

Neuropsychiatric profiles of patients with Alzheimer's disease and Vascular Dementia in Taiwan

Chia-Jung Hsieh¹, Chia-Chi Chang¹ and Chia-Chin Lin^{2*}

¹*School of Geriatric Nursing and Care Management, College of Nursing, Taipei Medical University, Taipei, Taiwan, ROC*

²*School of Nursing, Taipei Medical University, Taipei Medical University Hospital, Taipei, Taiwan, ROC*

SUMMARY

Background Previous studies have reported several conflicting findings regarding neuropsychiatric symptoms when comparing patients with Alzheimer's disease (AD) and patients with vascular dementia (VaD).

Objectives The purpose was to: (1) compare the prevalence of neuropsychiatric symptoms among patients with AD and VaD after controlling for demographic characteristics in difference setting and (2) rank and contrast the severity the common symptoms between the two groups in north of Taiwan.

Methods This study was a cross-sectional comparative design. Data were collected from clinical interviews using three instruments: the Mini-Mental Status Examination (MMSE), the Clinical Dementia Rating Scale (CDR), and the Neuropsychiatric Inventory (NPI).

Results A total of 154 subjects participated in this study. The male subjects with VaD from the outpatient setting had lower NPI scores. In the OPD, the subjects with AD had more nighttime behavior than subjects with VaD. In the nursing home setting, the subjects with VaD had higher prevalence of depression, irritability, and appetite changes than subjects with AD. The subjects with AD had more euphoria and nighttime behavior than subjects with VaD. The average of total NPI scores for people with AD and VaD from the nursing home setting indicate higher scores. In the nursing home group, the VaD subjects evidenced significantly higher irritability scores than the AD subjects.

Conclusions This was first care unit based study in north Taiwan. Our results showed the significant differences between AD and VaD groups of NPI symptoms. Understanding those differences may aid differential diagnosis of dementia subtypes and help develop proper interventions. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — neuropsychiatric symptoms; dementia subtypes; Neuropsychiatric Inventory

INTRODUCTION

Over the disease course of dementia, 80–90% of people with dementia evidence neuropsychiatric symptoms (Steinberg *et al.*, 2004). Non-cognitive behavioral and psychiatric disturbances such as apathy, disinhibition, agitation/aggression, depression, psychosis, and sleep disturbances are frequently observed in people with dementia (Chung and Cummings, 2000). Those disturbances can contribute to the clinical differen-

tiation of various subtypes (Srikanth *et al.*, 2005). Such symptoms interfere with the quality of life for both patients and caregivers, and may be an important factor in the decision to place an elder in long-term care (Aalten *et al.*, 2005a). Moreover, such symptoms are associated with caregiver distress, increased caregiver burden (Sink *et al.*, 2006) and higher costs of care (Lyketos *et al.*, 1999). On the basis of the Cache Country study, which is a large community population of elderly people, the authors conclude a wide range of dementia-associated mental and behavioral disturbance distress the majority of individuals with dementia. Because of their frequency and their adverse effects on patients and their caregivers, these disturbances should be determined

*Correspondence to: Dr C.-C. Lin, School of Nursing, Taipei Medical University, Taipei Medical University Hospital, 250 Wu-Hsing Street, Taipei 110 Taiwan, ROC. E-mail: clin@tmu.edu.tw

and attended in all cases of dementia (Lyketsos *et al.*, 2000).

Few studies have compared non-cognitive behavioral and psychiatric disturbances between dementia subgroups (Srikanth *et al.*, 2005) and differences in neuropsychiatric symptoms between patients with Alzheimer's disease (AD) and patients with vascular dementia (VaD). Results from the comparison between two groups are conflicting (Aalten *et al.*, 2005a, 2005b; Fuh *et al.*, 2005). For example, one study found that people with VaD had a significantly higher rate of apathy and sleep disturbances than people with AD; VaD patients had more disrupted sleep/wake cycles and decreased sleep quality (Fuh *et al.*, 2005). However, several study have reported that sleep disturbances were higher in the AD group with the most common sleep behaviors being a tendency to confusion in early evening and wandering at night (Ancoli-Israel *et al.*, 1994; Grace *et al.*, 2000). More definite symptoms such as delusions and aberrant motor behavior (ABM) were found in AD patients than VaD patients (Ikeda *et al.*, 2004). One study suggest that depression is specifically more common in VaD than AD (Payne *et al.*, 1998), but another study disagreed with that result (Sultzer *et al.*, 1993). Nevertheless no significant differences in neuropsychiatric symptoms were found between people with AD and VaD in a study by Srikanth *et al.* (2005). No previous studies have been conducted by matching important confounding variables.

Different types of dementia present varied neuropsychiatric symptoms, which may lead to differing medical treatments and contribute differently to caregiver distress (Chung and Cummings, 2000). In addition, differentiating neuropsychiatric symptoms among people with AD and VaD could aid diagnosis of dementia subtypes.

Previous studies have found inconsistent results in the relationship between neuropsychiatric symptoms and demographic characteristics such as age, sex, and severity of dementia (Levy *et al.*, 1996; Devanand *et al.*, 1997). One possible explanation is that such studies did not control for demographic characteristics (Ikeda *et al.*, 2004; Srikanth *et al.*, 2005; Peters *et al.*, 2006; Tatsch *et al.*, 2006).

Understanding differences in neuropsychiatric symptoms between people with AD and VaD may help clinicians to better predict the clinical course and to develop better treatment strategies (Lyketsos *et al.*, 2000). Despite being amenable to therapeutic interventions, neuropsychiatric symptoms are among the most important factors predicting institutionalization of the demented (Heyman *et al.*, 1997; Mortimer *et al.*, 1992).

Therefore, we tested the hypothesis that participants with AD or VaD would experience difference in neuropsychiatric symptoms. In this article our goal was to: (1) compare the prevalence of neuropsychiatric symptoms among patients with AD and VaD in different settings after controlling for demographic characteristics and (2) rank and contrast the severity of the common symptoms between the two groups.

METHODS

Subjects and study design

This study used a cross-sectional design. Research participants were recruited by random sampling from ten nursing homes and three neurology outpatient department (OPD) in northern part of Taiwan. These were outpatient residential facilities. The study subjects consisted of 154 individuals. The subjects were interviewed by researchers with a structured questionnaire. Participants' physical examinations were performed by their clinician. Physicians used the Diagnosis and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) for the diagnosis of AD (American Psychiatric Association, 1994) and completely reviewed the subjects' medical history, laboratory findings, and physical examination in order to differentiate subtypes of dementia. The subtypes of dementia were based on standard clinical criteria currently in use (Srikanth *et al.*, 2005). The VaD subjects met the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for AD (Knopman *et al.*, 2001). Subjects were excluded if they suffered from delirium or had a history of alcohol or substance abuse. This study was approved by the Institutional Human Subjects Committee of Taipei Medical University. Permission to conduct this study was given by the administrations of several long-term care facilities, and written informed consent was obtained from the patients and their caregivers.

Instruments

Data were gathered from the clinical interviews using a structured protocol and questionnaires.

Mini-Mental State Examination (MMSE). Cognitive statuses were measured by MMSE (Folstein *et al.*, 1975). The MMSE scores were adjusted below specific education norms. The MMSE cutoff point

for people who are illiterate is less than 20, but for those who have over 9 years of schooling is less than 28. Lower MMSE scores indicate increased cognitive impairment (Folstein *et al.*, 1975).

Clinical Dementia Rating Scale (CDR). The severity of dementia was measured by CDR. This is a five-point scale with scores ranging from 0 (no impairment) to 3 (severe impairment). CDR1 indicated a mild stage; CDR2 was equal to a moderate stage (Morris, 1993; Srikanth *et al.*, 2005). In this study we excluded the CDR3 which indicated severe impairment, as the subjects were almost totally dependent on their carers to maintain human contact and showed more severe impairment in all cognitive functions.

Neuropsychiatric Inventory (NPI). A clinician conducted a brief standardized interview with an informant and rated the frequency and severity of 12 specific behavioral and psychiatric symptoms of dementia (Cumming *et al.*, 1994). Included are: delusions; hallucinations; agitation; apathy; anxiety; depression; euphoria; irritability; disinhibition; aberrant motor behavior; changes in appetite; and nighttime behavior disturbances. If the answer to this screening question was 'no', then no further questions were asked. If the answer was 'yes', caregivers needed to rate the frequency and severity of the behavior based on scores with anchor points (frequency: 1 = occasionally, 2 = often, 3 = frequently, 4 = very frequently; severity: 1 = mild, 2 = moderate, 3 = severe). The frequency scores multiplied by the severity scores produced a composite score for each kind of behavior. A global score for each patient's NPI was generated by summing up the scores of the subscales. The total NPI score is the sum of intensity score for all items (0–144). Cronbach's α for overall score of the NPI was 0.88 score. The concurrent validity was good, as shown by an acceptable correlation between NPI scores and other validated measurements (Cummings *et al.*, 1994).

Procedure

A trained research assistant administered all scales to maintain uniformity. Caregivers (usually spouses or adult offspring) were asked to rate the frequency and severity of various disturbances measured by the NPI, as noted in the preceding month. If a spouse or

offspring was not available, a reliable alternative informant such as a professional caregiver was sought.

Statistical analysis

Statistical analysis was performed using the SPSS package version 12.0. The data analysis included descriptive statistics that contained means, standard deviations, frequencies, and percentages. Differences in frequencies of symptoms on the NPI were assessed for the two groups using the chi-square test. The student *t*-test was used to compare the difference in mean MMSE, CDR, and NPI scores and item scores between AD and VaD groups. A two-tailed level of significance ($p < 0.05$) was used for all tests.

RESULTS

Descriptive statistics of demographic and clinical data

A total of 154 subjects underwent neurological cognitive and psychiatric evaluation, including 77 in the AD groups and 77 in the VaD groups after being matched by age, gender, education, and severity of dementia. Demographic and clinical data for the two diagnostic groups and the two settings are reported in Table 1. There were no significant differences in demographic characteristics between the two groups. The average scores on the MMSE, CDR were 15.71 ± 4.74 , 1.36 ± 0.48 , respectively at baseline for all patients. There were no significant differences in clinical variables between the two groups.

Relationships of demographic characteristics to neuropsychiatric profiles within groups

The variance of demographic characteristics and NPI scores within each group are shown in Table 2. The male subjects with VaD from outpatient unit who had lower NPI score than the male subjects with AD, and has the significant difference ($t = -2.15$, $p < 0.05$).

Prevalence and ranking of neuropsychiatric symptoms

In this study, all participants showed one or more mental or behavioral disturbances, while 9.7% subjects had at least three symptoms in the NPI. The most common neuropsychiatric symptoms in order of ranking were nighttime behavior, apathy, aberrant

Table 1. Demographic and clinical data of subjects for the two groups

Variables	Total (n = 154) Mean (SD)	OPD		χ^2 (t)	Nursing home		χ^2 (t)
		AD (n = 25) Mean (SD)	VaD (n = 26) Mean (SD)		AD (n = 52) Mean (SD)	VaD (n = 51) Mean (SD)	
Demographic variables							
Age(year)	71.08 (6.89)	69.96 (6.86)	68.76 (5.22)	-0.112	71.56 (7.14)	72.80 (6.97)	0.897
Education-literate, n (%)	139 (90.3)	23 (92.00)	23 (88.50)	0.180	46 (88.50)	47 (92.20)	0.401
Female subjects, n (%)	74 (48.1)	11 (44.00)	14 (53.80)	0.494	26 (50.00)	23 (45.10)	0.248
Live with spouse, n (%)	43(27.9)	12 (48.00)	16 (61.50)	0.943	7 (13.50)	8 (15.70)	0.102
Clinical variables							
MMSE	15.71 (4.74)	16.04 (6.42)	15.58 (4.98)	-0.288	14.83 (3.93)	16.51 (4.39)	1.278
CDR	1.36 (0.48)	1.32 (0.48)	1.42 (0.50)	0.750	1.38 (0.49)	1.33 (0.48)	0.000

AD = Alzheimer's disease; CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; OPD = Outpatient Department; VaD = vascular dementia.
 $p < 0.05$; $p < 0.01$; $p < 0.001$.

motor behavior (ABM) and depression among all dementia patients (Table 3). At least 50% of subjects showed at least one of the above symptoms. The prevalence and intensity of neuropsychiatric symptoms are listed in Table 3. The most frequently observed neuropsychiatric symptom for participants with AD in the outpatient group was nighttime behavior (96.0%) and similar results were found in people with VaD in the outpatient group (73.10%), the other neuropsychiatric symptoms occurring in over 50% of participants with AD from the outpatient units were apathy (88.0%) and ABM (56.0%). The contrast between the nursing home groups was similar.

Table 3 contains the prevalence for each NPI item by diagnostic group.

In the OPD setting, the subjects with AD displayed more nighttime behavior than the subjects with VaD, and this reached statistical significant ($\chi^2 = 5.06$, $p < 0.05$). In the nursing home setting, the subjects with VaD had a higher prevalence of depression

($\chi^2 = 7.31$, $p < 0.05$), irritability ($\chi^2 = 7.27$, $p < 0.05$), and appetite changes ($\chi^2 = 5.92$, $p < 0.05$) than the subjects with AD. The subjects with AD had more euphoria ($\chi^2 = 9.78$, $p < 0.05$) and nighttime behavior ($\chi^2 = 5.47$, $p < 0.05$) than the subjects with VaD.

Comparison of the NPI scores between the AD and VaD groups

The average of total NPI scores for people with AD and VaD in the outpatient unit were 28.72 (± 12.43) and 26.69 (± 9.92), respectively. The subjects from nursing home had higher average scores of total NPI. To determine the difference in mean scores in the NPI items observed for both groups, the mean for individual symptoms evaluated with the NPI for each group is presented in Table 4. In the nursing home group, the VaD subjects evidenced significantly higher irritability scores (3.39 ± 4.05) than the AD subjects (1.17 ± 2.38) ($t = 3.40$, $p < 0.001$). In addition, there were no significant differences between the two

Table 2. Relationships of demographic characteristics to neuropsychiatric profiles within each group

Variables		OPD		t	Nursing home		t
		AD (n = 25) Mean(SD)	VaD (n = 26) Mean(SD)		AD (n = 52) Mean(SD)	VaD (n = 51) Mean(SD)	
Gender	Male	27.93 (12.74)	19.08 (4.64)	-2.15*	29.88 (12.48)	29.07 (10.82)	-0.26
	Female	29.73 (12.57)	33.21 (8.46)	0.83	33.19 (11.92)	37.35 (14.27)	1.11
Dementia Severity	Mild	26.76 (13.38)	26.07 (9.57)	-0.17	32.19 (13.11)	34.21 (12.63)	0.64
	Moderate	32.88 (9.57)	27.55 (10.78)	-1.11	30.50 (10.08)	30.000 (13.78)	-0.12
Education Level	Illiterate	50.00 (4.24)	22.00 (0.00)	-12.52	44.17 (8.32)	38.75 (16.56)	-0.69
	Literate	26.87 (11.09)	27.30 (10.41)	0.14	29.89 (11.70)	32.30 (12.79)	0.95

* $p < 0.05$; $p < 0.01$; $p < 0.001$.

Table 3. Prevalence and differences of neuropsychiatric symptoms between the two groups

NPI item	All subjects (n = 154)		Rank	OPD				χ^2	Nursing home				χ^2
				AD (n = 25)		VaD (n = 26)			AD (n = 52)		VaD (n = 51)		
	n	(%)		n	(%)	n	(%)	n	(%)	n	(%)		
Delusions	45	29.20		7	28.00	7	26.90	0.01	12	23.10	19	37.30	2.46
Hallucinations	61	39.60		9	36.00	8	30.80	0.16	21	40.40	23	45.10	0.23
Agitation	66	42.90		11	44.00	8	30.80	0.95	25	48.10	22	43.10	0.25
Depression	88	57.10	4	12	48.00	17	65.40	1.57	23	44.20	36	70.60	7.31*
Anxiety	63	40.90		7	28.00	9	34.60	0.26	27	51.90	20	39.20	1.68
Euphoria	63	40.90		12	48.00	9	34.60	0.94	29	55.80	13	25.50	9.78*
Apathy	118	76.60	2	22	88.00	17	65.40	0.27	37	71.20	39	76.50	0.78
Disinhibition	0	0.00		0	0.00	0	0.00	0.00	0	0.00	0	0.00	0.00
Irritability	50	32.50		3	12.00	6	23.10	1.08	14	26.90	27	52.90	7.27*
ABM	89	57.80	3	14	56.00	16	61.50	0.16	28	53.80	31	60.80	0.51
Nighttime behavior	132	85.70	1	24	96.00	19	73.10	5.06*	49	94.20	40	78.40	5.47*
Appetite changes	18	11.70		1	4.00	0	0.00	1.06	4	7.70	13	25.50	5.92*

* $p < 0.05$; $p < 0.01$; $p < 0.001$.

ABM = Aberrant Motor Behavior.

groups for the remaining neuropsychological variables (see Table 4).

DISCUSSION

This is the first study in Taiwan to systematically investigate and compare the prevalence of neuropsychiatric profiles in patients with AD and VaD after controlling for important confounding variables.

Firstly, the result of this study revealed that female elderly with VaD had more neuropsychiatric symptoms than male elderly from the OPD setting and these results are in line with a previous study (Levy *et al.*, 1996). The declining level of oestrogen hormones in elderly women causes a higher incidence of dementia, as oestrogen has purported neurotoxin effects (Morris, 2005). However, in one longitudinal study to investigate the course of neuropsychiatric symptoms

Table 4. Comparison of mean NPI scores and severity stratified between AD and VaD groups

NPI item	OPD				<i>t</i>	Nursing home				<i>t</i>
	AD (n = 25)		VaD (n = 26)			AD (n = 25)		VaD (n = 26)		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Total NPI	28.72	12.43	26.69	9.92	-0.65	31.54	12.98	32.80	13.04	0.51
Delusions	2.44	4.16	2.46	4.34	0.02	1.85	3.65	2.78	4.12	1.22
Hallucinations	1.36	2.78	1.46	2.77	0.13	2.27	3.21	1.63	2.37	-1.15
Agitation	1.72	2.41	1.73	3.19	0.01	2.71	3.16	1.71	2.60	-1.76
Depression	3.60	4.47	3.30	2.81	-0.28	3.04	3.83	4.29	3.95	1.64
Anxiety	1.60	3.11	1.23	2.05	0.50	2.62	3.40	2.68	4.22	0.09
Euphoria	2.24	2.47	2.00	3.09	-0.31	2.38	2.57	1.55	3.00	-1.51
Apathy	5.00	3.33	5.04	2.90	-0.04	4.44	3.79	3.55	3.38	-1.26
Disinhibition	0.00	0.00	0.00	0.00	0.0	0.00	0.00	0.00	0.00	0.00
Irritability	0.32	0.94	0.92	1.89	1.43	1.17	2.38	3.39	4.05	3.40*
ABM	3.28	3.53	3.31	3.08	0.03	3.40	3.71	3.78	4.13	0.49
Nighttime behavior	6.80	3.15	5.23	4.07	-1.54	7.02	3.27	5.96	4.11	-1.45
Appetite changes	0.36	1.80	0.00	0.00	-1.02	0.63	2.32	1.47	2.80	1.65

* $p < 0.05$; $p < 0.01$; $p < 0.001$.

ABM = Aberrant Motor Behavior; NPI = Neuropsychiatric Inventory.

in dementia, gender was not associated with specific neuropsychiatric symptoms (Aalten, 2005a).

Secondly, regarding the prevalence of neuropsychiatric symptoms between the two groups, it is important to point out that frequency of symptoms measured by the NPI was higher than in previous studies (Lyketsos *et al.*, 2000; Volicer *et al.*, 2001; Ikeda *et al.*, 2004; Srikanth *et al.*, 2005; Peters *et al.*, 2006). Our participants showed one or more mental and behavioral disturbances. One explanation for the higher percentage of symptoms in the current study might relate to the sampled patients being referred by nursing homes or dementia clinics using DSM-IV and NINCDS/ADRDA definition criteria. Neuropsychiatric symptoms of dementia increase caregiver stress and nursing home placement (Sink *et al.*, 2006). Neuropsychiatric symptoms are an important feature of individuals referred to dementia clinics (Peters *et al.*, 2006). Therefore, it is not surprising that the study participants showed a higher prevalence of neuropsychiatric symptoms than other subjects in community based studies.

The most common neuropsychiatric symptoms of dementia were problems with sleeping (nighttime behavior), apathy, and ABM, found in both groups. This pattern is very consistent with the results reported in earlier studies in dementia patients (Chung and Cummings, 2000; Ikeda *et al.*, 2004; Peters *et al.*, 2006; Tatsch *et al.*, 2006). Behavioral symptoms of dementia may occur at any time of the day, but some individuals experience behavioral symptoms mostly in the afternoon and evening or at night, possibly influenced by circadian rhythms. They usually have irregular sleep-wake cycles (Volicer *et al.*, 2001). In general, our study showed that people with AD type had a higher prevalence of nighttime behavior (sleep disturbance) than people with VaD type in both OPD and nursing home setting. This may be an important factor in the decision to place an elder in a long-term care facility (Aalten *et al.*, 2005a). Therefore, the interventions focus on sleep disturbance may need to be targeted towards patients with AD.

In addition, the result indicated that people with VaD had a higher prevalence of depression than people with AD type but a significant difference was only found in the nursing home setting. Our results lend modest support to previous studies indicating higher rates of depression in VaD (Payne *et al.*, 1998; Lyketsos *et al.*, 2000). Screening for depression and treatment for depression may need to be particularly targeted towards people with VaD.

A surprising finding of the current investigation is that there was no difference between the AD and VaD

groups in the prevalence of positive of psychiatric symptoms (e.g. delusions, hallucinations, and agitation), but the euphoria symptom score was higher in the AD group in the nursing home setting. Recent studies show delusions occur in approximately one-third of AD patients, and AD patients with psychosis have an increased rate of cognitive decline (Fischer, 2004). In our study delusions were present in 23.1–28.0% of patients in nursing home and OPD settings. The absence of significant differences between two groups may be because the prevalence rate was similar, and as our subjects were referred by physicians, they may have been treated for their positive symptoms meaning the symptoms were in remission.

In the Cache County study the least frequent symptom was elation, reported in only 1%, and the prevalence of disinhibition was 9.1% (Lyketsos *et al.*, 2000). In our study, the patients in the AD groups had more euphoria symptoms, that may reflect the damaged areas often associated with psychosis (Zubenko *et al.*, 1991). More evidence is needed to confirm this. Furthermore, euphoria in the AD patients is a challenging behavior for the caregiver and consequently monitoring their individual response to treatment was important. No patients in this study had disinhibition, this may be because this had been treated by pharmacological intervention.

Result from this study showed that caregivers reported patients with VaD had more severe irritability in the nursing home setting and OPD than patients with AD. Irritability is a challenging symptom for caregivers and strategies for managing this in the clinical setting, particularly nursing homes, need to be developed. In general, the results showed that people with VaD had a higher prevalence of depression,

KEY POINTS

- The most common neuropsychiatric symptoms in order of rank were nighttime behavior, apathy, aberrant motor behavior (ABM), and depression among all dementia patients.
- The people with VaD had higher prevalence of depression, irritability, and appetite change; but people with AD had higher prevalence of euphoria and nighttime behaviors in nursing home setting.
- In the nursing home group, the VaD subjects evidenced significantly higher irritability scores than the AD subjects.

irritability, and appetite change; but people with AD had a higher prevalence of euphoria and nighttime behaviors in the nursing home setting.

This study is limited in a number of ways. Although the variables were matched to a greater extent than in previous reported studies, we did not perform factor analyses of neuropsychiatric symptoms because of the small sample size of those subjects. Information regarding the NPI was obtained from the caregiver, not the patient. Therefore, subjective measures relying on memory have potential problems of accuracy. Multiple observations should be developed for future studies. In addition, subjects were recruited by referral from physicians in northern Taiwan, thus findings may not be generalizable to dementia patients in other areas.

In conclusions, this study is a comprehensive type-specific prevalence surveys of neuropsychiatric symptoms of dementia performed to date. The result showed that people with VaD had a higher prevalence of depression, irritability, and appetite change; but people with AD had a higher prevalence of euphoria and nighttime behaviors. These results have clinical implications. Our data may help clinicians establish an approach to manage the neuropsychiatric symptoms. Dealing with neuropsychiatric problems is challenging for caregivers and strategies regarding neuropsychiatric symptoms need to be developed in clinical settings, especially in nursing homes. This study could also help clinicians to develop different treatment approaches and alleviate caregiver distress.

CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

This study was supported by grants from Department of Health, Executive Yuan, ROC (Taiwan), grants number DOH95-TD-M-113-062-(2)(1/2).

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