Johns Hopkins
Medical Institutions

9330 '00 FEB 15 A11 :09

February 11th, 2000

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket 00N-0088

Ladies and Gentlemen:

We were pleased to note your announcement of a hearing on March 17th to be conducted by the agency's Psychopharmacologic Drugs Advisory Committee. According to the announcement, the hearing will address the development of drugs for treatment of the psychiatric and behavioral disturbances associated with Alzheimer's disease and related dementias (AD). An associated Position Paper poses several questions about the prevalence, measurement, and (especially) the classification of behavior disturbances in AD.

The authors of this letter have substantial research experience in the area of behavioral disturbances in AD. Represented by Dr. Lyketsos, we therefore will be available to attend the hearing in order to discuss new epidemiologic data, presented in the following paragraphs, which support a syndromic approach to the classification of behavior disturbances in AD. These data come from the first U.S. population study of behavioral disturbances in Alzhemeimer disease (see below) directed by Dr. Breitner. Dr. Lyketsos

00N-0088

C2

leads this project's efforts in the study of behavioral disturbencs in AD. We also propose new diagnostic criteria for two AD-associated behavioral syndromes. To support this letter and our hearing presentation, we offer the attached references, some of which are articles in press or under review.

First, we agree fully with the Position Paper's finding that non-cognitive psychiatric or behavioral disturbances are a frequent and serious complication of AD. It is well established that over half, perhaps as many as 80%, of patients with AD develop such disturbances during the course of their illness. Behavior disturbances may be more frequent and more complex in the middle stages of dementia, but their prevalence has not been studied adequately in the late stages of dementia. As the Position Paper notes, these disturbances are serious in that they are associated with considerable suffering and patient morbidity. They are further associated with significant caregiver burden and caregiver morbidity. Finally, they have adverse economic and social costs and are major contributors to institutionalization in long-term care facilities, and in psychiatric hospitals

Several studies have investigated the phenomenology, correlates, prognostic importance, and treatment of these behavior disturbances. We will not review these studies in depth, as we suspect that they are already familiar or will be addressed by others. However, we do wish to emphasize that most research in this area has been conducted using *clinical samples* that are subject to referral biases. Most such research has focused on relatively small case series with AD or on elderly with memory loss or dementia that has not been formally diagnosed.

The most widely used measures of these symptoms (1) are the NeuroPsychiatric Inventory (NPI) of Jeffrey Cummings and collaborators (from UCLA) and the Behavioral Pathology in Alzheimer's Disease Scale (Behave-AD) developed by Barry Reisberg and collaborators (from NYU). These measures have been used, for example, to assess clinical outcome in a variety of clinical trials of treatments for behavioral disturbances in Alzheimer's disease. Both the Behave-AD and the NPI have been used in studies of

atypical antipsychotics, and the NPI has also been used in studies of cholinesterase inhibitors. Several other scales are available to identify specific syndromes such as depression and apathy (for example, the Cornell Scale for Depression in Dementia and the Apathy Evaluation Scale).

However, in our view, the issue of the *classification* of the behavioral disturbances associated with AD has not been adequately addressed. The Position Paper identifies two approaches to this matter. The first is an individual symptom approach in which "target symptoms" are identified for intervention. The second approach, preferred in the Position Paper and by us, is a syndromic approach that attempts to classify behavioral disturbances along broader patterns of disturbance. The advantage of the syndromic approach is its verisimilitude relative to clinical practice, given that most disturbances of behavior in Alzheimer's disease occur in clusters (see new data presented below). By contrast, the symptom approach is narrowly focused and does not consider the substantial inter-correlations that exist between the various behavioral symptoms that occur in AD.

In the remainder of this letter, we will present recent results from the Cache County Study of Memory in Aging (CCSMA)[1]. Findings from this population study suggest a substantial prevalence of behavioral disturbances among community residing persons with dementia (not selected by self-referral to a specialty clinic). As well, CCSMA findings indicate that these disturbances cluster in identifiable patterns that suggest the appropriateness of diagnostic criteria for two syndromes. We should note, however, that what we present here may be less applicable to clusters of behavioral disturbance in very advanced dementia, often in institutionalized patients, such as wandering (2) or calling out repetitively. It is also noteworthy from these findings, as well as from other research (3), that agitation/aggression does not appear to be a primary disturbance. Instead, as we discuss below, agitation/aggression is a symptom that becomes manifest in the context of other disturbances. Finally, one cannot overstate the importance of general medical co-morbidity and environmental precipitants, including caregiver approach, to the genesis or

maintenance of these behavioral disturbances. These factors must therefore be taken into account when data are used to develop diagnostic criteria.

The Cache County Study of Memory and Aging (CCSMA) invited enrollment from the entire elderly population of Cache County, Utah, known for being among the longest lived populations in the United States, and for yielding extraordinary rates of participation in research. The CCSMA was designed as primarily an epidemiologic study of Alzheimer's disease. After an initial screening procedure, community residing individuals with suspected dementia, as well as a probability sample of the entire population (including, specifically, large numbers with no symptoms apparent on screening), were examined in detail by the study team. Approximately 330 individuals with dementia were thus ascertained and compared to approximately 670 individuals without dementia. All were administered the NeuroPsychiatic Inventory (NPI) to investigate possible behavior disturbances. Results that follow are referred to in Tables 1-3, currently in press (4).

Table 1 compares the frequencies of individual NPI disturbances in among Cache County elders with and without dementia. As expected, participants with dementia had significantly higher rates of behavioral disturbance. Table 2 compares the frequencies of NPI-ascertained behavior disturbances between patients with AD or Vascular dementia (VaD), the most frequent types of dementia, both diagnosed clinically. As can be seen, there were a few differences between the two groups. Depression was somewhat more frequent in VaD, and delusions were more frequent in AD. Table 3 compares the frequency of different disturbances across different stages of dementia, as defined using the Clinical Dementia Rating (CDR). This instrument classifies dementia as mild, moderate, or severe. Once again, few differences were noted across stages, although specific disinhibited behaviors and agitation/aggression were more frequent in more severe dementia.

The next analyses (5) focused on the behavioral disturbances of the subset of 198 participants in the Cache County study who had clinically diagnosed Alzheimer's disease. This investigation applied a statistical method called "latent class analysis" to determine

whether there were subgroups of study participants defined by their profile of behavioral disturbance. Table 4 shows the individual interrelationships between different behavioral disturbances in the study participants with AD. The table shows odds ratios and 95% confidence intervals relating individual disturbances, e.g. depression, to other disturbances, e.g. irritability. For example, the odds of irritability in the presence of depression was 3.15 times higher than when depression was absent. This is a statistically significant finding. It should be clear from the Table that there are many complex inter-relationships between individual behavioral symptoms and that individual symptoms rarely occur in isolation arguing against the use of a symptom based approach and in favor of a syndromic approach. For this reason, we engaged in the latent class modeling to investigate whether there a coherent behavior disturbance *profiles* that might be identified pointing to specific syndromes of disturbance

Table 5 shows the results of the latent class analyses. It appears that the AD patients can be classified into three groups based on their behavioral disturbance profile (the final statistical model was such that hallucinations constrained participants to the third class based on early statistical analyses.) The first group of approximately 60% (Class A) had few or no behavioral disturbances. This group had, on average 0.35 symptoms of behavioral disturbance, and none had more than two symptoms. We therefore refer to this group as the "minimally behaviorally disturbed" group. Their most frequent behavioral symptom was apathy, followed closely by agitation. Of note is that, while 9% had delusions, none had hallucinations. The second group (Class B), including about 28% of participants with AD, is an "affectively disturbed" group. Apathy, present in approximately 60%, was again their most frequent symptom, but depression and irritability were almost as common, each occurring in about 48% of patients. Participants in this group had, on average, 3.29 symptoms, and some had as many as 6 individual disturbances. About one-third had delusions. Agitation, aberrant motor behavior, and anxiety were also quite prevalent but not universal in this group.

Finally, the third group (Class C) evidenced predominately psychotic disturbance, and had slightly larger numbers of individual symptoms than Class B. They all had one or more psychotic symptoms, with 100% suffering from hallucinations and 58% suffering from delusions. Some participants in this group had as many as 7 symptoms. Thus, these analyses suggest that there are three natural groupings of AD victims based on behavioral disturbance profile. The majority of patients have few or mild disturbances, but there are two other groups, comprising about 40% of all, who suffer from either predominantly affective or psychotic disturbances.
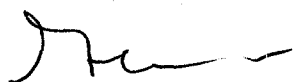
We have relied in part upon the above findings to develop operational criteria for the affective or psychotic disturbances associated with Alzheimer's disease. These criteria may prove useful as a basis for treatment studies and for the evaluation of new medications. The criteria are based on an approach articulated by Lyketsos and Treisman (6). They argue that, in order to attribute a syndrome to a brain disease, it is necessary to describe a characteristic set of symptoms *and* a temporal and coherent association between the causative disease and the syndrome. Table 6 shows the resulting criteria for the AD affective syndrome (6a) and psychotic syndrome (6b). It remains to be demonstrated whether these criteria can fulfilled operationally in practice through the use of one or more of the available behavioral symptom scales for AD. Given that the data gathering to date in our studies has relied on the Neuropsychiatric Inventory, we would prefer to begin our investigations with that inventory. Of note, the NPI now has a newer version that has added disturbances of sleep and appetite; these were not enumerated in Cache County.

In summary, we present findings that support the high prevalence and importance of behavioral disturbances in Alzheimer's disease. We propose that these disturbances are best approached in a syndromic fashion. We show population data that indicate a natural clustering of psychiatric and behavior disturbances in AD into two groups, one predominately affective and one predominantly psychotic. We also propose operational

criteria that might be used by the FDA and/or others to measure the effect of treatments, particularly drug treatments, for these disturbances.

We hope you will find the above information useful. We look forward to further discussions on this important topic at the hearing.
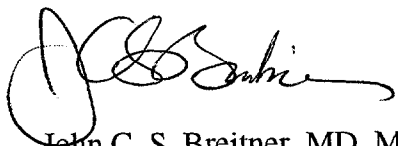
Sincerely,

Constantine G. Lyketsos, MD, MHS
Associate Professor of Psychiatry,
Director of the Neuropsychiatry Service

Peter V. Rabins, MD, MPH
Professor of Psychiatry
Director of Geriatric Psychiatry

John C. S. Breitner, MD, MPH
Professor and Chair, Department of Mental Hygiene
School of Hygiene and Public Health

References

1. Lyketsos CG, Steinberg M. Delirium, and the non-cognitive behavioral disturbances of dementia. Handbook of Psychiatric Measures, American Psychiatric Association (in press)
2. Klein DA, Steinberg M, Galik E, Steele C, Sheppard JMES, Warren A, Rosenblatt A, Lyketsos CG. Wandering behavior in Community-Residing Persons with Dementia. Int J Ger Psychiatry 1999; 14:272-279
3. Lyketsos CG, Steele C, Galik E, Rosenblatt A, Steinberg M, Warren A, Sheppard JM. Physical aggression in dementia patients and its relationship to depression. Am J Psychiatry 1999; 156:66-71
4. Lyketsos CG, Steinberg M, Tschantz J, Norton M, Steffens D, Breitner JCS. Mental and behavioral disturbances in dementia: Findings from the Cache County Study On Memory In Aging. Am J Psychiatry (in press)
5. Lyketsos CG, Steinberg M, Tschantz J, Norton M, Steffens D, Breitner JCS. Behavioral disturbances in Alzheimer's disease: Findings from the Cache County Study On Memory In Aging. Am J Psychiatry (under review)
6. Lyketsos CG, Treisman GT. Mood syndromes and causal associations (Editorial). Psychosomatics 1996 ; 5:407-412

Table 1. Comparison of CCSMA participants with and without dementia on frequency of individual NPI disturbances

	DEMENTIA PRESENT* (N=329)		DEMENTIA ABSENT (N=673)	
	Absent (n, %)	Present (n, %)	Absent (n, %)	Present (n, %)
Delusions	259 (81)	61 (19)	653 (98)	16 (2)
Hallucinations	276 (86)	45 (14)	668 (99)	4 (1)
Depression	249 (76)	78 (24)	624 (93)	47 (7)
Anxiety	266 (83)	56 (17)	628 (94)	38 (6)
Apathy	235 (72)	90 (28)	650 (97)	21 (3)
Irritability	258 (79)	67 (21)	640 (96)	30 (4)
Elation	325 (99)	3 (1)	669 (99.7)	2 (0.3)
Aggression	245 (76)	78 (24)	652 (97)	19 (3)
Disinhibition	294 (91)	30 (9)	665 (99)	6 (1)
Aberrant motor	275 (85)	47 (15)	662 (99.5)	3 (0.5)
TOTAL NPI	116 (39)	185 (61)	551 (84)	106 (16)

*for all comparisons, p<0.01

Table 2. Comparison of CCSMA participants with Alzheimer disease and participants with Vascular dementia on frequency of individual NPI disturbances and on NPI domain and total scores

	ALZHEIMER DISEASE (N=214)			VASCULAR DEMENTIA (N=62)		
	Absent (n, %)	Present (n, %)	NPI Mean (sd)	Absent (n, %)	Present (n, %)	NPI Mean (sd)
Delusions[a]	161 (78)	48 (23)	1.3 (6.19)	54 (92)	5 (8)	0.24 (0.98)
Hallucinations	180 (87)	28 (13)	0.72 (5.86)	53 (87)	8 (13)	0.29 (0.96)
Depression[b]	17 (80)	43 (20)	0.78 (2.3)	41 (67)	20 (33)	2.78 (10.8)
Anxiety	175 (83)	31 (17)	0.61 (1.9)	48 (81)	11 (19)	0.57 (1.7)
Apathy	150 (71)	61 (29)	1.66 (3.3)	46 (76)	14 (24)	0.43 (3.3)
Irritability	168 (80)	43 (20)	0.78 (2.18)	50 (82)	11 (18)	0.41 (0.94)
Elation	213 (99.5)	1 (0.5)	0.01 (0.21)	60 (98)	1 (2)	0.1 (0.79)
Aggression	163 (77)	48 (23)	1.2 (6.12)	41 (67)	20 (33)	1.1 (2.03)
Disinhibition	194 (92)	17 (8)	0.38 (1.79)	54 (89)	7 (11)	0.52 (1.8)
Aberrant motor	173 (83)	36 (17)	1.02 (2.7)	56 (92)	5 (8)	0.19 (0.76)
TOTAL NPI	79 (41)	114 (59)	8.1 (14.3)	18 (33)	37 (67)	7.7 (13.5)

[a] Wald Chi Square (df,1)=5.36, p=0.02 for difference in prevalence of delusions between AD and VaD
[b] Wald Chi Square (df,1)=4.17, p=0.041 for differences in the prevalence of depression between AD and VaD

Table 3. Comparison of CCSMA participants with dementia across CDR stages on frequency of NPI disturbances and on NPI domain/total scores

	CDR 0.5 or 1.0 (n=134)			CDR 2 (n=90)			CDR 3-5 (n=106)		
	Absent (n, %)	Present (n, %)	Mean (sd)	Absent (n, %)	Present (n, %)	Mean (sd)	Absent (n, %)	Present (n, %)	Mean (sd)
Delusions	115 (86)	18 (14)	1.7 (7.0)	64 (72)	24 (28)	1.2 (2.9)	80 (80)	20 (20)	0.78 (2.25)
Hallucinations[a]	123 (92)	11 (8)	0.18 (0.92)	69 (78)	19 (22)	0.79 (2.2)	84 (84)	16 (16)	1.15 (8.4)
Depression	103 (77)	31 (23)	0.80 (2.0)	59 (67)	29 (33)	1.3 (2.73)	85 (81)	20 (19)	1.78 (8.7)
Anxiety	112 (85)	20 (15)	0.48 (1.6)	65 (86)	21 (14)	0.99 (2.35)	89 (86)	14 (14)	0.46 (1.85)
Apathy	97 (73)	36 (27)	1.2 (2.35)	67 (77)	20 (23)	1.1 (2.41)	70 (67)	34 (33)	2.33 (4.1)
Irritability	111 (84)	21 (16)	0.41 (1.48)	66 (78)	21 (22)	0.8 (1.74)	81 (77)	24 (23)	0.97 (2.6)
Elation	133 (99)	1 (1)	0.02 (0.17)	87 (99)	1 (1)	0.07 (0.66)	105 (99)	1 (1)	0.03 (0.31)
Aggression[b]	114 (87)	17 (13)	1.0 (7.0)	64 (74)	22 (26)	0.9 (1.8)	66 (69)	30 (31)	1.57 (3.2)
Disinhibition	123 (92)	11 (8)	0.30 (1.34)	79 (91)	8 (9)	0.50 (1.98)	92 (88)	12 (12)	0.47 (1.9)
Aberrant motor[c]	119 (91)	12 (9)	0.28 (0.91)	72 (83)	15 (17)	1.17 (3.0)	84 (81)	20 (19)	1.1 (2.97)
TOTAL NPI	58 (47)	65 (53)	5.8 (12.5)	26 (32)	56 (68)	8.8 (11.1)	31 (33)	63 (67)	10.6 (17)

[a] Wald Chi Square (df,1)=3.39, p=0.066

Table 4. Matrix of Odds Ratios (95% Confidence Intervals in Parentheses) between domains (bottom half). Cells in bold indicate intersections between domains that deviate significantly from expectation under the null hypothesis of no association. Number and percentage of individuals endorsing each domain are on diagonal. Number of individuals endorsing combinations of domains are in top half.

	Apathy	Depression	Anxiety	Irritability	Elation	Delusions	Hallucinations	Agitation	Aberrant Motor	Disinhibition
Apathy	54 (27.3)	22	17	20	1	19	9	17	17	7
Depression	5.14 (2.45-7.83)	39 (19.7)	19	14	1	14	10	12	14	3
Anxiety	3.95 (1.80-8.66)	10.67 (4.58-24.87)	32 (16.2)	14	1	13	6	11	14	6
Irritability	4.11 (1.96-8.64)	3.15 (1.44-6.91)	3.86 (1.69-8.80)	38 (19.2)	0	15	6	19	18	9
Elation	.269 (.214-.339)	.193 (.145-.257)	.157 (.114-.217)	.807 (.754-.864)	1 (0.5)	1	1	0	1	1
Delusions	2.46 (1.22-4.97)	2.31 (1.08-4.96)	2.87 (1.28-6.40)	2.83 (1.32-6.06)	.223 (.17-.29)	45 (22.7)	15	18	14	12
Hallucinations	1.49 (.62-3.59)	3.08 (1.27-7.47)	1.69 (.62-4.59)	1.31 (.49-3.53)	.127 (.09-.183)	6.46 (2.70-15.44)	26 (13.1)	8	7	3
Agitation	2.30 (1.12-4.73)	1.99 (.90-4.39)	2.38 (1.04-5.44)	6.27 (2.88-13.67)	.792 (.74-.85)	3.77 (1.79-7.92)	1.87 (.75-4.68)	41 (20.7)	14	12
Aberrant Motor	3.43 (1.59-7.38)	3.89 (1.74-8.70)	5.68 (2.45-13.16)	8.1 (3.57-18.39)	.168 (.12-.23)	3.00 (1.37-6.60)	1.98 (.76-5.16)	3.55 (1.60-7.89)	34 (17.2)	9
Disinhibition	2.53 (.87-7.36)	1.02 (.274-3.81)	4.03 (1.32-12.26)	7.97 (2.63-24.09)	.071 (.043-.12)	18.18 (4.86-68.07)	1.74 (.46-6.63)	21.24 (5.64-80.0)	9.48 (3.11-28.93)	15 (7.6)

Table 5. Conditional Probabilities and Distribution of Symptoms by Class in Model M3R

N (%) *cond* *p*	Apathy	Delusions	Agitation	Depression	Irritability	Aberrant Motor	Anxiety	Hallucinations	# of symptoms, (SD) min-max
Class A (117; 59%)	12 (10.3) *.11*	11 (9.4) *.09*	10 (8.5) *.10*	2 (1.7) *.02*	4 (3.4) *.05*	0 (0) *.01*	2 (1.7)	0(0) *0*	0.35 (0.53) 0-2
Class B (55; 28%)	33 (60.0) *.59*	19 (34.5) *.35*	23 (41.8) *.39*	27 (49.1) *.48*	28 (50.9) *.48*	27 (49.1) *.47*	24 (43.6) *.44*	0 (0) *0*	3.29 (1.29) 1-6
Class C (26; 13%)	9 (34.6) *.35*	15 (57.7) *.58*	8 (30.8) *.31*	10 (38.5) *.38*	6 (23.1) *.23*	7 (26.9) *.27*	6 (23.1) *.23*	26 (100.0) *1.0*	3.35 (1.74) 1-7

Table 6. Proposed diagnostic criteria for dementia-associated affective or psychotic disturbance

6A. Affective Disorder

A. Dementia by DSM-IV criteria

B. A prominent disturbance of affect, that represents a change from the patient's baseline, as evidenced by the presence of one or more of the following symptoms:
   - a. depression
   - b. irritability
   - c. apathy
   - d. anxiety
   - e. euphoria

C. Associated symptoms, also representing a change from baseline that are less prominent than the disturbance of affect. Two or more of the following must be present (for a total of three when added to the one(s) from "A"):
   - a. aggression
   - b. psychomotor agitation
   - c. delusions
   - d. hallucinations
   - e. sleep disturbance
   - f. appetite disturbance

D. The symptoms from "A" above cluster together in time, occur most days, and the disturbance has a duration of two weeks or longer

E. The disturbance first onset after (or within two years before) the onset of cognitive symptoms that eventually developed into dementia

F. The disturbance cannot be explained in its entirety by another cause such as a general medical condition, caregiver approach, environmental precipitant or life stressor (such as relocation of residence or death of a spouse)

6B. Psychotic Disorder

A. Dementia by DSM-IV criteria

B. Prominent delusions or hallucinations that impact on the patient's behavior

C. Associated symptoms, also representing a change from baseline that are less prominent than the delusions or hallucinations. Two or more of the following must be present (for a total of three when added to the one(s) from "A"):
   - a. depression
   - b. irritability
   - c. apathy
   - d. anxiety
   - e. euphoria
   - f. aggression
   - g. psychomotor agitation

D. The symptoms from "A" above cluster together in time, occur most days, and the disturbance has a duration of two weeks or longer

E. The disturbance first onset after (or within two years before) the onset of cognitive symptoms that eventually developed into dementia

F. The disturbance cannot be explained in its entirety by another cause such as a general medical condition, caregiver approach, environmental precipitant or life stressor (such as relocation of residence or death of a spouse)

To Open Envelope, Pull Tab Slowly from Either Side

Attach Airborne Express Shippers Label within the dotted lines.

FROM

JOHNS HOPKINS UNIV
PSYCH 320 OSLER
600 N WOLFE ST

BALTIMORE   MD 21287

Lyketsos

410-955-615

TO

FOOD AND DRUG ADMINISTRATION

5630 Fishers Lane   Room 1061

Rockville   MD   20852

DOCKETS MANAGEMENT BRANCH

1789954784

Preprint Format No. 4781293

Origin BWI

Airbill Number 1789954784

Method of Payment — *Assumed sender unless otherwise noted*
☐ Bill Sender
☐ Bill Receiver
☐ Bill 3rd Party
☐ Paid in Advance

AIRBORNE EXPRESS.

EXP (Letter - 150 lbs)
NAS (Letter - 5 lbs)
SDS (Letter - 150 lbs)

Billing Reference *will appear on Invoice*

No. of Pkgs	Weight(LBS)	One box must be checked		
		Letter Express	Express Pack	Other Packaging
1	1	☑	☐	☐

Special Instructions
☐ ◄SAT   ☐ ◄HAA
☐ ◄LAB   ☐

PEEL BACK FROM

178 995 4784

MLDA 4x ABH

United States Shipping

1. Complete applicable white sections of the U.S. Airbill. Sign and date the Airbill at the Sender's Signature line. Please press hard.
2. Peel off protective covering from back of Airbill.

Limitation on Contents

The maximum acceptable contents of a Letter Express are forty (40) 8-1/2 x 11 pages. If the gross weight of the contents, envelope and airbill exceeds 1/2 pound, the next higher rate will apply. Contents