Depression in Alzheimer Dementia

순천향 의대 신경과
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Axes of evaluation for dementia

- Historical axis: history taking
- Cognitive axis: screening neuropsychological test
- Motor axis: neurologic examination
- **Behavioral axis: evaluation of BPSD**
- Functional axis: functional evaluation
- Medical axis: medical review

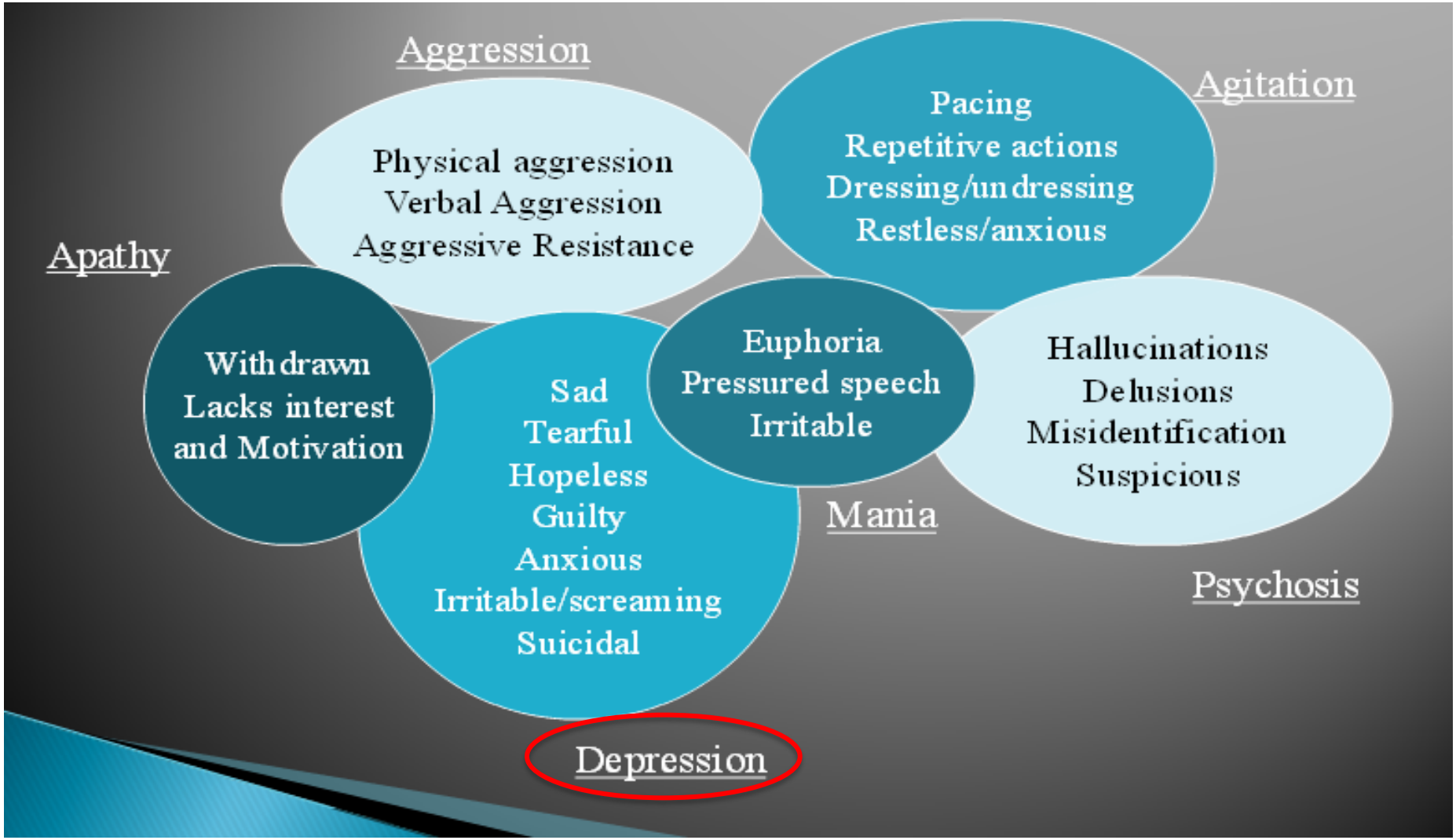
Severe dementia(2006). 3-20

Definition of BPSD

- Symptoms of disturbed perception, thought content, mood or behavior that frequently occur in patients with dementia

- Umbrella term for a heterogeneous group of non-cognitive symptoms that are almost ubiquitous in dementia

BPSD Symptom Clusters



Classification of BPSD

Psychological symptoms	*Behavioral symptoms*
Delusion	Aggression
Hallucination	Wandering
Paranoia	Sleep disturbance
Depression	Inappropriate eating disord.
Anxiety	Inappropriate sexual beh.
Reduplication	
Misidentification	

Luxenberg JS. Clinical issues in the BPSD of dementia. Int J Geriatr Psychiatry. 2000;15:S5-S8

Change of BPSD as *progression*

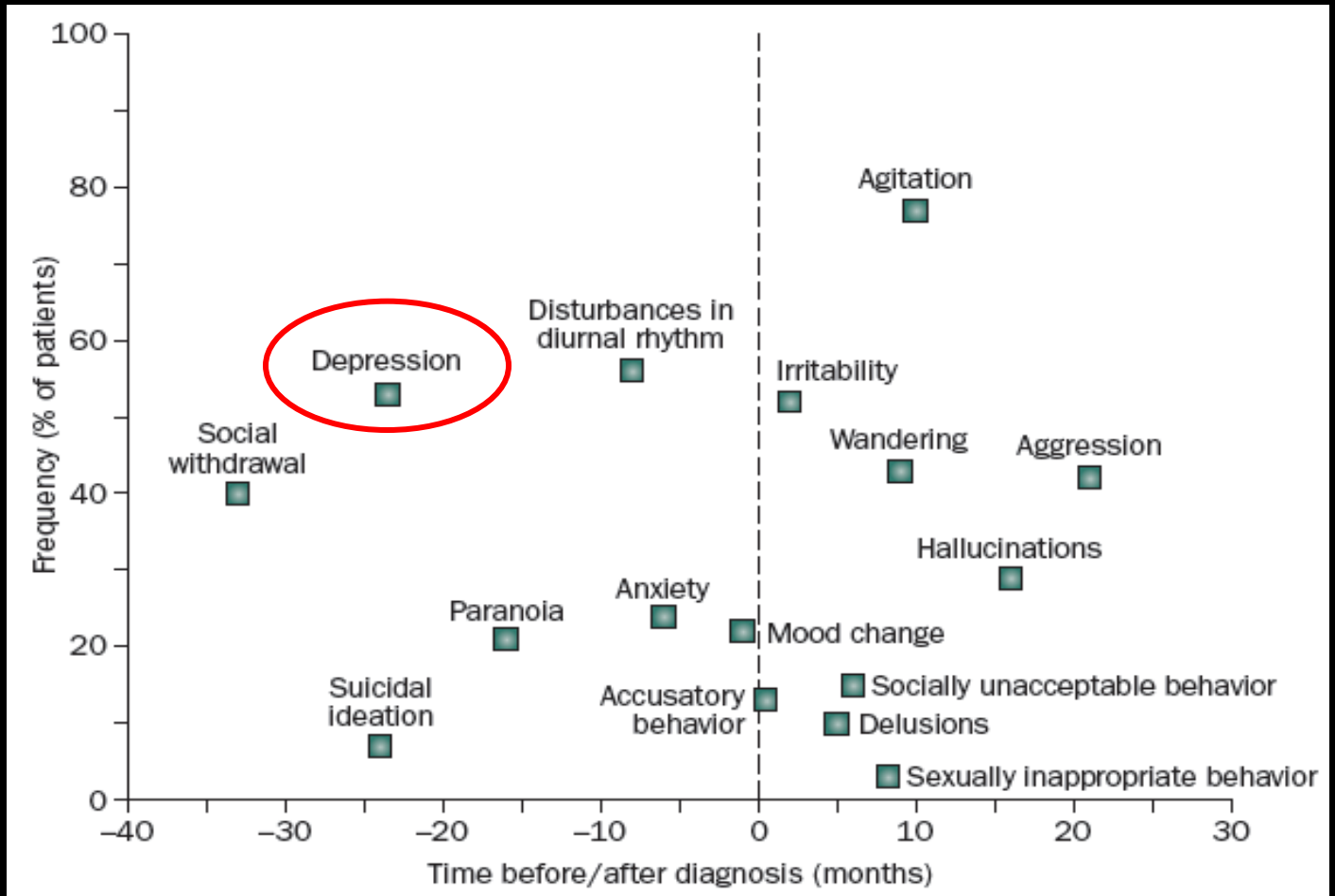
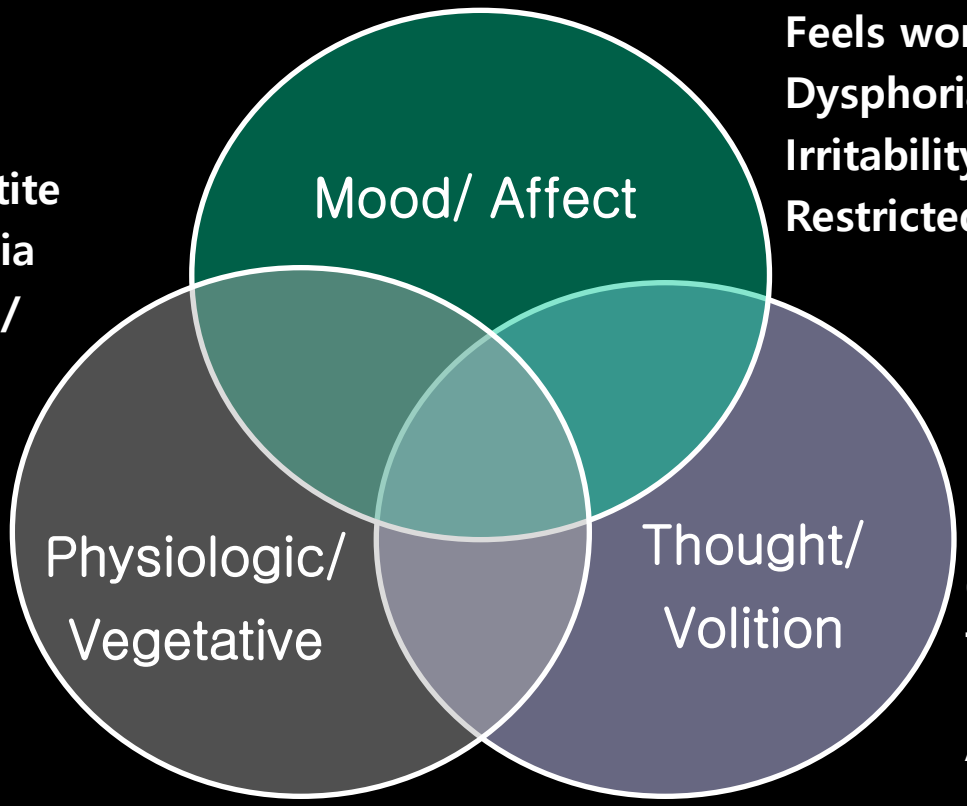


Figure 1 | Peak frequency of behavioral symptoms as Alzheimer disease progresses. Permission obtained from Blackwell Publishing © Jost, B. C. & Grossberg, G. T. *J. Am. Geriatr. Soc.* **44**, 1078–1081 (1996).

Nat. Rev. Neurol. 2009; 5: 245-255

Major Categories of Depression Symptomatology

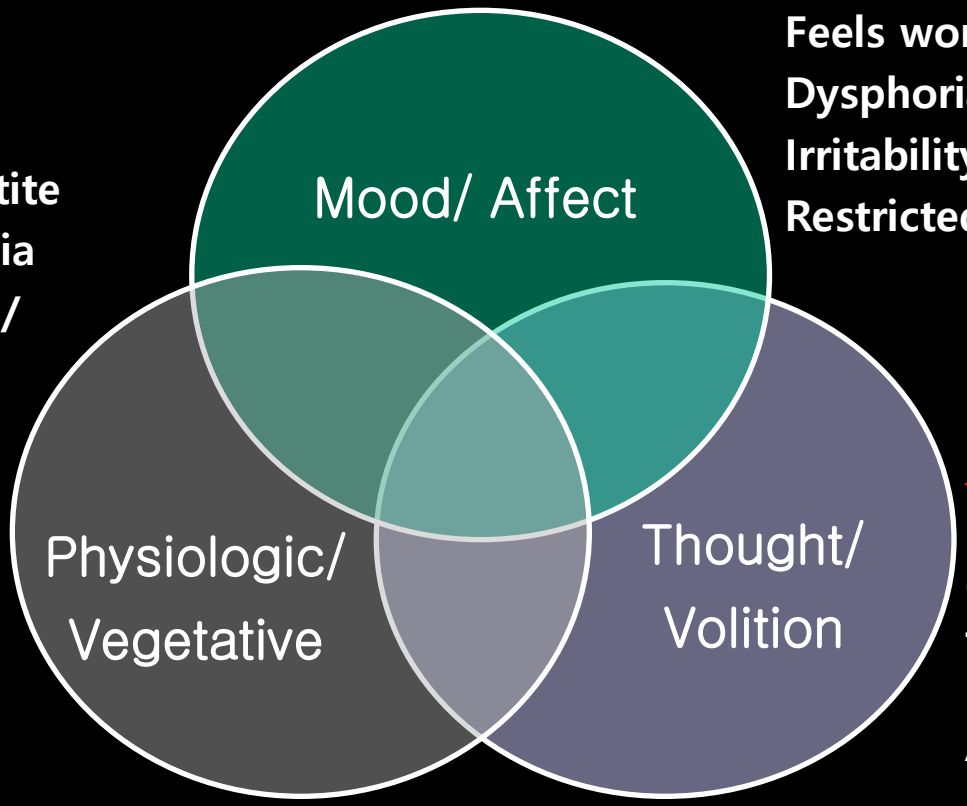


Depressive mood
Feels worthless/ guilt
Dysphoria
Irritability
Restricted affect

Loss/ change of appetite
Insomnia/ hypersomnia
Psychomotor agitation/ retardation
Loss of libido
Somatic symptoms

Loss of interest
Loss of energy
Cognitive impairment
Thoughts of death/ suicidal ideation
Apathy
Delusion /hallucination

Major Categories of Depression Symptomatology



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Loss of energy
Cognitive impairment
Thoughts of death/ suicidal ideation
Apathy
Delusion /hallucination

Major Depressive Episode: DSM-IV

> 5 including 1 or 2, > 2 weeks

1. ***Depressed mood***
2. ***Loss of interest***
3. Loss or change of appetite
4. Insomnia/ hypersomnia
5. Psychomotor agitation/ retardation
6. Loss of energy
7. Feeling of worthlessness/ guilt
8. Cognitive impairment
9. Recurrent thoughts of death/ suicidal ideation

DSM-IV에 정의된 우울 증상(APA, 1997)

주요우울삽화(Major depressive episode)

- 2주 동안 다음 아홉 가지 증상 중에서 다섯 개 이상이면서 1)이나 2) 중 하나는 반드시 포함
  1) 우울감, 2) 흥미의 소실, 3) 체중이나 식욕의 변화, 4) 수면의 변화, 5) 정신운동 항진이나 지체, 6) 피로감과 활력소실, 7) 무가치감과 죄책감, 8) 집중력 감퇴, 9) 죽음에 대한 사고

주요우울증(Major depressive disorder)

- 상기 주요우울삽화가 있으면서 다른 질환에 의한 것이 아닐 때
- 경도, 중등도, 중증의 여부, 정신증적 양상의 존재 여부, 급성 만성의 여부, 비정형 양상의 존재 여부, 산후 발병의 여부 등을 명기

기분저하증(Dysthymic disorder)

- 2년 이상 다음 여섯 가지 증상 중 두 개 이상을 포함하는 우울감
- 또한, 증상 없이 2달 이상 지낸 적이 없어야 한다.
  1) 식욕의 변화, 2) 수면의 변화, 3) 피로감과 활력소실, 4) 자존감의 저하, 5) 집중력과 결단력 감퇴, 6) 비관적 생각

경도우울증(Minor depressive disorder)

- 주요우울증에서와 같으나 아홉 가지 증상 중에서 2-4개의 증상에만 해당할 경우

주요우울장애의 DSM-5 진단 기준

1번과 2번 중에 하나는 반드시 포함되고, 다섯 가지 이상이 동일한 2주 동안에 나타난다.

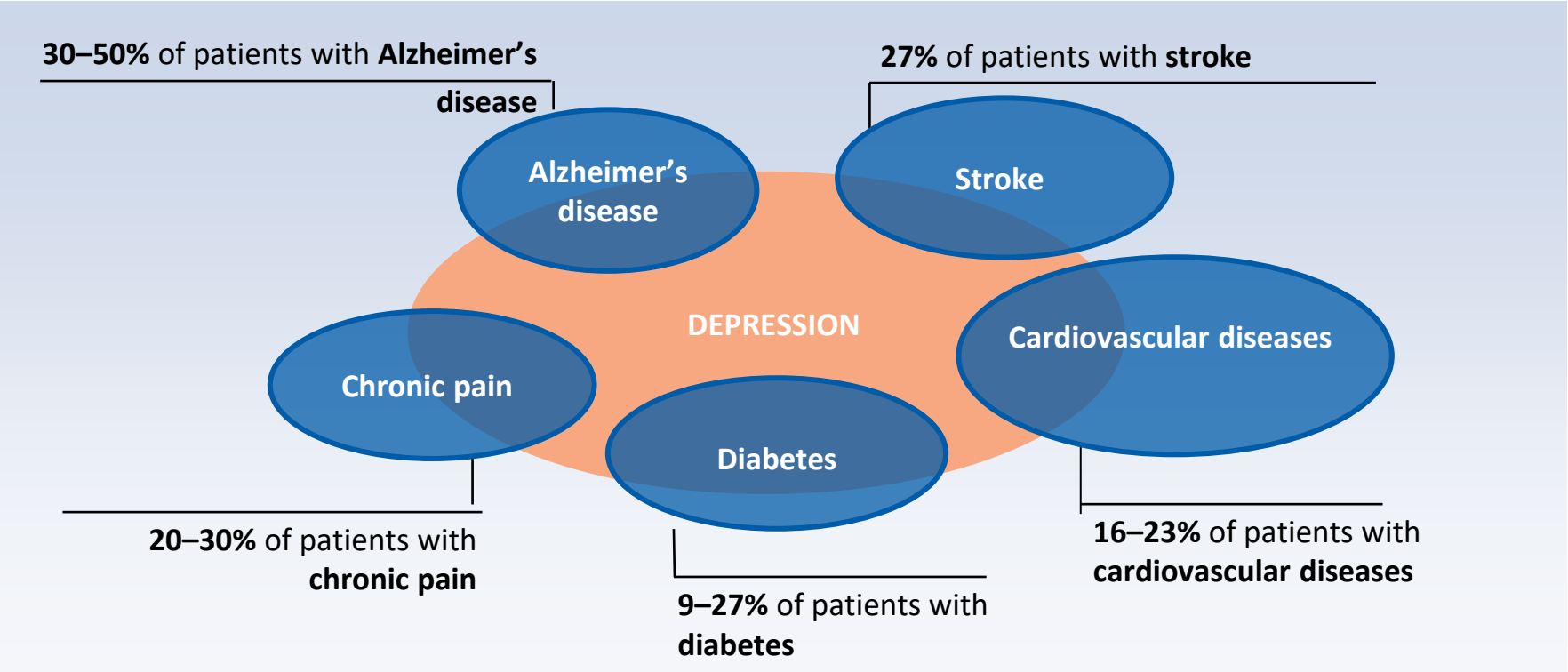
1. 거의 하루종일 우울한 기분이 거의 매일 이어지며, 이는 주관적 느낌 (예컨대 슬픔, 공허감, 아무런 희망이 없음)이나 객관적 관찰 소견(예컨데 자주 눈물을 흘림)으로 확인된다.
2. 거의 하루종일 거의 모든 활동에 대한 흥미나 즐거움 감소된 상태가 거의 매일 이어짐.
3. 체중 또는 식욕의 심한 감소나 증가
4. 거의 매일 반복되는 불면이나 과수면
5. 정신운동의 초조 (예: 안절부절 못함) 또는 지체 (예: 생각이나 행동이 평소보다 느려짐)
6. 거의 매일 반복되는 피로감 또는 활력 상실
7. 무가치감, 또는 지나치거나 부적절한 죄책감이 거의 매일 지속됨.
8. 사고력 또는 집중력의 감퇴, 결정을 못 내리는 우유부단함이 심해져 거의 매일 지속됨.
9. 죽음에 대한 생각이 되풀이되어 떠오르거나, 특정한 계획이 없는 자살 사고가 반복되거나, 자살을 시도하거나, 구체적인 자살 계획을 세움.

The effect of the depression

Heart disease	Most reviews conclude that depression is a risk factor for heart disease
Stroke	Depression is a risk factor for stroke
Diabetes mellitus	Depression is a risk factor for Type 2 diabetes. Depression is associated with poor adherence to treatment recommendations and poorer outcomes
Asthma	Significant association between depression or depressive symptoms and severity of asthma (e.g., psychological dysfunction is a risk factor for frequent exacerbation)
Cancer	Untreated depression can lead to decreased compliance with medical care, prolonged hospital stays, increased morbidity and possibly increased mortality
Arthritis and osteoporosis	Some evidence for depression as a risk factor for osteoporosis

Adapted from Clarke & Currie. Med J Aust 2009; 190: S54–S60

Late-life depression prevalence is higher in those patients with other medical illness



Comorbid diseases need to be considered when prescribing an antidepressant

Dolder et al. ADIS, Drugs Aging 2010; 27: 625–640; Chemali et al. Harv Rev Psychiatry 2009; 17: 242–253

The Prevalence of Depression in Alzheimer's Disease

Diagnostic Criteria	Major Depression (DSM) (25 studies, n=7549)	Specific Criteria for Dementia* (33 studies, n=11842)	
Total of 63 studies	12.7%	42%	
Population based	5%	35%	
Multiple source	8%	42%	
Single source	17%	43%	
Mild AD	14%	40%	MMSE ≥ 17
Severe AD	8%	48%	MMSE < 17
* NPI, PDC-dAD, CERAD-BRSD, CUSPAD, ADAS-Noncog, BEHAVE-AD, CADD, CSDD, HADS, GDS, MADRS			

- **Depression in patients with dementia is associated with**
  - Poorer quality of life
  - Greater disability in activities of daily living
  - Faster cognitive decline
  - Higher nursing home placement
  - Higher mortality rate
  - Higher burden in caregivers

Banerjee, et al. Lancet. 2011;378(9789):403-11

Depressive symptoms, cognitive decline, and risk of AD in older persons

R.S. Wilson, PhD; L.L. Barnes, PhD; C.F. Mendes de Leon, PhD; N.T. Aggarwal, MD; J.S. Schneider, MD; J. Bach, MSW; J. Pilat; L.A. Beckett, PhD; S.E. Arnold, MD; D.A. Evans, MD; and D.A. Bennett, MD

Abstract—*Background*: Cross-sectional and retrospective case-control studies suggest an association of depression symptoms with cognitive impairment and AD, but there have been few prospective studies and their results have been inconsistent. *Methods*: Participants are Catholic clergy members who were aged ≥65 years and who did not have clinical evidence of AD. During a 7-year period, they underwent annual clinical evaluations that included clinical classification of AD and detailed cognitive function testing from which global and specific measures of cognition were derived. Number of depressive symptoms was assessed at baseline with a modified, 10-item Center for Epidemiologic Studies Depression Scale (CES-D). The association of CES-D score with incident AD, using proportional hazards models, and cognitive decline, using random effects models, was examined. *Results*: At baseline, participants reported an average of about one depressive symptom on the CES-D scale (range, 0 to 8). During the 7 years of follow-up, 108 persons developed AD. In analyses that controlled for selected demographic and clinical variables including baseline level of cognitive function, CES-D score was associated with both risk of AD and rate of cognitive decline. For each depressive symptom, risk of developing AD increased by an average of 19%, and annual decline on a global cognitive measure increased by an average of 24%. *Conclusions*: The results raise the possibility that depressive symptoms in older persons may be associated with risk of developing AD.

NEUROLOGY 2002;59:364–370

Prevalence of Neuropsychiatric Symptoms in Dementia and Mild Cognitive Impairment

Results From the Cardiovascular Health Study

Context Mild cognitive impairment (MCI) may be a precursor to dementia, at least in some cases. Dementia and MCI are associated with neuropsychiatric symptoms in clinical samples. Only 2 population-based studies exist of the prevalence of these symptoms in dementia, and none exist for MCI.

Objective To estimate the prevalence of neuropsychiatric symptoms in dementia and MCI in a population-based study.

Design Cross-sectional study derived from the Cardiovascular Health Study, a longitudinal cohort study.

Setting and Participants A total of 3608 participants were cognitively evaluated using data collected longitudinally over 10 years and additional data collected in 1999-2000 in 4 US counties. Dementia and MCI were classified using clinical criteria and adjudicated by committee review by expert neurologists and psychiatrists. A total of 824 individuals completed the Neuropsychiatric Inventory (NPI); 362 were classified as having dementia, 320 as having MCI; and 142 did not meet criteria for MCI or dementia.

Main Outcome Measure Prevalence of neuropsychiatric symptoms, based on ratings on the NPI in the previous month and from the onset of cognitive symptoms.

Results Of the 682 individuals with dementia or MCI, 43% of MCI participants (n=138) exhibited neuropsychiatric symptoms in the previous month (29% rated as clinically significant) with depression (20%), apathy (15%), and irritability (15%) being most common. Among the dementia participants, 75% (n=270) had exhibited a neuropsychiatric symptom in the past month (62% were clinically significant); 55% (n=199) reported 2 or more and 44% (n=159) 3 or more disturbances in the past month. In participants with dementia, the most frequent disturbances were apathy (36%), depression (32%), and agitation/aggression (30%). Eighty percent of dementia participants (n=233) and 50% of MCI participants (n=139) exhibited at least 1 NPI symptom from the onset of cognitive symptoms. There were no differences in prevalence of neuropsychiatric symptoms between participants with Alzheimer-type dementia and those with other dementias, with the exception of aberrant motor behavior, which was more frequent in Alzheimer-type dementia (5.4% vs 1%; $P=.02$).

Conclusions Neuropsychiatric symptoms occur in the majority of persons with dementia over the course of the disease. These are the first population-based estimates for neuropsychiatric symptoms in MCI, indicating a high prevalence associated with this condition as well. These symptoms have serious adverse consequences and should be inquired about and treated as necessary. Study of neuropsychiatric symptoms in the context of dementia may improve our understanding of brain-behavior relationships.

JAMA. 2002;288:1475-1483 www.jama.com

Physical Aggression in Dementia Patients and Its Relationship to Depression

Constantine G. Lyketsos, M.D., M.H.S., Cynthia Steele, R.N., M.P.H., Elizabeth Galik, R.N., M.S.N., Adam Rosenblatt, M.D., Martin Steinberg, M.D., Andrew Warren, M.B.B.S., and Jeannie-Marie Sheppard, B.A.

Objective: The goal of this study was to determine the frequency of physically aggressive behavior in community-residing patients with dementia and its relationship to depression. **Method:** A consecutive series of 541 patients with DSM-IV-defined dementia underwent comprehensive neuropsychiatric evaluation and were rated on the Cornell Scale for Depression in Dementia, the Mini-Mental State, the Psychogeriatric Dependency Rating Scale, and the General Medical Health Rating. **Results:** Physically aggressive behavior was exhibited by 79 patients in the 2 weeks before evaluation. Aggressive behavior was closely associated with moderate to severe depression, male gender, and greater impairment in activities of daily living, even after adjustment for delusions, hallucinations, sleep disturbance, and severity of cognitive impairment. After adjustment for depression, gender, and impairment in activities of daily living, there was no association between physically aggressive behavior and the presence of either delusions or hallucinations. **Conclusions:** A substantial minority of patients with dementia exhibit physically aggressive behavior, and this aggression is strongly linked with the presence of depressive symptoms. It is possible that the identification and treatment of depression in dementia may be a means of preventing and managing physically aggressive behavior.

(Am J Psychiatry 1999; 156:66–71)

Dementia and Neurocognitive Disorders
2012; 11: 87-94

■ ORIGINAL ARTICLE ■

Clinical Characteristics of Behavioral and Psychological Symptoms in Patients with Drug-naïve Alzheimer's Disease

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Background: Behavioral and psychological symptoms of dementia (BPSD) are less well-defined aspects of Alzheimer's disease (AD). We designed this study to explore the followings: 1) the clinical profiles of BPSD 2) the clustered-groups domains of the Korean-Neuropsychiatric Inventory (K-NPI) assessment of BPSD 3) the clinical characteristics of the clustered-groups of BPSD in patients with drug-naïve probable AD. **Methods:** Descriptive and cluster analyses of the 12 K-NPI domains were done in 220 patients with drug-naïve probable AD. After clustering these domains, characteristics of these positive symptoms clustered-group of patients were compared with the negative symptoms groups of patients. **Results:** The mean Korean-Mini Mental Status Examination (K-MMSE), Clinical Dementia Rating (CDR) scale, and K-NPI scores were 15.0, 1.6, and 14.2, respectively. The CDR and K-MMSE scores correlated with total K- NPI scores, and depression was the most common symptom. According to cluster analysis, five major clusters were identified. Using the associated neuropsychological dysfunctions, characteristics of each group were defined. **Conclusions:** This study identified the clustered-domains for K-NPI, and suggested the possible anatomical substrates for these groups in drug-naïve AD patients. These attempts may clarify the complex and bizarre behavioral and psychological symptoms as more neurologically relevant symptoms.

Key Words: *Behavioral and psychological symptoms of dementia, Drug-naïve, Alzheimer's disease, Cluster analysis*

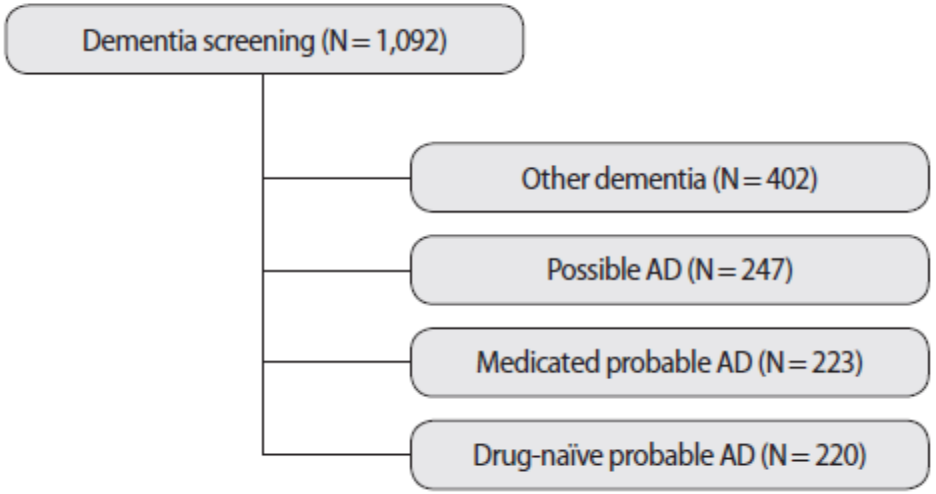

Fig. 1. Flow diagram of patient screening and inclusion.
AD, Alzheimer's disease.

Table 1. Demographic and clinical features of study subjects

Characteristics	CDR 0.5 (n = 69)	CDR 1 (n = 103)	CDR 2 (n = 37)	CDR 3 (n = 11)	Total (n = 220)
Age (yr)	72.8 ± 8.4	75.0 ± 7.4	75.5 ± 8.4	79.7 ± 5.1	74.5 ± 8.0
Female gender (%)	40 (60%)	62 (60%)	21 (57%)	10 (91%)	133 (60%)
Age at onset	70.9 ± 7.8	71.4 ± 9.4	71.9 ± 8.2	74.4 ± 4.9	71.4 ± 8.6
Disease duration, months	24.8 ± 21.0	42.2 ± 29.1	43.2 ± 21.8	65.2 ± 21.8	33.4 ± 25.6
Education years	10.4 ± 5.3	8.6 ± 5.7	6.5 ± 6.4	5.1 ± 5.8	8.7 ± 5.9
K-MMSE	23.0 ± 4.1	18.5 ± 5.1	12.2 ± 3.7	7.1 ± 5.0	15.0 ± 6.7
CDR					1.6 ± 0.8
Barthel index	20.0 ± 0	19.6 ± 1.2	18.3 ± 2.9	17.4 ± 2.7	19.4 ± 1.6
GDS	12.8 ± 6.9	14.2 ± 23.3	15.6 ± 7.0	14.6 ± 7.0	13.9 ± 7.2
K-NPI total	5.2 ± 9.8	15.4 ± 12.2	29.8 ± 20.0	41.1 ± 30.7	14.5 ± 23.0

K-MMSE, Korean Mini-Mental State Examination; CDR, Clinical Dementia Rating Scale; GDS, Geriatric Depression Scale; K-NPI, Korean Neuropsyhicatirc Inventory.

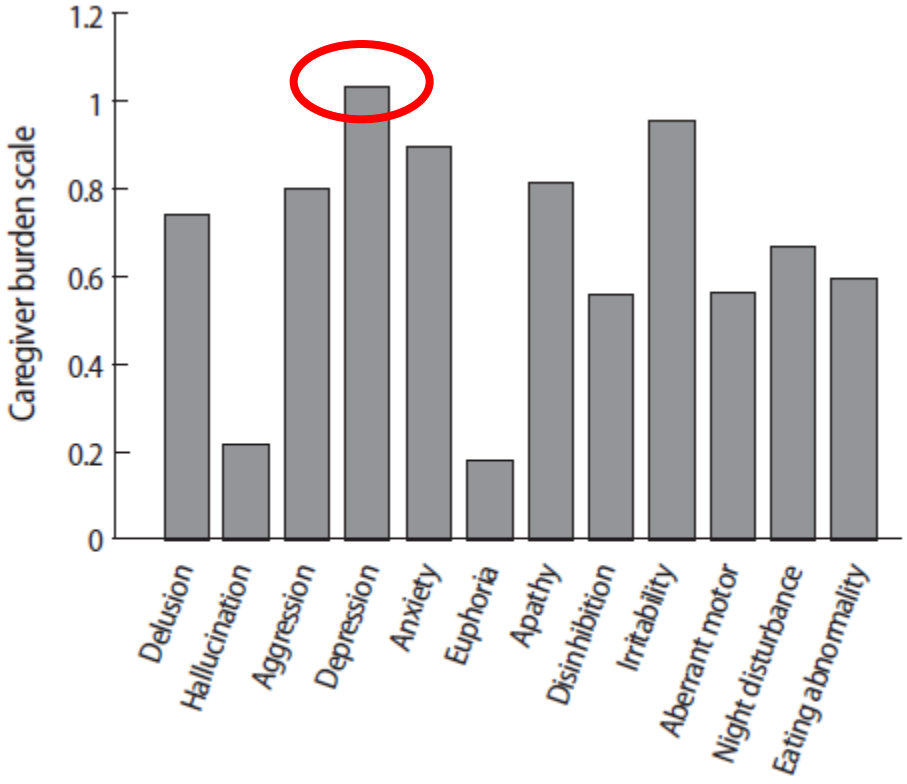

Fig. 2. Caregiver burden (in K-NPI) according to behavior and psychiatric domain.

Table 2. K-NPI domain prevalence according to CDR staging

Symptoms	CDR 0.5 (N = 69) N (%)	CDR 1 (N = 103) N (%)	CDR 2 (N = 37) N (%)	CDR 3 (N = 11) N (%)	Total study group (N = 220) N (%)
Delusions	6 (8.7)	23 (22.3)	20 (54.1)	8 (72.7)	57 (25.9)
Hallucinations	1 (1.4)	6 (5.8)	7 (18.9)	3 (27.2)	17 (7.7)
Aggression	8 (11.4)	27 (26.2)	19 (51.4)	10 (90.9)	27 (29.1)
Depression	31 (44.9)	64 (62.1)	18 (48.6)	5 (45.4)	118 (53.6)
Anxiety	15 (21.7)	44 (42.7)	19 (51.3)	5 (45.4)	83 (37.7)
Euphoria	2 (2.9)	8 (7.8)	4 (10.8)	3 (27.2)	17 (7.7)
Apathy	12 (17.4)	48 (46.6)	16 (43.2)	4 (36.3)	80 (36.4)
Disinhibition	9 (13.0)	23 (22.3)	12 (32.4)	6 (54.5)	22 (40.7)
Irritability	18 (27.7)	43 (41.7)	21 (9.5)	6 (54.5)	88 (40.0)
Motor behavior	3 (4.3)	21 (20.4)	20 (54.1)	8 (72.7)	52 (23.6)
Nighttime behavior	12 (17.4)	28 (27.2)	14 (37.8)	7 (63.6)	61 (27.7)
Eating change	11 (15.9)	40 (38.8)	19 (51.3)	4 (36.4)	74 (33.6)
Total	50 (72.5)	86 (83.4)	27 (73.0)	10 (90.9)	173 (78.6)

K-NPI, Korean Neuropsyhicatirc Inventory; CDR, Clinical Dementia Rating Scale.

AD vs VD vs FTD

Baseline characteristics of patients in the three groups

	AD ($n=44$) Mean (SD)	VaD ($n=31$) Mean (SD)	FTD ($n=23$) Mean (SD)
Age* (years)	67.2 (9.3)	59.6 (9.9)	55.2 (10.7)
Duration of symptoms* (months)	22.9 (30.5)	4.4 (2.8)	8.0 (4.4)
MMSE*	14.7 (5.6)	17.6 (4.7)	19.5 (5.2)
CDR	1.7 (0.7)	1.7 (0.5)	1.6 (0.7)
EASI	7.9 (2.5)	7.9 (2.2)	7.8 (2.6)
Total NPI*	23.8 (8.2)	24.4 (8.2)	32.1 (6.2)

AD—Alzheimer's disease.
VaD—vascular dementia.
FTD—frontotemporal dementia.
MMSE—mini-mental state examination.
CDR—Clinical Dementia Rating Scale.
EASI—Everyday Abilities Scale for India.
NPI—Neuropsychiatric Inventory.
* $p<0.01$ by one0way ANOVA.

Srikanth S, JNS, 2005

AD vs VD vs FTD

Frequencies of NPI domain disturbances in the three groups

NPI domains	AD ($n=44$) any (Sig.) [%]	VaD ($n=31$) any (Sig.) [%]	FTD ($n=23$) any (Sig.) [%]	Whole cohort ($n=98$) any (Sig.) [%]
Total NPI	100 (100)	100 (100)	100 (100)	100 (100)
Delusions	9.1 (9.1)	3.2 (3.2)	17.4 (17.4)	13.3 (13.3)
Hallucinations	4.6 (2.3)	9.7 (9.7)	0	7.1 (5.8)
Agitation	93.2 (68.2)	93.5 (77.4)	100 (91.3)	96.7 (82.4)
Depression	93.2 (75.0)	71 (54.8)	69.6 (56.5)	88.1 (75.0)
Anxiety	11.3 (6.8)	9.7 (6.5)	13 (8.7)	14.5 (10.1)
Euphoria	9.1 (6.8)	12.9 (9.7)	17.2 (8.6)	15.7 (11.4)
Apathy	95.5 (93.2)	96.8 (93.6)	95.7 (95.7)	96.9 (95.9)
Disinhibition	56.8 (45.4)	81.6 (64.6)	91.3 (82.6)	75.9 (67.8)
Irritability	95.5 (77.3)	96.8 (77.5)	95.7 (82.6)	96.7 (84.6)
ABM	43.2 (20.5)	64.5 (29.0)	91.3 (73.9)	64.5 (46.0)
Night-time behavior	43.2 (18.2)	51.6 (16.1)	52.2 (26.1)	50.0 (26.4)
Appetite changes	0	0	34.6 (21.6)	12.0 (7.5)

Srikanth S, JNS, 2005

AD vs DLB

Table 1. Patient characteristics

	Alzheimer's disease	Dementia with Lewy bodies	p values
Patients	126	57	
Age	75.6±7.8	76.6±7.9	0.413
Men, n	36 (28.6%)	32 (56.1%)	<0.005
MMSE scores	23.7±2.2	23.1±3.4	0.143
NPI total scores (median, range)	11.5 (0–64)	24 (0–89)	<0.005
NPI total caregiver distress (median)	6	12.5	<0.005

Numbers represent mean ± SD if not otherwise indicated.

Bjoerke-Bertheussen J, Dement Geriatr Cogn Disord, 2012

AD vs DLB

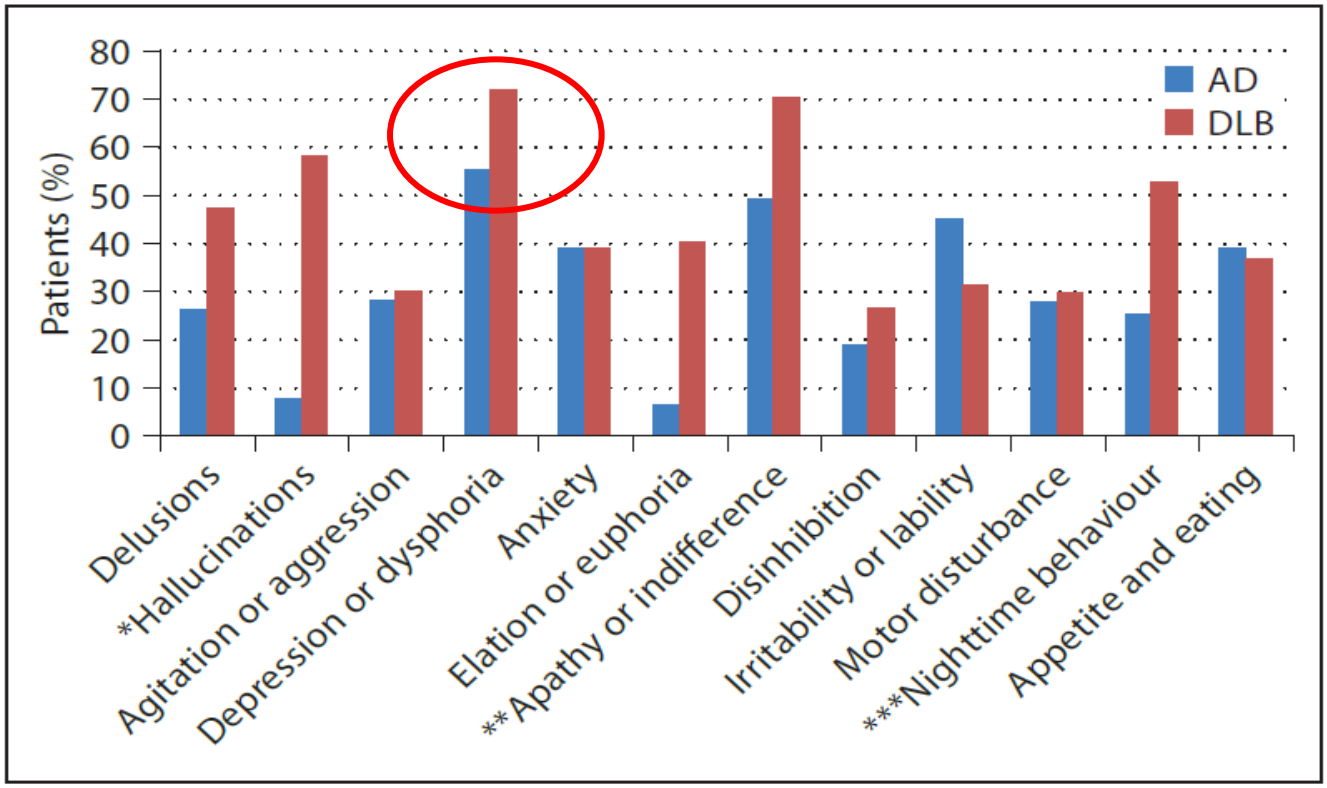

Fig. 3. Percentage of patients with a score >0; * $p < 0.005$; ** $p = 0.005$; *** $p < 0.005$.

Bjoerke-Bertheussen J, Dement Geriatr Cogn Disord, 2012

Depressive Symptoms in Alzheimer's Disease: Natural Course and Temporal Relation to Function and Cognitive Status

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Table 1. Demographic Characteristics of the Sample (N = 536) at Baseline and Follow-Up Information

Characteristic	Value	N
Age, mean ± SD	74 ± 8.7	
Education, years, mean ± SD	13 ± 4.1	
3MS score, mean ± SD	38.2 ± 6.1	
Blessed score, mean ± SD	37.5 ± 23.5	
Charlson index, mean ± SD	0.48 ± 0.82	
Illness duration, years, mean ± SD*	4.06 ± 2.30	
Female, %	59	
Depressed, %	39.2	
Cohort 1, %	45	
6-month follow-up visits, mean ± SD	5.6 ± 5.5	4,142
Depression evaluations, mean ± SD	5.43 ± 5.4	3,557
Function (Blessed) evaluations, mean ± SD	5.45 ± 5.4	3,592
Cognitive (3MS) evaluations, mean ± SD	4.0 ± 3.9	2,940

* Duration of illness from onset to baseline visit per neurologist's estimate.
SD = standard deviation; 3MS = modified Mini-Mental State Examination.

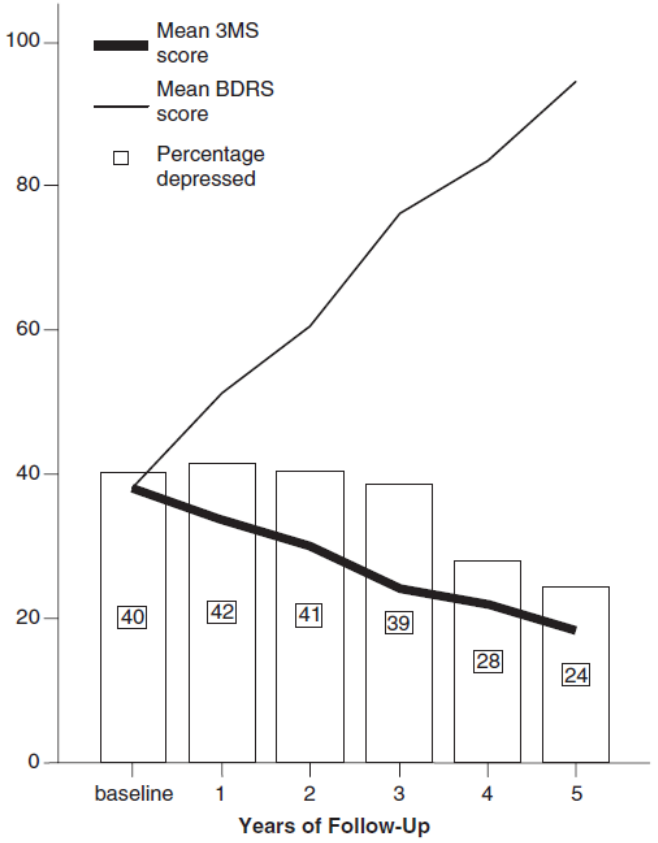

Figure 1. Percentage of patients deemed depressed at baseline through the fifth year of follow-up in relation to yearly mean modified Mini-Mental State Examination (3MS) and Blessed Dementia Rating Scale (BDRS) total scores.

Temporal course of depressive symptoms during the development of Alzheimer disease

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ABSTRACT

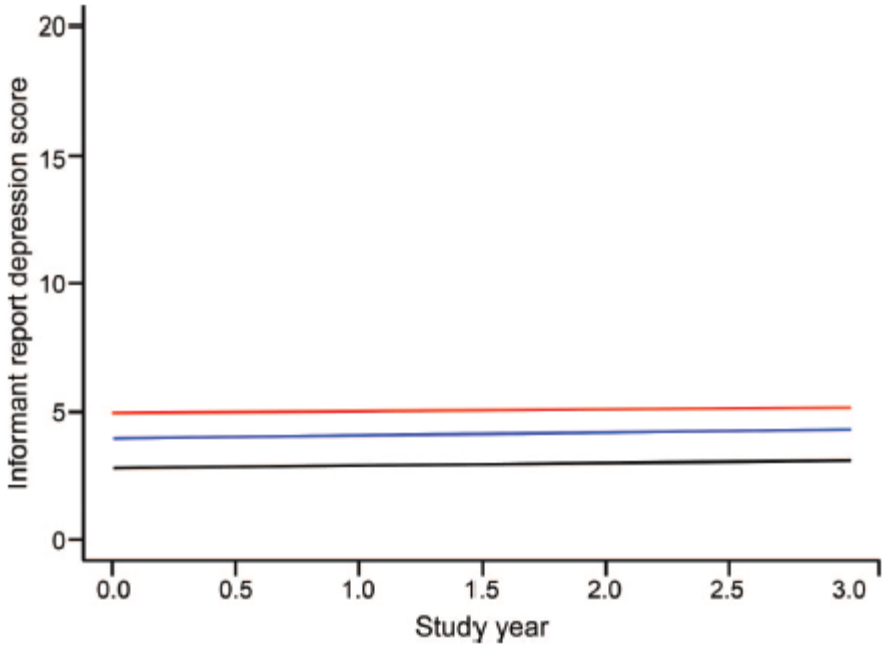
Objective: To character
tia in Alzheimer disease

Method: We used data f
factors for AD in a geog
357 individuals who de
(Center for Epidemiologi
to 9 years. In 340 indiv
symptoms (Hamilton De
AD (n = 107), mild cogn

Results: The incident AD
6 to 7 years of observat
3 years of observation a
annual follow-up, neither
in informant report of de

Conclusion: Depressive
AD to a moderate level

Figure 2 Change in informant report of depressive symptoms



Predicted 3-year paths of change in informant report of depressive symptoms in persons with no cognitive impairment (black line), mild cognitive impairment (blue line), or Alzheimer disease (red line), adjusted for age, sex, race, and education.

Dementia and Neurocognitive Disorders
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■ ORIGINAL ARTICLE ■

Clinical Characteristics of Behavioral and Psychological Symptoms in Patients with Drug-naïve Alzheimer's Disease

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Background: Behavioral and psychological symptoms of dementia (BPSD) are less well-defined aspects of Alzheimer's disease (AD). We designed this study to explore the followings: 1) the clinical profiles of BPSD 2) the clustered-groups domains of the Korean-Neuropsychiatric Inventory (K-NPI) assessment of BPSD 3) the clinical characteristics of the clustered-groups of BPSD in patients with drug-naïve probable AD. **Methods:** Descriptive and cluster analyses of the 12 K-NPI domains were done in 220 patients with drug-naïve probable AD. After clustering these domains, characteristics of these positive symptoms clustered-group of patients were compared with the negative symptoms groups of patients. **Results:** The mean Korean-Mini Mental Status Examination (K-MMSE), Clinical Dementia Rating (CDR) scale, and K-NPI scores were 15.0, 1.6, and 14.2, respectively. The CDR and K-MMSE scores correlated with total K- NPI scores, and depression was the most common symptom. According to cluster analysis, five major clusters were identified. Using the associated neuropsychological dysfunctions, characteristics of each group were defined. **Conclusions:** This study identified the clustered-domains for K-NPI, and suggested the possible anatomical substrates for these groups in drug-naïve AD patients. These attempts may clarify the complex and bizarre behavioral and psychological symptoms as more neurologically relevant symptoms.

Key Words: *Behavioral and psychological symptoms of dementia, Drug-naïve, Alzheimer's disease, Cluster analysis*

Table 2. K-NPI domain prevalence according to CDR staging

Symptoms	CDR 0.5 (N = 69) N (%)	CDR 1 (N = 103) N (%)	CDR 2 (N = 37) N (%)	CDR 3 (N = 11) N (%)	Total study group (N = 220) N (%)
Delusions	6 (8.7)	23 (22.3)	20 (54.1)	8 (72.7)	57 (25.9)
Hallucinations	1 (1.4)	6 (5.8)	7 (18.9)	3 (27.2)	17 (7.7)
Aggression	8 (11.4)	27 (26.2)	19 (51.4)	10 (90.9)	27 (29.1)
Depression	31 (44.9)	64 (62.1)	18 (48.6)	5 (45.4)	118 (53.6)
Anxiety	15 (21.7)	44 (42.7)	19 (51.3)	5 (45.4)	83 (37.7)
Euphoria	2 (2.9)	8 (7.8)	4 (10.8)	3 (27.2)	17 (7.7)
Apathy	12 (17.4)	48 (46.6)	16 (43.2)	4 (36.3)	80 (36.4)
Disinhibition	9 (13.0)	23 (22.3)	12 (32.4)	6 (54.5)	22 (40.7)
Irritability	18 (27.7)	43 (41.7)	21 (9.5)	6 (54.5)	88 (40.0)
Motor behavior	3 (4.3)	21 (20.4)	20 (54.1)	8 (72.7)	52 (23.6)
Nighttime behavior	12 (17.4)	28 (27.2)	14 (37.8)	7 (63.6)	61 (27.7)
Eating change	11 (15.9)	40 (38.8)	19 (51.3)	4 (36.4)	74 (33.6)
Total	50 (72.5)	86 (83.4)	27 (73.0)	10 (90.9)	173 (78.6)

K-NPI, Korean Neuropsyhicatirc Inventory; CDR, Clinical Dementia Rating Scale.

Major and Minor Depression in Alzheimer's Disease: Prevalence and Impact

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우울증과 알츠하이머병과의 관계는 매우 복잡하며 여러 가지 방법으로 연관되어 있을 수 있다.
첫 번째로 알츠하이머병과 우울증이 독립적으로 나타날 수 있고
두 번째로는 인지기능 장애의 이차적 반응으로 우울증이 발생할 경우이며,
마지막으로 우울증이 알츠하이머병의 위험인자이거나 알츠하이머병의 병태생리적인 원인에 의해 발병되는 경우이다.
우울증 가족력유무, 우울증 개인병력, 여성, 그리고 젊은 나이에 발병할 경우 등이 알츠하이머병에서 우울증과 연관된 위험인자로 보고 되었다.

One hundred nine outpatients with Alzheimer's disease (AD) were neuropsychiatrically evaluated and rated on standardized measures of depression, activities of daily living (ADL), nonmood behavioral disturbance, and burdensome events such as serious wandering, falls, and accidents. Distribution of depression scores revealed three patient groups: very few depressive symptoms (51%), minor depression (27%), and major depression (22%). Major depression was associated with substantially greater impairment in ADL, worse nonmood behavioral disturbance (such as aggression), and more frequent serious wandering, even after adjusting for severity of dementia or comorbid health problems. Minor depression was also associated with nonmood behavioral disturbance and wandering. The authors conclude that both major and minor depression are common in AD and produce considerable mood and nonmood morbidity affecting both patients and caregivers. Efforts are warranted to identify and treat depression in AD.

(The Journal of Neuropsychiatry and Clinical Neurosciences 1997; 9:556–561)

Longitudinal Assessment of Symptoms of Depression, Agitation, and Psychosis in 181 Patients With Alzheimer's Disease

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Objective: *The goal of this study was to define the recurrence or continuation of neuropsychiatric symptoms in patients with Alzheimer's disease who were observed serially for a 1-year period.* *Method:* *One hundred eighty-one patients with probable Alzheimer's disease were assessed five times at 3-month intervals with a standardized neuropsychiatric rating instrument.* *Results:* *Recurrence rates of neuropsychiatric symptoms during the 1-year period were 85% for depression, 93% for agitation, and 95% for psychosis. Symptom frequency at any point in time underestimated the cumulative 1-year frequency. Recurrence rates were significantly greater among patients who had multiple symptoms. Women exhibited more symptoms than men. Patients in the oldest age group (76–87 years) had more psychosis, less depression and agitation, and slower cognitive decline. Psychosis was associated with more rapid cognitive decline, and agitation was associated with more rapid functional deterioration.* *Conclusions:* *These results indicate that once psychiatric symptoms are present in patients with Alzheimer's disease, they frequently recur. These symptoms vary with age, sex, and rate of illness progression.*

(Am J Psychiatry 1996; 153:1438–1443)

Depressive symptoms and risk of dementia

The Framingham Heart Study

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ABSTRACT

Objectives: Depression may be associated with an increased risk for dementia, although results from population-based samples have been inconsistent. We examined the association between depressive symptoms and incident dementia over a 17-year follow-up period.

Methods: In 949 Framingham original cohort participants (63.6% women, mean age = 79), depressive symptoms were assessed at baseline (1990–1994) using the 60-point Center for Epidemiologic Studies Depression Scale (CES-D). A cutpoint of ≥16 was used to define depression, which was present in 13.2% of the sample. Cox proportional hazards models adjusting for age, sex, education, homocysteine, and *APOE* ϵ4 examined the association between baseline depressive symptoms and the risk of dementia and Alzheimer disease (AD).

Results: During the 17-year follow-up period, 164 participants developed dementia; 136 of these cases were AD. A total of 21.6% of participants who were depressed at baseline developed dementia compared with 16.6% of those who were not depressed. Depressed participants (CES-D ≥16) had more than a 50% increased risk for dementia (hazard ratio [HR] 1.72, 95% confidence interval [CI] 1.04–2.84, $p = 0.035$) and AD (HR 1.76, 95% CI 1.03–3.01, $p = 0.039$). Results were similar when we included subjects taking antidepressant medications as depressed. For each 10-point increase on the CES-D, there was significant increase in the risk of dementia (HR 1.46, 95% CI 1.18–1.79, $p < 0.001$) and AD (HR 1.39, 95% CI 1.11–1.75, $p = 0.005$). Results were similar when we excluded persons with possible mild cognitive impairment.

Conclusions: Depression is associated with an increased risk of dementia and AD in older men and women over 17 years of follow-up. *Neurology*® 2010;75:35–41

PAPER

Depressive symptoms and cognitive decline in a community population of older persons

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See Editorial Commentary, p 5

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Background: An association between depressive symptoms and cognitive decline has been observed in selected cohorts of older people, but studies of defined populations have had conflicting results.
Objective: To test whether the level of depressive symptoms predicted the rate of cognitive decline in a biracial community of older persons.
Methods: 4392 older people (88% of those eligible) from a defined community in Chicago completed two or three structured interviews at approximately three year intervals for an average of 5.3 years. At the baseline interview, the number of depressive symptoms was assessed with a 10 item version of the Center for Epidemiologic Studies Depression scale. Cognitive function was assessed at each interview with four performance tests, from which a previously established measure of global cognition was derived. Random effects models were used to assess change in cognition and its relation to depressive symptoms, controlling for age, sex, race, education, and baseline cognitive function.
Results: Participants reported a median of one depressive symptom at baseline (interquartile range, 0 to 2). For each depressive symptom, the rate of cognitive decline increased by a mean of about 5%. Results were not substantially changed when persons with cognitive impairment at baseline were excluded, or when chronic illness or participation in cognitively stimulating activities was controlled, and the association was not modified by age, sex, race, or education.
Conclusions: The results suggest that depressive symptoms predict cognitive decline in old age.

BJPsych
The British Journal of Psychiatry (2008)
193, 373–377. doi: 10.1192/bjp.bp.107.044974

Severity of depression and risk for subsequent dementia: cohort studies in China and the UK*

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Background
Depression and dementia often exist concurrently. The associations of depressive syndromes and severity of depression with incident dementia have been little studied.

Aims
To determine the effects of depressive syndromes and cases of depression on the risk of incident dementia.

Method
Participants in China and the UK aged ⩾65 years without dementia were interviewed using the Geriatric Mental State interview and re-interviewed 1 year later in 1254 Chinese, and 2 and 4 years later in 3341 and 2157 British participants respectively (Ageing in Liverpool Project Health Aspects: part of the Medical Research Council – Cognitive Function and Ageing study).

Results
Incident dementia was associated with only the most severe depressive syndromes in both Chinese and British participants. The risk of dementia increased, not in the less severe cases of depression but in the most severe cases. The multiple adjusted hazard ratio (HR)=5.44 (95% CI 1.67–17.8) for Chinese participants at 1-year follow-up, and HR=2.47 (95% CI 1.25–4.89) and HR=2.62 (95% CI 1.18–5.80) for British participants at 2- and 4-year follow-up respectively. The effect was greater in younger participants.

Conclusions
Only the most severe syndromes and cases of depression are a risk factor for dementia.

Declaration of interest
None. Funding detailed in Acknowledgements.

Prodromal Alzheimer's Disease: Successive Emergence of the Clinical Symptoms

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Objective: Whereas cognitive deficits are known to be detectable long before the typical symptoms of Alzheimer's disease (AD) are evident, previous studies have failed to determine when cognitive functioning actually begins to decline before dementia. Utilizing the long follow-up of the PAQUID study, we examined the emergence of the first clinical symptoms over a 14-year period of follow-up before the dementia phase of AD.

Methods: This study relies on a case–control sample selected from the PAQUID cohort. Of the 3,777 initial subjects of the cohort, 350 subjects experienced development of AD during the 14 years of follow-up. The cases were matched to 350 elderly control subjects. The evolution of scores on cognitive, functional, and depression scales was described throughout the 14-year follow-up using a semiparametric extension of the mixed-effects linear model.

Results: The first decline in cognitive performances appeared as early as 12 years before dementia in measures of semantic memory and conceptual formation. Then, more global deficits appeared that were concomitant with an increase in memory complaints and depressive symptoms. About 2 years later, as a consequence of cognitive dysfunction, the subjects started to become slightly dependent in their activities of daily living. In the last 3 years, the impairment significantly worsened until the subjects reached the dementia phase.

Interpretation: This approach, describing the 14 years preceding dementia, provides a clear illustration of the particularly long and progressive prodromal phase of AD, and shows the successive emergence of cognitive deficits, depressive symptoms, and functional impairment during this phase.

Ann Neurol 2008;64:492–498

Depressive Symptoms, Sex, and Risk for Alzheimer's Disease

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Depression associates with increased risk for dementia and Alzheimer's disease (AD), although it is unclear whether it represents an actual risk factor or a prodrome. To determine the relative hazard of premorbid depressive symptomatology for development of dementia and AD, we studied risk for incident dementia and AD over a 14-year period in 1,357 community-dwelling men and women participating in the 40-year prospective Baltimore Longitudinal Study of Aging. Screening for depressive symptoms, comprehensive medical and neuropsychological evaluations were prospectively collected every 2 years. Time-dependent proportional hazards of development of AD or dementia were calculated separately for men and women, with symptoms of depression detected at 2-, 4-, and 6-year intervals before onset of dementia symptoms. Vascular risk factors were analyzed as covariates. Premorbid depressive symptoms significantly increased risk for dementia, particularly AD in men but not in women. Hazard ratios were approximately two times greater than for individuals without history of depressive symptoms, an effect independent of vascular disease. We conclude that the impact of depressive symptoms on risk for dementia and AD may vary with sex. Further studies assessing separately the role of depression as a risk factor in men and women are necessary.

Ann Neurol 2005;57:381–387

Article

A Collaborative Study of the Emergence and Clinical Features of the Major Depressive Syndrome of Alzheimer's Disease

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Trey Sunderland, M.D.

Objective: This report provides a description of the prevalence and clinical features of the major depressive syndrome of Alzheimer's disease using data derived from structured diagnostic assessments of 243 patients with probable Alzheimer's disease and 151 nondemented elderly comparison subjects.

Method: Subjects were characterized by a consortium of four Alzheimer's disease research centers and the Geriatric Psychiatry Branch of the National Institute of Mental Health. All sites administered the Clinical Assessment of Depression in Dementia, a structured, anchored diagnostic interview that was developed to reliably diagnose and characterize major depressive episodes in this population.

Results: Despite the use of a common, reliable methodology for the assessment and diagnosis of major depressive episodes, the prevalence of major depression in Alzheimer's disease ranged widely from 22.5% to 54.4% across the recruitment sites. The prevalence of major depressive episodes among Alzheimer's disease patients in the aggregate sample exceeded that for elderly comparison subjects and reached nearly 50% among the most severely demented patients. Alzheimer's disease patients with a current major depressive episode had earlier mean ages at onset, a higher mean Hamilton Depression Rating Scale score, and were more likely to be experiencing psychotic symptoms than those who had not developed a major depressive episode. Although the major depressive episodes of Alzheimer's disease patients and nondemented elderly comparison subjects included similar numbers of depressive symptoms, patients with Alzheimer's disease were more likely to report a diminished ability to concentrate or indecisiveness and less likely to experience sleep disturbances and feelings of worthlessness or excessive guilt during their major depressive episodes. None of the clinical features of major depression differed significantly in frequency among depressed Alzheimer's disease patients with mild, moderate, or severe dementia. Concurrent psychotic symptoms progressively increased with dementia severity.

Conclusions: The high rate of major depressive episodes that occur after the onset of cognitive impairment among patients with Alzheimer's disease (the majority of whom had no premorbid history of major depression), common emergence in the early stages of dementia when symptoms of cognitive impairment are least likely to contribute to the syndromal diagnosis of major depression, and differences in the clinical presentations of the major depressive episodes of Alzheimer's disease patients and nondemented elderly comparison subjects, all support the validity of the major depressive syndrome of Alzheimer's disease. Our findings suggest that the major depressive syndrome of Alzheimer's disease may be among the most common mood disorders of older adults.

(Am J Psychiatry 2003; 160:857–866)

알츠하이머병 우울증과 조기발병 우울증은 유병율, 과거력, 가족력, 심한정도, 자살기도, 증상의 지속기간, 예후, 치료에 대한 반응 등이 차이가 난다.

예를 들면 **알츠하이머병에서 우울증은** 조기발병 우울증에 비하여 증상이 덜 심하며, 호전과 악화를 지속적으로 반복하는 경향이 있고, 자살욕구나 기도가 거의 없으며, 성별차이가 없고, 심리사회적 요인이 뚜렷하지 않다.

또한 **알츠하이머병 우울증 환자는** 종종 슬픈 감정(sad feelings)을 보이지 않으며 우울감 보다는 동기결여(lack of emotion,)나 쾌감손실(loss of pleasure)이 더 심하고, 종종 망상이나 무감동과 같은 다른 행동증상을 동반한다.

BPSD 평가 도구

- BEHAVE-AD
- Behavioral Rating Scale for Dementia (BRSD) of CERAD
- Dementia Symptom Scale
- Columbia University Scale for Psychopathology in AD (CUSPAD)
- California Dementia Behavior Questionnaire
- Neurobehavioral Rating Scale
- Cornell Scale for Depression in Dementia
- Cohen-Mansfield Agitation Inventory (CMA)
- Neuropsychiatric Inventory (NPI)

Neuropsychiatric Inventory (NPI)

Neuropsychiatric Inventory (NPI)

Cummings JL (1994)에 의해 제작
Korean version of NPI (최성혜 등, 2000)
1994년 이후 전세계적으로 가장 많이 사용되고 있음

구성
1. 12 이상 행동: screening question, subquestion
2. 빈도, 심한 정도, 보호자 고통 정도를 평가
3. 환자를 잘 알고 있는 보호자와의 면담을 통해 평가

발병 이후에 새로이 생기거나 변화가 있는 행동 중에서
과거 4주동안에 관찰되어진 행동에만 적용

Neuropsychiatric Inventory

J Korean Med Sci. 2000 Dec;15(6):609-15. Choi SH et al.

1. 망상 (Delusions)
2. 환각 (Hallucinations)
3. 초조/공격적 행동 (Agitation/Aggression)
4. **우울/낙담 (Depression/Dysphoria)**
5. 불안 (Anxiety)
6. 다행감/기분의 들뜸 (Euphoria/Elation)
7. 무감동/무관심 (Apathy/Indifference)
8. 탈억제 (Disinhibition)
9. 과민/불안정 (Irritability/Lability)
10. 비정상적인 운동행동 (Aberrant motor behavior)
11. 야간의 행동 (Night-time behavior)
12. 식욕/식습관의 변화 (Appetite/Eating change)

4. 우울/낙담(Depression/Dysphoria)

환자분께서 슬퍼 보이거나 우울해 보입니까? 환자분 스스로 자기가 슬프거나 우울하다고 말합니까?
아니오 (다음 선별질문으로) 예(아래의 세부 질문으로)

(둘 중 한 곳에 표시)

	예	아니오
1. 환자 분께서 슬퍼서 눈물을 흘리거나 흐느낄 때가 있습니까?	_____	_____
2. 슬프거나 기분이 쳐진 것처럼 행동하거나 말합니까?	_____	_____
3. 자신은 실패자라고 말하거나, 자기 자신을 과소평가하곤 합니까?	_____	_____
4. 환자 분께서 자신이 나쁜 사람이라고 얘기하거나 벌을 받아도 마땅하다고 얘기합니까?	_____	_____
5. 매우 낙심한 것처럼 보이거나 자기에게 미래가 없다고 말합니까?	_____	_____
6. 환자 분 스스로 자신이 다른 가족에게 짐이 된다고 말하거나 또는 자신이 없으면 다른 가족들이 더 잘 지낼 것이라고 얘기합니까?	_____	_____
7. 죽고싶다고 말하거나 자살하겠다는 얘기를 한 적이 있습니까?	_____	_____
8. 그밖에 우울해 하거나 슬퍼하는 증상이 있습니까?	_____	_____

빈도 ☐	1. 드물다 – 일주일에 1회 미만 2. 가끔 – 일주일에 1회 정도 3. 자주 – 일주일에 몇 번 그러나 매일은 아님 4. 매우 자주 – 근본적으로 계속 있음
심한 정도 ☐	1. 경함 - 우울증이 고통이 되기는 하지만 안심을 시키거나 주위를 환기시키면 조절된다. 2. 보통 - 우울증을 유발하고, 환자 스스로 먼저 우울 증상을 말하며, 우울 증상을 경감시키기 힘들다. 3. 심함 - 우울증 때문에 고통스럽고, 우울증이 환자의 고통의 주원인이 된다.

항목	N/A	없음	빈도	정도	빈도x정도	보호자고통 정도
망상			1 2 3 4	1 2 3	9	1 2 3 4 5
환각		O	1 2 3 4	1 2 3	0	1 2 3 4 5
초조/공격적행동			1 2 3 4	1 2 3	4	1 2 3 4 5
우울/낙담			**1 2 3 4**	**1 2 3**	**6**	**1 2 3 4 5**
불안			1 2 3 4	1 2 3	4	1 2 3 4 5
다행감/기분의 들뜸		O	1 2 3 4	1 2 3	0	1 2 3 4 5
무감동/무관심			1 2 3 4	1 2 3	6	1 2 3 4 5
탈억제		O	1 2 3 4	1 2 3	0	1 2 3 4 5
과민/불안정		O	1 2 3 4	1 2 3	0	1 2 3 4 5
비정상적인 운동행동			1 2 3 4	1 2 3	4	1 2 3 4 5
야간의 행동			1 2 3 4	1 2 3	12	1 2 3 4 5
식욕/식습관의 변화		O	1 2 3 4	1 2 3	0	1 2 3 4 5
총 점					45	

Cornell Scale for Depression in Dementia

※ 지난 1주일 간 환자가 보인 증상을 평가하시오.

평가방법/ 평가기간:지난 1주일, 평가기준: 0=없었음,
1=경도 또는 간헐적, 2=중증 또는 자주, 9=평가 불능

1. 불안 (불안한 표정, 불안감 표현, 반복적 고민, 지나친 걱정 등)	⓪ ① ② ⑨
2. 슬픔 (슬픈 표정, 슬픈 감정 표현, 서글픈 목소리, 눈물을 흘리거나 글썽거림, 등)	⓪ ① ② ⑨
3. 즐거운 일에 대한 반응 소실	⓪ ① ② ⑨
4. 과민 (쉽게 신경질을 냄, 참을성이 없음)	⓪ ① ② ⑨
5. 초조 (가만히 있지 못함. 손을 쥐어 짬, 머리카락을 뜯는 모습 등)	⓪ ① ② ⑨
6. 지체 (느린 행동, 느린 말소리, 반응 지연, 등)	⓪ ① ② ⑨
7. 다양한 신체 증상 호소 (소화기 증상만 호소하는 경우 0으로 평가)	⓪ ① ② ⑨
8. 흥미상실 (일상 활동에 참여하지 않으려고 함, 최근 일 개월 이내에 갑작스럽게 발생한 경우에만 점수를 부여함)	⓪ ① ② ⑨
9. 식욕 저하 (평소에 비해 적게 먹음)	⓪ ① ② ⑨
10. 체중 감소 (지난 1개월간 2Kg 이상의 감소가 있을 경우 2로 평가)	⓪ ① ② ⑨
11. 활력 상실 (쉽게 피로함, 지속적으로 활동을 할 수 없음; 최근 일 개월 이내에 갑작스럽게 발생한 경우에만 점수를 부여함)	⓪ ① ② ⑨
12. 하루를 주기로 기분이 변하며, 아침에 증상이 심해짐.	⓪ ① ② ⑨
13. 잠들기 힘듬 (평상시보다 늦게 잠 듬)	⓪ ① ② ⑨
14. 수면 도중 자주 깸	⓪ ① ② ⑨
15. 너무 일찍 깸 (평상 시보다 아침에 일찍 깸)	⓪ ① ② ⑨
16. 자살 사고 (삶이 가치 없다고 느낌, 자살에 대한 바램, 자살기도, 등)	⓪ ① ② ⑨
17. 자존심 저하(자신을 책망, 자신이 가치 없다고 생각, 실패했다는 생각, 등)	⓪ ① ② ⑨
18. 비관 (가장 나쁜 쪽으로 전망, 희망이 없다고 생각 등)	⓪ ① ② ⑨
19. 기분에 일치되는 망상 (병에 걸리거나, 망하거나, 다 잃어버릴 것이라는 망상)	⓪ ① ② ⑨
총 점	**/38점**

CSDD
: 환자와 보호자와 인터뷰를 시행하며 작성

Reliability and Validity of the Korean Version of CSDD in Dementia

- A cut-off score of 7 for the CSDD-K
  : sensitivity - 87.5%, specificity - 100%.

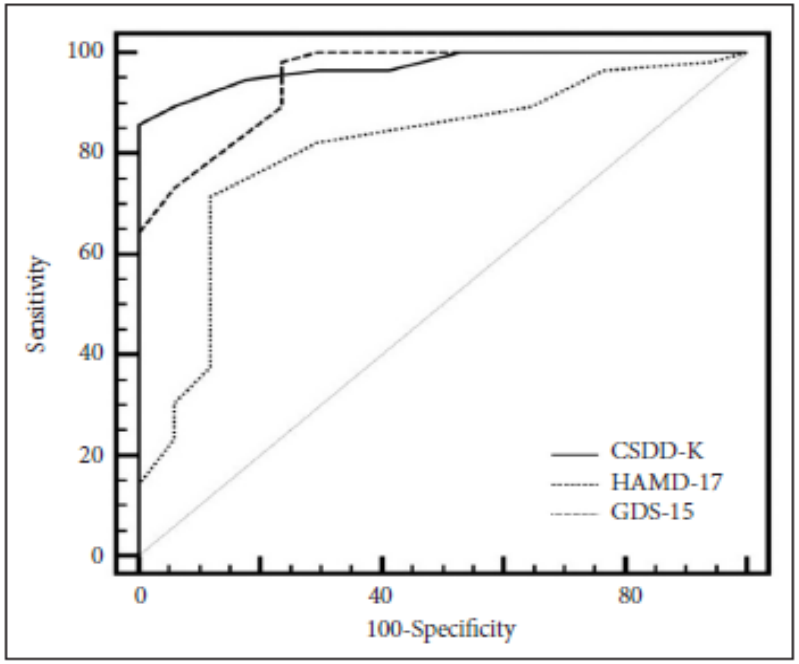

Figure 1. The ROC curves of CSDD-K, HAMD17 and GDS for the prediction of the diagnosis of depression in AD. ROC: Receiver Operation Characteristics, CSDD-K: Korean version of Cornell Scale for Depression in Dementia, $HAMD_{17}$: 17-item Hamilton Depression Rating Scale, GDS_{15}: 15-item Geriatric Depression Scale, AD: Alzheimer's disease.

<Lim HK et al. Psychiatry Investig 2012;9(4):332-8>

Hamilton Depression Rating Scale (HDRS)

Hamilton Depression Rating Scale (HDRS)

Validity and reliability of the Korean version of the Hamilton Depression Rating Scale(K-HDRS) *J Korean Neuropsychiatr Assoc 2005;44:456-465*

1. 우울한 기분 (슬픔, 절망감, 무력감, 무가치감)
0 없다
1 물어보았을 때만 우울한 기분이라고 말한다.
2자발적으로 우울한 기분이라고 말한다.
3 얼굴표정, 자세 , 목소리, 쉽게 우는 경향과 같은 비언적 표현을 통해 우울한 기분을 나타낸다.
4 오로지 우울한 기분만을 언어적, 비언어적 표현을 통해 나타낸다.

2. 죄책감
0 없다
1 자책하거나 자신이 사람들을 실망시킨다고 느낀다.
2 죄를 지었다가 생각하던가, 과거의 실수나 자신의 한 나쁜 행위에 대해 반복적으로 생각한다
3.현재의 병을 벌로 여긴다. 죄책망상이 있다.
4. 비난 또는 탄핵하는 목소리를 듣거나 위협적인 환시를 경험한다.

3. 자살
0 없다
1인생이 살 가치가 없다고 느낀다.
2.차라리 죽었으면 하거나 죽는 것에 대한 상상을 한다.
3. 자살사고가 있거나 자살기도처럼 볼 수 있는 행동을 한다.
4.심각한 자살 기도를 한다.

4. 초기 불면증
0 잠드는데 어려움이 없다
1 간간이 잠들기가 어렵다
2 매일 밤 잠들기가 어렵다

5. 중기 불면증
0 어려움이 없다
1 편하고 깊게 자지 못한다
2 한밤중에 깨어 뒤척이거나 잠자리에서 벗어난다.

6. 말기 불면증
0 어려움이 없다
1 새벽에 깨지만 다시 잠이 든다
2 일단 깨어나면 다시 잠들 수 없다.

7. 일과 활동 0 어려움이 없다 1 제대로 할 수 없다고 느낀다. 일이나 취미와 같은 활동에 대해 피로하거나 기력이 떨어졌다고 느낀다. 2.일이나 취미와 같은 활동에 흥미를 잃는다 3. 활동시간에 줄거나 생산성이 떨어져 있다. 4. 현재의 병 때문에 일을 중단한다.	**8. 지체(생각과 말이 느려짐; 집중력 저하; 운동활성의 저하)** 0정상적으로 말하고 생각한다. 1면담할 때 약간 지체되어 있다. 2면담할 때 뚜렷이 지체되어 있다. 3 면담이 어려울 정도로 지체되어 있다. 4 완전한 혼미상태에 있다.
9. 초조 0없다 1 조금 초조한 듯하다 2 손이나 머리카락 등을 만지작거린다. 3가만히 앉아 있지 못하고 몸을 자꾸 움직인다. 4손을 비비꼬거나 손톱을 물어뜯거나 머리카락을 잡아당기거나 입술을 깨문다.	**10. 정신적 불안** 0없다 1긴장감과 과민함을 느낀다 2사소한 일들에 대해 걱정을 한다 3얼굴표정이나 말에서 염려하는 태도가 뚜렷하다 4묻지 않아도 심한공포가 드러난다.
11.신체적 불안 0없다 1경도 2중등도 3고도 4최고도	**12. 위장관계 신체증상** 0없다 1 입맛을 잃었지만 치료진의 격려없이도 먹는다. 2치료진의 강요없이는 잘 먹지 않는다.
13. 전반적인 신체증상 0없다 1팔,다리, 등, 머리가 무겁다 2매우 뚜렷한 신체증상이 있다.	**14. 성(性)적인 증상 (성욕감퇴, 월경불순 등)** 0없다 1경도 2고도
15. 건강염려증 0없다 1몸에 대해 많이 생각한다 2건강에 대해 집착한다. 3건강이 나쁘다고 자주호소하거나 도움을 청한다 4건강염려증적 망상이 있다.	**16. 체중감소 (A 또는 B로 평가한다)** A 병력에 의해 평가할때 0 체중 감소가 없다 1현재의 병으로 인해 체중감소가 있는 것 같다 2확실한 체중감소가 있다.
17. 병식 0 자신이 우울하고 병들었다는 것을 인식한다. 1 병들었다는 것을 인정하지만 음식, 날씨, 과로, 바이러스, 휴식부족 등이 이유라고 생각한다.	2 자신의 병을 전적으로 부인한다.

Depression: PHQ-9

- 주요우울장애의 진단을 위한 총 9 문항의 자가보고형 척도로 DSM-IV의 우울삽회 진단 기준을 반영함
- 무쾌감, 우울감,수면 변화, 피로감, 식욕 변화, 무가치감, 집중력 저하, 좌불안석 또는 쳐진 느낌, 자살사고
- 일반적으로 3분 미만 소요
- Score (0~27): 점수가 높을수록 우울증이 심각함
  - 0-4 (normal), 5-9 (mild), 10-19 (moderate), 20-27 (severe)

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-13.
한글판 우울증 선별도구 (Patient health questionnaire-9 PHQ-9)의 신뢰도와 타당도 – 박승진 외, 대한불안의학회지 2010;6(2):119-124

PHQ-9

- Patient Health Questionnaire(PHQ)는 1999년 일차의료기관에서 흔하게 보는 몇 가지 정신질환의 criteria-based diagnosis를 위해 개발된 Primary Care Evaluation of Mental Disorder의 자기 보고형식으로 Spitzer에 의해 개발되었으며, PHQ의 우울증 모듈이 PHQ-9이다.
- 한국에서는 2008년 Han 등, 2010년 Park 등에 의해 한국어로 번역이 되어 만족할 만한 타당성과 신뢰성을 보였으며, 절단점이 연구되었다.
- Patient Health Questionnaire-9은 DSM-IV의 진단기준에 의거하여 지난 2주간의 무쾌감, 우울감,수면의 변화, 피로감, 식욕의 변화, 죄책감, 무가치감, 집중력 저하, 좌불안석 또는 쳐진 느낌, 자살사고의 9가지 요소로 구성되어 있다.
- 각각의 요소는 0점(전혀 그렇지 않다)에서 3점(거의 매일 그렇다)까지로 채점이 되어 총점 27점으로 점수가 높을수록 우울증의 심각도가 높다는 것을 반영한다.

PHQ-9

- 2001년 Kroenke 등이 6000명을 대상으로 타당도 검증을 하였을 때 절단점은 10점이었으며, 절단점을 12점으로 하였을 때 95%의 민감도와 84%의 특이도를 보였다.
- 한국판으로 번역이 되어 노인 인구에서 5점을 절단점으로 하였을 때 우울증의 선별에 있어 타당성과 신뢰성을 보였으며, 우울증의 진단뿐 아니라 증상 변화의 추적관찰에도 도움이 될 것이라고 평가하였다.
- 또한 2010년 번역된 한국판 PHQ-9의 주요우울장애 또는 양극성 장애의 우울삽화 환자를 대상으로 한 신뢰도와 타당도 연구에서 0~4점을 우울증이 아님,5~9점을 가벼운 우울증, 10~19점을 중간 정도 우울증, 20~27점을 심한 우울증으로 분류하였다.

For the Investigator: Please fill in the date of rating.

Date of Rating: Day Month Year

Patient Health Questionnaire-9 (PHQ-9)

Reference : Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief
Intern Med 2001 Sep;16(9):606-13.

Over the last 2 weeks, how often have you been bothered by any of the following problems ? *(please tick to indicate your answer)*	(0) Not at all	(1) Severa days
1 Little interest of pleasure in doing things	☐	☐
2 Feeling down, depressed, or hopeless	☐	☐
3 Trouble falling or staying asleep, or sleeping too much	☐	☐
4 Feeling tired or having little energy	☐	☐
5 Poor appetite or overeating	☐	☐

Patient Health Questionnaire-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems ?	(0) Not at all	(1) Several days	(2) More than half the days	(3) Nearly every day
6 Feeling bad about yourself – or that you are a failure or have let yourself or your family down	☐	☐	☐	☐
7 Trouble concentrating on things, such as reading the newspaper or watching television	☐	☐	☐	☐
8 Moving or speaking so slowly that other people could have noticed ? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	☐	☐	☐	☐
9 Thoughts that you would be better off dead or of hurting yourself in some way	☐	☐	☐	☐
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people ?	Not difficult at all ☐	Somewhat difficult ☐	Very difficult ☐	Extremely difficult ☐

Thank you. Please sign and date below, after you have checked that you have answered all questions.

Patient's Signature: _____ Date: DD MMM YYYY

환자 건강 질문지-9
(Korean version of the PHQ-9)

72883

THIS SECTION FOR USE BY STUDY PERSONNEL ONLY.

Were data collected? **No** ☐ *(provide reason in comments)*

If **Yes**, data collected on visit date ☐ or specify date: _____
DD-Mon-YYYY

Comments:

Only the patient (subject) should enter information onto this questionnaire.

지난 2 주일 동안 당신은 다음의 문제들로 인해서 얼마나 자주 방해를 받았습니까?	**전혀 방해 받지 않았다**	**며칠 동안 방해 받았다**	**7 일 이상 방해 받았다**	**거의 매일 방해 받았다**
1. 일 또는 여가 활동을 하는 데 흥미나 즐거움을 느끼지 못함	0	1	2	3
2. 기분이 가라앉거나, 우울하거나, 희망이 없음	0	1	2	3
3. 잠이 들거나 계속 잠을 자는 것이 어려움, 또는 잠을 너무 많이 잠	0	1	2	3
4. 피곤하다고 느끼거나 기운이 거의 없음	0	1	2	3
5. 입맛이 없거나 과식을 함	0	1	2	3
6. 자신을 부정적으로 봄 – 혹은 자신이 실패자라고 느끼거나 자신 또는 가족을 실망시킴	0	1	2	3
7. 신문을 읽거나 텔레비전 보는 것과 같은 일에 집중하는 것이 어려움	0	1	2	3
8. 다른 사람들이 주목할 정도로 너무 느리게 움직이거나 말을 함. 또는 반대로 평상시보다 많이 움직여서, 너무 안절부절 못하거나 들떠 있음	0	1	2	3
9. 자신이 죽는 것이 더 낫다고 생각하거나 어떤 식으로든 자신을 해칠 것이라고 생각함	0	1	2	3

SCORING FOR USE BY STUDY PERSONNEL ONLY

0 + _____ + _____ + _____

=Total Score: _____

만일 당신이 위의 문제 중 하나 이상 "예" 라고 응답하셨으면, 이러한 문제들로 인해서 당신은 일을 하거나 가정일을 돌보거나 다른 사람과 어울리는 것이 얼마나 어려웠습니까?

전혀 어렵지 않았다	**약간 어려웠다**	**많이 어려웠다**	**매우 많이 어려웠다**
☐	☐	☐	☐

Depression: PHQ-9

- 주요우울장애의 진단을 위한 총 9 문항의 자가보고형 척도로 DSM-IV의 우울삽회 진단 기준을 반영함
- 무쾌감, 우울감,수면 변화, 피로감, 식욕 변화, 무가치감, 집중력 저하, 좌불안석 또는 쳐진 느낌, 자살사고
- 일반적으로 3분 미만 소요
- Score (0~27): 점수가 높을수록 우울증이 심각함
  - 0-4 (normal), 5-9 (mild), 10-19 (moderate), 20-27 (severe)

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-13.
한글판 우울증 선별도구 (Patient health questionnaire-9 PHQ-9)의 신뢰도와 타당도 – 박승진 외, 대한불안의학회지 2010;6(2):119-124

Geriatric Depression Scale

Geriatric Depression Scale (GDS-15)

Development of the Korean version of the Geriatric depression scale and its short form among elderly psychiatric patients, *J Psychosom Res 2004:57:297-305*		
1	당신은 평소 자신의 생활에 만족합니까?	예/아니오
2	당신은 활동과 흥미가 많이 저하되었습니까?	예/아니오
3	당신은 앞날에 대해서 희망적입니까?	예/아니오
4	당신은 대부분의 시간을 맑은 정신으로 지냅니까?	예/아니오
5	당신은 대부분의 시간이 행복하다고 느끼십니까?	예/아니오
6	당신은 지금 살아있다는 것이 아름답다고 생각합니까?	예/아니오
7	당신은 가끔 낙담하고 우울하다고 느낍니까?	예/아니오
8	당신은 지금 자신의 인생이 매우 가치가 없다고 느끼십니까?	예/아니오
9	당신은 인생이 매우 흥미롭다고 느끼십니까?	예/아니오
10	당신은 활력이 충만하다고 느끼십니까?	예/아니오
11	당신은 자주 사소한 일에 마음의 동요를 느끼십니까?	예/아니오
12	당신은 자주 울고 싶다고 느낍니까?	예/아니오
13	당신은 아침에 일어나는 것이 즐겁습니까?	예/아니오
14	당신은 결정을 내리는 것이 수월합니까?	예/아니오
15	당신의 마음은 이전처럼 편안합니까?	예/아니오

Original GDS
: Yesavage et al.(1983)
•30문항
•>11 depression
•11~20: mild depression
•21~30:moderate depression

GDS-15문항
5점이하: 정상
6~9: 중등도 우울증상
10이상: 우울증

Geriatric Depression Scale (GDS)

GDS (Geriatric Depression Scale)

"이제부터는 평상시의 생각이나 느낌에 대해서 여쭈어 보겠습니다. 제가 말씀드리는 내용이 지난 1주일 동안의 자신의 기분이나 생각과 같다고 생각하시면 '네,' 그렇지 않다고 생각하시면 '아니오'라고 대답하여 주십시오."

지난 한 주 동안의 느낌	응 답	
1. 평소 내 생활에 기본적으로 만족한다.	예	아니오
2. 활동과 흥미가 많이 줄었다.	예	아니오
3. 사는 게 허전하다.	예	아니오
4. 자주 따분해진다.	예	아니오
5. 앞날에 대해 희망적으로 생각한다.	예	아니오
6. 쓸데없는 생각들이 자꾸 떠올라 괴롭다.	예	아니오
7. 몸과 마음이 가뿐하다.	예	아니오
8. 나쁜 일이 일어나지 않을까 두렵다.	예	아니오
9. 대체로 행복하다고 느낀다.	예	아니오
10. 아무 것도 할 수 없을 것처럼 무기력하게 느낀다.	예	아니오
11. 안절부절 못하고 초조할 때가 자주 있다.	예	아니오
12. 밖에 나가기보다는 주로 집에 있으려 한다.	예	아니오
13. 앞날에 대해 걱정할 때가 많다.	예	아니오
14. 기억력이 많이 약해졌다.	예	아니오
15. 지금 내가 살아있다는 것이 참 기쁘다.	예	아니오

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Diagnosing Depression in Alzheimer Disease With the National Institute of Mental Health Provisional Criteria

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TABLE 1

NIMH Provisional Diagnostic Criteria for Depression in Alzheimer Disease

A. Three (or more) of the following symptoms must be present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms must either be 1) depressed mood or 2) decreased positive affect or pleasure

1. Clinically significant depressed mood
2. Decreased positive affect or pleasure in response to social contacts and usual activities
3. Social isolation or withdrawal
4. Disruption in appetite
5. Disruption in sleep
6. Psychomotor changes
7. Irritability
8. Fatigue or loss of energy
9. Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
10. Recurrent thoughts of death, suicidal ideation, plan or attempt

B. All criteria are met for Dementia of the Alzheimer Type (DSM-IV)[7]

C. The symptoms cause clinically significant distress or disruption in functioning

D. The symptoms do not occur exclusively in the course of delirium

E. The symptoms are not due to the direct physiological effects of a substance

F. The symptoms are not better accounted for by other conditions such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer disease, anxiety disorders, or substance-related di sorders

Adapted from Olin et al., 2002. [22]

Causes of BPSD

- Intellectural and cognitive changes
  - Amnesia, agnosia, apraxia, aphasia, apathy
- Neurotransmitter dysfunction
  - Dopamine, serotonin, cholinergic, adrenergic, GABA
- Instinctual behaviors under stress
  - Territoriality
  - defensiveness

BPSD & Structural changes in Neuroimage

Symptoms	Findings	References	Sample
	Computerized tomography		
Delusional misidentification	Right frontal and temporal atrophy	Förstl et al. (1994)	56 AD patients
	Magnetic resonance imaging		
Depression	Decreased gray matter volume in right hippocampus and amygdala	Egger et al. (2008)	14 AD patients
Apathy	Anterior cingulated gyrus, orbitofrontal, and frontosubcortical areas atrophy	Tunnard et al. (2011)	111 AD patients
		Bruen et al. (2008)	31 mild AD patients
		Massimo et al. (2009)	40 FTLD patients
Delusions	Decreased GM volume in frontal, temporal, and limbic regions	Bruen et al. (2008)	31 mild AD patients
		Massimo et al. (2009)	40 FTLD patients
Visual hallucinations	Lesions on visual cortex and association areas detected in MRI	Holroyd et al. (2000)	14 AD patients
Agitation	Anterior cingulated cortex and left insula atrophy	Bruen et al. (2008)	31 mild AD patients
Aggressive behavior	Amygdala atrophy	Poulin et al. (2011)	264 AD patients
Disinhibition	Cingulate frontal cortex atrophy and medial orbital frontal cortex atrophy	Serra et al. (2010a)	54 AD patients
		Massimo et al. (2009)	40 FTLD patients
Anxiety, sleep disorders, and aberrant motor behavior	Increased WMH volume	Berlow et al. (2010)	37 AD patients

AD, Alzheimer disease; FTLD, fronto-temporal lobar degeneration; GM, gray matter; MRI, magnetic resonance imaging; WMH, white matter hyperintensities.

BPSD & functional changes in Neuroimage (PET & SPECT)

Symptoms	Findings	References	Sample
Depression	Hypoperfusion and hypometabolism in some areas of temporal, frontal, and parietal lobes	Hirono et al. (1998) Staffen et al. (2009)	53 AD patients 149 MCI + 131 DA + 127 DCI patients
Apathy	Decreased perfusion and hypometabolism in anterior cingulated gyrus, orbitofrontal, and frontosubcortical areas	Lanctôt et al. (2007b)	51 AD patients
		Benoit et al. (1999)	63 AD patients
		Marshall et al. (2007)	41 AD patients
		Craig et al. (1996)	31 AD patients
Psychosis	Hypometabolism in frontal lobe	Sultzer et al. (1995)	21 AD patients
Hallucinations	Hypoperfusion in parietal lobe	Kotrla et al. (1995)	30 AD patients
Delusions	Hypometabolism of prefrontal, anterior cingulate, right temporal, and parietal cortex Increased metabolism in the inferior temporal gyrus and decreased metabolism in the occipital lobe	Staff et al. (2000) Sultzer et al. (2003) Hirono et al. (1998)	45 AD patients 25 AD patients 65 AD patients
Agitation	Changes in metabolism in frontal and temporal cortices	Sultzer et al. (1995)	21 AD patients
Aggressive behavior	Hypoperfusion in the temporal cortex (right middle and left anterior)	Lanctôt et al. (2004) Hirono et al. (2000)	49 AD patients 10 dementia patients

AD, Alzheimer disease; MCI, mild cognitive impairment; FTLD, fronto-temporal dementia; DCI, depression with cognitive impairment (DCI).

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DND

ORIGINAL ARTICLE

The Neuropsychological Characteristics in Early Stage of Alzheimer's Patients with Depression

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[2]Department of Neurology, Hyoja Geriatric Hospital, Yongin, Korea

Background and Purpose Although depression is a common psychiatric symptom in Alzheimer's disease (AD), there has not been a lot of research on neuropsychological characteristics of this symptom. To determine the characteristic neuropsychological deficit in patients with depression compared to patients without depression, this study compared each neuropsychological test between AD patients with depression and without depression.

Methods Psychotropic-naïve (drug-naïve) early stage [Clinical Dementia Rating Scale (CDR)=0.5 or CDR=1] probable AD patients with depression (n=77) and without depression (n=179) were assessed with the Seoul Neuropsychological Screening Battery, which includes measures of memory, intelligence, and executive functioning.

Results AD patients with depression had lower scores on the digit forward, digit backward, calculation, and Color Word Stroop Test tests compared to AD patients without depression.

Conclusions Our study showed that AD patients with depression have disproportionate cognitive deficit, suggesting frontal (especially in the left dorsolateral), left hemisphere and left parietal dysfunction. Considering the neuropsychological differences between AD patients with depression and without depression, depression may have specific anatomic substrates.

Table 2. A comparison of neuropsychological tests between AD patients without depression and with depression

	Depression (-)	Depression (+)	*p*-value*
Digit forward	5.15±1.38	4.61±1.24	0.005
Digit backward	3.21±1.17	2.63±0.66	0.000
K-BNT	31.89±10.83	30.46±11.18	0.362
Calculation	9.49±3.24	7.94±3.44	0.001
Ideomotor praxis	3.65±1.62	3.42±1.57	0.321
SVLT immediate recall	12.90±4.77	12.30±4.35	0.359
SVLT delayed recall	1.68±2.56	1.58±2.21	0.763
RCFT copy	24.32±9.49	21.75±9.15	0.076
RCFT immediate copy	5.08±5.61	4.42±3.84	0.413
RCFT delayed copy	4.44±5.42	3.74±4.14	0.379
Contrasting	16.96±6.08	16.68±6.04	0.751
Go-no-go	14.02±6.80	13.16±6.80	0.394
Fist-edge-arm	2.08±0.94	2.00±1.18	0.678
Alternating hand	2.30±0.93	2.21±1.15	0.618
Alternating square	1.53±1.32	1.47±1.65	0.433
Luria	1.52±1.32	1.61±1.75	0.800
COWAT animal	10.26±3.71	9.70±3.71	0.262
COWAT supermarket	10.35±5.08	9.63±5.25	0.327
COWAT phonemic	16.43±8.40	14.26±8.42	0.165
CWST word correct	106.66±14.37	96.67±21.28	0.003
CWST color correct	52.95±26.70	40.58±23.72	0.033

*Independent *t*-test was performed.
AD: Alzheimer's disease, COWAT: Controlled Oral Word Association Test, CWST: Color Word Stroop Test, K-BNT: Korean version of the Boston Naming Test, RCFT: Rey-Osterrieth Complex Figure Test, SVLT: Seoul Verbal Learning Test.

Table 3. Correlation between GDS15 and specific neuropsychological tests in AD patients with depression

	Correlation coefficient	*p*-value*
Digit forward	-0.159	0.013
Digit backward	-0.237	0.000
K-BNT	-0.059	0.368
Calculation	-0.229	0.000
Ideomotor praxis	-0.030	0.642
SVLT immediate recall	-0.122	0.058
SVLT delayed recall	-0.033	0.668
RCFT copy	-0.118	0.084
RCFT immediate copy	-0.046	0.503
RCFT delayed copy	-0.005	0.937
Contrasting	-0.070	0.287
Go-no-go	-0.064	0.331
Fist-edge-arm	-0.012	0.887
Alternating hand	-0.117	0.331
Alternating square	-0.021	0.797
Luria	0.069	0.381
COWAT animal	-0.097	0.131
COWAT supermarket	-0.117	0.069
COWAT phonemic	-0.138	0.075
CWST word correct	-0.308	0.000
CWST color correct	-0.215	0.023

*Pearson bivariate correlation was performed.
AD: Alzheimer's disease, COWAT: Controlled Oral Word Association Test, CWST: Color Word Stroop Test, GDS15: Geriatric Depression Scale 15, K-BNT: Korean version of the Boston Naming Test, RCFT: Rey-Osterrieth Complex Figure Test, SVLT: Seoul Verbal Learning Test.

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DND

ORIGINAL ARTICLE

The Neuropsychological Characteristics in Early Stage of Alzheimer's Patients with Depression

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[1]Department of Neurology, Seoul Veterans Hospital, Seoul, Korea
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Methods Psychotropic-naïve (drug-naïve) early stage [Clinical Dementia Rating Scale (CDR)=0.5 or CDR=1] probable AD patients with depression (n=77) and without depression (n=179) were assessed with the Seoul Neuropsychological Screening Battery, which includes measures of memory, intelligence, and executive functioning.

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■ ORIGINAL ARTICLE ■

Clinical Characteristics of Behavioral and Psychological Symptoms in Patients with Drug-naïve Alzheimer's Disease

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Background: Behavioral and psychological symptoms of dementia (BPSD) are less well-defined aspects of Alzheimer's disease (AD). We designed this study to explore the followings: 1) the clinical profiles of BPSD 2) the clustered-groups domains of the Korean-Neuropsychiatric Inventory (K-NPI) assessment of BPSD 3) the clinical characteristics of the clustered-groups of BPSD in patients with drug-naïve probable AD. **Methods:** Descriptive and cluster analyses of the 12 K-NPI domains were done in 220 patients with drug-naïve probable AD. After clustering these domains, characteristics of these positive symptoms clustered-group of patients were compared with the negative symptoms groups of patients. **Results:** The mean Korean-Mini Mental Status Examination (K-MMSE), Clinical Dementia Rating (CDR) scale, and K-NPI scores were 15.0, 1.6, and 14.2, respectively. The CDR and K-MMSE scores correlated with total K- NPI scores, and depression was the most common symptom. According to cluster analysis, five major clusters were identified. Using the associated neuropsychological dysfunctions, characteristics of each group were defined. **Conclusions:** This study identified the clustered-domains for K-NPI, and suggested the possible anatomical substrates for these groups in drug-naïve AD patients. These attempts may clarify the complex and bizarre behavioral and psychological symptoms as more neurologically relevant symptoms.

Key Words: *Behavioral and psychological symptoms of dementia, Drug-naïve, Alzheimer's disease, Cluster analysis*

Table 3. Clustered group among K-NPI domains

	Group 1	Group 2	Group 3	Group 4	Group5
K-NPI domain	Agitation-aggression Aberrant motor behavior Delusion Irritability Disinhibiton Hallucination	Seep disturbance	Depression apathy	Eating abnormalities	Anxiety euphoria

Table 4. Clinical characteristics of clustered group

Characteristics	Group 1 (N = 21)	Group 2 (N = 65)	Group 3 (N = 60)	Group 4 (N = 74)	Group 5 (N = 19)
MMSE	12.6 ± 5.2†	18.1 ± 5.8*	18.8 ± 5.2	18.7 ± 5.0	18.5 ± 6.0
CDR	2.1 ± 0.7†	1.3 ± 0.8†	1.2 ± 0.6	1.2 ± 0.6*	1.5 ± 0.8*
CDR-SB	11.3 ± 3.4†	7.2 ± 4.2†	6.4 ± 3.2*	6.3 ± 3.2*	8.3 ± 3.6†
Barthel	17.7 ± 2.5†	18.9 ± 2.1†	19.2 ± 1.7†	19.0 ± 2.2*	18.2 ± 2.3
GDS	14.9 ± 6.1	14.4 ± 6.7	15.1 ± 7.2†	14.1 ± 6.9	12.3 ± 7.0
Seoul Verbal Learning Test immediate recall	7.3 ± 5.4†	11.0 ± 4.6	10.4 ± 4.7†	10.0 ± 4.5†	12.4 ± 3.6
Seoul Verbal Learning Test delayed recall	0.4 ± 1.1†	1.3 ± 1.8	0.9 ± 1.9	0.8 ± 1.5	1.8 ± 2.0
Controlled oral word association test	11.3 ± 7.9†	17.0 ± 6.9	15.6 ± 7.6*	16.5 ± 7.6	16.2 ± 4.8*
Stroop color	59.5 ± 31.8	50.8 ± 22.7	45.4 ± 24.6	55.5 ± 26.6	38.0 ± 16.6
Calculation	8.3 ± 3.5	8.3 ± 3.5	8.5 ± 3.9	8.3 ± 3.8	7.1 ± 4.2
Rey-Osterrieth Complex Figure Test	19.1 ± 12.3	19.4 ± 9.7†	23.0 ± 10.2	22.0 ± 9.3*	15.7 ± 10.7*

Each positive group was compared with each negative group, i.e. apathy and depression-positive group was compared to apathy and depression negative-group. If one symptom was positive and other symptom was negative, this data was not compared. Statistical significance means that positive symptom groups had a lower score than the negative symptom groups.

*p value < 0.05; †p value < 0.01 (One-Way ANOVA test was used).

MMSE, Korean Mini-Mental State Examination; CDR, Clinical Dementia Rating Scale; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes; GDS, Geriatric Depression Scale.

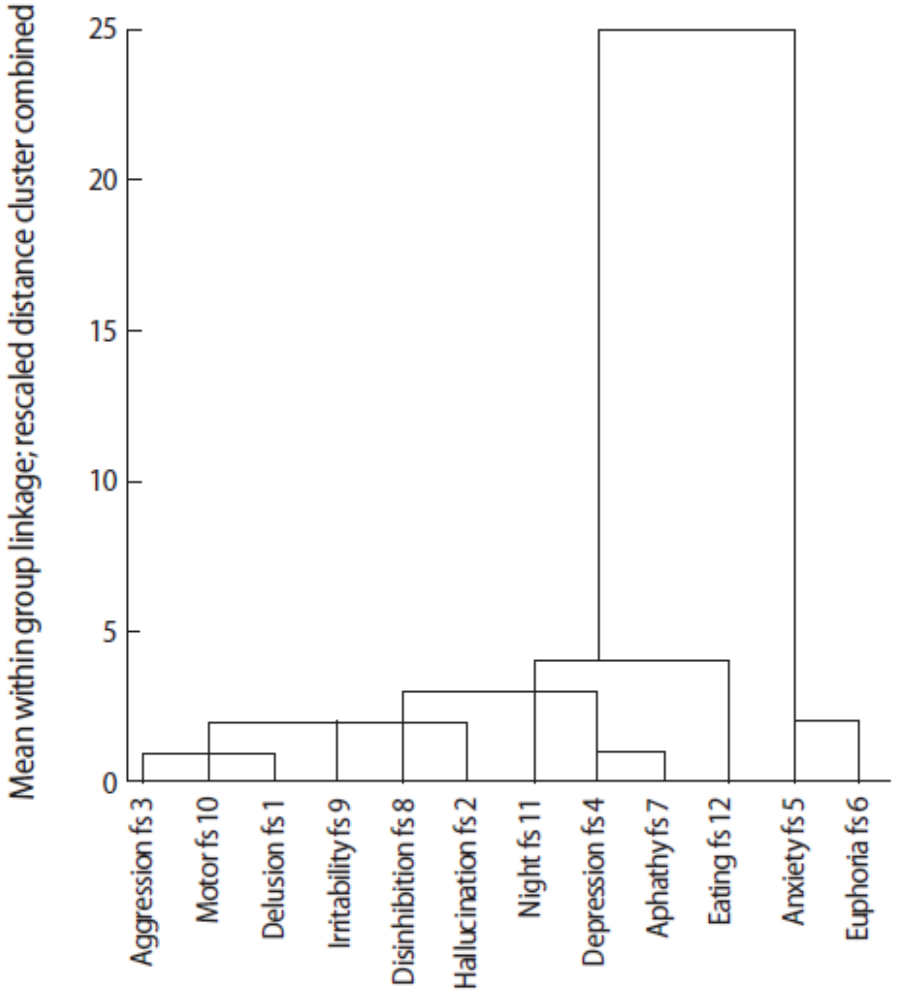


Fig. 4. Dendrogram for clustered variable of K-NPI domains. Closely intercorrelated variables are joined at an early stage in the analysis (left of the dendrogram) and less closely intercorrelated variables are joined at a later stage in the analysis (right of the dendrogram). Fs, frequency x severity; K-NPI, Korean Neuropsyhicatirc Inventory.

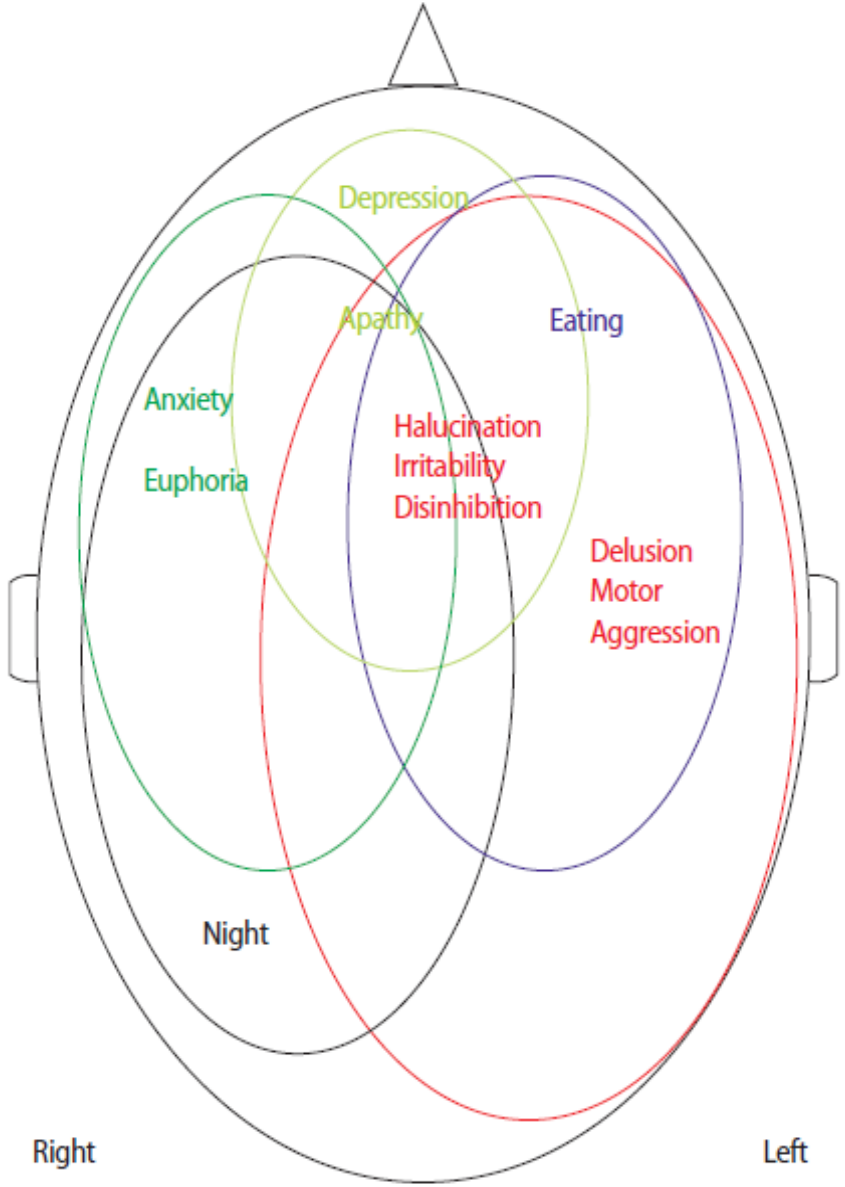


Fig. 5. Hypothetical mapping for K-NPI domains.

BPSD that will not respond to medication

- Wandering
- Inappropriate urination/ defecation
- Inappropriate dressing/ undressing
- Annoying repetitive activities (perseveration) or vocalization
- Hiding/ hoarding
- Eating inedibles
- Tugging at/ removal of restraints
- Pushing wheelchair bound co-residents

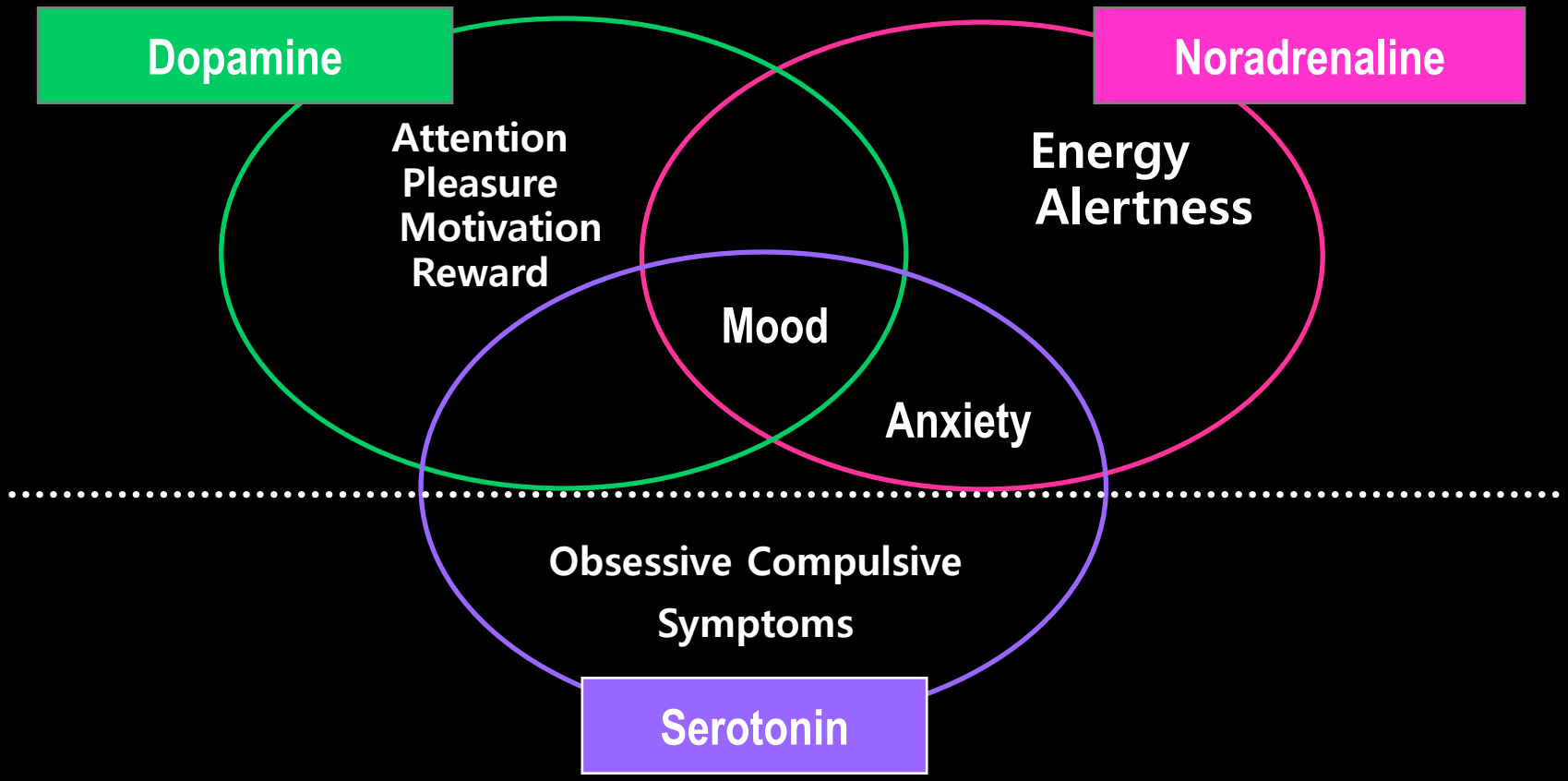
BPSD that may respond to medication

- Anxiety
- **Depressive symptoms**
- Sleep disturbance
- Manic-like symptoms
- Persistent and distressing delusions or hallucinations
- Persistent verbal and physical aggression
- Sexually inappropriate behavior

Antidepressants in Depression

- In general,
  - Clinical improvement : 60~70% (cf. Placebo 30%)
  - Onset of antidepressant effects : several weeks
  - All antidepressants act on 5-HT or NE system, some on DA
  - Similar efficacy, different safety and side effect profiles
  - Side effects are related with action on various neurotransmitter system

Neurotransmitter Regulation of Mood, Cognition, and Behavior



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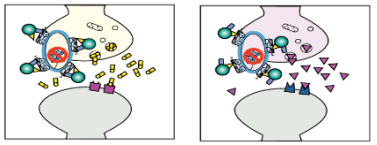
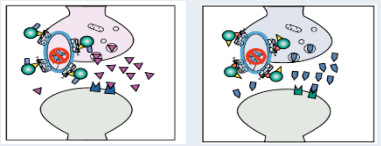
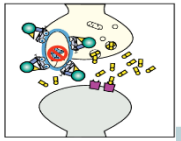
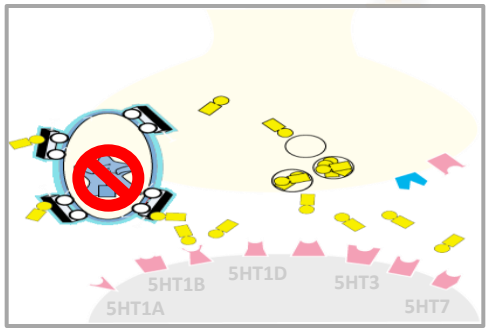
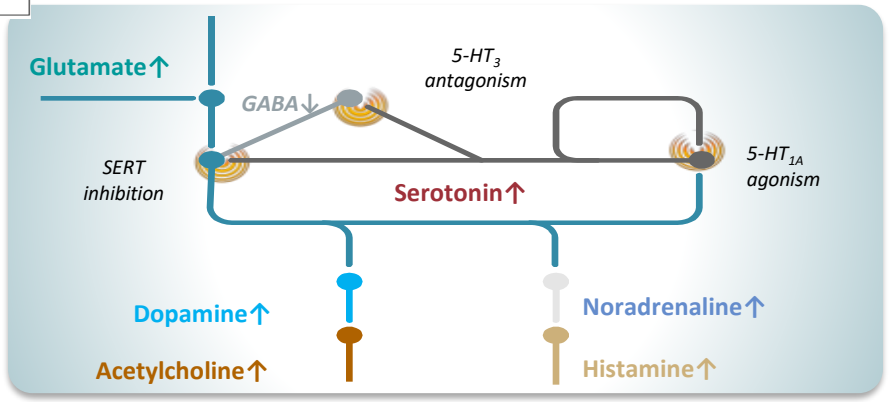
Foote SI. *Psychopharmacology*. 1995.

Comparison of AD's Mechanism

Classification		Examples	Mechanism	Indirect Effect
SSRI	**Selective Serotonin Reuptake Inhibitor**	Fluoxetine/Fluvoxamine/Paroxetine/Sertraline/Citalopram/Escitalopram		**5HT↑**
SNRI	**Serotonin Norepinephrine Reuptake Inhibitor**	Duloxetine/Venlafaxine/Desvenlafaxine		**5HT↑ & NE ↑**
NDRI	**Norepinephrine Dopamine Reuptake Inhibitor**	Bupropion		**NE ↑ & DA ↑**
Multi-modal	**Serotonin Modulator and Stimulator**	Vortioxetine	  	**5HT↑ & NE, DA, Ach, His↑**

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ORIGINAL ARTICLE

Depression in Alzheimer's disease: is there a temporal relationship between the onset of depression and the onset of dementia?

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(Received 3 July 2001; accepted 5 March 2002)

Summary – Alzheimer's disease (AD) patients often present with concurrent major depression (MD). To investigate the reasons for this comorbidity, e.g. MD being a risk factor for AD, or both diagnoses having a common neurobiology, the temporal relationship between the first onset of AD and of MD during lifetime was investigated—57 out of 146 AD patients had a lifetime diagnosis of MD. The correlation between the ages at onset of MD and dementia was calculated. The incidence of MD in AD patients in several 5-year-intervals before and after the onset of AD was compared with the average incidence of MD in the present AD sample and with the expected incidence of MD in the general population. No significant correlation between the onset of AD and of MD could be found after controlling for age, gender and the Mini-Mental-State. However, the incidence of MD 5 years before and after the onset of AD significantly exceeded the expected incidences—MD is only partially related to AD. However, the increased incidence of MD within 5 years before and after the onset of dementia may indicate that a common neurobiological process causes cognitive decline and depression in a subsample of AD patients. © 2002 Éditions scientifiques et médicales Elsevier SAS

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Original Research Article

The Effects of Donepe… Geriatric Depression S… Patients with Alzheime…

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[a]Department of Neurology, Veteran Health Service M…
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Table 3. Correlation between GDS15/GDS factors and general cognitive function/Barthel index

	GDS15	Factor 1	Factor 2	Factor 3
GDS15				
Factor 1	0.842**			
Factor 2	0.055	–0.401**		
Factor 3	0.506**	0.187**	–0.142	
K-MMSE	–0.017	0.102	–0.155*	–0.184**
CDR	–0.042	–0.122	0.099	0.145*
Barthel index	0.190**	0.296**	–0.157*	0.101

GDS = Geriatric Depression Scale; K-MMSE = Korean Mini-Mental State Examination; CDR = Clinical Dementia Rating scale. * p value <0.05, ** p value <0.01.

Table 4. Parameter change after 3 months of donepezil treatment

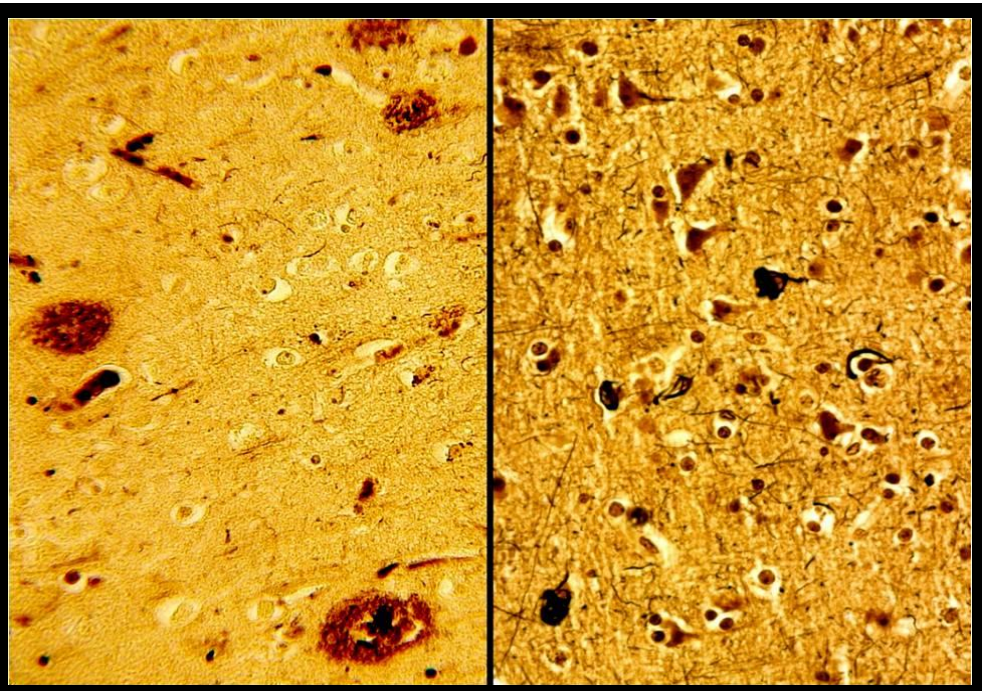
Characteristics	Baseline	3 months	p value
K-MMSE	16.8±5.7	18.6±5.8	0.013
CDR	1.2±0.5	1.2±0.6	0.874
Barthel index	19.2±2.7	19.6±3.0	0.865
GDS15	8.5±4.0	7.1±4.2	0.009
Factor 1	4.3±2.4	4.1±2.8	0.242
Factor 2	1.9±1.4	1.3±1.4	0.001
Factor 3	2.3±0.9	1.9±1.0	0.000

K-MMSE = Korean Mini-Mental State Examination; CDR = Clinical Dementia Rating scale; GDS = Geriatric Depression Scale.

Increased Neurofibrillary Tangles in Patients With Alzheimer Disease With Comorbid Depression

Michael A. Rapp, M.D., Ph.D., Michal Schnaider-Beeri, Ph.D., Dushyant P. Purohit, M.D., Daniel P. Perl, M.D., Vahram Haroutunian, Ph.D., Mary Sano, Ph.D.

Without depression



With depression

ORIGINAL ARTICLE

Treating Depression in Alzheimer Disease

Efficacy and Safety of Sertraline Therapy, and the Benefits of Depression Reduction: The DIADS

Constantine G. Lyketsos, MD, MHS; Lourdes DelCampo, MD; Martin Steinberg, MD; Quincy Miles, BA; Cynthia D. Steele, RN, MPH; Cynthia Munro, PhD; Alva S. Baker, MD; Jeannie-Marie E. Sheppard, BA; Constantine Frangakis, PhD; Jason Brandt, PhD; Peter V. Rabins, MD, MPH

Context: Major depression affects about 25% of the patients who have Alzheimer disease and has serious adverse consequences for patients and caregivers. Results of prior antidepressant treatment studies have produced contradictory findings and have not fully assessed the benefits of depression reduction.

Objectives: To assess the efficacy and safety of sertraline hydrochloride for the treatment of major depression in Alzheimer disease, and to evaluate the effect of depression reduction on activities of daily living, cognition, and nonmood behavioral disturbance.

Design: Randomized, placebo-controlled, parallel, 12-week, flexible-dose clinical trial with a 1-week, single-blind placebo phase. The study was conducted between January 1, 1998, and July 19, 2001.

Setting: University outpatient clinic.

Participants: Forty-four outpatients who have probable Alzheimer disease and major depressive episodes.

Intervention: Sertraline hydrochloride, mean dosage of 93 mg/d, or identical placebo, randomly assigned.

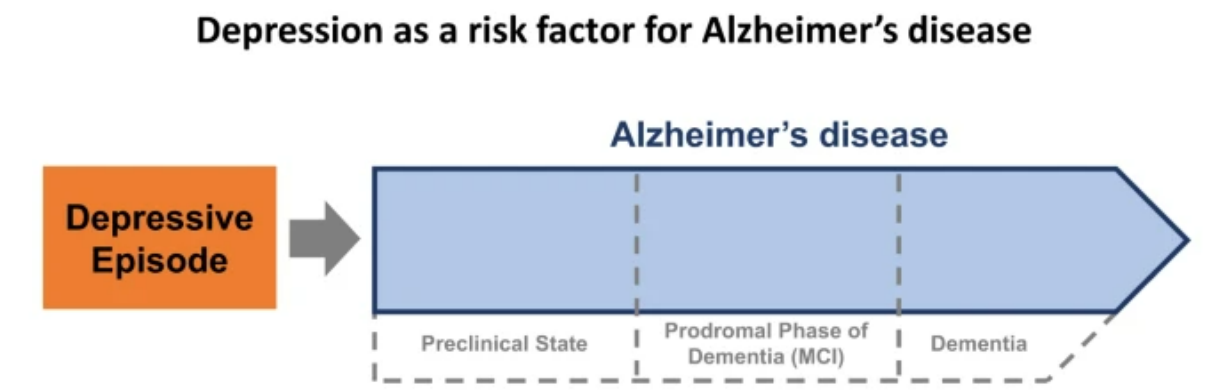
Main Outcome Measures: Response rate, Cornell Scale for Depression in Dementia, Hamilton Depression Rating Scale, Mini-Mental State Examination, Psychogeriatric Depression Rating Scale–activities of daily living subscale, and Neuropsychiatric Inventory to quantify patient behavior disturbance and caregiver distress.

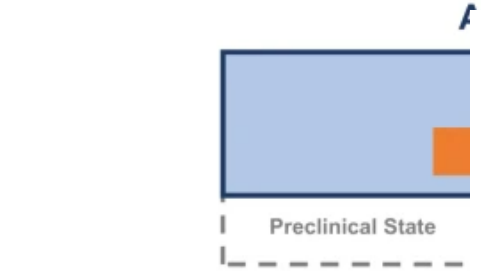
Results: In the sertraline-treated group 9 patients (38%) were full responders and 11 (46%) were partial responders compared with 3 (20%) and 4 (15%), respectively, in the placebo-treated group ($P = .007$). The sertraline-treated group had greater improvements in the scores for the Cornell Scale for Depression in Dementia ($P = .002$) and Hamilton Depression Rating Scale ($P = .01$), and a statistical trend toward less decline in activities of daily living on the Psychogeriatric Depression Rating Scale–activities of daily living subscale ($P = .07$). There was no difference between the treatment groups in Mini-Mental State Examination ($P = .22$) or Neuropsychiatric Inventory ($P = .32$) ratings over time. When full responders, partial responders, and nonresponders were compared, full responders only, or full and partial responders had significantly better ratings on activities of daily living ($P = .04$), behavioral disturbance ($P = .01$), and caregiver distress ($P = .006$), but not on the Mini-Mental State Examination ($P = .76$). Safety monitoring indicated few differences in adverse effects between the 2 treatment groups.

Conclusions: Sertraline is superior to placebo for the treatment of major depression in Alzheimer disease. Depression reduction is accompanied by lessened behavior disturbance and improved activities of daily living, but not improved cognition.

Arch Gen Psychiatry. 2003;60:737-746

Fig. 1: The relationship between depression and cognitive decline throughout the development and clinical course of Alzheimer's disease (AD).





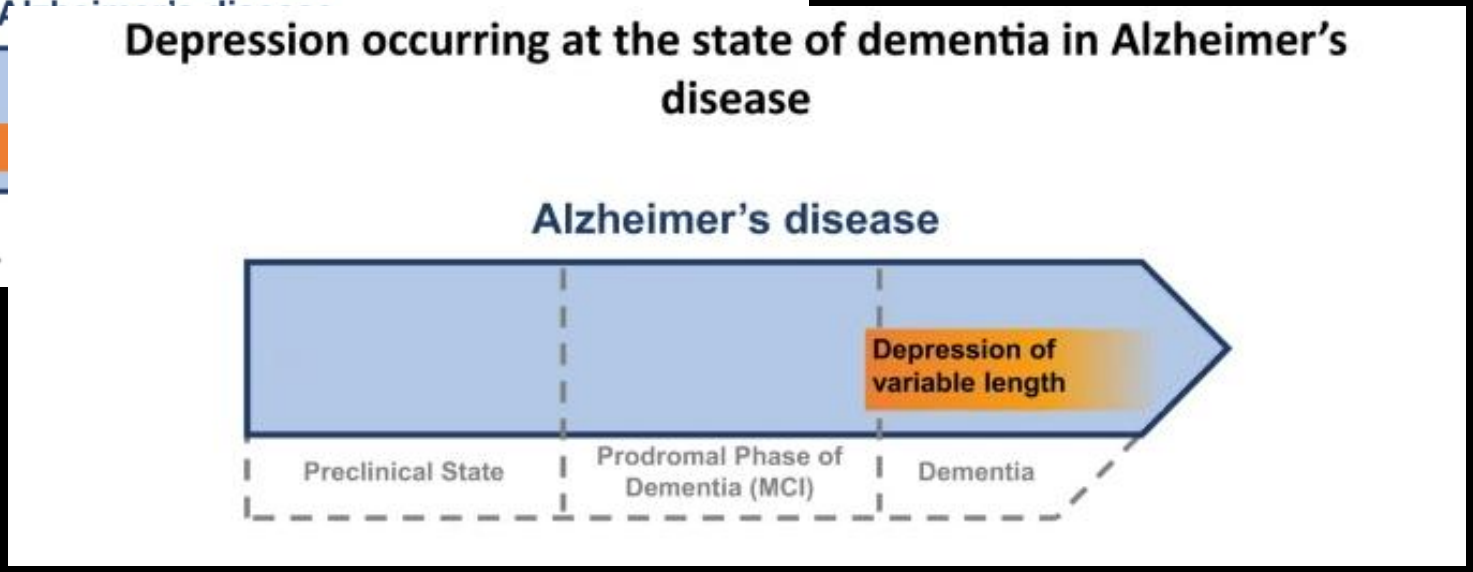
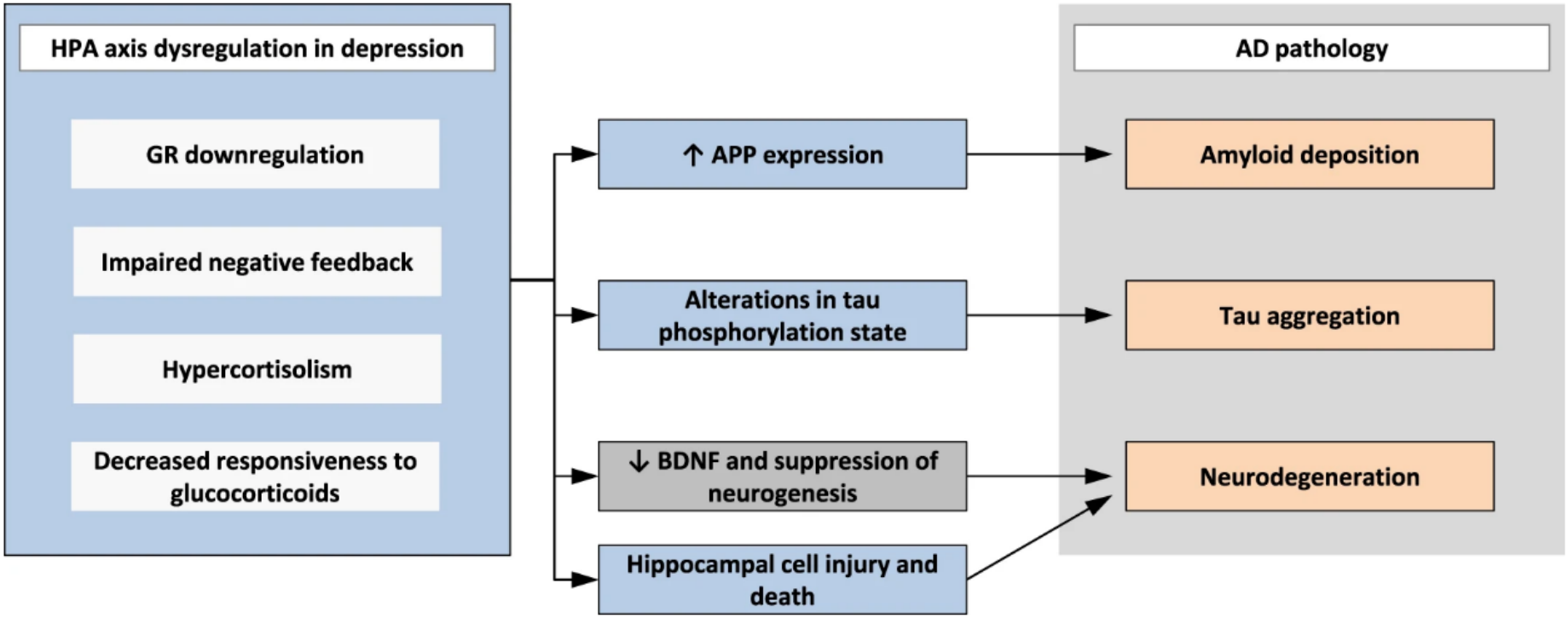


Fig. 2: Impact of HPA axis dysregulation in depression on AD pathology.

From: Depression—an underrecognized target for prevention of dementia in Alzheimer's disease



HPA axis: hypothalamic-pituitary-adrenal axis, GR: glucocorticoid receptor, APP: amyloid precursor protein, BDNF: brain-derived neurotrophic factor, AD: Alzheimer's disease.

알츠하이머병 환자의 우울장애에 대한 잠정 진단기준

1. 알츠하이머병치매(DSM-IV-TR)의 기준에 부합될 것
2. 주요우울장애에서의 아홉 개 증상 중 다섯 가지가 아니라 세 가지의 증상에 부합
   1) 우울감, 2) 흥미의 소실, 3) 체중이나 식욕의 변화, 4) 수면의 변화, 5) 정신운동 항진이나 지체, 6) 피로감과 활력 소실, 7) 무가치감과 죄책감, 8) 집중력 감퇴, 9) 죽음에 대한 사고
3. 두 개의 증상이 추가됨. 1) 이자극성, 2) 사회적 고립이나 위축
4. '흥미의 소실'은 '사회적 접촉이나 일상생활로부터의 긍정 반응의 감소'로 변경
5. 주요우울장애와 마찬가지로 2주 이상 증상이 존재해야 하나 거의 매일 증상이 있어야 하는 것은 아님

Antidepressants: suggested dosage, side effects and evidence in BPSD

Medication	Suggested dosage	Side effects	Highest level of evidence available	Notes
Sertraline	50–200 mg/day	Nausea, insomnia, diarrhoea, increased risk of bleeding, hyponatremia	RCTs	Preferred SSRI in older adults due to fewer drug interactions; monitor for hyponatremia and bleeding, especially in patients on CHEIs or anticoagulants.
Escitalopram	5–10 mg/day	Nausea, insomnia, fatigue, increased risk of bleeding, hyponatremia	RCTs	A safer alternative to citalopram due to a lower risk of QTc prolongation. Monitor for bleeding risk.
Citalopram	10–20 mg/day	Nausea, dry mouth, QTc prolongation, increased risk of bleeding, hyponatremia	RCTs	Not recommended as a first-line treatment due to QTc prolongation risk. Use with caution, especially with QTc- prolonging drugs.
Trazodone	Agitation/Psychosis: 50–150 mg/day; Sleep disorders: 25–100 mg/day	Sedation, dizziness, dry mouth, orthostatic hypotension	RCTs	Effective for agitation and sleep disorders. Monitor for sedation and fall risk, especially in older adults.

Antidepressants: suggested dosage, side effects and evidence in BPSD

Medication	Suggested dosage	Side effects	Highest level of evidence available	Notes
Mirtazapine	Depression: 15–45 mg/day Sleep disorders: 7.5–15 mg/day	Weight gain, sedation, increased appetite	RCTs	Effective for depression and sleep disorders. Limited benefit for agitation in dementia.
Esmirtazapine	Sleep disorders: 1.5–4.5 mg/day	Sedation, dizziness, dry mouth	RCTs	Effective for sleep disorders at low doses with minimal side effects.
Doxepin	Sleep disorders: 3–6 mg/day	Sedation, dizziness, dry mouth	RCTs	Safe for sleep maintenance insomnia in older adults at low doses.
Agomelatine	25–50 mg/day	Nausea, headache, dizziness, fatigue, increased liver enzymes	Observational study	Liver function should be monitored regularly due to the risk of hepatotoxicity. No significant risk of sexual dysfunction or weight gain, making it potentially beneficial in long-term use.

Depression in Dementia (Summary)

Definition	DSM-V criteria
Prevalence	Wide range (0%~87%), less common than apathy Much more attention than apathy
Cognitive funcion **ADL**	The relationship between depression and cognition: controversial
Symptom	Sleep disturbances and fatigue >sad mood, loss of interest, psychomotor changes>loss of weight> loss of appetite and guilt feelings> suicidal ideation
Neuropathology	Frontal-striatal and subcortical limbic circuits/Serotonergic deficit/ NFT
Scale	Hamilton depression scale, Geriatric depression scale, NPI, CSDD
DDx	Hypothyroidism, Electrolyte imbalance, Steroid, Beta-blocker, Digoxin, Pseudodementia, NSAIDS
Treatment	SSRIs, TCAs
Associated **Behavior problems**	Anxiety/Agitation/Irritability/Hallucinations
Related Disease	Stroke (anterior, left sided) , HD, PD

경청해 주셔서 감사합니다

SCH