faster than moderate to severe depressive symptoms because they were more disruptive to the family rather than the individual.

So, really what you are bringing up is an old problem, not a new problem, and just saying how do you deal with it in this situation. I think the best way to handle it is to define the patient's functional interference from the disorder that is there and, if it is treatable, then you treat it. If the family member is having a problem, that is something that you would work with the family member on but it is then part of a psychosocial environmental patient interaction.

DR. TAMMINGA: Dr. Whitehouse?

DR. WHITEHOUSE: It is a difficult issue. It is not unique to this particular circumstance obviously. I think there clearly are circumstances in which I, anyway, would view in the diad that the symptoms are not distressful to the patient and not particularly distressful to the caregiver even though they have psychotic features. So, that would not exceed my threshold and it wouldn't be a conflict because both parties would agree. In circumstances where it is distressful to both and that would exceed a threshold, you treat.

The circumstance we are talking about is when it appears to be distressful to the caregiver but you are not

sure whether it is distressful to the patient or not. I think that is relatively -- relatively rare. Obviously, there is an element of clinical judgment just because when the patient is distressed by his or her own symptoms that converts into behaviors that tend to make it more likely that it also distresses the caregiver.

DR. KATZ: I guess I would really just like to know how we know that. One can easily imagine any number of scenarios where the patient's behavior appears to all the world to represent some internal distress but, in fact, is just a response to what is happening. You know, they are screaming because they don't want to be given a bath or a shower. They are not upset about the screaming; they perhaps are upset about the fact that somebody wants to give them a shower when they don't want to take one. One would assume that the response of the caregiver or the observer would be that this is a representation of some internal distress. And, I would just like to know how we know that the behaviors that we interpret as being a manifestation of some internal state are, in fact, that.

DR. WHITEHOUSE: I guess it does depend on the stage of disease we are talking about because, I mean, we have been talking about mild to moderate patients where, frankly, you can ask them and you will get your sense clinically from just interviewing the individual. In

situations where it is a person who is less verbal, there are actually specific distress scales which you can use looking for non-verbal manifestations of distress, and some of those have recently been well studied.

But, I guess I have two discomfort levels. One, I agree with Jeff, we are moving more to this more difficult area of agitation because we are trying to do it in the context of diagnosing psychosis and then saying whether you have this difference between the caregiver and the patient as to whether you want to treat or not. So, my own feeling is that through any means a clinician has -- conversation and/or non-verbal communication -- there are ways of establishing with a reasonable degree of certainty that somebody is distressed.

Now, the issue you are raising is a different one. Having identified somebody is distressed, in the practical realities of nursing homes they may not spend the time to identify that that person is distressed because they stood on a nail in the shower rather than it being part of a more general drug appropriate therapy. So, clearly, environmental precipitants need to be addressed, whether they are or not in all circumstances is kind of another issue.

DR. TAMMINGA: Dr. Grundman?

DR. GRUNDMAN: I think we have to accept that

psychosis and the distress that it causes to the patient and to the family are real and prevalent, otherwise we wouldn't be here right now having this meeting and discussing it. I think the other question though about how to treat it is an empirical one, and I think once having defined a syndrome that we think is problematic we can then use different approaches, pharmacologic and non-pharmacologic, to treat that syndrome and see, using a variety of assessment scales, both from the patient's perspective, the clinician's perspective and the caregiver's perspective, which treatment is most effective at treating that syndrome.

DR. TAMMINGA: I think Dr. Jeste was next.

DR. JESTE: In psychiatry, as we know, most of the diagnoses as far as treatment decisions are based on the information we get from the patient, from the caregiver, the patient's clinician and the charts and then the clinician makes his judgment, not from any single source. I think to the same extent it will have to be the clinician's decision whether the condition is causing functional disruption for the patient. If the patient says that it is not causing functional disruption and yet it is clear that the patient is pulling out his IV and is suffering because of that I think the patient would need to be treated. So, the point is that we need to get information from multiple sources and expect that the clinician will make the right decision.

DR. TAMMINGA: Dr. Tariot?

DR. TARIOT: Well, at the risk of repeating what other people have said, in the scenario you described, Dr. Katz, of a nursing home resident with dementia who didn't want to be fed at noon and got upset over this happening on a recurrent basis and demonstrated this with psychomotor agitation of some kind, I didn't hear anything about a psychotic syndrome. I heard about a dementia syndrome with some motor and verbal manifestations. So, I would say that person hasn't met syndrome criteria for anything so far, other than dementia. But if you told me that the person had the delusion that he was being poisoned at noon and that it was associated with all these other behaviors that in the aggregate, using the kinds of principles that Dilip just went over, I judged were functionally impairing, then I would say there was a dementia syndrome and a syndrome of psychosis that meets syndrome or criteria that exceeds this threshold.

DR. TAMMINGA: Dr. Caine?

DR. CAINE: Yes, I think that Pierre has really hit it. The other issue is that no other part of medicine has ever used distress as its entry criteria for finding a diagnosis. What we have talked about is impairment. Impairment can be objectively defined as well as subjectively defined. Distress can only be subjectively

defined. I think it is very clear that you can go to a great number of Alzheimer patients and elicit whether they are distressed. The point has been well made. I mean, these are not mute people, by and large, until they are very far into the disease process. So, I think that we are sort of going down the wrong path in the sense of saying is there a decision that can be made on the basis of impairment. Yes, it is an all-sources data collection process and it can be done in a standardized fashion where people can be held accountable.

DR. TAMMINGA: Dr. Laughren?

DR. LAUGHREN: Just one last question on this, I don't think it makes any difference so much where the information comes from. It is true that functional impairment is part of a lot of diagnostic criteria in psychiatry. What seems unusual to me is this is the first time I have seen functional impairment of the caregiver -- wait a minute, let me finish -- as being sufficient to meet the criterion. I mean, this is what this says; it says patient or other's functioning. So, you could meet all the syndromal requirements for psychosis of AD and you could meet D only if the caregiver's level of functioning was impaired.

DR. CAINE: Yes, that is a proposal on the floor that some of us would definitely not accept.

DR. TAMMINGA: I haven't heard general agreement amongst the whole group on that point, and maybe Dilip wants to respond to that.

DR. JESTE: These criteria were not proposed as criteria for treatment, definitely not criteria for treatment. So, there is a difference.

DR. CAINE: Let's put it this way, and I can say this as a guardian of the gate, this would never make it into the DSM as it was published because it, in some ways, just doesn't fit sort of criteria-land. It would be revolutionary in a way that I don't think is acceptable to put in the distress of the caregiver as meaning that there is enough stuff around -- I mean, my wife would be medicating me on multiple occasions --

[Laughter]

-- if this was a criterion. Since I am not going to let that happen, I think we ought to sort of, you know, dispense with that one real quick.

DR. TARIOT: Not to mention your faculty.

DR. CAINE: No, they would be murdering me on multiple occasions.

DR. TAMMINGA: Let's hear from Dr. Banister.

DR. BANISTER: I guess one of the comments that I have, particularly when we are talking about the nursing home patients, is that most of the physicians that would be

prescribing this medication are not psychiatrists. So, I am just wondering in terms of their level of skill, when we are talking about psychiatrists having many, many years of experience with this, primary physicians may not have that specificity or that level of skill.

DR. CAINE: Let me put this sort of from the diagnostic point of view, a number of us have been interested in seeing this evolve over the past decade because most of the people who prescribe now do it with no sense of specificity and often barely see the patient. So, the more that we can push the field towards specificity, towards trials, towards empirical science as opposed to snow the whole room, the better we are. So, we view this as an effort to deal just with that problem. I think there is less risk, in fact, and more likely to do good the further we drive this towards criteria and studies than where we are now because, you know, people do off-label stuff all the time.

DR. TAMMINGA: Dr. Cummings?

DR. CUMMINGS: One way to be helpful might be to add another exclusion criterion. That is, we already have exclusion where the patient is in a delirium. Perhaps we can add an exclusion along the lines of not directly attributable to environmental provocation. That would then require that the clinician ask this question before

prescribing the medication. That might be a helpful way.

DR. TAMMINGA: Dilip?

DR. JESTE: Also, I think in order to bring this discussion to a close, I will say that I agree with you that for FDA purposes we can drop functional disruption of the caregiver as a criterion. I mean, if that makes it easier, we could do that.

DR. LAUGHREN: From my standpoint it does because we would be setting a precedent that I think would be very hard to live with.

DR. TAMMINGA: Furthermore, there is not general agreement around that particular phrase. So, it would be a proposal that was originally made that wouldn't achieve much in the way of consensus.

DR. SCHNEIDER: It seems, Drs. Katz and Laughren, that many of the questions that you are asking you actually have control of when you are reviewing protocols, and when you notice a protocol that purports to take in patients with psychosis associated with Alzheimer's disease but uses rather loose criteria or does not rule out criteria for concurrent medical illness for some of the agitation being caused by that; does not rule out criteria for cataracts possibly being associated with hallucinations, and, by framing and reviewing the protocols you are also, in essence, working with the sponsor to frame, review and

propose the likely labeling which would be fairly specific on how the study was done, and who the patients were who were chosen, and hopefully that would guide the general practitioner who is prescribing medications.

DR. KATZ: Well, I guess I would agree with you that distress is clearly a subjective thing that is very difficult, perhaps even in the best of cases, for an observer to assess. So, if you look at functional impairment, I still sort of have questions about how we know that we can assess reliably some functional impairment resulting specifically from the particular psychotic behavior in this patient population, at least in a large part of this patient population. Is that something you want to give guidance to people on? That sort of thing.

DR. CAINE: I think it is clear that you have a decade's worth of research, whether it is Barry's research, or Jeff's research, or research from Pierre and Lon, where people have looked at this in a fairly systematic fashion. They have looked at the interference of psychotic symptoms, although they didn't label them this way, and were able to define functional impairment that in a rigorous and standardized fashion they saw as related to these manifestations.

DR. TAMMINGA: Dr. Grundman?

DR. GRUNDMAN: Again, I think it is an empirical

question. If we accept the syndrome and we try to treat it, we can throw in activities of daily living scale into a clinical trial that we design and see whether or not it improves with treatment.

DR. COHEN-MANSFELD: I think that we have shown lots of correlations between psychotic symptoms and stage of ADL functioning, etc. But I don't think that we have shown the causality in having a specific delusion and that impairing. I am not saying it never does. I could think of scenarios where it does and where the environment determines whether it does or doesn't.

DR. CAINE: I think it is important that we not create a new standard of excellence in Alzheimer's disease that doesn't exist for schizophrenia or major depression. There has been no data that I would know of which shows causality between a delusion and the functional impairment because that is not how we have studied it. So, we accept the relationship at face validity. But to suddenly say that we have to show this in a world where we haven't done this with a lot of other disorders I think would be putting a hurdle there which hasn't existed before.

DR. WHITEHOUSE: I think it is a little different in Alzheimer's disease because I agree that, you know, just correlating at a scale level function and psychiatric symptomatology doesn't get you the full answer because the

demented people have another reason to have functional disability, i.e., their dementia. So, it seems to me, having made that point, that there are clear examples of where a particular belief, whether it be the poisoning or whether it be people outside the house are out to get you, it is clear that those individual delusions relate to behaviors that the patient then exhibits and, it seems to me, fairly reasonably links the functional disability to that particular psychotic symptom. But it is more of a one-to-one kind of situation, not one that you would pick up by studying it at the level of the scale comparison.

DR. TAMMINGA: Dr. Tariot?

DR. TARIOT: If I could just extend what Eric was talking about, I mean, we have experts here on affective disorders and schizophrenia. I mean, what are the standards there for establishing DSM syndromal criteria? What is the threshold for saying that somebody with schizophrenia has psychosis severe enough that it interferes with functioning?

DR. TAMMINGA: Well, I was trying to think about that while this discussion was going on, and in schizophrenia, anyway, when there is psychosis first of all you ask the question is there psychosis and the answer to that is yes or no. Even the very mildest psychosis, even if you detected very mild delusions or very mild thought disorder, you could answer yes. Then, the second question

is whether or not you decide to treat it, and that is a treatment threshold question. And, it sounds like a lot of what we are discussing here is a threshold question and perhaps in dementia, just like you said, Peter, it is really much more difficult to decide where the threshold is. If you are treating psychosis it is hard to differentiate whether the functional disability comes from the dementia or the psychosis. I am not sure if that is true, Pierre. You may wish to comment.

DR. TARIOT: Well, I guess part of my response would be that, but certainly many of those same variables come into play for schizophrenia or, indeed, affective disorders. There is cognitive impairment. There are relationship issues, environment issues, and so on and so forth. So, this is really a generic problem, not unique to psychosis in Alzheimer's disease. That would be my assertion.

DR. TAMMINGA: I would think that would be true. And, in any case, you would tend to treat rather than not treat if something productive happened.

DR. SCHNEIDER: Carol, I think the similar threshold issue exists both in schizophrenia and in psychosis of Alzheimer's disease at least in regard to implementing any of a number of treatments. Cost Lyketsos' data that he showed earlier on -- he kind of showed that

threshold by taking people who scored in Utah on either a 1, or I believe it was a 3 or 4 level on the NPI. If you put words onto that, a 1 level is mild but not particularly distressing, essentially there; whereas a level of 3 or 4 is moderately distressing and it is clearly of clinical significance. I think you saw the continuum of scoring 1, 2 and I think 4.

DR. TAMMINGA: Dr. Caine?

DR. CAINE: I think actually Dr. Katz has raised a really important issue, but I guess maybe I would come back to what Dr. Grundman was saying. Clearly, what you are also defining is how you are going to tell about these drugs in the long run, and one of the things that I would think, from a regulatory point of view, is that were one to be studied and treated and come in and say, gee, I have a drug that works, not only are they going to show a symptomatic improvement in the target symptoms of psychosis but they are also going to show functional improvement. This is certainly what we do in antidepressant studies, and this is certainly what we do in any psychotic studies, whether it is a clinical global rating, a GAFF score or the like, someone has to show that they are functioning in life better. Certainly as a clinician, you know, someone may be less psychotic but if they are no more functional and you can't discharge them from the hospital you haven't really done

them much good.

DR. KATZ: Well, that does raise a question about what is the best way to measure or what ought to be the standards for trial design or outcome measures. For example, for cognitive treatments for Alzheimer's you know the standard is an effect on some cognitive task, the core symptom, so-called, but also an effect on the global which, at least theoretically, was supposed to ensure that the cognitive effect meant something clinically useful. But this sort of double outcome or two primary outcome measures, whatever you want you call it, as a standard is unusual. Ordinarily we pick a scale that measures some symptoms and that is it. I mean, it would be useful if we do sort of reify this diagnosis of psychosis and dementia, to know how the group felt about what ought to be the way to assess it in a trial.

DR. TAMMINGA: So, you are suggesting that you would like some feedback about not only how to make the diagnosis of the syndrome but, once you have made that diagnosis and once you have entered into a clinical trial design what scales you would do, where you would set the threshold, and what you would look at as outcome measure.

DR. KATZ: Well, I am not particularly interested -- well, I am interested to hear what the group says, but I wouldn't necessarily want to come down as endorsing a

particular scale or a particular outcome measure. But, in principle, what are the sorts of spheres of behavior that people think ought to be included in a valid trial in this condition, and if it would be this sort of double outcome, that would be very interesting to hear.

DR. TAMMINGA: Dr. Whitehouse?

DR. WHITEHOUSE: Well, you said if we have reified. It sounds like we may be doing that, or maybe have done it or tried to do it, but I guess I would answer the question yes. To call it a double standard seems to be the wrong word but it is in part what we were talking about before, that you can have psychotic features and you can have a treatment for it but you want to make sure that you have had an impact on something that is clinically meaningful. I think we were talking about function, and I think there are differences about how people view activities of daily living as a measure of clinical meaningfulness, but certainly you could look at clinical globals, as has been looked at. You could look at activities of daily living. You could also potentially look at quality of life measures, which is an ill-developed area but one that is rapidly evolving. That would be another way I think you could legitimately consider that a drug has not only improved the symptoms but also improved somebody's life.

DR. TARIOT: But, just for argument's sake, I

thought the proposal you made for assessing significance of change in a behavior rating scale makes great good sense. It does parallel what happens with the typical antidementia trial. What is the clinical relevance of a change in a score on a cognitive test? Well, that is assessed at least in part by the clinician's clinical global impression of change. It seems to me there is a useful parallel that could be discussed for rating scales for psychopathology. Is it relevant? Well, that would be assessed in part by the clinical global impression.

DR. TAMMINGA: Dr. Caine?

DR. CAINE: You are also bringing up the notion of dual reading or looking at function as some summative process. It is also one that you really confront whenever you start to look at psychopathology that exists in the context of systemic diseases.

The point was brought up this morning -- to get away from psychosis for a minute, how are you going to study mood disorders, and you get something like lack of energy, lack of initiative, apathy, disinterest. Is that an inherent part of the "dementia" or is it an inherent part of the "depression"? And, people will debate that but, in fact, some of us have taken the approach of saying we don't know because we can't infer what is going on in the brain and which system is affected. We will study it but then we

will not only look at how that responds to an intervention such as, say, an antidepressant in that case, but also how does an overall functioning rating improve; how does someone's behavior change, and the like, not trying to make the split a priori about what is in someone's head because you were asking about that earlier, but rather, saying this is a potential target and we are going to monitor it and see it how it comes.

So, I think the more "impure" the system or the disease process or syndrome or condition that you are looking at, where you are really trying to look at psychopathology and medical pathology and brain pathology and every other kind of level of analysis you want to look at, the more careful you have to be about this and open and frank about the shortcomings of some of the things, and then try to compensate. So, using a dual scale system in some sense is trying to compensate for what we don't know.

DR. COHEN-MANSFELD: Well, I basically agree but I think that what you call for is a very thoughtful process in terms of developing this double outcome because, for example, if someone has a hallucination of the caregiver as an impostor and they, therefore, attack them and if you have a drug that stops this behavior the caregiver is probably going to have a global rating of improvement because there are no more attacks. However, if at the same time all

behavior is reduced and, therefore, they don't go to the bathroom though they used to go before, we have lost something which may not be obvious on the global rating. This is maybe not suggesting an easy answer but to point out the importance of looking at those double outcome variables.

DR. TAMMINGA: Dr. Cummings?

DR. CUMMINGS: I think a global might be an impossibly high standard because the amount of variance that the psychosis is contributing to the patient's global state might be quite small and, yet, still very important. That is, the patient's suffering may well be tied much more to the fearfulness of the delusion than to the severe memory and cognitive abnormalities of which they are not aware. It might be very useful to the patient by relieving the delusion and not have a global effect and, therefore, the drug would fail.

DR. TAMMINGA: Jeff, do any of the scales that are used as the rating scales, your scale or the BEHAVE-AD, have sub-scales or clusters so you can look at the psychosis score separate from the total score?

DR. CUMMINGS: Yes, both of them do.

DR. SCHNEIDER: I believe that actually a global is extremely important in all of these studies, and it certainly is in depression and schizophrenia as well because it is asking the blinded physician, you know, doctor, please

state clearly, all in all, is this patient better, or worse, or not changed? Almost by definition, that is clinically significant.

I would elaborate on Jeff's comments and say that if a drug is hypothetically effective at treating just the delusion that that has got to be translated into improvement in some other aspects of behavior for a patient to be judged to be meaningfully improved. If it happens to knock out a delusion -- this is almost absurd, knock out the delusion but the agitation and the aggression is still there, there is not going to be much meaningful change.

DR. TARIOT: Just to mention briefly, of course, there are examples where the standard that has been proposed has been met in clinical trials in dementia. So, it can happen where there is both a rating scale change and an improvement in the global.

DR. TAMMINGA: Dr. Reisberg?

DR. REISBERG: Really just to expand on that, I think there are two different kinds of globals. One is a global with respect to the psychotic or BPSD symptoms per se and the other is a broader global with respect to dementia. Clearly, with respect to globals with respect to the psychotic and BPSD symptoms per se there have been studies and, in fact, in the studies where one has gotten statistically significant effects on scales it seems that

they tend to go along with statistically significant effects on globals.

With respect to the disease per se, I don't think it has been looked into, but I think just on a conceptual basis it certainly would seem to be quite possible that clinicians would think that the changes that they are seeing are significant. It would include cognition and functioning as well as behavior if one is looking at disease per se, and one would get a dilution effect and I am not sure that one would wish that.

DR. KATZ: There seems to be some general agreement, I think, that one of the criteria for this syndrome would be that the symptoms are interfering with the patient's functioning somehow as opposed to, let's say, distress. All I am saying is that it makes some sense, if everyone agrees with that, that assessing functioning ought to be a part of the assessment of the treatment, in addition to an assessment of the specific symptoms of delusions, hallucinations, or whatever. How one goes about assessing functioning of a patient -- I mean, presumably there are ways to do that. How reliable they are I personally don't know.

DR. LAUGHREN: I think that makes a lot of sense but, again, if you look at other areas that we have dealt with in the past -- schizophrenia, major depression and so

forth, it has not been a requirement in other areas to have, you know, these dual criteria on some primary rating instrument, like the HAM-D as well as the CGI or some other measure of functioning. In a sense, it is a higher standard to set. Maybe it makes sense.

DR. TAMMINGA: Dr. Grundman?

DR. GRUNDMAN: I think what you are maintaining is useful and a good way to go. I think the two-pronged approach with a targeted symptoms rating scale and clinician global impression would parallel what we are doing in dementia currently as far as cognition goes, and I think would make sense also for the behavioral component.

Getting back to your point about function, that might be minimal criteria but I think, in addition, in studies that are performed it might be very helpful to get an assessment of activities of daily living, which is frequently done, or also an assessment of caregiver burden, which also might be a very useful concurrent measure.

DR. CAINE: It is true that other parts of psychiatry haven't looked at function but, you know, geriatric psychiatry always does need to lead the way into the future. Since geriatric psychiatrists always think about function as the integration of all of someone's capabilities, it really becomes an extremely useful target for what we do. So, you are partly hearing a bias, if you

would, or if you want to call it a field-specific view on the need for functional assessment and looking at the integrated aspects of human behavior.

DR. TAMMINGA: Dr. Reisberg?

DR. REISBERG: Just a few additional words on this, one is that there is the functional decline associated with dementia, and that is one aspect of assessing functioning. But here, associated with disturbance with the psychosis, it would seem to be another aspect of functioning, and that is the extent to which one is participating in activities, interacting with other individuals.

For those other aspects that you are alluding to we might need, as a field, really to develop new kinds of measures. With regard to the traditional aspects, as I have mentioned before and at the risk of repeating, I think we do need to look at that and covary it and look in terms of therapeutic effects and side effects.

DR. SCHNEIDER: Well, I think that many of us are, in fact, explicitly stating that there should be a higher standard towards FDA clinical trials, towards a judgment of efficacy at least by requiring multiple outcomes in at least dementia in geriatrics. It is simply not suitable to measure something on one scale to observe a small difference and to pronounce that effective.

Since it is getting late, I just wanted to mention one other aspect of clinical trials, and that is that traditional, typical clinical trials run for 6 weeks, 12 weeks, even 24 weeks, and then take an endpoint rating, and a decision is made on efficacy on the basis of that endpoint rating.

Some of us presented data today showing that psychosis at least waxes and wanes a bit. So does depression if you consider depression of Alzheimer's disease. It tends to be mild and waxes and wanes, and it would seem important that when one does these clinical trials, whether it is for 6 weeks or 12 weeks or longer, that intermediate outcomes be taken so that one is able to show that over the course of time particular patients are benefiting from medication, rather than simply showing an overall group effect on a continuous scale.

DR. TAMMINGA: We have talked a lot this afternoon -- why don't you go ahead before I start this?

DR. HAMER: I am afraid as a statistician, you know, if you are talking about multiple measures in clinical trials you have to decide about whether you are going to connect with them with an "and" or an "or." It wasn't clear to me that you were proposing to connect them with an "and."

DR. SCHNEIDER: Can I respond to that? In dementia and in cognitive studies of dementia FDA connects

it with an "and" but uses group statistics. EMEA, amongst other things, expresses the sponsor's data as somebody must improve by a certain level on a cognitive test and on a global. They will show breakdowns, categorical breakdowns in their information. So, we are doing it both ways.

DR. HAMER: Because if you don't connect it with an "and" you have an error rate problem. The same thing holds for taking interim looks. The more you look at your data, the more you somehow need to adjust for that, and the more you adjust for that, the higher a hurdle you wind up setting for yourself to get over. I don't have any objection to that in a sense but it does make it harder to gain approval.

DR. TAMMINGA: Dr. Laughren?

DR. LAUGHREN: Well, there are many ways of dealing with that. One thing you can do is, rather than looking at endpoints, looking at some sort of an AUC approach. But the discussion is getting fairly far down the road in terms of looking just at this one entity, and I am wondering, given that it is getting late, how are we going to discuss other syndromes and other issues.

DR. TAMMINGA: Well, that was just what I was going to bring up. We have discussed psychosis with dementia for a prolonged period of time, perhaps mostly as a model of what one might look for in other syndromes and

because there were diagnostic criteria already proposed for this. But I think that we ought to move on to discuss the question of if there are other syndromes that would be important in dementia and what those would be. Perhaps we wouldn't want to necessarily -- unless the room is rented until midnight -- discuss each of these syndromes so thoroughly, but at least it would be good to know what the target is. I mean, what do people think about which other syndromes are out there to be delineated, and what kind of consensus amongst all the experts is there on those sub-syndromes? Eric?

DR. CAINE: Well, clearly in sort of leaving the five standing mental disorders "due to" there was a sort of mini-consensus among about four of us who were writing the criteria that there was substantial evidence or clinical need for psychosis due to mood disorder, due to sleep, anxiety and personality changes being five conditions related to Alzheimer's disease.

DR. TAMMINGA: You mean demential due to?

DR. CAINE: I am sorry, psychosis due to Alzheimer's disease, mood disorder due to Alzheimer's disease, anxiety disorder due to Alzheimer's disease, sleep due to Alzheimer's disease, and personality change due to Alzheimer's disease. We saw those as five areas where there was substantial data in the literature. I think it is fair

to say though that there is a difference in maturity or development among those, such that it is possible to present robustly today a discussion about psychosis.

DR. TAMMINGA: And how would you rank that? Would you put psychosis first and then rank them in the order in which you gave them?

DR. CAINE: Oh, I would put mood and sleep as charging in the second, and then in the third tier I would put anxiety and personality change. I left out delirium on purpose.

DR. TAMMINGA: Any other comments or thoughts about that? Yes, Dr. Grundman?

DR. GRUNDMAN: Yes, I don't know if we are trying to include in the idea of psychosis but I think, as has been pointed out by several people already, agitation in and of itself is probably a concomitant of Alzheimer's disease due to the pathology of Alzheimer's disease, and is more frequent actually than psychosis and I think should be a target for treatment, assuming one can define a constellation of symptoms that can be studied.

DR. TAMMINGA: I would suggest continuing on with the discussion for a minute about sub-syndromes and then talk about agitation in a different class as a different kind of an indication but, clearly, we need to touch on that this afternoon too. Dr. Whitehouse?

DR. WHITEHOUSE: I just agree with Eric in terms of the ranking exactly. I think anxiety is problematic because of the potential overlap with agitation, but I think depression and sleep are second rank and the other ones follow.

DR. TAMMINGA: Within mood disorder, would one include secondary mania and what you were talking about, Pierre?

DR. TARIOT: Well, I think what I was trying to say this morning and perhaps didn't convey clearly is that it is a plausible idea on the face of it that a secondary manic syndrome could exist and be due to Alzheimer's disease, but the level of evidence for that is fairly weak, whereas it is also face valid to me that psychosis in Alzheimer's disease exists but the level of evidence is much greater. So, I think it is unproven.

Lastly, I think there will be a large, more heterogeneous group of features that many of us would end up calling agitation and perhaps not conceptualize as secondary mania, but that is hazier and if Costa Lyketsos were still here he would say, I believe, that a lot of these are driven by affective features which could include depressed mood but also irritability. And, I think he would ask us to not rule out the possibility that in essence a lot of these "agitated" features are affective, either irritable or

depressed mood driven.

DR. TAMMINGA: Dr. Whitehouse?

DR. WHITEHOUSE: I think the mania illustration is interesting from kind of a historic perspective. This is my interpretation but I think it is not unreasonable, I mean, clinicians do not refer to mania in Alzheimer's disease. That whole effort was an attempt to get around or look at the issue of agitation in a different way. It was a recognition that the regulatory authorities might treat mania with greater favor, just as they are perhaps interested in treating psychosis as a more defined entity than agitation. So, honestly, my interpretation of this is -- and we haven't talked about the data so we can't see how the experiment really worked out, but basically these were agitated patients which were relabeled as mania, and I am not sure whether it will prove to be a useful exercise or not.

DR. TAMMINGA: Dr. Schneider?

DR. SCHNEIDER: I think you are quite right, Peter. In that one particular study, one particular clinical trial was designed that way explicitly. On the other hand, as Pierre was mentioning, the concept of manic symptoms within dementia or so-called secondary mania has been prevalent for a long time, but I think also for a long time some of those symptoms were called differently

depending on one's particular specialist outlook or neurobehavior outlook. So, disinhibition, for instance, would be used to define a behavior that otherwise might be called manic. In the European view of bipolar disorder and of mania irritable mania is recognized to a greater extent than elation related mania. But I do agree, this is a fuzzier area than psychosis.

DR. TAMMINGA: I would like to get an idea from all of you about what consensus there is amongst our experts about Dr. Caine's proposal of psychosis being the most well-developed, if you will, sub-syndrome, mood disorders and sleep disorders being second, anxiety and personality disorders being third within the "due to" Alzheimer's disease.

DR. TARIOT: I just have a question to Eric perhaps. When you talk about personality change due to, is that where you are subsuming what for the moment we are loosely calling agitation?

DR. CAINE: In fact, there are multiple types of personality change, including aggressive, labile, disinhibited. So, I think there are some real research questions there in terms of are these states or traits. Then, this overlaps with the issue that Dr. Grundman brought up about the question of agitation and is that a syndrome or a symptom. So, one of the reasons why I see that as a very

fuzzy area is because there hasn't been enough research to clarify this.

DR. TAMMINGA: Andy?

DR. WINOKUR: I can think of some very clear reasons, and most of them have been mentioned already, why sleep or sleep and circadian rhythm disturbances in Alzheimer's could be viewed as being a very separable, distinct and unique entity, which might also then be a very productive target for therapeutic treatment.

We started to talk a little bit about a question I had asked Dr. Cummings this morning about to what extent depression in Alzheimer's is unique and distinctive or, you know, if there are chronology or past history issues. I am also thinking of an earlier meeting that we had this year where we were talking about depression in the context of another disorder and how we or the FDA would look at proof that a drug was helping because we already know that is an established antidepressant or that there was some unique profile in this condition. So, I am wondering to what extent aspects of both of those issues would be interesting challenges in this context.

DR. TAMMINGA: Dr. Grundman?

DR. GRUNDMAN: Could I go back to the issue of agitation at this point?

DR. TAMMINGA: I wouldn't mind getting the idea of

the syndromes cleared up --

DR. GRUNDMAN: Well, I think part of the problem is that lurking in everybody's minds is this issue that agitation is really an important problem. It is an important problem for the patients and for the caregivers, and somehow we need to include that in this nosology, or whatever, and whether or not sort of the psychiatric approach to this, whether it is reflective of mood, or sleep, or anxiety, or personality change, or manic syndrome really hits the nail on the head for what we are trying to do. I think there are certain behaviors that can be measured and that are observable, and we have aggressive behaviors, for example, uncooperativeness, verbal aggression, physical aggression, those types of things, which can be measured. So, aggression might be one type of behavior that could be targeted. Another type might be the sort of motor restlessness, wandering, purposeless behaviors, getting up and down, all these types of things that are sort of disruptive either to the patient in terms of their functioning or to their caregivers, which may not lend themselves easily to being assumed under one of these other descriptions.

DR. CAINE: Again, I want to be very cautious about this but in the DSM-IV personality change due to a general medical condition, due to Alzheimer's disease has a

series of subtypes, including labile -- I had to write them down because I can never remember them all -- labile, disinhibited, aggressive, apathetic, paranoid, other, combined and unspecified. So, if you can't include all of human behavior in that, I don't know what you can. Nonetheless, there are some very substantive research issues that need to be addressed in terms of are these persisting characteristic changes and how someone functions in an inter-personal and environment setting on a day-to-day basis. Are they episodic -- a sort of down-played personality change and saying, hey, this is an area that needs a lot of research versus the issue of behavioral disturbances as a qualifier because there are a substantial number of questions which may, in the long-run, have substantial therapeutic implications.

So, I think there is a lot of sense in saying clearly what we know well -- psychotic disorder due to Alzheimer's disease, and then here is the second level which we don't know quite as well, and here is the third level which we are more ignorant about because part of our job today, as I understand it, is to help give guidance about what we know well and what we don't know so well, and then to say, fine, you know, something like agitation, if there is enough data, how do you define it; what are its clinical characteristics; what are its inclusion and exclusion

criteria -- fine, then I think we can move ahead towards that. But when you start to get to things like lability, disinhibition, is that all part of so-called frontal lobe type things or not, I think that you get very complicated very fast.

DR. SCHNEIDER: Mike, certainly as a clinician I agree with you entirely. Agitation is the signal. Agitation is what draws our attention to patients. But, at the same time, it is so heterogeneous -- it involves, you know, such things as uncooperativeness, restlessness, verbal aggression, a screaming patient, pacing, attention seeking, irritability. You know, the first step is to notice that. Then, I think a whole series of other steps in terms of analyzing, evaluating the behavior, asking the question whether some of those behaviors might be better understood as part of a depressive syndrome or as part of a psychosis syndrome -- and this is, of course, after ruling out that these are not due to the urinary tract infection, to the acute abdomen, and to any of a number of other problems that are occurring.

DR. TAMMINGA: Dr. Reisberg?

DR. REISBERG: I think it would be wrong not to address Dr. Winokur's question with respect to the issue of depression in dementia more directly. In addressing this, I think we need to first point out that there was a very good

presentation, but I don't remember who gave it, that did begin to address these issues. Clearly, there is a depression which is the harbinger of subsequently manifest Alzheimer's disease. Except by way of noting this and perhaps the interesting analogy to Huntington's, I am not sure we need to say more about this but it is part of the story here.

In addition to that, particularly early on in Alzheimer's disease, one does see something akin to a major depression which can occur in the early stages of the disease and the mild to moderate stages. One only sees it then in a form which is akin to a major depression that we would identify. Then there is something much more complex which is, if you will, the depression of Alzheimer's disease and I am not sure it is that per se, but whatever it is, it does lead clinicians to prescribe what we would call antidepressant medications for Alzheimer's patients on a massive basis currently and I think that needs to be better defined. We have done some research in this area. This particular research is the only thing I have referred to that we have not published at this point, but it seems to indicate that certain clusters of symptoms that we have mentioned today -- anxiety, mood, indeed, but also other symptoms seem to respond to medications which we would call antidepressants. Certainly, antidepressants do need to be

studied not only perhaps with this ineffable entity but also with respect to the major issue of today, which is the psychosis of Alzheimer's disease.

DR. TAMMINGA: Dr. Whitehouse?

DR. WHITEHOUSE: We are kind of bouncing around here a bit but I was going to say that when Mike rightfully kept persevering on agitation here, I think I have a sense that we agreed with the ranking that Eric had made pretty much, and I wanted to say that and just see if there were any disagreements.

Barry has brought us back to depression, which I think we didn't address as seriously perhaps as you would like, and I think Barry has just enumerated why it is a bit more complicated and is in the second grouping. I think the fact of the matter is that we have to look at the fact that people are prescribing antidepressants and they are also prescribing antipsychotics for agitation. So, there is a practical need to clarify these issues and provide clinicians more information.

That was the comment I was going to make. I think with regards to agitation, if we are in that category now or if we are bouncing between depression and agitation -- I think the question I asked Jiska and the question that Alan raised in his talk is really the principal empirical question that we don't have an answer to in agitation. I

think Rusty or Tom was saying the FDA isn't sure whether to put agitation in the non-specific pain category or whether to believe Jeff's unpublished study, which is certainly novel, that agitation actually may be syndromic and there may be biological differences between agitated and non-agitated patients.

But, it seems to me, this is a vast research agenda which does principally hinge on whether we can define the symptomatology to agitation that crosses several diseases; whether we can use instruments that can cross these different diseases; and whether we can find therapeutic effects that are, in fact, supportive of a non-specific kind of approach; or whether we do the research and find, in fact, that the syndromes of agitation look different in different diseases. So, it seems to me that, roughly speaking, is the agenda in my opinion for agitation.

DR. COHEN-MANSFELD: Though I agree with you, Peter, that we don't have the answer across diseases, I disagree with Lon. I believe that we are short-changing the literature on agitation. There are dozens, if not hundreds, of papers on agitation. Even though they use different terminology -- some will use motor restlessness; some use disinhibition; some use physical non-aggressive behaviors and the various types of aggressive behaviors -- it is amazing that despite the different instruments and despite

the different labels a lot of this literature does converge. So, I don't think we have to assume that we are starting from step one. Sure, we still have some questions but we also have a lot of answers available.

People, coming from many different ways, came up with aggression as an entity that exists, is worthy of study, can be characterized pretty well and, again, yes, there are many instruments and so you will get little variations in the exact points but, depending on the instrument you use and what frequency scale or intensity scale they used, the interesting thing is that the final conclusions are pretty similar. So, we are talking about the same entity.

Similarly, motor restlessness exists in British studies and in other studies, and I don't even remember the names of the instruments or the exact definitions, but if you look at what behaviors they are looking at, it clusters at the same issues. The same is true for vocal and verbal. This is not all psychiatric research. There is nursing research. There are other types of professionals who have dealt with this. There are also some longitudinal data as to how those behaviors change over time and we can look at those papers. So, there are some things that are known.

I also disagree with the assertion that agitation or these three syndromes of agitation are all secondary to

depression. Some of these are related to depression and some are not. Even when they are, it is far from very high levels of variance that are accounted for so their relationship is very complex, of course. The definition of depression in late-stage dementia is also complex. So, we didn't get into that yet.

Finally, all of that doesn't necessarily mean that we should jump on the drug trials on this. Personally, I think that the only category of these that may be appropriate for drug trials is the aggression part, and even there we need to have all kinds of exclusions looking at environmental issues and other issues but I think there is something to look into in that category.

DR. TAMMINGA: I am struggling to understand what people mean by agitation or how people view agitation in dementia. I work in schizophrenia and in this field of schizophrenia schizophrenic patients are agitated a lot but we would never consider that agitation would be a group of things, and they really match a lot of these descriptors here. We would never really think of agitation as being what ought to be the target for a drug study but, rather, consider it secondary to the psychosis and if we treat the psychosis the agitation goes down.

Now, I think the situation in dementia may be a little bit more complicated because you may have more than

one thing. You have dementia and you have psychosis, or you have dementia and depression. So, I don't know if it is more complicated in depression or if people are actually looking at it as a primary syndrome -- agitation as a primary syndrome, not secondary to any other psychiatric thing.

DR. TARIOT: In case I created the impression that I thought all agitation and dementia was related to affective disturbance, I didn't mean that.

[Slide]

What is up here, for those who are able to read it, is simply half a list of actual target symptoms seen in demented nursing home residents who are enrolled in a placebo-controlled trial for agitation. It illustrates how heterogeneous the phenomenology is and how difficult it is to make simple sense of it.

I would be curious what Jeff is going to say here, but my own view would be that we are charged with trying to make the kinds of connections Carol was just talking about. In this particular case, do you think that the agitation is driven by psychosis; in this particular case, do you think it is driven by affective features? Indeed, sometimes the answer is yes to those, and in some cases, my experience and my view of the literature is that you can't say yes to either of those and you end up with this other kind of

unformed type of agitation. I think, Jeff, that is what your data also concluded.

DR. CUMMINGS: Yes, let me comment on that and then I would like to comment on depression. I think you can defend a case for agitation as a symptom of many disorders that we are talking about, but when you have accounted for all of that there is still a group of patients who are agitated and who are not obviously psychotic or depressed, or in pain or have any other explanation for their disorder. This may be a disorder where there is both a syndromic manifestation and a symptom manifestation. I think there is not sufficient data to allow us to conceptualize this in the same way that we can psychosis.

A couple of points on depression before I give up the microphone, one is that it really is terribly important. We saw from Costa's data that it is the third of the three syndromes of Alzheimer's disease, and I think that spoke to it very nicely from an evidence base. It is important to recognize that, for the most part, these patients don't meet criteria for major depressive episode. Therefore, in conceptualizing what the syndrome should consist of, I think it should not map straightforwardly onto our existing DSM-IV criteria. The core psychological symptoms are critical because so many patients have sleep disorders, apathy, and other ancillary symptoms common in depression and dementia.

So, looking at the sadness, and tearfulness, and worthlessness, and hopelessness is very important.

To reinforce Barry's point, it is really important to measure the associated symptoms. When you treat depression secondary outcomes have to involve agitation for example, so that we discover this relationship even if agitation is not the primary outcome.

Then, the point was made how few antipsychotic trials there have been, with Lon being able to identify seven or nine of good quality. There are fewer such antidepressant trials. I think there are only four or five double-blind, placebo-controlled antidepressant trials. We greatly need a stimulus to move ahead in the treatment of depression in this arena.

DR. CAINE: A couple of things -- I will replicate Jeff's path and touch on agitation and then go to depression so Lon can then get back into depression. I think your discussion about agitation both as a symptom or part of the constellation of psychosis, depression or other kinds of things and sleep-wake disturbance, as an example, really underscores one of the reasons why, at least at this juncture, we are left with behavioral disturbance as a subtype because there appear to be some people with dementia due to Alzheimer's disease who are agitated where there is no other apparent explanation. Whether this is an

independent cluster -- Barry was debating earlier about whether this should be an independent cluster that could be attached or not, I don't know the answer to that, and I don't think anyone does at this point. So, I think clearly this is an area that needs investigation but it is one that makes it more problematic in terms of giving guidance to the agency relative to how it proceeds.

The issue of mood disorder I think is an interesting one. Let me see if I can reframe, Jeff, what you said while agreeing with you, which is that the entry criteria to defining whether someone has a mood disorder in Alzheimer's disease ought to be different because the issues of energy, spontaneity, sleep disturbance and those are phenocopies -- I am using that generically. We don't know where they come from. So, when we would set up a trial it would be on the basis of the kinds of things of sadness, hopelessness, distress, subjective and other kinds of psychological symptoms of depression. But, once one started the trial, one would want to look at all the array of manifestations that might be potentially amenable -- I don't intend to use the word associated symptoms, but certainly including energy and all the sort of psychovegetative signs that one had previously looked at in more traditional mood disorders, but I wouldn't use them as the entry criteria.

DR. LEBOWITZ: I want to keep it on agitation for

a minute, before Lon gets to depression. That is, to really ask all of us whether, sort of by having this discussion in this way, we are rejecting the agency's position and rejecting Alan Breier's recommendation that we deal with agitation as a non-specific kind of phenomenon that goes across a whole series of things. We are sort of talking about agitation as if it is, well, gee, we know a lot about psychosis; we know less but still quite a lot about depression and circadian disruption. The other things, the anxiety and personality are not next in order because they are close; they are kind of, you know, out there somewhere that maybe some day somebody will develop that stuff to get to the point of being as good as what we know already in these other areas. This discussion, de facto, is saying do we think of agitation as being closer in terms of what we know to the depression stuff or to the psychosis stuff, but by having that discussion we are essentially rejecting the alternate point of view, which is that it is different from the psychosis and the depression and the sleep-wake disturbance. It is different and needs to be treated differently. If that is what we are saying, then I am not sure I agree with it.

DR. TAMMINGA: We are going to listen to Dr. Laughren first and then I will get back to you, Eric.

DR. LAUGHREN: I just wanted to clarify that we

don't have a position on that. You know, we are raising the question. I mean, what I am hearing here from most people is that either you view what is called agitation as secondary to some other syndrome, like psychosis or depression or something else, or you view it as an independent entity but in some sense specific to Alzheimer's disease. The sense I am getting from most of you is that in whichever form it occurs, it is a fairly specific disease; that you don't see it as a non-specific thing in the same sense as one sees pain and fever as non-specific. Am I reading that correctly or not?

DR. CAINE: Let me try to address this in response to Barry and also to you. I think if I were setting up a study and I wanted to study agitation in Alzheimer's patients, I would take those who are non-psychotic and not depressed, if I was going to try to do an agitation study. There certainly is a population of plenty of Alzheimer's patients who don't have one of these mental disorders due to, let's call, it a second axis on diagnosis, who would have dementia due Alzheimer's where there is a lot of agitation. So, I think that is a studiable population and that is a behavioral set of constructs that could be studied.

On the other hand, I also think there are people with Huntington's disease and other neurodegenerative

diseases who also have that agitation. I don't know yet whether those are distinct entities or non-specific. I would tend to suspect they are non-specific, and disagree with Jeff, but I think honorable people could disagree on that.

DR. TAMMINGA: Dr. Whitehouse?

DR. WHITEHOUSE: I agree with Eric. I didn't get the same sense you did, Tom, that we were moving towards identifying your position as thinking they were non-specific and rejecting it. My intent was to say we don't know. My gut reaction is, in the diseases that I am involved with which is Alzheimer's disease and other adult dementias and mental retardation with and without dementia, that agitation is a non-specific but definable entity. I do agree with Jiska. There has been an awful lot of work done in agitation in dementia specifically, and I think what needs to be done, because it is always a difficult thing to do in medicine, is to put together the agitation literature from some of these different conditions, not only the different dementias but also other conditions. I think if you did that, my intuition is that there is a core that it is non-specific and that would be the way to go. But, I do agree with Eric that we don't know yet.

DR. SCHNEIDER: This still comes back to how do you define agitation and, you know, what do you mean

agitation -- you know, to paraphrase the President. You know, this is what you find in a nursing home when you look for agitation, and I invite you to read what Pierre finds in a nursing home. You find uncooperativeness, assaultiveness, restlessness, verbal aggression, sleep-wake cycle disturbances, etc. in 17 percent. This is just a starting point in the evaluation of a patient. So, how would you do a clinical trial of this kind of symptomatology? You certainly can do it, but you would then have a fairly large clinical trial and you would have a lot of multiple outcomes. That is fine. What you don't know about some of these symptoms of agitation is the natural history of some of them. Some of them you do and, therefore, they may start to constitute a syndrome; others you don't. Some of this can be better explained as psychosis or depression but it depends on the evaluation of the individual patient.

DR. TAMMINGA: Dr. Grundman?

DR. GRUNDMAN: I think this gets down to lumping and splitting. I think you can study agitation but you shouldn't call it agitation. You should call it aggression in one instance; you might call it motor restlessness in another; you might call it vocal outbursts in another. So, each one of those could be separate targeted symptoms for which you would be recruiting patients into an individual study to look at whether or not a treatment was effective.

But as far as the other issue that came about before, whether or not agitation should be non-specific or specific for Alzheimer's disease, I think Jeff actually brought up some points earlier which I think are very relevant. One is that the agitation, say, in Parkinson's disease and Alzheimer's disease may have a different pathophysiology. The agents that you might want to use to treat the agitation associated with Alzheimer's disease might be different. For example, cholinergic treatments might work where they might not work in another circumstance. Finally, the safety of the agents might e different in a frail, elderly Alzheimer patient as opposed to other patients with agitation.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: Michael, your point about you can call it aggressive behavior in one and verbal outbursts in another and study each of those things, that is precisely the point. We have to think about how we would label something for something called agitation. You know, I take Lon's point, there are thirty things there that somebody subsumed under something called agitation. They are wildly different. They may have nothing to do with each other but somebody thought they were agitation. I mean, that is precisely the point, how do we define this thing? Are we at the stage where there is a consensus on what constitutes

this thing called agitation? Are we there yet? Whether it is specific for a particular condition like Alzheimer's disease or whether it is a symptom that occurs in many different clinical settings, do we really know what it is? Is there agreement?

DR. GRUNDMAN: You know, Jiska pointed out that when you do these analyses of symptom clusters and patient clusters, there are patients that experience certain types of agitation versus other types of agitation, and I would say that you could split them apart and that you don't have to develop a label for agitation in Alzheimer's disease. You could develop a label, say, for aggressive behavior in Alzheimer's disease and potential treatments for that.

DR. KATZ: I suppose we don't have to. The question is where is the field so that we can say yes in an affirmative way, yes, there is something called agitation. There is general agreement about what constitutes it, what symptoms are subsumed under that heading and, yes, it occurs in multiple clinical settings or, no, this type of agitation (a) occurs in Alzheimer's disease and agitation (b) or something like it but different occurs in the setting of depression. I mean, we are looking for guidance about where we are on that continuum. The sense I am getting is that there isn't really a good, clear understanding or agreement at least about what agitation is, let alone whether it is

the same from one clinical setting to another. But, I would like to hear what people say about that.

DR. TAMMINGA: Let me hazard a proposal that the experts can respond to. In fact, there is a considerable degree of disagreement about this concept of agitation in terms of what its etiology is, how it should be treated, how it should be viewed -- not that it exists. There seems to be broad agreement that it exists but there seems to be a lot of disagreement about really what to do with it, and that the academic community needs to do some more investigation before the FDA hangs its hat on any particular peg. Now I would like the experts to respond to that proposal. Peter?

DR. WHITEHOUSE: I don't disagree with the last point, which is that there needs to be more research, but I am feeling a little bit uncomfortable with the kind of degree of chaos with which people seem to be characterizing this. I think you can define agitation, and I would invite Jiska to do this because I like her definition and I am sure she can remember it better than I do. There is a definition in the dictionary. I think we all have an internal sense of what it means to become agitated. So, I do think there is more there than perhaps I sense the conversation has been supporting.

I think that the issue of etiology or pathogenesis

I object to a little bit in the FDA's sense that with non-specific symptoms -- well, with all these syndromes they would like to have pathophysiological mechanisms. But I think with pain and with fever at some kind of rudimentary peripheral level we do have some understanding of the pathogenesis but, as somebody pointed out in one of their position papers, the central understanding of pain perception, I think, is probably ahead of agitation but I wouldn't want to necessarily hold as high criteria that an understanding of pathogenesis of this particular what I think or as non-specific cluster of symptoms necessarily be counted as a major weakness. But I am not disagreeing with the fact that there needs to be more phenomenological work in different conditions with instruments across different diseases, and so on.

DR. COHEN-MANSFELD: I would partially second what Peter said, but I think we have definitions. I think this list is misleading because this list is where we were 15 years ago. We had those lists. Everybody had different lists but we have gone some steps ahead of those lists. We have some studies that deal with etiology. We have some studies that deal with groupings. As I said, even though those are not all identical, I really believe that there is plenty there that is converging both cross-culturally and across assessments. I think in that sense it is maybe

beyond where the delusions are. The delusions have generally had two or three assessments that have been universally used and, therefore, defined the field. Here, we have used I think forty types of assessments and still most of the data do converge. So, I think there is much there.

The issue that you raised, what is the explanation for it? Is it secondary to psychosis? Obviously, you brought out it can't be secondary to psychosis if psychosis is so much less frequent. I think there are lots of other issues that have to do with just the experience of being demented. There is boredom; there is loneliness; there is physical pain that is not detected; there is the discomfort of sitting in a chair all day; there are all kinds of things that are not the things that we usually deal with. Then, there may also be some things that people here do deal with that need to be addressed. As I said, I personally think those are more in the aggressive syndrome than in the other two. But, I think to just look at the list and say this is bewildering -- sure, it is bewildering but it is not where the field is.

DR. TAMMINGA: Dr. Laughren?

DR. LAUGHREN: Dr. Cohen-Mansfeld, just one question about your view of agitation, you have these three agitation syndromes, do you view those as specific to

Alzheimer's disease or do you view those in some sense, you know, as broader, cutting across diagnoses?

DR. COHEN-MANSFELD: I don't have a good enough answer to that. Personally, I think they do relate to dementia. I think a lot of these have to do with the interaction between the person's ability to take care of themselves and communicate and their interpretation of reality and the way reality deals with them. So, as you proceed with stages in dementia, your ability to take care of your needs decreases and your need to communicate versus different agitated behaviors increases. So, that is sort of part of the picture where it relates to dementia. Whether it depends on which type of dementia, my first guess is no but this is not a very educated answer.

DR. TARIOT: If I could just clarify what is in your handout and what I showed up there, I probably didn't say clearly enough that these were not features that we were calling agitated. These were idiosyncratic target symptoms recorded in demented nursing home residents who were enrolled in placebo-controlled trials for operationally defined agitation, essentially according to your three factors. The point of it was that even with that kind of purified sample these were people who did not meet syndromal depression criteria or psychosis criteria. Even with that relatively purified sample -- and I know you know this,

Jiska, but in essence it was for the other part of our audience -- you see all kinds of other phenomenology, and that is the kind of thing that is confusing for the uninitiated and even for the experienced clinician trying to, in an individual case, figure out what is the best thing to do for this person.

DR. TAMMINGA: Dr. Caine?

DR. CAINE: I will try to respond to your question and your surveying, as it were, the consensus of the panel or not. It is clear that you can set up studies of the sort that Pierre did which excluded people with syndromal psychosis and syndromal depression, and there are people there who then have substantial agitation, who have many behaviors that fall under it, who can be clustered in a variety of ways. I think what is also clear in the literature is that there aren't enough studies like that that have removed people or have excluded people who qualified for psychosis due to Alzheimer's disease, or depression due to Alzheimer's disease, or other major disruptions of that form who then had agitation and were studied prospectively.

So, if you are going to set up an approach, then it gets again to how you define your entry and how you define your exclusion, and can you be clear enough about that. Otherwise, you know, certainly agitation would be

valuable to look at as a dependent variable in the context of a psychosis study or in the context of a depression study, but that is a different set of questions.

DR. TAMMINGA: Dr. Reisberg?

DR. REISBERG: Just a brief comment as a member of the panel and also as a clinician, clinicians are treating agitation in hundreds of thousands of dementia patients at any given time. Also, there are excellent methodologies for assessing agitation, and clearly good studies need to be done in this area.

DR. TAMMINGA: Dr. Whitehouse?

DR. WHITEHOUSE: I think this is a discussion where we don't have a clear-cut yes or no. I mean, I think there are some areas of consensus around agitation but exactly how much knowledge we have and how far we are down the line, I guess you are getting some differences of opinion. I mean, I think people have said you can get agitation with affective symptoms; you can get agitation with psychosis. You can get it without either of those other two. My own sense, as I was thinking about this big shopping list, I mean, if you asked a similar question about pain you would have all kinds of other things -- this may not be a helpful analogy but you would have all kinds of other things associated with that non-specific symptom in other diseases. So, the fact that when you get agitated

there is kind of a whole laundry list of things that may go along with that in terms of behaviors may, in fact, be part of what it means to be non-specific. I am not sure, but I think the fact that there are lots of different manifestations of it doesn't worry me specifically and might be characteristic of what you mean by non-specific.

DR. TAMMINGA: Dr. Grundman?

DR. GRUNDMAN: Just one other point, in terms of trying to fiddle agitation into a psychiatric type syndrome you have a big problem because agitation type of behaviors tend to increase as the dementia gets worse, and it becomes more and more difficult for people to express their delusions and hallucinations and depressive feelings and all you are left with is the direct observation that they appear to have these agitative behaviors which are very disruptive and need some sort of treatment, whether it is behavioral or pharmacologic.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: Maybe I am asking a more basic question. I will grant that the list we were looking at was a list of associated symptoms, but they were associated presumably with agitation, something that somebody called agitation. I will ask the same question I asked before, is there a common understanding of what the term agitation means, and what would that common understanding be if there

is a common understanding, and is it something that can be studied as of now? In other words, the criteria for agitation, are they sufficiently well developed and commonly accepted so that they can be studied now whether as a specific syndrome or as sort of a general symptom that occurs, and if there is a common understand I would be interested to know what it is.

DR. COHEN-MANSFELD: I would like to answer both yes and no. On the one hand, if you ask is there a common understanding of what is agitation, even the term agitation -- maybe people don't use it; they call it behavior disturbances, behavior problems. There are half a dozen terms used for these behaviors. However, despite that there are core symptoms that seem to repeatedly cluster together that we can define, with a definition -- aggressive behaviors, either by a list or by half a dozen assessment instruments for each of them. So, I think that the common literature has a well-defined group of behaviors that is examined here but the terminology is not accepted by all. There are different terms that are used by different researchers but I think that is masking an underlying agreement, actually.

DR. TARIOT: Could you just reiterate the major factors when you looked, when you just observed large numbers of these patients? You did it this morning but I

think it is worth reiterating.

DR. COHEN-MANSFELD: Well, there is a pretty large Chinese study, a pretty large Japanese study, a Dutch study, a nursing home study, an adult day care study and probably others because I didn't do a search. These just happened to come across my way as I was preparing this paper. They all found basically these three syndromes -- aggressive behaviors, motor restlessness and verbal-vocal. Now, there are still issues to be clarified. For example, verbal aggression -- does it belong in verbal; does it belong in aggression? It behaves a little bit like each of these. So, I don't want to pretend that we know everything here, but these have been pretty reliably found. In addition, some researchers have just looked at aggression, or just looked at motor restlessness because that was reasonable to them through common sense; that is what clinicians see. So, beyond the factor analysis or other statistical methods, I believe there are clinical phenomena here.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: I don't know the data, but it might be the case that aggressive behavior correlates well with motor restlessness. Do we really believe those are the same things? Remember, we have to write labeling. We have to be able to say to people this is the condition, the symptom, the setting that this drug is going to work for. And, do we

really believe that aggressive behavior is the same thing as motor restlessness? They may go together but are they the same thing? If we call those two things together, and add the third one, agitation, and one drug treats one of those and another drug treats another one do they both get a claim for agitation? I am not clear on that yet.

DR. COHEN-MANSFELD: I am saying just the opposite. I am saying these are three separate syndromes. Yes, they do correlate if you do correlations but they behave differently enough, however, that hitting, kicking, pushing, biting do tend to co-occur and all these would be under the aggressive syndrome. Pacing, wandering, moving things from one room to another tend to co-occur and all these are under the motor restlessness. But I believe these are separate and should not be labeled together.

DR. SCHNEIDER: Maybe this isn't the time to do it but just as a point of clarification, when you say kicking, biting, etc. co-occur, do you mean an individual patient is far more likely to have several of those behaviors than a single behavior? If you could elaborate on the co-occurrence?

DR. COHEN-MANSFELD: Yes, basically if someone has one of these behaviors they are more likely to have another of them than if they didn't.

DR. TAMMINGA: I would like the group of experts

to consider that this morning Dr. Breier suggested that agitation be considered as a non-specific indication. Is it my impression that the experts think it is really premature for the FDA to do this? Is there disagreement about that? Or, do you all think that we should recommend to the FDA, just like we did with psychosis with Alzheimer's disease, that the FDA move ahead with considering this seriously and soon for an indication?

DR. WHITEHOUSE: The psychosis is clear, and that is why we are asking the FDA, I think, to help companies in making that a more clear target for therapy, but I think we are also saying let's not forget agitation. Let's do what people do, which is measure agitation either as the concept or in its three components, as Jiska was saying, because it is going to be very valuable to clinicians to know as part of the research agenda what effect these drugs have on those particular syndromes. Now, that is different than labeling but, frankly, as so many people have said already, these drugs are being used for agitation. People may say I am treating the hyperactivity; I am treating the verbal aggressiveness, or whatever because, as Jiska says, the language is not that common. But, honestly, I think to a certain extent this is an area where patients, and families, and clinicians are already doing it. They have a sense of what this is and I don't think we should relegate this to

another five years of research -- not that it doesn't need five years of research, it needs to be addressed in our studies maybe not as a primary indication as I said already, but I would not want measurement and studies of this particular phenomenology to be removed from the kind of therapeutic research area while we are doing a whole lot of phenomenology.

DR. TARIOT: So your answer was what?

[Laughter]

DR. WHITEHOUSE: It was, as you just detected, somewhat grey, agreeing with looking at psychosis but looking at agitation or its components in these studies to see what we can learn about it.

DR. TARIOT: I didn't mean to tease. My answer, in a sense, would be both as well. It seems plausible, based on the available evidence, that there is a somewhat unique form of agitation that can occur in dementia of the Alzheimer type. Jeff Cummings has left but he has very interesting data showing that there is a specific clinical pathological correlate that he can identify in these people. That will be an important advance in the field.

On the other hand, if I think about Marshall Folstein's data that I presented today, it would be an example of the sort of non-specific approach that patients with mania due to bipolar disorder and patients with

Alzheimer's disease looked quite similar on a behavior rating scale that looked at features of agitation. I think both are, in fact, likely to be true.

DR. TAMMINGA: I don't want us to end the day before considering the safety question because Dr. Laughren raised it specifically, and there are people here who are experienced enough to provide some feedback.

The safety question, I will remind you, was that there certainly is some evidence for a different tolerability profile in this population of patients, and do we need a policy in evaluating risk of psychotropic drug treatment in people with dementia of the Alzheimer's type? I should have just let Tom frame this question.

DR. LAUGHREN: Can I just try and clarify what I meant a little bit? As I said, we have had very little data to look at from a regulatory standpoint, and I realize that there is a large literature on this and many of you are probably familiar with many of these studies.

I want to just focus on two data sets that we looked at. I am not going to name drugs because I don't want to pick on any particular drugs, but with one drug in a very elderly Alzheimer's population, you know, we saw excess sedation. In some patients we saw dehydration, decreased nutritional intake. In fact, the study was stopped because of these problems and that kind of finding causes us a great

deal of concern. In another study with a totally different kind of drug we also saw excess sedation; a clear difference from placebo on an effect on gait; and, again, a suggestion of dehydration.

All of those kinds of things raise in our mind the possibility that if you look at a large enough sample there is a potential for seeing an increase in mortality. Those kinds of things lead to bad outcomes. So, it is that kind of finding that raises a concern in our mind that something more needs to be done in looking at the safety of these drugs and a lot more thinking needs to go into, for example, how large a sample one might need to look at to rule out the possibility, say, of a slight increase in mortality.

DR. CAINE: I don't think there is much question that you are correct on this. Let me sort of take it from two perspectives. This is just the sort of area where you need the research because the drugs are already being used quite rampantly and, therefore, what we have is a large national experiment under way without any regulatory oversight or other kind of view. So I think it is really critical to take something like psychosis due to Alzheimer's disease and clarify exactly what the rules of the road are so that this can be done. Then, clearly, when you say, okay, fine, I am dealing with an elder population, this is one of the issues why functional outcome is so important.

If someone is asleep all the time, their function is going to going down, not up; and looking at physical parameters that have to do with gait, falls, the like -- falls are complicated.

Let's take falls. You know, a lot of elders fall. How are you going to deal with it? They are going to get observed more in a study like this than they would under any other circumstance. So, you are probably going to detect those falls more. A placebo group is going to be very important. Right now, the national experiment, of course, has no placebo group.

So, I think there is compelling data or compelling reasons to go ahead with this, and then to be clear-cut about the safety and potential liability issues in the long run.

DR. REISBERG: Here I need to come for the fourth time to the issues of cognition and functioning. First of all, certainly one needs to assess safety in terms of traditional side effects of these medications but, in addition, one needs to assess safety very specifically in the context of dementia in terms of the impact on cognition and the impact on functioning. This is true in a very real sense. So, for example, we have had medications which have been widely prescribed in our time for dementia patients. There has been a time when medications which we might even

consider BPSD medications -- and I will name a name just to give an example, Haldol for example was routinely prescribed for dementia patients, and what we have already heard is that the psychosis of AD peaks at a certain point at a certain stage in the illness and you can actually move patients with medication down into greater stages of dementia, later stages of dementia and decrease the psychosis but you are not improving the patient. You control for that in part by looking at cognition.

Similarly, if one uses the Haldol example, what happened in our field -- and Haldol used to be the most widely prescribed medication in this area -- is that doctors at one time in our history used to routinely freeze Alzheimer's patients. They literally froze them, and this was considered to be improving the patient because there was less disruption. Without covarying for functioning one is not judging whether or not the medication is therapeutic. It does not apply, I think, to current medications or medications which are likely to be studied in such an overt way at this time, but I think our history dictates a special approach to dementia with respect to these issues.

DR. SCHNEIDER: I think safety is a critical issue and, of course, part of FDA's charge is to ensure that medications are safe and effective, and I agree with Barry with respect to the cognitive safety or possible lack of

safety of some of these medications causing potentially impairment in cognition or function. Some of these medications can also improve cognition. But the elderly also are a highly heterogeneous group of people and they go from maybe age 70 on up. It depends where these clinical trials are being carried out. And, when we are carrying out clinical trials with 85-year olds and 83-year olds in nursing homes, who are medically frail and perhaps only have a few months of life expectancy it is a very different safety issue than carrying out clinical trials in, for instance, in medically healthy 72-year old patients with mild Alzheimer's disease who are going into cholinesterase inhibitor trials.

I guess I would urge the agency to take safety very seriously, to look at the pharmacoepidemiologic literature, especially the literature from Tennessee on nursing home side effects on the potential safety of a whole wide range of medications, and also have this built into clinical trials. Efficacy in an outpatient population and safety is not necessarily similar to efficacy and safety in a nursing home population.

DR. TAMMINGA: Dr. Whitehouse?

DR. WHITEHOUSE: I guess I would like some clarification of the word policy that you used in your written statement because it seems to me that what has been

said is fairly obvious and that, in fact, it is the big issue around the comparisons between the drugs that we are studying and comparing. It is the side effect profile. So, when you say policy or advice about policy, that is an internal policy you would develop in relationship specifically to this topic of safety?

DR. LAUGHREN: Actually, what I was referring to is what kind of guidance we would be putting together for industry in doing these trials. Other than the obvious kinds of safety outcomes that you do in a standard size controlled trial, based on what you are seeing in standard controlled trials, you are seeing findings that could conceivably lead to a very bad outcome like mortality. And, there is a possibility that giving these drugs actually increases the mortality. Granted, this is a population that already has a very high mortality. In the studies that are done in patients with a mean age of 85 and very low MMS scores, you know, it looks like background mortality rates are anywhere from 5-10 per 100 patient years, perhaps even higher than that. So, you already have a very high background rate, but the question is if you are seeing in routine studies findings like excess sedation, decreased nutritional intake, disturbances in gait do you need to look beyond that? Do you need to worry about the mortality question? I am just raising that as an issue.

DR. WHITEHOUSE: I think you are doing the kinds of things that you need to do, that is to say, monitoring for all these expected side effects. So, I am not sure there is anything you need to do differently, other than, as Lon said, look very carefully at your base rate problem here, mortality.

I want to say one other thing that may sound rather strange but it is a somewhat geriatric perspective. You know, people are going to die when they are old, and we certainly don't want to contribute to deaths unnecessarily but it is perfectly conceivable to me, and we make these decisions to a certain extent, that you may take risks to improve quality of life and diminish quantity of life.

DR. TAMMINGA: Dr. Reisberg?

DR. REISBERG: Just to respond very specifically to the mortality question, there is data -- I believe it is from Columbia; I don't see Dev here at this moment -- that indicates that BPSD more generally or psychosis more specifically is actually an indicator of increased mortality. So, mortality with respect to treatment of these issues relates not only to medication but also to the morbidity associated with the entity.

DR. TARIOT: I wonder if what is lurking in the question here -- again, we talk about the standards for clinical research in this area, should the standards be

different in this frail population that may not have the ability to understand what is going on to more fully address safety and mortality than would ordinarily occur? I take it you mean perhaps larger studies or longer studies.

DR. SCHNEIDER: We have focused so much in these studies on efficacy and effect size of efficacy, and often these effect sizes are rather mild or moderate and, again by comparison, we don't focus on such statistics as number needed to harm. If some of these medications are causing symptomatic bradycardia, are causing syncope, are causing falls it may be occurring in a relatively "low" absolute rate, 5 percent, 6 percent over a period of time of 3 months, 6 months or beyond the ability of an individual clinical trial of 200 patients to really pick out. Yet, that can be hugely harmful to the public health in general, and that small effect can also detract rather markedly from the positive clinical effect size.

Again I am repeating myself, in the elderly there are at least two populations that need to be looked at, the outpatient ambulatory and nursing homes, and there are different issues but safety I think is quite important. Unfortunately, you need the placebo-controlled comparisons in order to get a good fix on this.

DR. TAMMINGA: Dr. Grundman?

DR. GRUNDMAN: Not to repeat too much the obvious,

but there are always going to be tradeoffs. When you elect to treat a patient you may improve their behavior and, at the same time you may put them at risk of having some side effect. I think the best thing you can do is to do your trial with a sizeable number of patients where you can measure both, and then at the end of the trial try to assess whether or not the risks are worth the benefits.

DR. TAMMINGA: Dr. Laughren?

DR. LAUGHREN: I think the issue here for me is that this population already has a substantial mortality and if you are introducing something like sedation that can lead to a variety of bad outcomes, you may not detect that because patients are already dying from pneumonia; they are already falling. This is the concern. That is why I think this population is particularly vulnerable to that kind of a bad outcome, and it is very difficult to detect in that setting. I am just raising this as one possible concern that, you know, we need to think about how to look at, and I think it would mean larger studies. I don't know how to get around it, other than looking at a larger -- you are not going to learn this in a small trial.

DR. TAMMINGA: Nor are you going to learn it in a trial without a placebo.

DR. LAUGHREN: Well, that is absolutely true.

DR. TAMMINGA: Dr. Winokur?

DR. WINOKUR: I had a question for Dr. Cohen-Mansfeld related to your presentation this morning. You made reference briefly to a concern about the pharmacological representativeness and mentioned problems entering. If this is not relevant to the current discussion, then just go past it, but I was concerned about what that was about and whether, for example, if it was necessary to do studies on patients that were the tip of the extension, and if safety issues were much more of a concern at a different point and yet clinically we would be extrapolating from such studies, then there could be safety issues that would were not well elucidated by such studies.

DR. COHEN-MANSFELD: Well, I want to thank you because I have been trying to get the opportunity to talk exactly about this. I think the safety issues that you are rising hide an even greater problem because, it is my understanding, that everybody is justifiably concerned about safety in this population. In fact, in our little non-pharmacologic study 20 percent died, many of them just between consent and starting the music. So, there is a very high mortality rate and this is a very vulnerable population. So, what happens is that companies which are doing pharmacological studies are concerned that too many people will die on the study, which does not look good. So, entry criteria require the relatively healthier portion of

this population. Therefore, we don't represent the most vulnerable. However, the most vulnerable do get the drugs and may get more side effects because they are more vulnerable, because they have more other drugs, etc., etc.

I think a mechanism to look at who is pre-screened out would be helpful. Now, I hear from colleagues that this is not unique only to dementia, that some of these issues may occur elsewhere. I think it is a very important issue in this vulnerable population, and I realize that it is raising more hurdles but I think if we are speaking about the public's health and safety it is extremely important.

DR. TAMMINGA: Dr. Reisberg?

DR. REISBERG: I wanted to respond to Dr. Laughren's question with respect to specific safety issues in this population, and you wanted more specifics. Patients, particularly severe dementia patients, patients who are likely to have either psychosis or agitation, are very, very susceptible to loss of ambulation. Although one would not see it immediately, loss of ambulation down the road is associated with increasing rigidity, ultimately increasing decubiti, increasing infection and increased mortality. So, this is a particular safety issue that really needs to be specifically addressed.

DR. HAMER: I want to agree with Dr. Cohen-Mansfeld in that this sort of issue is not particular

dementia. When we do clinical trials with the depressed we exclude suicidal people. In fact, when we give antidepressants to people we give them in high proportion to suicidal people. So, we exclude from the samples the very population we are studying. When we do antipsychotic clinical trials we exclude people abusing alcohol and drugs, and then we go out there into the big, wide world and use those medications in people abusing alcohol and drugs. So, this particular situation is not unusual or particular to the elderly demented.

DR. TAMMINGA: Dr. Lebowitz?

DR. LEBOWITZ: I want to react to Tom Laughren's challenge in kind of a different way, and that is we can't expect trials in the dementia population to address all the problems of geriatric psychopharmacology, and particularly to address them from the perspective of the agency and from agency policy. Clearly, at some point we need to think, or you need to think, or everyone needs to think collectively about what kinds of incentives there might be for everybody to do more geriatric trials in general to look at general issues of cognitive and behavioral toxicity in geriatric patients, regardless of the indication and regardless of the drug class that is being pursued.

There is a real need for study here though because you can't just take the labeling and then say, well, this

compound is going to be terrible for older people. The best example I know is clozapine. If you looked at the labeling for clozapine you would say anybody who ever prescribed this drug for an older person ought to go to jail -- there is no circumstance in the world, yet, there are reasonable data, good series of case reports and other things that say under certain circumstances clozapine is an absolutely appropriate drug to be used in older people despite what it says, and despite all the warnings, and everything else.

There are special issues here and we have to be careful about over-interpreting some of these special issues. Yes, you can reduce the risk of falls and consequent hip fractures by keeping people so depressed that they never get out of bed. If they never get out of bed they never get up and walk around, and if they never get up and walk around they are never going to fall over. So, it is hard to come to sort of generalizable conclusions without really digging in and investigating these kinds of issues in a specific case.

Is there a higher standard required for studies in a demented population? Sure, for a whole variety of reasons and, sure, we need to be careful about a whole lot of things. I am not convinced that there are any problems in your current processes. I think that you are able to identify, follow, determine issues of causality or at least

close correlation. I don't see that there is any need to do anything beyond that; simply to say that we had better made sure we follow our own procedures.

DR. LAUGHREN: Yes, I was just raising the question to see what the committee of experts thought about it, and if it is something that would need to be explored as part of a drug development program. Again, our experience is limited. We have seen only a few trials because companies have not submitted applications for these disorders. Is there enough of a signal of concern here that something more needs to be done?

DR. SCHNEIDER: As a matter of fact, people stay on these medications or are prescribed these medications for longer periods of time. Even though consensus guidelines might say, well, you should probably only prescribe for 16 weeks or so and then taper, people stay on for longer than even the 16 weeks.

On the other hand, some of the efficacy studies that are proposed or that have been in both depression and psychosis and dementia only go for 6 weeks or 12 weeks. So, there is no information on safety or efficacy for 12 weeks or 16 or 20 weeks. It would seem at least trials can gather the safety information up until the average time that you would expect to use the medication.

DR. LAUGHREN: Just one response, the difficulty,

of course, is that unless you have a controlled trial that goes for a longer period of time you are not going to learn very much in this population that has all kinds of bad outcomes and events.

DR. WHITEHOUSE: I find this kind of an awkward thing to say but I guess there is a possibility -- there is a bit of kind of "age-ism" floating in here that I am sure you are not intending because it sounds like what you want to be is excessively protective of people who are more likely to die and who are frail, and I certainly don't object to that. But, one would have to be careful that any additional protections that you set up actually did, in fact, end up somehow excluding that population from the opportunity to have studies done. I am just raising that as an issue.

But having said that, there is one concrete suggestion because I know we have had situations in which there have been in our field concerns about excess deaths, and then people go back and retroactively look at the deaths more intensively -- I mean, maybe there is a policy that you should set up to more intensively look at deaths in relationship to the potential concerns of the drug. Maybe you do this already, but my understanding is that in the case of some drugs you kind of identify the deaths and then there is a long process looking back to see if you could tie

them to the drug or not. Maybe you could more proactively try to see if there is some connection. Maybe you are doing it already but that is just one suggestion.

DR. KATZ: Well, of course, if we see deaths in an NDA database we take it very seriously. Attempts to establish causality outside the context of a controlled trial, a placebo-controlled trial, are very treacherous. It would be the rare case where you would see some sort of cause of death that would strike you as being odd in that population, and these people die of the things that older people die of.

Tom has said it several times and I agree, there is no good way to get at the question of increased mortality in this population without large, long-term placebo-controlled or appropriately controlled trials, unless you had an incredibly huge mortality associated with a drug which was way out of proportion of anything you would expect from the background rate, which is essentially inconceivable.

So, as Tom pointed out, I think in the few data sets we have seen so far there has been a signal that bad things happen to people on drug at a higher rate than placebo, things that could ultimately result in increased mortality but there is no way to know that unless you did the studies which are big, longer and placebo-controlled. I

just don't think there is any way around it.

DR. GRUNDMAN: As far as concrete suggestions go, I don't think I would power the study based on safety since I think you can collect that in the course of the study, and I think the primary outcome that you are after has to do with whether or not you are improving the patient's primary problem to begin with and quality of life.

Just in terms of how you can monitor these side effects more carefully, I think if you look at the side effect profiles of certain drugs as well as the risks associated with patients who are agitated and severely demented, you might be able to develop a list of safety items that you could query or monitor on a regular basis with each visit, for example, as opposed to leaving it in a free-form style. We have done that on occasion with some of the studies that we have done in the Alzheimer's Cooperative Study.

DR. TAMMINGA: We may be on the cusp of exhausting our experts. So, it is with some trepidation that I ask whether the FDA wants to address our attention to another topic. Tom?

DR. LAUGHREN: I just have a couple of very short questions. Getting back to psychosis in Alzheimer's disease, one question that will inevitably come to us, assuming that we can get agreement on this and it sounds

like we are almost there, that this is a real entity and should be studied -- the question comes up of how many studies you need to establish efficacy. Ordinarily, with a new indication you want two studies but it is not so obvious in a situation like this where you already have a drug, say, that is approved for another psychotic disorder that the answer is necessarily two studies. I am just raising that as a question to see if anyone here has any advice for us or opinions about that issue of how much additional data you need to establish efficacy in this additional psychotic population.

DR. TAMMINGA: For instance, how many studies do you require for a bipolar indication, for psychosis in bipolar illness?

DR. LAUGHREN: We have required two in that situation.

DR. SCHNEIDER: I will respond by asking a question. What is the difference between two small studies or one large study in the way you look at studies?

DR. LAUGHREN: If the small studies are big enough to show a difference between drug and placebo, I think ordinarily we would find them persuasive unless they are so small that one wouldn't believe the outcome. I don't think a big study necessarily carries, you know, more weight.

DR. TAMMINGA: I might add that we did have a

meeting for indications maybe half a year or three-quarters of a year ago where the Ns of the studies were quite small, although they were independent studies and they were considered independent studies and they were highly significant in outcome, but they were maybe Ns of 25 or something like that.

DR. KATZ: I am just wondering about the motivation of your question. Are you asking the other side of the coin? Are you saying if we have one multi-center trial that is positive, should that be considered the equivalent of two independent trials?

DR. SCHNEIDER: It seems you are coming at two studies from more of a regulatory point of view and a Code of Federal Regulations requirement that there be adequate and well-controlled studies. You know, I am putting up for a point of discussion that you could have two studies, each multi-centered, each with 200 patients in it, one of which may be positive, the other may be nominally positive or they both can be statistically significant. On the other hand, you could have a large multi-centered study with more sites in it with, let's say, 350 patients in it. So, it is not quite double. It would seem that it depends on how the studies are done and the quality of the studies on whether you value them and whether you value the results.

DR. KATZ: Well, ordinarily a multi-center trial,

if it is designed to be analyzed as a single trial, is taken to be a single trial. I suppose if they had multi-centers, all of which independently showed statistically significant differences you might argue that that provides the sort of independent replication and confirmation that truly independent studies do, but traditionally, unless there is some compelling reason to conclude otherwise, even a large multi-center trial is considered a single trial. If nothing else, two trials really do have sort of that independence, particularly if there are slightly difference designs. For example, if you have one multi-center trial you only have one design. If there is some sort of bias in there that you really can't detect, then you have no independent replication, or confirmation, or corroboration of its results. So, that is the usual way it is done.

DR. TAMMINGA: Tom?

DR. LAUGHREN: It is actually fairly common for drug company development programs to do two identical studies under the same protocol to get, you know, the two studies but it is replication. It is not so much the size of the study, it is replication.

DR. TAMMINGA: Dr. Caine?

DR. CAINE: I think practical issues are going to raise enough energy that you may end up with two studies anyway. If I were a pharmaceutical company I would be

really loathe to lump far progressed people perhaps with people who have developed their psychosis relatively earlier in the disease course and who might be ambulatory. They may have very different parameters to them. So, I think that there are some issues that might get two population samples and the like, and it may be that independent studies emerge anyway. There is also the question of size and how much you need for your side effect monitoring.

DR. TAMMINGA: Dr. Grundman?

DR. GRUNDMAN: I will just cut to the chase. I think two studies is a good idea.

DR. KATZ: As far as different studies enrolling different sets of subpopulations, that would ordinarily not be a requirement unless you folks said it should be the whole spectrum of severity or different subsets of a particular indication be studied. I think what Tom's question gets at is that ordinarily you need two studies to prove a point from a regulatory point of view for, let's say, a new indication. But the question is how much strength, if any, can we borrow from the approval in schizophrenia to say, well, we really only need one study in this psychosis of dementia to sort of give us the sort of replication that we ordinarily have.

DR. TAMMINGA: Tom, do you want to say something?

DR. LAUGHREN: Just to elaborate on that, in some

other areas, for example in epilepsy, it would not be uncommon to get an approval for another subtype of epilepsy on the basis of a single study, and that would be true in other therapeutic areas as well.

But just to follow up on Dr. Caine's point, that was actually the second question I wanted to ask, is there a need to do studies in different strata of this population, in both mildly impaired and in severely cognitively impaired patients?

DR. GRUNDMAN: I think if you are looking for labeling for treatment of psychosis or agitation in Alzheimer's disease or associated with Alzheimer's disease, then I think it would be reasonable to do two studies in that context.

DR. CAINE: Yes, I am sort of a bit quizzical -- I will come to the strata issue in a minute -- because I thought we spent the whole morning saying that this was highly distinctive from schizophrenia and that its rationale was that it was a separate, definable entity and there was not an overlap and, therefore, two studies, it seems to me, is the logical outgrowth of that.

The other issue, of course, I don't know from a regulatory point of view whether you need different strata. Clearly, in the long-run I think it is going to be useful guidance for the field if one understand the different side

effects in far advanced disease patients versus relatively less impaired individuals. But I don't know that from a regulatory point of view you need to separate that out.

DR. WHITEHOUSE: I guess it is an epistemological point about whether you need replication. I don't think there is an easy answer to that. I think it depends on the weight of evidence you have, how big it is, whether you can split it and what the evidence is in the other condition that you either think is uniquely different or somehow related, but it is different if it is psychosis or depression.

I guess the question I would like to raise, which is a bit of a corollary, is we know that we have some studies that have been done using a different approach to developing drugs for psychosis. That has been alluded already, the studies of alanzopine and respiredol. We know that in those studies, although the entry criteria were based on scores on instruments like the BEHAVE and the NPI, in those studies there were patients that would meet the criteria for psychosis which we are almost approaching. So, that is a very specific question but that is another issue where I would consider that those studies -- and this is very practical and talking about the field and where we are now -- ought to be considered in the weight of the equation as to whether you would want one or two more studies. So,

it is another part of the data set, and you might have other circumstances in which that would be the case. That is the situation now, so it might be interesting to see if the other experts feel as I do, that the evidence that has been collected really ought to count in terms of the evaluation of any subsequent studies that are done with more strict criteria.

DR. SCHNEIDER: There is a generalizability issue between outpatients and nursing home patients. They are a decade apart in age. They have different medical problems. They might represent some heterogeneity within a psychosis of Alzheimer's designation. As Tom pointed out, there may be excess sedation or there may be non-ambulatory patients in the nursing home. It would seem that a study in each of those groups would be highly informative but you may not need it for regulatory purposes. But certainly for utilization purposes and effectiveness purposes it is important.

Also, in terms of a public health point of view, it is the outpatients who stand to benefit the most from effective treatment of their psychosis, agitation, depression, etc. The inpatients -- there is kind of a fixed cost associated with them and already a lower life expectancy. So, just relatively speaking, there is a greater public health impact on effective treatment of

outpatients.

DR. REISBERG: I guess the general question was raised whether we need one of two studies, whether we can bootstrap Alzheimer's disease with data from other entities. I think we all generally responded by saying that certainly what we went over this morning was that the psychosis of Alzheimer's disease is different; the side effect issues are different.

But something that we didn't address at all, and we certainly won't want to address in any detail, is that the psychosis of Alzheimer's disease, although different from those other entities, does have much in common with respect to other dementing entities which might ultimately also be studied in this area. So, for example, although we didn't go into it, cerebral vascular dementia, we know, is really an entity which is very much on a continuum with Alzheimer's disease and it has long been known that cerebral vascular dementia comprises primarily what used to be called mixed cases, which express the pathology of both Alzheimer's disease and vascular risk factors. In addition, we now know that even if one looks at pure Alzheimer's cases cerebral vascular factors seem to be risk factors not only for cerebral vascular dementia but also for Alzheimer's disease. So, I think when ultimately one turns to some of those other entities the points about the number of studies that one

needs might be readdressed.

DR. COHEN-MANSFELD: I am not sure if this is a regulatory issue, but it seems to me that both from the point of view of efficacy and safety it does make a difference if the person is in early or late stages of dementi. Both co-occurring conditions and response to various interventions differ. So, there is an issue of course. What is mitigating it is if you take delusions, if they tend to occur at stages around five, you are more likely to have that stage in your sample anyway, but the stage should make a difference.

DR. REISBERG: Maybe just a word, stage probably makes a difference. It probably also makes a difference in terms of dosages of medication. As the disease evolves and, if you will, the brain reserve shrinks the amount of medication which can impact very dramatically on a patient changes quite a bit.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: I have one more question, unrelated to the psychosis. I hesitate to bring it up but maybe we can dispense with it extremely rapidly. We had a long discussion about psychosis and how it ought to be measured, and we decided, I believe, that there ought to be a measure assessing the psychotic symptoms as well as a functional measure. With agitation we are sort of not as definitive,

but if we were to look at agitation, whether as a symptom that cuts across several clinical entities or whether agitation of dementia, would the group also recommend that there be a second outcome looking at the functional concomitant as primary in addition to the effect on agitation per se? I see a lot of heads nodding. Yes?

DR. TAMMINGA: Is there anybody that would answer no to that? Dr. Grundman?

DR. GRUNDMAN: Just going back to your original supposition, I wasn't sure that we agreed that there should be as the primary outcome measure a functional assessment. I thought we had agreed that there would be a targeted symptom rating and a global, and then the functional assessment would be sort of a secondary outcome measure.

DR. KATZ: Well, I didn't hear that there was agreement that there ought to be a global. In fact, I guess maybe I was hoping it was going to be a functional measure, but some other measure that looks at something other than the core symptoms in an attempt to get at the sort of functioning. Maybe a global could do that; maybe it can't. Whatever we think we decided, I want to know whether an analogous sort of thing should be true for agitation, and I think I got the answer.

DR. REISBERG: I just think the point needs to be echoed. I think we did endorse a global, not necessarily a

functional measure.

DR. TAMMINGA: I will take this opportunity then to thank the experts who stuck with it until the bitter end, and even those experts who had to leave early, and all the committee members who were a part of this process, and say that I thought that it was a terrific day and a lot of very new issues were addressed. I suspect, because Dr. Laughren and Dr. Katz don't have any questions, maybe the ground that we covered will have been important to their considerations and what they are going to do with companies who come in with these indications. So, thank you all very much.

DR. KATZ: I just also want to thank the committee and invited guests. I think it has been a long day, very helpful and complicated issues, and I think you brought a fair amount of clarity and I appreciate it. And, we were in no danger of staying until midnight. The record for an advisory committee is 10:30.

DR. LAUGHREN: I just also wanted to add my thanks to the committee and our invited guests. For me, it has been a very helpful day and I think we have covered a lot of ground and made some real progress.

[Whereupon, at 5:10 p.m. the proceedings were adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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