatedly, they were only counted once in this analysis.

Across these three studies, which we summarized in the form of a meta-analysis, the overall rate of psychosis as an adverse event as I have described in these trials was 9.6 percent, with individual rates ranging from 7 percent to 10 percent, and being related to the entry level Mini-Mental State of the specific trials. The mean time to the first psychotic event across the three studies was approximately 200 days. Approximately two-thirds of the patients with these psychotic symptoms were rated as having them at a degree of severity of moderate or severe.

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In addition, we examined the co-occurrence of psychosis with the adverse event category of agitation, and in the case of agitation the key words that we were used

were agitation, combativeness, wandering, confusion, behavioral disturbance, irritability, anxiety, angry or some derivation of that word, and outbursts. Now, across the three studies the overall rate of agitation in these three studies was about 40 percent. Across these three studies, about 60 percent of those with psychosis also reported agitation, and this is a significant correlation.

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In terms of the resolution and the persistence of the symptom of psychosis, 70 percent of those with psychosis demonstrated persistence for more than three months, and about one-third of those with psychosis reported symptoms that had resolved by the end of the study, and two-thirds had not resolved by the end of the study.

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We also attempted to examine the overall incidence in terms of when the onset was occurring. of those who had some psychotic event as described, in 45 percent it occurred within the first 6 months and about 82 percent within the first year. The cumulative incidence by this method is about 8 percent per year.

Let me just review some of the points that I think are important here. First of all, among those who had psychosis, 54 percent did receive medication for this specific indication. Now, others may have received

medication for other symptoms, such as agitation or depression, which were not recorded as treatments for the psychosis. So, this number may actually be higher. Despite medication use, as I mentioned earlier, 70 percent of the patients demonstrated persistence for more than 100 days.

Now, we think that the present review of the data illustrates that, even among relatively healthy patients with Alzheimer's disease, psychosis of sufficient severity to be described as an adverse event occurs in nearly 10 percent of the population. A standard criterion for participation in these clinical trials is the likelihood of being able to follow the protocol for the entire duration of the study, as I mentioned, one to two years, without needing psychotic treatment. Regular use of antipsychotic medication is an exclusion in these trials and, in fact, this increases the likelihood that we have selected a very specific and healthy population. So, with this in mind, I think it is reasonable to suggest that this data is an under-representation of the total prevalence or incidence of psychosis in the population of individuals who have Alzheimer's disease.

I think there are several advantages to these data sets. First, the analysis includes data collected from more than 25 sites around the U.S., and reports of the psychosis were not captured on a structured format yet the data is

consistent or relatively consistent across trials and with other numbers that you have heard today. This suggests that the terminology and the phenomenology was commonly recognized, and possibly we could even state that it was valid terminology.

Finally, while the patients in the clinical trials are generally recognized as relatively homogeneous, these three studies actually represent a wide range of disease severities. Taken together, the findings do suggest that the phenomenon of psychosis in Alzheimer's disease may be universally observed.

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So, in summary, I think the eligibility criteria in this specific study select against those most likely to have psychosis, giving us a more conservative estimate. In addition, since we are not using a formal elicitation of symptoms, we are likely also to have a more conservative estimate. As I mentioned, the treatment of other conditions may even reduce the likelihood of observing psychosis.

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So, in summary, I would just like to simply repeat that it appears to us that this is a recognizable phenomenon -- psychosis in Alzheimer's disease. It has a predictable frequency. It has significant morbidity, and it is relatively persistent amongst a wide range of individuals.

[Applause]

DR. TAMMINGA: Thank you, Dr. Sano. Any questions or comments?

DR. GRUNDMAN: Mary, I agree that psychosis occurred in about 10 percent of patients. One of the things that you mentioned very quickly was that agitation seemed to occur in 40 percent of patients.

DR. SANO: Right.

DR. GRUNDMAN: So, even though psychosis is sort of easier to define, agitation is probably a more prevalent and important adverse event which is brought up by caregivers on a more regular basis.

DR. SANO: I think that is absolutely the case. The one thing to keep in mind is that we don't know the time course of which symptom occurred first and which symptom occurred second. Perhaps, as has been suggested, the agitation is an outcome of the psychosis.

DR. GRUNDMAN: Except that it occurred in 40 percent of the patients --

DR. SANO: That is correct, but in addition you will notice it is a wider range of key words that have been used. We haven't done the same refining of agitation. It cuts across a wide domain of phenomena I think.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: What did you say the range of

severities of Alzheimer's disease was in this cohort?

DR. SANO: The range is from mild to moderate by overall definition. In most cases there is little or no upper limit on the MMS. The lower limit was also not established in the first trial that was described of 341. There was no MMS requirement. So it could go as low as 0. The mean scores of the one trial that was ranging closer to 7 percent than 10 percent was about 2 points higher on the MMS.

DR. KATZ: Why did you choose to focus on these events as defined by a relevant observer as opposed to patient reports as being severe or problematic.

DR. SANO: I absolutely admit this is a post hoc analysis of the adverse event -- I think adverse event is an unusual word to use; perhaps inter-current event is the correct term to use. So, in the context of the trial, when a person reports that their patient had a significant adverse event the broad question is have there been any problems, and the caregiver may describe them or in the interview the clinician may observe them. That is the broad category.

DR. KATZ: Right, what I am trying to get at is that these were events that were defined as being problematic by someone other than the patient.

DR. SANO: Right.

DR. KATZ: Right, and I am asking why you chose to rely on those reports as opposed to patient reports, if you will.

DR. SANO: What I am saying is that this was the collection of adverse event and for regulatory purposes and the typical procedure is for the clinician to determine the severity of the event using all information. He can either observe the patient or use the caregiver.

DR. TAMMINGA: Dr. Tariot?

DR. TARIOT: But, Mary, is it not correct that if a patient said I am in terrible distress that would be picked up also?

DR. SANO: Oh, absolutely. Absolutely. I am sorry, what I meant to suggest is it was both observed as well as reported.

DR. KATZ: Let me then just ask a follow up, if I can, do you have any sense of how many of these were observed by the patients or reported by the patients as opposed to how many of these were observed by someone else?

DR. SANO: Right, my impression is it is highly representative of the patient state, primarily because the clinician evaluates it in the context of the patient's experience.

DR. TAMMINGA: Dr. Grundman?

DR. GRUNDMAN: One other point is that if the

patients have delusions and hallucinations they might not be the most likely people to complain about it.

DR. TAMMINGA: Dr. Schneider?

DR. SCHNEIDER: Just, Dr. Katz, a point maybe of clarification, two of these data sets are essentially typical of patients who are in cholinesterase inhibitor studies or in galantamine, and I think a reason we wanted to look at this was similar to the reason Janssen looked at their galantamine data to try to get an appreciation of Alzheimer's patients in the community who volunteer for these studies and who really do not have significant behavioral problems to the extent that would cause interference in the studies. We were just trying to get a sense of what the incidence of psychosis was in this group, and I think Mary reported a fairly predictable incidence.

DR. SANO: Right. Let me reiterate the fact that most of this is reflective of the patient's experience. The possibility that it is reflective of a report is based on the fact that in advanced patients the information could have been collected without observing the patient. That represents a relatively small number across this whole study.

DR. CUMMINGS: I think it is worth making the point, Dr. Katz, that it is common for patients who have psychosis to not be psychotic during the 30 minutes that

they are observed in the evaluation in the clinic and, therefore, if it was strictly patient-based in terms of observation that would greatly underestimate the prevalence of psychosis in these populations. So, we always do depend on the caregiver for the report in addition to patient observation.

DR. TAMMINGA: We have a comment from Dr. Reisberg.

DR. REISBERG: We have actually investigated and published the relationship between observations in actually a little bit less than 30 minutes, approximately 20 minutes on average and reporting of symptomatology by knowledgeable observers over the previous two-week interval, and if one correlates actually rating scales that are similar and comparable with respect to the issues -- we have looked at 6 of the seven BEHAVE-AD categories because, for example, sleep disturbance could not be observed in that 20-minute interval. So, we excluded that. We get a 0.54 correlation overall, which is very highly statistically significant. So, actually, there is a very strong relationship when one actually does begin to observe patients in a systematic way between what one can observe over a brief 20-minute interval and what is reported by caregivers. We did this on a routine basis and it is absolutely remarkable how much one can actually see if one observes the patient. This includes

things like delusions. So, for example, patients will tell you about their delusions in a few minutes just the way caregivers will report it, and one can go on and on in that regard.

DR. TAMMINGA: These issues will be picked up this afternoon, if I could ask you, Dr. Hamer, to hold your comment until this afternoon. And, I want to thank Dr. Sano and thank all of the people who presented during the open public hearing. We will now break for lunch -- oh, yes, Dr. Jeste needs a minute.

DR. JESTE: Yes, this is my fourth FDA meeting and I want to publicly disclose that I too have worked as a consultant to several pharmaceutical companies.

DR. TAMMINGA: We are breaking for lunch now and perhaps even a little walk outside on a beautiful Washington day. The committee, both the guests and the committee itself has a separate room to eat in. So, if you would kind of keep your eyes out for that. We will come back and 1:45, please, 60 minutes from now. Thank you.

[Whereupon, at 12:45 p.m., the proceedings were recessed for lunch, to be resumed at 1:50 p.m.]

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

Committee Discussion

DR. TAMMINGA: I would like to reopen this afternoon's meeting. What I would like to do is attempt to bring a touch of focus to at least the beginning of the discussion in the afternoon by turning back to Dr. Laughren's presentation this morning. The FDA is interested in hearing from the psychopharm. committee and from its invited experts answers to some of the questions and dilemmas posed by Dr. Laughren this morning.

The overall topic of our afternoon is psychiatric and behavioral disturbances associated with dementia, and the practical question is really for us as a committee to pull together our advice, our best advice for the FDA on the issues of their legal requirements -- efficacy, safety and acceptable labeling.

Now, going back again to what Dr. Laughren articulated this morning, what is required for a particular clinical entity to be considered an acceptable indication for treatment is, number one, accepted in the clinical and academic community; number two, operationally definable; and, number three, a reasonably homogeneous patient group.

From the things that we have already talked about this morning, we have an awful lot of data that people have presented, although not extensively discussed, around those

points. As an example, perhaps to help us as a committee get started in our discussion, Dr. Laughren reviewed what approaches have already been proposed for addressing the psychiatric behavioral aspects of dementia, and proposed -- didn't exactly propose but suggested that what that has been evolving into lately is something more specific, like psychosis associated with Alzheimer's disease.

So, I would like us to see, using the data that was presented this morning and reviewing what we know from our clinical work, what we as a group might recommend to the FDA about these various syndromes, the psychiatric and behavioral disturbances associated with dementia, first of all, the exact syndromes and then also I think that it would be useful to have a discussion about the non-specific psychiatric signs and symptoms, particularly about agitation since that has been a topic that has been raised before.

There is one topic that Dr. Laughren raised this morning that I thought was particularly important and that I would like us to address, not initially but before the end of the afternoon, and that is the safety of these drugs in the elderly and whether or not there might be some need for a policy for evaluating risk of psychotropic drug treatment in this population.

So, I would like to open the floor for some discussion amongst the committee and its invited experts on

these topics of psychiatric and behavioral disturbances associated with dementia.

DR. WHITEHOUSE: Let me address your topic. Let me first take the opportunity to make my conflict of interest statement since I didn't give an address but will be making some comments. As the facilitator of the International Working Group for the Harmonization of Dementia Drug Guidelines, our institution has received grants from over twenty-five different companies, and I am interested in extending my conflict of interest and will be happy to talk to you about our activities.

[Laughter]

I have also served as a personal consultant to some of the companies as well.

I should say that the International Working Group identifies that in Europe and in Japan the importance of behavioral symptoms has been recognized by the regulatory bodies, but they have not taken any particular actions with regards to open discussion or coming to some concrete closure on this. So, again, I thank the FDA for having this meeting and taking us in that direction.

I am also an academic, which is a conflict of interest because we tend to promote our own interests -- in my case that happens to be quality of life -- and also tend to make statements to make sure that research is never-

ending. But I think I agree with Carol, it is time to focus the discussions because we want to have more than an ongoing and richer discussion; we need to take on specific actions and recommendations.

I should say that the other committee of the FDA that has addressed this topic in the past is the Central and Peripheral Nervous System Committee, which was the committee in which antidementia drug guidelines, focusing particularly on drugs to improve cognition, were developed in parallel as some of the cholinesterase inhibitors were evaluated by that committee. Again, different committees have different styles and we appreciate being guests here. That committee actually passed a unanimous motion that the FDA should develop guidelines which, in fact, is the language you used several years ago.

Now, I am not being critical of the FDA for not taking that forward, nor am I suggesting here that we should take votes, nor am I suggesting that guidelines are exactly the appropriate way that we should go forward. I think operational criteria and recognizing what I think we have heard this morning, that psychosis is clearly an area where there is a lot of agreement; depression very close -- we have heard some small minority voices around topics we haven't had time to discuss, like sleep-wake cycles and, clearly, agitation is the messier area. But I do think we

have clearly heard this morning a considerable amount of consensus and I would just like to make sure that we do identify that explicitly as the afternoon's discussions go on.

DR. TAMMINGA: Thank you, Dr. Whitehouse. One of the things that seemed apparent to me this morning is that some of the discussions about the psychiatric and behavioral disturbances associated with dementia really came up around the issue of psychosis and around the issue of the use of antipsychotic drugs in dementia. In fact, the category of psychosis associated with Alzheimer's disease or the entity that you made criteria for, Dilip, may be a model for some of the ways to conceptualize these sub-areas.

So, maybe I would like to ask you, Dr. Jeste, to really reformulate what you talked about this morning and have us listen to you and see to what extent there is agreement amongst the committee and to see on which points people have differences of opinion.

DR. JESTE: Thank you, Carol. The criteria that Sandy and I proposed are modeled after the DSM-IV criteria for schizophrenia, and those are meant for clinical diagnosis. As Tom pointed out, in a clinical trial one will have to first use the clinical criteria and then use some additional criteria for a specific clinical trial.

So, we could talk about the clinical criteria

themselves, although we will have to realize that they are not necessarily criteria for a specific clinical trial. In the criteria, I think the main aspects will be having characteristic symptoms which I think will have to be either delusions or hallucinations with a certain minimum duration, say, of one month; certain severity, that is, to cause functional disruption; and exclusion of other possible causes of psychosis in these patients.

I thought there was some liberality about the chronology, whether the symptoms of dementia should necessarily precede the symptoms of psychosis. The general consensus I thought is that, yes, they should although, as Eric pointed out quite rightly, once we know more about the idiopathology of Alzheimer's and are able to diagnose Alzheimer's even before dementia is manifest, then we may be able to associate earlier developing psychosis with dementia.

I thought one other area where there was some discussion was about the type of hallucinations or delusions. Jeff pointed out that there should probably be specific types of hallucinations/delusions. My feeling is probably it may be better to leave it at that stage right now for a clinical diagnosis and just say delusions/hallucinations and then, depending on the specific clinical trial, one might want to expand that further.

The last point on which there was some discussion, an important point, was functional disruption for whom -- the patient or the caregiver. And, I think we all agree that it has to be functional disruption for the patient. The only question that comes up is whether we make that determination strictly based on the patient report or we take the caregiver report into account. Just as with schizophrenia, if you ask the patients, the patients will say they have no problems even when they are severely agitated, aggressive and so on. So, I think taking into account the caregiver's input is critical. Actually, if you look at both BEHAVE-AD and NPI, they do depend on the caregivers' reports.

So, I think there is large consensus in terms of clinical criteria. We may have to think a little bit about specific clinical trials and what specifications we use for that.

DR. TAMMINGA: Bob?

DR. HAMER: Actually, I would like to back off just one second in a couple of ways. The first thing is that the title of Dr. Laughren's talk was regulatory issues in the development of drug treatments for various psychiatric and behavioral disturbances associated with dementia. But, in fact, the huge bulk of what we talked about this morning was dementias of the Alzheimer's type. I

think that it ought to be clear that, at least in terms of what we have discussed, thus far, we haven't talked about vascular dementias, we haven't talked about Lewy body disease, we haven't talked about Parkinson's disease, and any of the other host of things that can cause dementias. And, from the data we have been presented so far, the scope of our discussion probably ought to be limited to Alzheimer's disease. We have no business whatsoever in generalizing or attempting to persuade the FDA to generalize indications to any dementias beyond that.

DR. TAMMINGA: Dr. Caine?

DR. CAINE: I very much agree and I think that is why it is really important, again, to use the term dementia due to Alzheimer's disease, psychosis due to Alzheimer's disease -- put your money where your data are.

I want to follow up on what Dilip says, and I think that really, clearly, there is a very straightforward process, it seems to me, that can unfold expeditiously. Actually, the coding for the DSM has officially been changed because the National Center for Health Statistics changed the coding on dementia more than a year ago. So, the codes of 294, dementia "due to," is already in place. The .10, .11 won't be in place until this October. In fact, the DMS-IV categories with simple criteria for psychosis due to Alzheimer's disease, mood disorder due to Alzheimer's

disease -- those have been in existence throughout this past decade.

Thus, really the question is not are those diagnostic constructs available but how are they used, and then really I think Dilip has given an example, an illustration of their use of bringing to life, if you would, or bringing to greater degree of specificity. So, in fact, as a number of us have foreseen, sort of getting rid of the subtypes, the simplifying of the rules, is really just the next step. What we would then hope to see fall into place are much more specific criteria sets. This is an excellent model. One should rapidly be able to follow for mood disorder. There certainly would then be, after that, I would hope in the future, things around personality change, anxiety and sleep-wake disruption, all of which have been found to be in elevated prevalence in Alzheimer's disease, some of which, of course, are targets for pharmacotherapeutic intervention but others aren't at this point in time.

Obviously, the field has been driven to a great extent by the needs of industry and the needs of investigators working with industry. But I think that the outlines and the constructs are already in place. This isn't something that has to be legislated and is new. This is really presently available and it is really the question,

to me, today of are the model criteria with some modest modification useful for giving clinical substance or specificity to what is already in the book? Then, beyond that, how would one want to measure in a standardized, reproducible fashion, these syndromes or disorders, however you want to describe it, and are the tools there? I think the answer to that is at least yes for some of them. And, are they acceptable at a level of scientific rigor which would allow for further investigations?

DR. TAMMINGA: Eric, I thought we were having this discussion because what we are talking about isn't in the book yet; that what Dilip is proposing for dementia with Alzheimer's disease and psychosis actually isn't in DSM-III.

DR. CAINE: Well, it is DSM-IV. III was 1980, III-R was 1987. Dilip's criteria or the Jeste-Finkel criteria are not in DSM-IV. What is in DSM-IV is an unpublished change by the National Center for Health Statistics, but in terms of what record rooms do the discarding of the 290.-whatever diagnosis was discarded actually over a year ago, and the 294 base, dementia due to a specified medical problem is the current standard that the United States government applies to diagnosis of dementia.

The diagnosis of mood disorder due to Alzheimer's disease is already in DSM-IV. There is a chapter called Mental Disorders Due to General Medical Problems. The

criteria, as I said this morning, for how do you decide "due to" were modeled on the Bradford-Hill criteria. They are not called criteria. They are really just written guidelines. They are not enumerated but they are really embedded there, and they were modeled on the Bradford-Hill material that was first published in the mid-1960s and then in his textbook in 1971. So, that base work is already done, and this really is, as I view it, just the next logical step, which is to give specificity to what was a rather vague category.

DR. TAMMINGA: Dr. Cummings has some remarks.

DR. CUMMINGS: Just a few responses, one with regard to diagnosis. I don't know why we would need to restrict just to AD. I think the process we are trying to decide on is how does one define a syndrome, operationalize it, use it in a clinical trial for legitimate drug development, and I think that the rules that emerge today could be used for vascular dementia or Alzheimer's disease, or dementia with Lewy bodies as long as the specific dementia was defined in each type. So, I think the process we are engaged in here could be more widely applicable than just to Alzheimer's disease.

DR. HAMER: Could I just respond to that for a second? The response is that, yes, you are absolutely right. What I was trying to say, however, was that if we

decide to do clinical trials of psychosis in Alzheimer's disease we should not attempt to generalize from those clinical trials to psychosis in any of the other dementias.

DR. CUMMINGS: I agree with that completely. Then, in terms of the chronology issue, it seems to me that it would be legitimate to say that if the psychosis appears coincident with the diagnosis of AD or following the diagnosis of AD -- I think the worry here is we can't diagnose a patient who comes in just with psychosis as having AD at this point. Maybe at some future point we will be able to but we can't at this point.

Then, the final worry that I have, and the reason that I was struggling with operationalizing the idea of delusion and hallucination is my continued fear that patients will be misidentified as having delusions when we are really looking at some other process in these patients. We know that trialists are motivated to liberalize the criteria as much as possible, and these will be used in trials even if that is not exactly how we intend them. So, I am still struggling with the idea of operationalization, and I wonder is there any other way to operationalize these criteria more specifically.

DR. TAMMINGA: Could you be more specific about in what kind of ways people could liberalize the current criteria and get down which wrong track?

DR. CUMMINGS: Yes, actually Barry gave a very nice example of a misidentification syndrome in which the patient says, no, this is not my mother, so now she is in a clinical trial, when that misidentification might well be prosopagnosia or a memory defect in which he remembers, let's say, his wife as being twenty years younger than she actually is now. So, that kind of patient I think we are trying to keep out of a trial of antipsychotics who is real open to misinterpretation and inclusion in a trial.

DR. TAMMINGA: But in the example that you used the person wouldn't be having a true delusion. You wouldn't call that a delusion. So, delusions and hallucinations would be still a fair way --

DR. CUMMINGS: Well, I think that some people might call that a delusion, and that is what I am worrying about because it is a belief held in spite of evidence to the contrary and, therefore, sort of meets general criteria for delusions. So, I think it is open to misinterpretation unless we operationalize it more carefully. That is my worry.

DR. TAMMINGA: Dr. Reisberg?

DR. REISBERG: Yes, just to endorse Jeff's points and to expand on the need, the problem is that, of course, a delusion is defined classically as a fixed false belief and in Alzheimer's disease the delusions are not so fixed, in

the schizophrenic sense of the word. Even though they tend to be there when you assess it some months later, they are not always there when you assess them a few hours later. So, I think there is a need to operationalize these kinds of symptoms really with respect to the entity that we are speaking of in terms of entry into clinical trials.

DR. TAMMINGA: Dilip?

DR. JESTE: I agree with that entirely, and I don't think there is any disagreement amongst us. I think we can take the DSM example. What the DSM does -- for example, there are specific criteria for schizophrenia, and then there is a more detailed description of each of the factors. What I think Jeff and Barry are talking about is detailed description along those lines, and I really think we are on the same page there.

DR. SCHNEIDER: I think what Jeff and Barry are talking about are very important heuristic issues in teaching physicians and others how to recognize delusions, how to recognize hallucinations, how to recognize depression, sleep disorder, etc. We should probably move off this though if we have agreement that there is a psychosis associated with Alzheimer's disease. The operationalization is very important when you get to the actual design of clinical trials.

But I suppose I am looking towards the FDA and

what I think the FDA wants to get out of this, and what we may all want to get out of that, and that is labeling. I mean, can we live with the concept of psychosis of Alzheimer's disease or depression of Alzheimer's disease.

Then just one last comment, remember that when you look at the criteria for dementia, whether it is the McCann criteria or the DMS-IV, very similar criteria, all the criteria are saying is that there is memory disorder and there is disorder in a number of other functions. It doesn't go so far as to describe precisely what the memory disorder is, or precisely what the other cortical functions are. It is presenting a concept, and I think we ought to try to do the same.

DR. TARIOT: I wonder if another way to say this is to back up to DSM and the kind of terminology Eric was advocating before. Perhaps if a patient with dementia of the Alzheimer type presented with this belief that somebody who was dead who was actually alive, and that was it, it seems to me that that wouldn't reach syndromal criteria and we would not call that psychosis. We could fuss over whether we wanted to call it a delusion or just cognitive impairment but, because it is not intense enough to interfere with social, occupational or other functioning, we wouldn't use the term psychosis due to Alzheimer's disease; we would just call it one of the symptoms that this demented

person is experiencing. So, it is really a question of whether you think that is a helpful way to conceptualize it, Jeff.

DR. TAMMINGA: Dr. Whitehouse?

DR. WHITEHOUSE: I agree with that. I also agree with Lon. I think going back not only to the issue of misidentification and that being a matter of either further specification for a particular trial or just training people to make sure they are aware of the difference between misidentification, hallucination -- all the things that Dilip so nicely summarized when you asked him to start -- the issue of whether we ask caregivers, the issue of the temporal relationships. I don't think there is much disagreement in this group on any of the number of issues that were identified as areas to consider and to operationalize further but basically going back to Lon's point that agreement exists that psychosis and dementia is a problem and is an appropriate target for therapy.

DR. CAINE: I think there are a couple of points. I want to underscore, obviously, what Pierre said, which is that inherent to the DSM is the notion that this is a disorder which rises to a threshold of social, occupational or other interference of function. So, there is a threshold requirement in every psychiatric diagnosis, and that is what separates something like this from a symptom rating scale.

Jeff and I used to do stuff on Tourette syndrome and I would write about the difference between obsessive-compulsive symptoms in Tourette and obsessive-compulsive disorder, the two being quite distinctive in the sense that one is functionally impairing and the other isn't. So, it is very clear that very much the thrust of getting rid of delusions or hallucinations with depression sub-codes is part of the confusion. Some people put it in when it wasn't functionally significant; other people put it in when it was functionally significant. It is very clear that text is often used as a clarifier and certainly that is a common thing to do.

I think the issue of something like misidentifications is really a studiable point, and I think the way to handle it is not to say you include it or exclude it arbitrarily but say, hey, we will either choose to include or choose to exclude people who have substantial misidentification, look at that quality, understand how it responds to medication. Many of these people are profoundly distressed. We would say, to use an old language, that their degree of distress and dysfunction rose to the level of a psychotic disorder, in the old sense that psychotic meant severe, and was severely disruptive.

But, quite frankly, you may be right that those are different and they may respond less well to medication.

So, trialists may, in fact, want to exclude some of those folks, not necessarily include some of those folks. But, in any case, I think that is really a dotting an "i" or crossing a "t" phenomenon. The fundamental concept is does psychosis exist, yes/no, and then do you want to include in this particular trial someone who has characterized by misidentifications? That can be a yes/no too and can be just an inclusion or exclusion criterion.

DR. TAMMINGA: Dr. Cohen-Mansfeld?

DR. COHEN-MANSFELD: I realize that nearly everybody used the term psychotic today, so it is somewhat out of line to go from a different point of view but I would like to suggest that most of the delusions that we see are, in fact, misinterpretations of reality accompanied by emotional and behavioral disturbances. Now, whether that can change the term or not, I don't know. Whether it makes a difference in terms of drug studies is also another question. This is a question to the panel in general.

I think other categories to consider when that final definition is made are issues -- for example, in hallucinations there are a number of studies that all show that severe visual impairments are associated with visual hallucinations. Are these included or is this an exclusion? Similarly, there are issues with reality, especially when you speak with these people, some of whom verge between

communicating and not communicating. Like theft -- I spoke about that. There is a lot of theft, say, in nursing homes that seems to occur and those are reality issues that need to be taken into account when making this definition.

DR. CAINE: Actually, I think Dr. Cohen-Mansfeld has just made a very eloquent argument for why psychosis in Alzheimer's disease is different from schizophrenia. So, rather than view this as a problem -- the word delusion is an umbrella word. I mean, there are many types of delusions in psychopathology. So, I think you have just made a very, very convincing case that in describing these people they don't have idiopathic schizophrenia; they have Alzheimer's disease which is causing this kind of -- I would use the word psychotic disorder but I understand that the quality of the psychotic disorder is not identical to the people who have idiopathic disease. So, I think that really we are almost into semantics now, but I think your point is well taken but I don't think it is really in contradiction to the other points. I think we are just using words slightly differently.

DR. TAMMINGA: Dr. Reisberg?

DR. REISBERG: I do agree that certainly there are environmental influences on what we will call the psychosis of AD, and those environmental influences would include the physiologic environment as well as the social environment.

So, for example, a patient who is isolated and living alone is more likely to show paranoid symptomatology. I think that there are environmental influences in all mental disorders. Certainly, somebody who has just lost a loved one is more susceptible to depression, as all of us know. Also, the psychosis of schizophrenia is very, very susceptible to environmental influences. I was describing earlier that where I trained, at Metropolitan Hospital, patients were very violent with the psychosis of schizophrenia. When I visited acute care settings in New Delhi where the family members lived with the patients and there was not this, if you will, culture of violence I didn't see this at all, even with low doses of medication. So, I think that these issues are not really foreign to other mental illnesses, just as they are not foreign to this one.

DR. TAMMINGA: Dr. Cummings?

DR. CUMMINGS: If it is possible to hear from Tom or Russ about whether or not they are satisfied with the consensus about psychosis in AD, then we could move on to something else if they think that they have heard enough here.

DR. LAUGHREN: In terms of what would go into labeling, it is always difficult for us to try and figure out how much information, including a definition or

description of a diagnostic entity, to put into labeling. Usually the rule that we try and use is the importance of the information. If a particular distinction is felt to be clinically important, for example if it were important to distinguish between certain kinds of delusions or hallucinations from a clinical perspective, we would be more inclined to include that; if not, we would not. So, there is no clear-cut answer to that.

The question again, from our standpoint is, is there enough agreement that there is such a thing as psychosis in Alzheimer's disease that makes it stand alone from other psychotic disorders to justify studying it as an entity. That is really the issue from our standpoint.

DR. TAMMINGA: We haven't heard either from Dr. Lebowitz or Dr. Grundman, if you would like to contribute.

DR. LEBOWITZ: Sure. My contribution is really very straightforward, and that is going back to Tom Laughren's introduction remarks, transition to more specific indications, which is the policy direction for the agency, doesn't necessarily mean different or higher standards of proof. It means only what it says, which is more specific indications.

I think much of the discussion in the last few minutes has been just how much higher the bar needs to be in terms of specificity, and it seems to me to be exactly of

the sort that now Tom Laughren has just clarified for us, which is a distinction doesn't make a difference unless it makes a difference, to quote our statistician friend who probably would have said it because statisticians have always said that better than I just have. So, it sounds like we are exactly on the right track here.

DR. TAMMINGA: Dr. Grundman?

DR. GRUNDMAN: I would agree. I think, you know, it has been pointed out before that psychotic symptoms are present in about 20 percent of individuals and maybe up to 50 percent over the course of the disease. If these are interfering with people's function and assessment of reality, and interfering with their ability to function at home, I think we should put this forward as a target for treatment.

DR. TAMMINGA: Dr. Winokur?

DR. WINOKUR: I have a comment and a question which several people might respond to, and this is from the perspective of someone who really doesn't work in this area. It really does sound like the psychosis of AD has some potential to meet a lot of the criteria that Dr. Laughren had laid out this morning, and sounds important and of interest. I think the issue of the extent to which this psychosis is different than others, particularly in schizophrenia, and even the comment that Dr. Cummings made

about the different neural environment is very fascinating.

Something that I heard from data from several people, Dr. Martinez, Dr. Sano, and I think a couple of others which surprised me from my different clinical experience is the number of people with persistent psychotic symptoms who are not getting treatment. I was wondering whether that related more to Dr. Caine's comment about the symptoms also being functionally important, or is that going to present some either operational or interpretation challenges in terms of treatment studies? In other words, why are people who are apparently having distinct and readily identifiable persistent symptoms at this point not being treated?

In Dr. Martinez' trial that he reviewed it was a different point. What interested me there was that people were on placebo trials for five or six months with persistent psychotic symptoms, whereas in other studies that I have been involved with that might have been problematic. So, as someone not familiar, I would be interested in some thoughts about what that is about.

DR. SCHNEIDER: The very quick answer to that is that these were clinical trials of cholinesterase inhibitors. So, the goal was to keep patients on the placebo or the cholinesterase inhibitors as long as possible and, perhaps understandably, try not to treat other things

to affect the validity of the study. Similarly, in the nursing home part of the Janssen presentation there was randomization to risperidone or placebo and the goal was to try to maintain even the placebo patients for twelve weeks. In the Sano group of studies, these were patients who didn't obviously have behavioral problems. In part though, the type of setting -- academic, largely neurological Alzheimer geriatric centers -- perhaps was not quite as sensitive to some of the behavioral problems as we might ordinarily be if we were operating in a psychiatric clinic.

DR. WINOKUR: Just to follow up, the scientific rationale for trying to keep the integrity of the study going is queer in the context of studies that I have primarily been involved in. For a variety of reasons that would not have been possible for that period of time as in the case here.

DR. TARIOT: I would say it slightly differently. I think if those patients met syndromal criteria for psychosis they would have been treated. But, again, that is this difference between signs and symptoms that may not reach a certain threshold and those that do. Carol, you said, you know, what are we having a discussion about, I think that is a key cleavage line. If we accept the notion that a certain threshold is necessary, it is a very clarifying concept but one that the field hadn't been using

-- hadn't even been using this terminology until fairly recently even though it is already in the textbooks.

DR. TAMMINGA: This is a threshold for diagnosis and for treatment, or just a threshold, once the diagnosis has been made, for treatment?

DR. TARIOT: I would say for both.

DR. WHITEHOUSE: Just to elaborate on that, I think in the field there is a threshold for treatment which is different than diagnosis, and the traditional teaching is that if somebody is developing these symptoms you do try behavioral or non-pharmacological approaches to treating the different behavioral disturbances, and I think it gets to the topic that Carol mentioned, that we need to be sure to address, which is the interest in developing policies about risk for therapy. So, because there is this perception that the non-pharmacological treatments may be better for milder patients and less harmful, these patients will probably be treated that way in part.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: Yes, I would like to raise an issue about one specific criterion of the syndrome of psychosis in Alzheimer's disease that has been alluded to but hasn't really been discussed in great detail yet, and I think it is a very important one. Dr. Cummings, in his remarks, suggested that he would make some modifications to the Jeste

and Finkel criteria along the lines that the symptoms have to be distressing to the patient, and other people have talked about it has to interfere with the patient's functioning, or words along those lines.

But, these are patients obviously who, in many cases, are incapable of articulating any particular distress or exactly what they mean when they are engaging in a particular behavior, and they engage in a whole host of behaviors that certainly have the potential to be unpleasant, disruptive to others, however you want to characterize it, but which may not be causing them any particular distress. So, I would like to hear people talk about how they know or how we know with any degree of certainty that a particular behavior that a patient is engaging in that is obnoxious or uncomfortable for others is, in fact, distressing to them because I think that is an important point to get at.

DR. JESTE: Just one quick point, this situation is not really unique to psychosis of Alzheimer's. It is very common in people with schizophrenia. We can interview a person with schizophrenia who has obvious psychotic symptoms and is severely sick and the patient says he is fine; he has no problems and, yet, the caregivers talk about all the disruption that the patient is causing and also how poor the quality of the patient's life is. So, what you

raised is a very good point but all I am saying is that it also applies to schizophrenia.

DR. REISBERG: I think if we add to the word distressing "dangerous" or, perhaps in parentheses, dangerous or harmful to the patient it is a true way out of this dilemma. So, for example, if a patient is staying up all night and not sleeping, at a certain point that can be judged as dangerous or harmful to the patient. If a patient is constantly asking the spouse -- I mean, not only to mention the psychotic symptoms -- the same question over and over again, and again, and the spouse says I can't take it anymore; I can't live with them; I am leaving, then at a certain point, if the spouse leaves, that becomes a very dangerous situation for the patient. When the spouse says I can't take it anymore; I am going to put them away, then that becomes a deleterious situation for the patient. I think we can go on and on in that light, but I think we need to recognize that if a patient is asking their roommate in the nursing home the same question over and over again and the roommate is responding by hitting the patient, then even though that is not necessarily directly distressing for the patient, it is potentially dangerous and harmful for the patient. I think if we look at it in that broader light, it is a way out of this.

DR. KATZ: You know, that is a part of what

concerns me. I think if we said it has to be limited to patients who are dangerous to themselves or others, in a common sense understanding we could all agree with that. But as you described, which is sort of my concern, you can probably take any of these behaviors and ultimately define them as being dangerous. I mean, if a patient is in a nursing home and they get fed at noon because that is the schedule but they are not hungry and they run into their room screaming because they don't want to eat, ultimately that is going to become dangerous because they are not going to eat, as you suggest, over time and the nursing home is not going to change their schedule; it is unwieldy and it is undoable. So, that behavior becomes, by definition, dangerous to the patient. I think you can define any behavior ultimately that is disruptive or unpleasant to others as dangerous to the patient. If there can be agreement on a definition of a syndrome in psychosis and dementia that drugs get approved for, what concerns me very much is how would you write labeling to prevent the inappropriate drugging, if you will, of patients who really are not distressed and are not really causing any direct physical threat to others?

DR. CAINE: You are touching on one of the core problems of making a diagnosis in somebody where you don't have a defined disease state. Now, I want to step back for

a couple of minutes because it is very clear that using subjective distress is a faulty criterion -- no offense, Jeff. So, for example, in someone who has major depression who is in great pain and psychological distress and finally decides that he is going to kill himself and his stress goes down, and he feels peace of mind and he looks calm, and then in the next 48 hours he kills himself, we wouldn't necessarily want to use distress as a good indicator that he needs help in that 48-hour interval. That is an absurd example but it is actually true in life and we see it.

Let me back up though, if someone had a well-defined genetic disorder that was already expressing its genetic abnormality at a molecular level but had no clear symptoms as yet, but we had a treatment for that genetic abnormality and the patient had no distress and no manifestation whatsoever, we would treat that person if we knew that this was going to unfold into a deleterious process. So, in making a diagnosis we really talk about two things. One is the disease state which has some deleterious process, if we can define it. The other is, when we can't, we try to define some threshold of dysfunction. DSM used social and occupational and personal function as the criterion. The Europeans use the concept of handicap which they see as interference in life and that kind of thing.

Those are purposefully not defined as being either

defined by the individual or the social surround, but really being subject to the sound judgment of clinicians in terms of how to best capture the handicap or the dysfunction. Obviously, in the dementia-land there are all the issues of misuse of chemical restrains and that sort of thing. Clearly, one wouldn't want to advocate that, but one wouldn't want to go to the opposite direction of taking someone who has no insight into his or her situation and using that either.

So, when we try to struggle around these diagnostic constructs we are using the notions of handicap or functional disruption with the notion that this is a disease state that is potentially remediable or worthy of treatment. So, it is an imperfect solution until the day that we have the genetic tests and treat the fundamental biologic abnormality.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: Well, I think there are some distinctions here between some of the scenarios you give as examples. If we had a genetic test for a condition which hadn't become symptomatic yet, the person, in general, would be able to say, okay, I know that information now; I want to take treatment for it or I don't want to take treatment for it. Patients with Alzheimer's disease who are already impaired, their functioning is impaired -- we have

treatments for Alzheimer's disease, good or bad, for the disease itself. We are now talking about ancillary symptoms which are, I recognize, part of the condition. I mean, the view is that it is part of the condition. But I still have concerns that there are going to be people who are going to be engaging in behaviors that are unpleasant and I don't know how we know that they are distressing to the patient. I guess that is what I am saying. I think people interpret certain behaviors of patients who can't tell you what they mean. I would like to know how we know what we know, if you will -- how we know that those interpretations are correct and we are not just treating the environment, if you will.

DR. CAINE: Let me come back to a couple of things that you said. I know Dr. Cohen-Mansfeld wants to chime in on this as well. I disagree with what you said a moment ago. We are not treating Alzheimer's disease. We have symptomatic treatments for dementia which is a manifestation of Alzheimer's disease. The question now is will we develop symptomatic treatments of other manifestations of Alzheimer's disease, and are those, like dementia, disruptive and impairing of function? Are they such that, if they were treated, someone would be able to function more effectively, more optimally in their environment?

The question you are bringing up is how do we avoid abuse, and abuse of treatment, to me, is not so much

the question of is the drug effective or not effective, is it used on target or not on target but, rather, what are the quality assurance mechanisms that we have for the appropriate use of medications once they have been developed for specific indications? That is somewhat different. I don't understand the scope of your agency, not exactly, but I know that in the department that I run and in the part of the hospital that I run, it isn't a question of do the drugs have a specific indication or not; it is what are the quality assurance, peer review and other utilization processes that we have to make sure that they are adequately and appropriately prescribed?

DR. TAMMINGA: Dr. Cohen-Mansfeld?

DR. COHEN-MANSFELD: I think that some of your comments have to do with the fact that both the occurrence of the behaviors and their definition has to do with the interplay between an environment and person which you spoke to. Although I agree with you, Peter, that behavioral approaches, change in the environment and improving the environment first is what we pay lip service to, and what is in the regulation, in fact it is not reimbursed, unlike medications, and most of the time it is not done and, therefore, I disagree with your word "abuse" here because I think there is too much of a grey area to let it loose. Even without the intention of abuse because of all the

restrictions on the system, it is easy to apply those diagnoses where probably they should not be applied. I think it is a real concern.

DR. REISBERG: I think a full answer to the concerns which Dr. Katz and others are properly expressing, that is to say the chemical straightjacket and how do we avoid abuse, really requires the risk of jumping ahead but I did allude to this to some extent in my talk, and that is that I think when we examine these kinds of medications we really need to very carefully look not only at BPSD disturbances and the psychosis per se, but also to look at separately, in terms of covarying and in terms of issues of side effects and issues of risk, the effects of substances on cognition and also the effects of substances on functioning.

DR. TAMMINGA: Dr. Cummings?

DR. CUMMINGS: I think also we have shifted here a little bit from thinking about psychosis to the problem of agitation, and I think you can tell when a psychotic patient is upset by the delusion or hallucination because they are fearful, they are really upset that this person is there. I don't think that there is nearly as much of a clinical issue surrounding the distress of the patient who is specifically psychotic versus this much more ill-defined entity of agitation. So, I think we could come to consensus on

distress associated with psychosis as long as we stay with that particular syndrome.

DR. KATZ: I would just like to know if there is general agreement about that, and are there some sorts of psychotic episodes that it can reliably be told ar a manifestation of distress or upset worthy of treatment, or are some delusions acceptable? I mean, if a patient is just walking around, talking to someone who isn't there, is that worthy of treatment? I am concerned about ultimately, as I say, if a syndrome is defined and felt to be appropriate for drug development how you would label it. How you would tell people these sorts of things are okay to treat, these sorts of things are not okay to treat? And, I don't know if it is a question of abuse or a question of the grey areas, but I think there is large room here for lots of people to get treatment who maybe don't need treatment. I would just like to know what the sense of the group is about these things.

DR. TAMMINGA: Dr. Laughren, do you want to continue?

DR. LAUGHREN: Just to follow up on that, again getting very specific, if you look at the criteria that have been proposed by Drs. Jeste and Finkel and then by Dr. Cummings, your criteria, Jeff, make it clear that it has to be a disruption of the patient's functioning or being

distressing to the patient. The other criteria say either/or. If there is agreement that psychotic symptoms in a patient can be detected as being distressing to a patient, could the group agree with that as a diagnostic element rather than this broader sweep, or not?

DR. TAMMINGA: Dr. Caine?

DR. CAINE: Well, two perspectives. Let me address what Dr. Laughren just brought up. Some of us would have disagreed with the Jeste-Finkel criteria in the sense of caregiver distress being a target for treatment of the patient. That is certainly a consideration when you start to evaluate a psychosocial situation but often treating the caregiver isn't done -- I mean, that is like the old joke of giving the medication for the nursing staff. That is not an appropriate use; it is not an appropriate indication. So, in that sense I would agree with Jeff but I wouldn't use the word subjective distress; I would use the word impairment of function in the patient.

The issue of environmental interaction with psychiatric symptoms, of course, has no limit on Alzheimer's disease. This is really across the board in all of psychiatry, whether it is schizophrenia, depression, bipolar disorder. I mean, forty of fifty years ago at the beginning of empirical research in the 1960s it was very clear that mild manic symptoms would get someone hospitalized much