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Original Research Article

The Effects of Donepezil on 15-Item Geriatric Depression Scale Structure in Patients with Alzheimer Disease

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Key Words

Alzheimer disease · Cognitive function · Donepezil · Factor analysis · Geriatric Depression Scale

Abstract

Background/Aims: In Alzheimer disease (AD), depression is among the most common accompanying neuropsychiatric symptoms and has different clinical manifestations when compared with early-life depression. In patients with drug-naïve AD, we tried to explore the structure of the 15-item Geriatric Depression Scale (GDS15) and the effect of donepezil on these substructures. ***Methods:*** GDS15, cognitive function, and activities of daily living function tests were administered to 412 patients with probable AD who had not been medicated before visiting the hospital. Using principal component analysis, three factors were identified. The patients with AD who received only donepezil were retrospectively analyzed and we compared the change of cognition and GDS15 subgroup after donepezil medication. ***Results:*** Our study identified three factors and revealed that the GDS15 may be comprised of a heterogeneous scale. The Barthel index was significantly correlated with factor 1 (positively) and factor 2 (negatively). The Korean version of the MMSE (K-MMSE) was significantly correlated with factor 2 and factor 3. Compared to the baseline state, K-MMSE and GDS15 showed significant improvement after taking donepezil. Among GDS15 subgroups, factor 2 and factor 3 showed significant improvement after donepezil treatment. ***Conclusions:*** These results suggest that the GDS15 may be comprised of a heterogeneous scale and donepezil differentially affects the GDS15 subgroup in AD.

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Introduction

Classically, patients with depression show a unique constellation of cognitive, mood, and somatic symptoms. However, the depression in Alzheimer disease (AD) patients often has different clinical presentations and shows significant variations compared with early-life depression [1].

Disturbances in mood of depression in AD are short-lived and frank sadness is less prominent than irritability, worry, anxiety, or fear. Patients with AD may concurrently exhibit lack of interest in the surrounding world and a gradual withdrawal from activities that were previously enjoyable. Patients may keep to themselves in current social settings. Somatic symptoms more often take on the form of a lack of ability to sustain activities, including activities of daily living (ADL). AD patients with depression initiate very few activities and their willingness to participate in activities tapers off after a short while, which eventually often leads to apathy. AD patients with depression typically have sleep disturbances, with trouble falling asleep or staying asleep being most common. They also have decreased appetite and mild persistent loss of weight. Cognitive symptom is relatively prominent and tends to be underestimated in AD patients with depression. Guilt and suicidal thoughts are uncommon. AD patients with depression often have little confidence in themselves and, as a result, avoid social interactions. They may report decreased self-esteem, and make self-deprecating statements [2]. Finally, the treatment of depression in AD is particularly problematic because antidepressants are less effective in patients with dementia compared to patients with early-life depression [3]. Due to these differences, depression that occurs in AD has been considered to be an atypical syndrome of depression [4].

In AD, the relationship between cognitive impairment and depression remains controversial. Cognitive impairment not only changes how we perceive ourselves and the world around us, it also changes the way we feel. Extensive studies have explored the association between cognitive aspects and depression in patients with AD. Some previous studies reported the negative impact of depression on general cognition [5], measures of dementia severity, working memory, processing speed [6], attention, motor functioning, visuospatial perception and construction [7]. Other investigators have found no cognitive differences between AD patients with and without depressive symptoms [8]. Due to this lack of consistent or weak relationships between cognitive abnormalities and depression, it is still uncertain whether the depression is secondary to cognitive impairment or epiphenomenal to AD.

Among the confounding factors for this inconsistency, the psychoactive medication effect may be critical. Not only can depression be influenced by antidepressants, it can also be influenced by other psychoactive medication. Due to the long-standing Korean tradition of caring for dementia patients by family members, there is a considerable number of patients with mild to severe AD who visit dementia clinics while having never been on medicated status. Therefore, we can build databases for drug-naïve probable AD patients, which will thus overcome this limitation.

The 30-item Geriatric Depression Scale (GDS30) has been a widely used depression screening tool in clinical work and research for elderly persons since its first development over 30 years ago [9]. However, because the original GDS (GDS30) is relatively time-consuming, a shortened 15-item version (GDS15) extracted from the GDS30 has been developed [10]. Sensitivity and specificity of the GDS15 have been assessed in a general elderly population [10], geriatric inpatients [11], primary care outpatients [12] and patients with AD [13], and proved good discriminant validity, content validity, concurrent validity and internal consistency reliability.

Patients with AD complain about multiple depressive symptoms, which often occur concurrently. One approach to better understand the depressive symptomatology of AD in

GDS15 is to evaluate whether specific GDS15 questionnaire items occur more in association with patients with AD. This approach can provide us with insight into how items of the GDS15 can be subgrouped (factors) and whether GDS15 can be used as a unidimensionality scale [14] or multidimensionality scale [15]. If the individual items of GDS15 are heterogeneous in AD, then these might be grouped in a more similar one and this clinical co-occurrence may suggest a common biologic mechanism for these symptoms. To extract the homogeneous subgroups, several factor analysis studies for GDS30 [4, 14, 15] and GDS15 [16–18] have been published.

Donepezil hydrochloride, a selective acetylcholinesterase (AChE) inhibitor, has received widespread approval for the symptomatic treatment of AD. Also, there is evidence that donepezil improves the neuropsychiatric symptoms of AD [19]. Secondary and subgroup analysis of donepezil studies showed that donepezil was effective for reducing dysphoric mood [20, 21]. As already known, potential antidepressant effects of AChE inhibitors are complex and have received mixed clinical reviews.

The aims of this study were the following: firstly, to examine the factor structure of the GDS15 in patients with probable AD. A second aim was to explore the donepezil effects according to GDS structure. Finally, using these results, we hypothesized the meaning of depressive symptomatology of patients with AD.

Methods

Patients

An initial 1,426 patients with dementia were screened from March 2003 to July 2015 at the Hyoja Geriatric Hospital and Veteran Health Service Medical Center. Among the 1,426 patients with dementia, the study subjects were 412 patients with probable AD who were not medicated before visiting the hospital. All study subjects met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD [22]. Patients who were taking psychoactive drugs, including antidepressants, antipsychotics, anticonvulsants, benzodiazepines, and cholinesterase inhibitors, were excluded from this study. All study subjects underwent a complete medical history, physical and neurological evaluation, comprehensive neuropsychological tests, routine laboratory tests, and a brain magnetic resonance imaging or computed tomography scan. Among them, 102 patients were medicated with donepezil alone and were re-checked with cognitive test and GDS15 3 months after donepezil medication according to the Dementia Registry.

Procedures

A structured interview and neuropsychological examination were performed with each subject. In the first, in order to assess cognitive functions, the Korean version of the MMSE (K-MMSE) [23] and Clinical Dementia Rating (CDR) scale [24] were used. A Barthel index [25] for ADL evaluation was adopted. Secondly, GDS15 was administered by a trained neuropsychologist. The cutoff screening criterion of the Korean version of GDS15 for depression is 8 or more endorsed items [12]. Finally, to assess the donepezil effects on cognitive function and GDS15, patients with AD who received donepezil alone were retrospectively evaluated using the Dementia Registry of our clinics, and the changes of cognition and GDS15 structures after donepezil medication were compared with baseline state.

This study was approved by the Institutional Review Board of the Veteran Health Service Medical Center and the Public Institutional Review Board Designated by the Ministry of Health and Welfare.

Table 1. Demographic and clinical features of study subjects[a]

Characteristics	No donepezil study subjects (n = 310)	Donepezil study subjects (n = 102)	p value
Age, years	74.5±7.2	74.9±6.3	0.821
Female gender (%)	192 (61.9)	74 (72.5)	0.10
Age at onset, years	70.2±8.1	73.0±7.6	0.672
Disease duration, months	34.5±28.8	23.7±17.2	0.349
Education, years	9.1±6.2	7.4±4.1	0.269
K-MMSE	19.0±6.2	16.8±5.6	0.382
Mean CDR	1.1±0.9	1.3±0.6	0.151
CDR, n			
0.5	60	8	0.456
1	189	60	
2	61	34	
Barthel index	18.1±2.4	19.2±2.7	0.202
GDS15	8.4±4.1	8.5±4.0	0.799
Factor 1	4.2±2.4	4.3±2.4	0.874
Factor 2	1.9±1.6	1.9±1.4	0.824
Factor 3	2.3±1.0	2.3±0.9	0.687
Number of GDS15 depression (%)	148 (47.7)	57 (57.0)	0.105

K-MMSE = Korean Mini-Mental State Examination; CDR = Clinical Dementia Rating scale; GDS = Geriatric Depression Scale. [a] 400 study subject were recruited from a previous study [12].

Statistical Analysis

Principal component analysis (PCA) was carried out on the GDS15. Before PCA analysis, two complementary methods, the Kaiser-Meyer-Olkin measure of sampling adequacy and Bartlett's test of sphericity, were used to evaluate the appropriateness of factor analysis. Factors, extracted by the PCA with Spearman correlation matrices and varimax rotation, were used for orthogonal rotation to get a simple structure. This rotation phase allows the identification of factors summarizing sets of closely related variables. Factors were selected if their eigenvalue was 1, and an item was included if its factor loading was 0.30. Second, to evaluate the factors and other cognitive and ADL parameters, bivariate correlation was performed. Finally, to assess the donepezil effects on cognitive function, ADL function and GDS15 subgroups, paired t test was performed. Statistical analyses were performed with the SPSS version 18.0 (SPSS, Inc., Chicago, Ill., USA) and p values of 0.05 were regarded as significant.

Results

Demographic Characteristics of the Study Subjects

The study included 152 men (36.9%) and 260 women (63.1%). The mean age was 74.8 ± 7.0 years. The average K-MMSE and CDR scores were 18.5 ± 5.5 and 1.1 ± 0.7, respectively, indicating that mainly subjects with mild to moderate AD were recruited. Among them, 102 patients were selected for further analysis of donepezil effects. Demographic data of these patients are shown in table 1.

Prevalence and PCA of the GDS15 Items

The prevalence of individual GDS15 items is presented in table 2. Item 8, 'Often feel helpless', was the most frequently endorsed item. Item 11, 'Wonderful to be alive now', was

Table 2. Three-factor structure of the GDS15 in study subjects

Item of GDS15	Endorsement, %	Factor 1	Factor 2	Factor 3
12/Feel pretty worthless	61.0	0.684		
8/Often feel helpless	69.8	0.645		
3/Feel your life is empty	58.7	0.640		
4/Often get bored	55.5	0.627		
14/Feel your situation is hopeless	66.4	0.600		
9/Prefer to stay at home	55.4	0.586		
6/Afraid something bad will happen	60.4	0.556		
15/Most people better off	69.5	0.540		
7/In good spirits most of the time (no)	35.9		0.601	
5/Hopeful about the future (no)	42.9		0.555	
11/Wonderful to be alive now (no)	34.5		0.511	
1/Basically satisfied with life (no)	37.2		0.499	
10/Have more memory problems than most	60.6			0.720
2/Dropped many activities and interests	49.9			0.652
13/Feel full of energy (no)	67.8			0.471
Eigenvalues		5.112	1.888	1.677
Variance, %		32.88	13.10	11.50
Cumulative variance		32.88	45.98	57.48

GDS = Geriatric Depression Scale.

the least frequently endorsed item. PCA and their factor loadings are presented in table 2. All GDS15 items reached the factor loading criterion of ≥0.30, and 3 subgroups were identified using PCA. These 3 subgroups explained 57.48% of the total variance in the data. The first subgroup, factor 1 (resembling previously named 'dysphoria' [6, 16]), was comprised of 8 items: 'Feel pretty worthless', 'Feel your life is empty', 'Often feel helpless', 'Often get bored', 'Feel your situation is hopeless', 'Prefer to stay at home', 'Afraid something bad will happen', and 'Most people better off', and this was composed of 32.88% of the total variance. The second subgroup, factor 2 (resembling previously named 'life satisfaction or apathy' [6, 16]), included 4 items: 'In good spirits most of the time (no)', 'Hopeful about the future (no)', 'Wonderful to be alive now (no)', and 'Basically satisfied with life (no)', and this explained 13.10% of the total variance. The third subgroup, factor 3 (resembling previously named 'cognitive impairment' [6, 16]), included 3 items: 'Have more memory problems than most', 'Dropped many activities and interests', and 'Feel full of energy (no)', and this was composed of 11.50% of the total variance.

Correlation among GDS15, GDS15 Subgroups, K-MMSE, CDR and Barthel Index

In table 3, the correlation between GDS15 factors and general cognitive function and ADL functions were summarized. Factor 1 and factor 3 were significantly correlated with GDS15, while factor 2 was not significantly correlated with GDS15. The Barthel index was significantly correlated with factor 1 (positively) and factor 2 (negatively). K-MMSE was significantly correlated with factor 2 and factor 3.

Changes in GDS15, GDS15 Subgroups, K-MMSE, CDR, and Barthel Index after Donepezil Medication

Compared to the baseline state, K-MMSE and GDS15 showed significant improvement after taking donepezil, while CDR and Barthel index did not show statistical differences

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.

Table 5. Factor 1 change-related demographic variables with intercept and corresponding weights (B) and probability levels in patients with AD

	Factor 1		Factor 2		Factor 3	
	B	p value	B	p value	B	p value
Intercept	–30.9	0.194	–9.874	0.194	–9.219	0.116
Age	0.853	0.253	0.289	0.229	0.143	0.399
Age at onset	–0.607	0.398	–0.174	0.445	–0.059	0.720
Symptom duration	–0.062	0.533	–0.026	0.411	0.008	0.727
Gender	–0.226	0.922	–0.828	0.290	–0.662	0.256
Education	0.247	0.446	–0.005	0.960	–0.068	0.379
K-MMSE	0.224	0.463	0.062	0.521	0.116	0.049
CDR	5.323	0.090	0.848	0.343	0.467	0.470
Barthel index	0.115	0.334	–0.257	0.685	0.094	0.694

Multiple regression analysis (R = 0.793).

(table 4). Among GDS15 subgroups, factor 2 and factor 3 showed significant improvement after donepezil treatment. In multiple regression analysis for identifying the factors associated with GDS subgroup change, factor 3 related significantly with baseline K-MMSE scores (table 5).

Discussion

The factor analysis of the GDS is useful not only for research application but also for clinical insight into depression. For example, the GDS factor structure might enable clinicians to understand the characteristics of a patient's subjective experience of depression. Our study used PCA methods and adopted factor when factor loading was above 0.40 (approximately 15–16% of variance), which exceeds the critical value of the Pearson r. In this way, a three-factor model was extracted and showed good overall fit using GDS15. As in previous studies, our study extracted three factors reflecting dysphoria [4, 17], life satisfaction [16, 18], and cognitive impairment [21]. Factor 1 consisted of 8 items and all these questionnaires were comprised of positively stated items. Factor 2 consisted of 4 items and, characteristically, all these items were comprised of negatively stated ones. Finally, factor 3 consisted of 3 items and was comprised of a mix of positively and negatively stated ones.

In the previous factor analysis study on GDS15 [16], three dimensions, general depressive affect (resembling our factor 1), life satisfaction (resembling our factor 2), and withdrawal (resembling our factor 3), were reported. In this study, the item 'Do you feel you have more problems with memory than most?' did not load highly on the cognitive impairment construct, but this item loaded highly on factor 3 in our study. The item 'prefer to stay at home' is included in withdrawal symptoms, but this is included in factor 1 in our study. The item 'dropped activity and interest' is included in the withdrawal or apathy symptom [4], but in our study, this item is a component of factor 3. The other study for AD, using GDS30, showed 4 factors. All items included in factor 2 of our study belong to the apathy factor. Most items in factor 1 of our study are consistent with dysphoric factors except item 3 (apathy factor) and item 9 (social withdrawal factor). Only memory problem items in factor 3 of our study are consistent with cognitive impairment factors. The 'dropped activity' item (factor 3 in our study) is included in the apathy factor and the 'Prefer to stay home' item (cognitive impairment item in our study) is included in the social withdrawal factor [5].

Statistically determined symptom clusters can be affected by many considerations, including which symptoms were assessed, how they were measured, their prevalence in the study sample, and the size and composition of the sample. Therefore, the slightly different cluster of our study from other previous studies might reflect these differences and the most possible causative factors might be different characteristics of the study subjects, e.g., normal elderly subjects or patients with dementia, and drug-medicated or drug-naïve patients.

To find the clinical characteristics of these subgroups, the correlations between these factors and cognitive functions and ADL function are analyzed. Interestingly, factor 1 was significantly positively correlated with the Barthel index but this was not correlated with cognitive functions. Why these are positively related to Barthel index is not certain. Factor 1 was related with mood symptoms, and ADL function might be more related with mood symptoms than cognitive functions. This hypothesis should be explored. Factor 2 is significantly correlated with K-MMSE and Barthel index. Factor 3 is significantly correlated with K-MMSE and CDR. These findings suggested that factor 2 and factor 3 are more or less related to cognitive function, while factor 1 is not significantly related to cognitive functions. Interestingly, in the multiple regression analysis for searching variable donepezil influencing GDS substructures, factor 3 was positively correlated with baseline K-MMSE. This means that lower baseline K-MMSE scores are related to lower factor 3 after donepezil medication.

Patients with AD accompanied multiple depressive symptoms reflecting in GDS15 and these items are often concurrent. Clinical co-occurrence may suggest a common biologic mechanism for some symptoms. In line with current concepts of brain function, these depressive subgroup symptoms are thought to arise from a certain anatomical area and failed

regulation of functional brain networks. To elucidate this hypothesis, the identified clusters were retrospectively analyzed after donepezil medication.

A number of studies for cholinesterase inhibitor drugs to augment antidepressant treatment in later life have been conducted. Positive antidepressant effects of augmentation with AChE inhibitors have been reported [20] but there is also a negative report [26] and the overall picture is somewhat obscure. Old previous studies have indicated that exposure to cholinomimetic drugs, such as pilocarpine, physostigmine and organophosphate insecticides, may in fact have a depressogenic effect [27].

AChE inhibitors increase synaptic levels of acetylcholine and this leads to stimulation of both muscarinic and nicotinic acetylcholine receptors. Muscarinic receptor antagonists appear to have antidepressant properties and there is previous literature describing antidepressant effects of atropine [28]. Conversely, antidepressant-like effects have been reported for nicotinic receptor agonists [29] and there is growing interest in the clinical potential of nicotinic agonists as antidepressants.

Because these two receptors may be differentially involved in depression, clinical outcomes may be variable. Thus, it is likely that the antidepressant-like effects of donepezil that were observed in the present study would be due to nicotinic stimulation. More generally, it seems likely that the outcome of anticholinesterase treatment of depression may depend on the balance of stimulation of muscarinic and nicotinic receptors, which might vary as a function of drug dose, mood status, and baseline level of cholinergic activity. Further investigation is needed to elucidate these relationships.

Another hypothesis is that antidepression effects of AChE inhibitor result from hippocampal neurogenesis by activation of the central cholinergic system. Destruction of cholinergic neurons is known to decrease hippocampal 5HT levels, suggesting that an adequate level of cholinergic activity is necessary for normal activity at hippocampal 5HT terminals, and that donepezil may enhance hippocampal 5HT activity in a manner comparable to conventional antidepressants [30].

Our study showed that there are individual GDS15 items that are more likely to be associated with cognitive functions. These items can be the nonaffective factors, even though they are comprised of depression scales such as the GDS. Therefore, we should be cautious in interpreting GDS15 results and re-appraise the clinical implications of these items.

However, the present study had several limitations. First, the sample size was relatively small. Second, the present study included mainly mild patients, and as a result, this study was mostly biased for mild cases (mean CDR score was 1.1). Third, the statistical method (correlation) and study design (retrospective study) cannot find any cause-effect relationship and only suggested the correlation among factors. Fourthly, correlation test is used for confirming the relationship between two variables. Though variables are statistically significant when the p value was under 0.05, the coefficient of correlation of some variables, which measures the strength and direction of the relationship between two variables, is low in our study. This means that though these variables are statistically related, the strength (not the relationship itself) can be somewhat low. So, statistical results should be taken cautiously. Finally, the present study was a hospital-based study and other factors such as social backgrounds were not evaluated, and so our subjects might not represent the real community.

In summary, our study showed GDS15 comprised of 3 different structures, and these factors are differentially related to cognitive symptoms. Moreover, donepezil showed differential effects on the substructure of GDS15. These findings are suggestive of cognitive aspects of GDS15 in patients with AD. Therefore, when we use this screening tool for depression, cautious and different application may be needed.

Disclosure Statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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