Table 1
Participants demographic and clinical characteristics

	Checkers ($n = 27$)			Washers ($n = 26$)			P
	Mean	SD		Mean	SD		
Age, years	36.2	7.0		33.8	8.2		.25
Gender (% female)	59			58			.91
Right-handed (%)	100			100			
Years of education	14.1	1.8		14.5	1.6		.37
Duration of illness (years)	6.8	2.9		5.3	3.0		.06
SRI, mg/day Clomipramine equivalent	224.1	32.1		228.9	37.9		.62
BDI-II	15.7	5.6		15.9	6.3		.89
STAI							
State anxiety	57.6	8.7		58.6	10.0		.72
Trait anxiety	59.2	9.4		61.6	10.5		.39
MOCI subscale score							
Checking	8.2	0.9		3.0	1.3		<.001*
Washing	1.9	1.4		9.5	1.3		<.001*
Slowness	3.4	1.3		3.4	1.7		.97
Doubting	4.6	1.5		3.7	1.2		.02*
Y-BOCS							
Total	33.7	4.3		34.4	4.3		.57
Obsessions	17.1	1.8		17.2	2.2		.77
Compulsions	17.1	1.8		17.2	2.7		.50
Number of patients of each score	Absent	Mild	Major	Absent	Mild	Major	
Contamination/cleaning	27	0	0	0	0	26	
Aggressive/checking	0	0	27	26	0	0	
Symmetry/ordering	10	17	0	13	13	0	.34
Hoarding	23	4	0	20	6	0	.44
Sexual/religious	23	4	0	24	2	0	.41

BDI, Beck Depression Inventory; STAI, Stait Trait Anxiety Inventory; MOCI, Maudsley Obsessional Compulsive Inventory; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale. Absent, patient did not have any of the symptoms; Mild, patient had at least one of the symptoms, but it was not considered as major problem; Major, at least one of the symptoms was considered as major problem.
* $P < .05$.

Table 2
Neuropsychological test results of participants

	Checkers ($n = 27$)		Washers ($n = 26$)		P
	Mean	SD	Mean	SD	
WMS-R					
General memory	125.1	23.8	134.8	14.6	.08
Verbal memory	64.5	20.5	72.3	13.0	.11
Visual memory	60.6	5.9	62.5	4.4	.18
Stroop test (false number)	3.4	2.5	1.0	1.0	<.001*
Stroop test (time)	12.8	11.2	8.0	3.2	.04*
TMT subtracted time	61.9	31.3	37.7	19.6	.002*
GO/NO GO test (omission errors)	7.6	3.6	7.1	2.9	.54
GO/NO GO test (commission errors)	33.5	13.7	13.4	7.9	<.001*
Letter fluency	16.7	5.7	19.2	5.8	.12
Category fluency	32.1	7.0	38.9	7.3	.001*
WAIS-R digit symbol	59.3	13.9	64.7	10.6	.12
WCST (perseverative errors)	7.7	9.3	9.7	9.8	.45
WCST (categories achieved)	4.7	1.5	4.9	1.2	.55
Dual task	91.1	9.5	94.8	6.4	.10

WMS-R, Wechsler Memory Scale Revised; TMT, Trail Making Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WCST, Wisconsin Card Sorting Test.
* $P < .05$.

performance include (a) clustering, the production of words within semantic or phonemic subcategories; and (b) switching, the ability to shift efficiently to a new subcategory. Switching relies upon frontal lobe processes such as strategic search processes, cognitive flexibility, and shifting. Therefore this factor was named "cognitive flexibility". The factor III accounted for 15.2% of the variance and included WCST (perseverative errors), WCST (categories achieved) and dual task. WCST is a complex problem-solving task that probably requires multiple cognitive processes

Table 3
Factor loadings from analysis of the scores of executive attention function

	Factor loadings			Total
	Factor I inhibition	Factor II cognitive flexibility	Factor III multi-tasking	
Stroop test (false number)	**.90**	−.13	.13	
TMT subtracted time	**.83**	.00	−.16	
Stroop test (time)	**.80**	.22	−.03	
GO/NO GO test (commission errors)	**.77**	−.16	.00	
Letter fluency	.23	**.92**	.02	
Category fluency	−.24	**.62**	.00	
Digit symbol	−.15	**.53**	−.03	
WCST (perseverative errors)	.05	.09	**.74**	
WCST (categories achieved)	−.01	−.02	**−.67**	
Dual task	−.20	−.14	**.40**	
% of variance	37.4	17.4	15.2	70.0
Correlations between factors	Factor I	Factor II	Factor III	
Factor I	1.00			
Factor II	−.39	1.00		
Factor III	−.04	.15	1.00	

Loadings ⩾.40 or ⩽−.40 are printed in bold face.
TMT, Trail Making test; WCST, Wisconsin Card Sorting Test.

rather than a single, unitary function (Dehaene and Changeux, 1991; Anderson et al., 1991). Dual task was a measure for assessing the ability to perform two tasks simultaneously. Therefore we named the third factor "multi-tasking".

Statistically significant differences were observed between the washers and the checkers on the inhibition and the cognitive flexibility scores, but not on the general memory or the multi-tasking score (Table 4).

We next investigated an interaction between each factor and general memory by OCD subtypes through analysis of covariance. There were no significant overall difference between the two groups with respect to the general memory score of the WMS-R, but there was a significant interaction between groups and the inhibition score [$F(1,49) = 6.9$, $P = .01$]. Only among 'checkers', a significant correlation was observed between general memory score and the inhibition score, indicating that the checkers

Table 4
General memory score of WMS-R and Factor score of each subtype

	Checkers ($n = 27$)		Washers ($n = 26$)		P
	Mean	SD	Mean	SD	
General memory	125.1	23.8	134.8	14.6	.08
Factor I: inhibition	.53	1.07	−.55	.39	<.001*
Factor II: cognitive flexibility	−.36	.88	.38	.80	.002*
Factor III: multi-tasking	−.05	.92	.05	.78	.67

* $P < .05$.

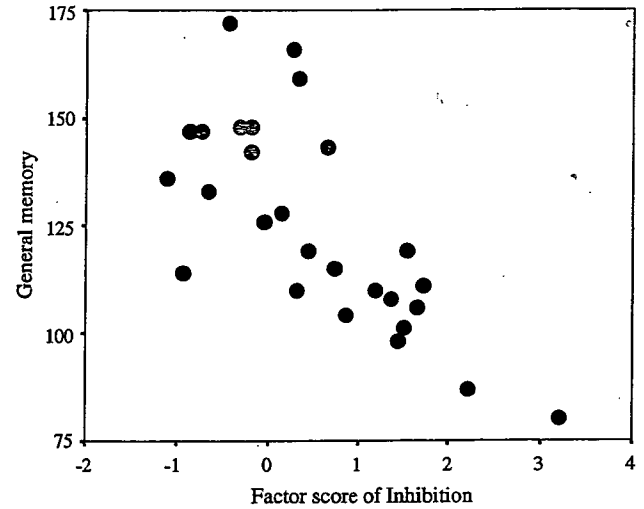

Fig. 1. Correlation between general memory and factor score of inhibition among checkers. Checkers with poorer inhibition had poorer memory. Pearson's correlation coefficient (r) = −.73. $P < .001$.

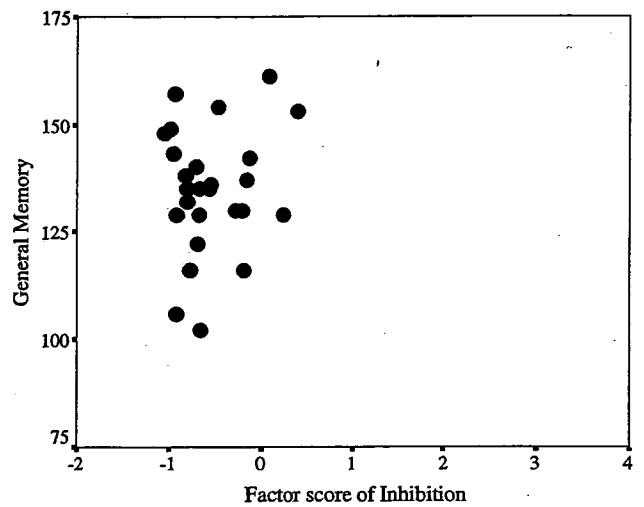

Fig. 2. No correlation between general memory and factor score of inhibition among washers.

with poorer inhibition had poorer memory. Pearson's correlation coefficient (r) and the corresponding P value for this correlation were $r = -.73$ and $P < .001$, respectively (Fig. 1). No such interaction was observed among 'washers' (Fig. 2).

4. Discussion

To the best of our knowledge, this study represents the first formal comparison of comprehensive neuropsychological functions among the "checking" and "washing" subtypes of OCD. The main findings of this study are that checkers, compared to washers, have deficits on neuropsychological tests that assess inhibition and cognitive flexibility and that general memory was affected by the inhibition score only among checkers.

4.1. Memory and inhibition

Our observation that there was no significant difference regarding general memory between the checkers and the washers is consistent with the recent cognitive theory suggesting that the checkers have memory confidence problems not attributed to primary memory deficits but to meta-memory impairment. Indeed, compulsive checking occurs when the checkers have low memory confidence (Clark, 2004).

On the other hand, we found differential deficits in executive attention functions between the washers and the checkers. Our results that checkers had poorer factor scores of inhibition were congruent with several studies using the negative priming paradigm to investigate cognitive inhibition reported that negative priming was more apparent among the checkers than among the non-checkers (Enright et al., 1995; Hoenig et al., 2002). Recent neuroimaging studies of OCD using PET or SPECT demonstrated the dysfunction of the OFC and/or anterior cingulate cortex and/or the caudate nucleus in OCD (Baxter et al., 1987; Swedo et al., 1989; Machlin et al., 1991; Busatto et al., 2000). The orbitofrontal-subcortical pathways subserve the response inhibition and therefore the inhibition may be the most vulnerable of various attention tasks by OCD subjects. Several studies have indicated that both GO/NO GO test and Stroop test required by response inhibition were impaired among OCD subjects (Bannon et al., 2002; Herrmann et al., 2003).

A possible explanation, then, for the observed association between the inhibition and the general memory in the checkers is that the deficits of inhibition may cause secondary memory deficits in checkers. The ability to respond effectively and recall prior information depends, in part, on the capacity to ignore or inhibit irrelevant information and to focus on the task at hand. The reason for checkers with poorer inhibition had poorer memory score may be due to interference effects resulting from a failure to inhibit irrelevant or distracting material.

4.2. Subtypes of OCD

Our findings demonstrating differential executive attention functions among checkers and washers indicate that distinct subtypes of OCD may exist with respect to cognitive function.

There is controversy over the method to identify specific subtypes of OCD because OCD is a clinically heterogeneous disease. Recent studies (Mataix-Cols et al., 1999, 2004, 2005) proposed that dimensional models of OCD have some advantage over categorical models of OCD. While categorical models identify homogeneous and mutually exclusive subgroups based on some clinical features, dimensional models are designed to characterize each patient according to symptom dimensions derived from factor analysis. According to the dimensional models of OCD, OCD is characterized by the overlapping syndromes that can coexist in the same subjects.

In our study, we assessed the five clinical dimensions of OCD (Mataix-Cols et al., 1999) using the Yale-Brown Obsessive-Compulsive Scale Symptom Checklist, and then identified the relatively pure washers and checkers.

4.3. Limitations and conclusions

Some possible limitations of the current study need to be mentioned before we conclude. First, we had no healthy controls because the present analyses focused on the contrasts between the washers and the checkers. Second, all the patients in this study were taking SRIs. Several single case reports have been published in which SRIs induced significant cognitive impairments in patients with OCD (Hoehn-Saric et al., 1991; George and Trimble, 1992). However, one recent study compared a group of SRI medicated with a group of SRI-free patients on a neuropsychological battery and found that the two groups were able to perform on cognitive functioning test at a comparable level (Mataix-Cols et al., 2002). Moreover, the effect of the SRIs is unlikely to be a significant confounder in the present comparison between the washers and the checkers, because there was no significant difference in the average daily dose of SRIs between the two groups. Third, it is well known that OCD is often accompanied by depressive symptoms. Some studies report that the deficits of executive function are influenced by the coexistent depression or subclinical depressive symptoms (Basso et al., 2001; Moritz et al., 2001; Aycicegi et al., 2003). In the present study, we excluded OCD subjects with current major depressive disorder and the participants reported only mild depressive symptoms according to the BDI-II and, more importantly, there was no significant difference in the severity of depression between the two subtypes. In the future, we plan to study the cognitive effect of the depressive symptoms on memory and executive attention functions among OCD subtypes. Fourthly, we cannot determine from these data whether the observed neuropsychological deficits may represent state markers of OCD patients rather than their trait markers. Chamberlain et al. (in press) reported impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of OCD and suggested that these impairments appear to reflect trait markers that can exist in the absence of clinically significant symptoms and medication confounds. Further studies are needed examining whether neuropsychological deficits observed in our study are independent of the acute illness state. Finally, the reported results of factor analysis need to be replicated in larger samples because statistical power may have been insufficient for this analysis. Although there are no formal methods to estimate sample size to obtain a robust factor solution, however, our sample size may have been relatively small. It is also to be noted that there are no formal rules to label the obtained factors and the names we chose remain somewhat arbitrary.

In summary, the present study found that a significant correlation between the general memory score and the inhibition score exists only among the checkers, supporting the view that inhibition regulates episodic memory in the checking subtype of OCD. Discrepancies reported in prior neuropsychological studies of OCD may be due to in part inclusion of patients with different subtypes. Findings from this study provide additional evidence that distinct neural systems might be involved in the development of different symptoms in OCD. Further studies examining neuropsychological functioning in OCD in larger samples and in comparison with normal controls are warranted.

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Regular Article

Two dimensions of anosognosia in patients with Alzheimer's disease: Reliability and validity of the Japanese version of the Anosognosia Questionnaire for Dementia (AQ-D)

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Abstract Although a number of studies have examined anosognosia of cognitive deficits in patients with Alzheimer's disease (AD), not much is known about the anosognosia of behavioral symptoms in AD. The aims of the present study were to establish a Japanese version of the Anosognosia Questionnaire–Dementia (AQ-D) and to examine its factor structure, reliability and validity, and to identify the effects of various variables on the AQ-D. Factor structure, internal consistency, test–retest reliability and concurrent validity of the Japanese version of the AQ-D were analyzed. Multiple regression was then done using the results of the AQ-D as dependent variables and entering all relevant predictor variables. Both the internal consistency and the test–retest reliability of the AQ-D were excellent. Factor analysis indicated four factors: anosognosia of basic and instrumental activities of daily living; that of episodic memory and orientation; that of disinhibited behaviors; and that of apathy and depression. The first two factors were regarded as anosognosia of cognitive deficits and were associated with Mini-Mental State Examination scores, while the latter two factors were regarded as anosognosia of behavioral symptoms and were associated with the Neuropsychiatric Inventory (NPI) score. A dissociation between the two domains of anosognosia was confirmed, namely of cognitive deficits and of behavioral symptoms using the Japanese version of the AQ-D. The knowledge that various factors may have different effects on different domains of anosognosia in patients with AD may serve as useful information for clinicians assessing anosognosia in AD.

Key words Alzheimer's disease, Anosognosia Questionnaire for Dementia, behavioral symptoms, cognitive deficits, Japanese patients, reliability, validity.

INTRODUCTION

In patients with Alzheimer's disease (AD), all domains of insight are not always lost. Starkstein *et al.* divided the domains of anosognosia (loss of insight) into two domains: lack of cognitive awareness and lack of behavioral awareness.[1] Recently they extended these findings by analyzing four domains of anosognosia in a large series of patients with AD.[2] While a number of studies on dementia have examined aspects related to the loss of insight into cognitive deficits, less is known about the loss of insight into behavioral disturbances. Neuropsychiatric symptoms (behavior disturbances) are commonly encountered in AD patients, and may not only increase the distress of caregivers but also affect the patients' own distress levels. Thus, it is important to

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investigate the clinical significance of anosognosia of behavior disturbances in patients with AD dementia.

However, to the best of our knowledge, a standardized anosognosia questionnaire covering both the cognitive and behavioral domains is not available in Japan. The aim of the present study was therefore to develop the Japanese version of the Anosognosia Questionnaire–Dementia (AQ-D), originally devised by Migliorelli *et al.*,[3] to examine its factor structure, and to confirm its reliability and validity. We also examined the effects of clinical variables, such as cognitive function and the presence of neuropsychiatric symptoms, on these domains of anosognosia in patients with AD. We hypothesized that the two domains, cognitive deficits and behavioral deficits, could also be validated in the Japanese version of the AQ-D.

METHODS

Participants

One hundred and forty-three consecutive Japanese outpatients with AD who visited Nagoya City University Hospital were recruited. The inclusion criteria consisted of (i) diagnosis of probable AD according to the National Institute of Neurology and Communicative Disorder and Stroke/Aizheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria;[4] and (ii) very mild to mild functional severity (grade 0.5–1 on clinical dementia rating [the CDR][5]). Patients were excluded if (i) other neurological diseases were present; (ii) there was a previous history of mental illness; (iii) focal brain lesions were seen on magnetic resonance imaging; or (iv) Mini-Mental State Examination (MMSE)[6] score was <11. Each patient's caregiver was defined as the principal family member providing day-to-day care.

The study protocol was approved by the Ethics Committee of Nagoya City University Graduate School of Medical Sciences. The examiner explained the study protocol including the study purpose, procedures and so on using simple and straightforward language to both AD patients and their caregivers. The examiner repeatedly explained the protocol to all AD patients and their caregivers as often as required to ensure adequate comprehension of the objective of the study. After a complete description of the study protocol, written informed consent was obtained from all AD patients and their caregivers.

Translation of AQ-D

The AQ-D is a 30-item questionnaire seeking responses from both the patients and their caregivers about the current level of impairment of the patients. With the original authors' permission, we translated the original English version into Japanese. We followed a standard back-translation procedure to ascertain the semantic equivalence of the Japanese version with the original English version.

Procedure

In accordance with the procedure recommended for the original AQ-D, the AD patients and their caregivers completed the questionnaire independently in different rooms. The AQ-D consisted of 30 questions covering the patient's insight of two domains (intellectual functioning and behavior). Each answer was rated as follows: never (0 points), sometimes (1 point), usually (2 points), or always (3 points). Higher scores indicated a more severe impairment of insight. The final score was obtained by subtracting the score on the patient's report version from that of the caregiver's report version. Therefore, a positive final AQ-D score indicated that the caregiver had rated the patient as more impaired than the patient had.

At the time of administering the AQ-D questionnaire, the following tests were also conducted.

(1) Neuropsychiatric Inventory (NPI):[7] a semiquantitative assessment based on information provided by the caregiver. This interview consists of 10 behavior-related questions. Hirono *et al.* confirmed the reliability and validity of the Japanese version of this interview.[8]

(2) Hyogo Activities of Daily Living Scale (HADL): a scale designed for a detailed and comprehensive assessment of the functional abilities of subjects with AD.[9] It consists of 18 questions related to basic and instrumental activities of daily living (ADL). Assessment using this scale is also based on information provided by the caregiver. The reliability and validity of this questionnaire was confirmed by Hirono *et al.*[9]

Statistical analysis

We used SPSS 11.0 J for Windows (SPSS, Chicago, IL, USA) for the statistical analysis.

Factor analysis

A principal component factor analysis using varimax rotation was performed on the 30 items of the AQ-D. The models included factors with an eigenvalue >1. An item was considered to load onto a factor if its factor loading score exceeded 0.30. In addition, we calculated the congruence coefficients for the components after varimax rotation between the present results and the Starkstein *et al.* results.[2] The congruence coefficients

range from −1 to +1, and values >0.90 are usually considered very high.

Reliability

The reliability of this scale was assessed in two ways. First, the test–retest reliability was assessed among a subset of 85 patient–caregiver pairs 1 month after the initial evaluation, using an analysis of variance intraclass correlation coefficient (ANOVA ICC). In general, an ANOVA ICC >0.7 indicates good reliability. Second, the internal consistency of the scale was estimated by determining Cronbach's alpha coefficients. Cronbach's alpha >0.70 is indicative of a good internal consistency.[10]

Validity

To examine the concurrent validity, we assessed the correlation between the Japanese version of the AQ-D score and the criteria described by Reed *et al.*[11] One of the authors (N.S.), an experienced psychiatrist, rated the patient's level of insight (4-point scale) without knowledge of the results of the AQ-D score.

Prediction of the AQ-D score

We conducted a multiple regression analysis to explore the correlation between the AQ-D score and cognitive or behavior symptoms and ADL functioning. The dependent variable was the final AQ-D score. The independent variables were the duration of AD (in years), the MMSE score, the NPI score, and the HADL score. We used the three dimensions (mood factor, psychosis factor, and euphoria factor) of the NPI score as demonstrated in our previous study.[12]

RESULTS

Subject characteristics

Table 1 presents the mean scores and standard deviations of the clinical and demographic characteristics. Among the caregivers ($n = 143$), 58% were spouses, 19% were daughters-in-law, 18.1% were adult children, and 5.8% were other close relatives.

Factor analysis

An exploratory principal component analysis reduced the 30 variables to five factors. The five factors explained 64.2% of the variance in the data. The first four factors were retained because of their clinical relevance. However, the fifth factor was composed of only one item. Thus, a four-factor model best fitted the Japanese version of the AQ-D (Table 2). The first factor loaded on the items corresponding to ADL abilities. This factor was termed 'anosognosia of basic and instrumental ADL'. The second factor included most of the items corresponding to episodic memory and orientation. Therefore, we named this factor anosognosia of episodic memory and orientation. The items in the third factor corresponded to increased irritability, laughing inappropriately. Therefore, the third factor was named anosognosia of disinhibited behavior. The fourth factor included such items as less interest in favorite things, more depressed. Therefore, the fourth factor was named anosognosia of apathy and depression. The factor congruence coefficients for the four factors between the present results and those derived from Starkstein *et al.*[2] were between 0.62 and 0.88 (Table 3). The factor congruence coefficient between the two studies was either substantive or moderate. Korth suggested that congruence coefficients tend to become smaller when larger numbers of factors are extracted,[13] as in the present study. Therefore, we consider that the observed factors in the present study were replicated in the original factor model.

Table 1. Subject data

	AD patients Mean ± SD ($n = 143$)	Caregivers Mean ± SD ($n = 143$)
Gender (male/female)	59/84	56/87
Age (years)	72.1 ± 7.3	61.5 ± 11.2
Education (years)	9.6 ± 0.8	10.4 ± 2.0
Duration of dementia (years)	1.9 ± 0.5	(–)
MMSE	20.1 ± 4.3	(–)

AD, Alzheimer's disease; MMSE, Mini Mental State Examination.

Reliability

The alpha coefficients for the patient responses (0.90; 95% confidence interval [CI], 0.88–0.92) and the caregiver responses (0.92; 95% CI, 0.88–0.93) indicated an excellent internal consistency for all 30 items of the AQ-D. The test–retest reliability ($n = 85$) of the total score after 1 month was excellent, with a good ICC (0.81; 95% CI, 0.72–0.88).

Validity

We observed a statistically significant and substantive correlation between the clinical assessment of anosognosia in AD according to the Reed *et al.* criteria[11] and the final AQ-D score ($r = -0.71$, $P < 0.01$).

Table 2. Factor analysis for 143 AD patients

Anosognosia characteristics	Factor 1	Factor 2	Factor 3	Factor 4
A-21. Problems with feeding oneself	**0.806**	0.148	0.059	0.062
A-14. Problems with communicating with people	**0.761**	0.201	0.066	0.086
A-15. Problems doing mental calculations	**0.739**	0.087	0.013	0.092
A-20. Problems with doing home activities	**0.686**	0.388	0.001	0.117
A-19. Problems with orientation in the house	**0.658**	0.391	0.041	0.088
A-22. Problems with doing clerical work	**0.619**	0.336	0.190	0.218
A-18. Problems with understanding the plot of a movie	**0.615**	0.498	0.021	0.109
A-13. Problems with practicing favorite hobbies	**0.586**	0.310	0.069	0.144
A-10. Problems with handling money	**0.389**	0.261	–0.031	0.287
A-17. Problems with bladder control	**0.350**	0.253	0.273	–0.055
A-16. Problems with remembering shopping lists	0.555	0.523	0.070	0.01
A-11. Problems with orientation in your neighborhood	0.511	0.489	0.058	0.232
A-6. Problems with understanding the newspaper	0.183	**0.675**	0.043	0.269
A-3. Problems with remembering telephone calls	0.138	**0.664**	0.026	0.179
A-2. Problems with orientation in new places	0.275	**0.664**	0.099	0.055
A-5. Problems with signing your name	0.407	**0.652**	–0.104	0.239
A-1. Problems with remembering dates	0.354	**0.637**	0.179	0.061
A-4. Problems with understanding conversations	0.341	**0.630**	–0.081	0.179
A-8. Problems with remembering where things were left	0.175	**0.627**	0.211	0.116
A-7. Problems with keeping belongings in order	0.389	0.470	0.031	0.208
A-12 Problems with remembering appointments	0.420	0.470	0.126	0.097
B-27. Laughing inappropriately	0.011	0.054	**0.795**	0.110
B-28. Increased sexual interest	0.002	–0.083	**0.708**	0.096
B-26. More frequent crying episodes	0.061	–0.039	**0.626**	0.181
B-25. More irritable	0.141	0.223	**0.528**	0.297
B-24. More egotistical and self-centered	0.210	0.191	0.315	**0.641**
B-29. Less interest in favorite activities	0.020	0.137	0.555	**0.633**
B-30. More depressed	0.064	0.218	0.460	**0.608**
B-23. More rigid and inflexible about decisions	0.169	0.244	0.216	**0.543**
A-9. Problems with writing	0.366	0.430	–0.064	0.190

A, Intellectual Functions; B, Behavior. **Bold**, loadings ≥0.30.
AD, Alzheimer's disease.

Table 3. Factor congruence coefficients for the present and Starkstein *et al.* studies[2]

Factor structure	First factor	Second factor	Third factor	Fourth factor
Factor 1 (iADL)	0.621			
Factor 2 (bADL)		0.644		
Factor 3 (depression)				0.833
Factor 4 (disinhibition)			0.655	

Vertical: factor structure for the Starkstein *et al.* study;[2] horizontal: factor structure for the present study.
First factor, basic and instrumental ADL; second factor, episodic memory and orientation; third factor, disinhibition; fourth factor, apathy and depression.
bADL, basic activities of daily living; iADL, instrumental activities of daily living.

Prediction of the AQ-D score

While multiple regression analysis showed that the MMSE and HADL scores predicted the score for anosognosia of cognitive deficits, the NPI scores (mood, psychosis, and euphoria factors) and the HADL scores predicted the score for anosognosia of behavior symptoms (Tables 4,5).

Table 4. Variables predicting score for anosognosia of cognitive deficits (first and second factor scores) on AQ-D

Variables	β	*t*	*P*
Duration of illness (years)	–0.016	–0.419	0.676
MMSE score	–0.329	–3.348	0.001*
HADL	0.608	6.119	<0.001**
NPI			
Mood factor	–0.069	–1.665	0.098
Euphoria factor	–0.038	–0.883	0.379
Psychosis factor	–0.055	–1.328	0.186

* $P < 0.01$, ** $P < 0.001$.

β, standardized regression coefficient.

AQ-D, Japanese version of Anosognosia Questionnaire–Dementia; HADL, Hyogo Activities of Daily Living Scale; NPI, Neuropsychiatric Inventory.

Table 5. Variables predicting score for anosognosia of behavior deficits (third and fourth factor scores) on AQ-D

Variables	β	*t*	*P*
Duration of illness (years)	–0.04	–0.674	0.501
MMSE score	–0.123	–0.818	0.415
HADL	0.498	3.275	0.001**
NPI			
Mood factor	0.181	2.87	0.005**
Euphoria factor	0.142	2.188	0.03*
Psychosis factor	0.144	2.272	0.025*

* $P < 0.05$, ** $P < 0.01$.

β, standardized regression coefficient.

AQ-D, Japanese version of Anosognosia Questionnaire–Dementia; HADL, Hyogo Activities of Daily Living Scale; NPI, Neuropsychiatric Inventory.

DISCUSSION

We confirmed that the Japanese version of the AQ-D had good internal and external reliability and satisfactory concurrent validity. Four factors of the AQ-D were identified in the present study: basic and instrumental ADL; episodic memory and orientation; disinhibition; and apathy and depression. In addition, while the MMSE and HADL scores predicted the scores for the domains of anosognosia of cognitive deficits on the AQ-D, the NPI score predicted the scores for the domains of anosognosia of behavioral symptoms on the AQ-D. As shown in Table 3, the factor congruence coefficient between the first factor in the present study and that in the Starkstein *et al.* study[2] was 0.621; that between the second factor in the present study and that in the Starkstein *et al.* study[2] was 0.644. The factor congruence coefficient is an index of similarity between factor loadings. Because factor congruence coefficients for the first and second factor between the two studies are modest, we can assume that there was good convergence of the first two factors between the present study and that by Starkstein *et al.*[2] In addition, the factor congruence coefficient for the third and fourth factors between the present and the Starkstein *et al.* studies[2] were either high or modest. Therefore, the present study suggests that the four-factor structure demonstrated by Starkstein *et al.*[2] was replicated in the present sample.

In contrast, we failed to observe the two different domains of basic ADL (bADL) and instrumental ADL (iADL) observed in the Starkstein *et al.* study.[2] Starkstein *et al.* demonstrated the four-factor structure of anosognosia in a large series of 750 patients with very mild to severe stage AD.[2] In that study the cognitive domains could be clustered into two subdomains, namely, bADL and iADL, and behavioral domains could also be clustered into two subdomains, namely, depression, and disinhibition. Unlike the present study, the patient series examined by Starkstein *et al.* included not only patients with mild AD, but also patients with moderate or severe AD.[2] They found a marked difference in the anosognosia score for the bADL domain between the moderate and severe stage. Tekin *et al.* suggested that while iADL impairment can be an early sign of dementia, bADL ability was maintained until late in the course of AD disease.[14] Thus, the subtle difference between the present results of those of Starkstein *et al.*[2] may be related to differences in the clinical severity among the two series of patients. Larger study groups of Japanese patients with all stages of AD will clarify the phenomenon of anosognosia into two different levels of ADL.

Although we named the second factor 'episodic memory and orientation', some items in this factor may correspond to the ability to perform bADL tasks. However, we could not term the second factor 'bADL' because the items in the second factor (except for 'problems with signing your name') did not include items among the bADL domains defined by Starkstein *et al.*[2] Several studies of patients with AD have suggested that ADL ability (particularly iADL ability) was associated with executive dysfunction.[15,16] The present data indicate that executive function may be associated with iADL (i.e. doing clerical work, handling money) in the first factor because the activities in these items are complex. However, episodic memory and orientation, rather than executive function, may contribute to the activities of items in the second factor (e.g. remembering the date, remembering where things were left). Therefore, different cognitive mechanisms likely underlie activities associated with ADL between the first and second factors in the present study.

The third and fourth factors identified in the present study were identical to the two factors, anosognosia for depression and for disinhibition, reported by Starkstein *et al.*[2] Unlike their study, we named the third factor 'apathy and depression' because apathy and depression may be distinct syndromes in patients with dementia.[17] Because the fourth factor included items corresponding to inappropriate activities, we termed this factor as 'disinhibited behavior'; this factor was identical to the fourth factor identified by Starkstein *et al.*[2]

Results from multiple regression support the existence of two domains of anosognosia in subjects with AD. While the score for anosognosia of cognitive deficits was correlated with the MMSE and HADL scores, the presence of neuropsychiatric symptoms identified by the NPI was correlated with the score for anosognosia of behavior deficits. The present study may also provide additional evidence supporting a previous hypothesis that anosognosia is not a consequence of cognitive deficits but is a wider behavioral disorder,[1–3] because the present study included patients with very mild or mild stages of AD. Several caveats should be addressed. First, although we confirmed the reliability and validity of the Japanese version of the AQ-D, the information obtained from the caregivers may have been influenced by various factors (i.e. reliability of emotional stress, and cognitive level).[2,18] Therefore, information obtained from the caregivers should be used with caution. Second, previous studies have identified deficits associated with specific neuropsychological findings (i.e. frontal lobe function).[2,19] Unfortunately we could not conduct comprehensive neuropsychological tests, except for the MMSE.

In conclusion the present study demonstrated that the Japanese version of the AQ-D was both reliable and valid for a large number of patients with AD. More importantly, the present study demonstrated a dissociation between the two domains of anosognosia, cognitive and behavior deficits, on the Japanese version of the AQ-D. We expect the Japanese version of the AQ-D to become a clinically useful standard assessment of anosognosia in patients with AD.

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ORIGINAL ARTICLES

Can psychiatric intervention improve major depression in very near end-of-life cancer patients?

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ABSTRACT

Objective: Although depression is a prevalent and burdensome psychiatric problem in end-of-life cancer patients, little is known about its susceptibility to treatment, especially when patients reach very close to the end of life. This study was conducted to evaluate response rate of that end-of-life depression to psychiatric intervention and to assess the feasibility of conventional evidence-based pharmacological therapy for depression.

Methods: The medical records of 20 patients who were referred to the psychiatry division for major depressive disorder and died within 3 months after the referral were reviewed. The Clinical Global Impression–Improvement (CGI-I) Scale was used for each case, and responders were defined as patients whose scores were much or very much improved. All pharmacological treatments were extracted, and the doses of the antidepressant prescribed were compared to their evidence-based-defined therapeutic doses.

Results: Of the 20 patients, seven were responders, but no response was achieved when the survival time was less than 3 weeks. Most patients were treated with antidepressants, but the doses prescribed were far less than the defined doses, especially the doses of the tricyclic antidepressants (TCAs).

Significance of results: These results suggested that patients' survival time largely determines susceptibility to psychiatric treatment, and it is hard to achieve response in patients whose survival time was less than about 1 month. Implementation of conventional evidence-based pharmacological treatment is difficult, especially with TCAs, and various antidepressants, which can be administrated by other routes, are needed when oral intake is impossible.

KEYWORDS: Terminally ill, End of life, Cancer, Major depression, Therapeutics

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INTRODUCTION

Depression is the most prevalent and distressing psychiatric issue in terminally ill patients with advanced cancer. The prevalence of depression in such patients deduced by rigorous methods (e.g., structured clinical interview) has been reported to be 5%–26%, with a median value of 15% (Hotopf et al., 2002) Several studies have indicated that depression can have a serious negative impact on terminally ill patients with advanced cancer, including reducing their quality of life (Grassi et al., 1996) causing severe suffering (Cherny et al., 1994), causing a desire for early death and requests for physician-assisted suicide and/or euthanasia (Brown et al., 1986; Chochinov et al., 1995; Breitbart et al., 2000; Akechi et al., 2002), and suicide (Henriksson et al., 1995) as well as psychological distress in family members (Cassileth et al., 1985).

Treatment of depression in patients very near the end of life is very challenging. The illness trajectory of cancer shows steady progression in the beginning, but a very rapid decline in the final few months. In about the last 3 months of the cancer journey, patients must confront one major stressful event after another, such as weight loss, reduction in performance status, and impaired ability for self care (Lunney et al., 2003; Murray et al., 2005). Pain and other burdensome physical symptoms may also exacerbate depression (Chochinov et al., 1995). Management that combines psychosocial and pharmacological intervention is recommended for end-of-life depression (Wilson et al., 2000; Pessin et al., 2003), and in our institution, psychiatrists specializing in psycho-oncology have tried to treat such depression aggressively. However, because of the very few empirical studies concerning its susceptibility to treatment, we have wondered if patients benefit from aggressive treatment, which may cause adverse events, as many palliative care physicians have been reluctant to prescribe antidepressants (Lawrie et al., 2004).

Focusing on pharmacotherapy, which is a key treatment for depression, to achieve conventional pharmacotherapy, which is defined based on evidence from physically healthy patients, may be difficult for these patients in regard to duration and dose prescribed. Some randomized controlled trials have shown that antidepressants can improve depression in advanced cancer patients (Costa et al., 1985; Holland et al., 1998; Fisch et al., 2003) However, there is not enough time to treat patients near the end of life, because, although side effects appears early, it takes 6–8 weeks to achieve full symptom reduction with antidepressants (Gabbard, 2000). Moreover, prescribing evidence-based therapeutic doses may be difficult in end-of-life cancer patients because of side effects, especially those of tricyclic antidepressants (TCAs; Popkin et al., 1985; Lloyd-Williams et al., 1999).

In this study, we reviewed our treatment experience and discussed future clinical implications. The primary aim of the study was to determine whether or not depression in very near end-of-life cancer patients is treatable, and we assessed the response of patients to psychiatric intervention. The secondary aim of the study was to determine the feasibility of pharmacotherapy, especially in regard to duration and dose prescribed.

METHODS

Study Sample

All psychiatric consultations referred to the Psychiatry Division, National Cancer Center Hospital East (NCCH-E), Japan, between August 2002 and December 2003 were reviewed. All psychiatric consultations were recorded in a computerized database (Akechi et al., 2001), and we constructed another database for consultations of major depression in advanced cancer patients in this period as a part of a pharmacological treatment algorithm study (Akizuki et al., 2002). This major depression database include patients' demographic factors, medical factors such as cancer site, performance status, and pain intensity, starting date of psychiatric consultation, selected antidepressant and its dose, and date of death. Using the above two databases, we extracted cases that met the following inclusion criteria: (1) clinical diagnosis of a major depressive disorder based on DSM-IV and (2) cancer death within 90 days of the start of psychiatric treatment. Patients were excluded from the study if follow-up was impossible for any reason, such as transfer. Because this study was a retrospective review of clinical practices, written consent and institutional review board approval were not obtained.

Psychiatric Intervention

Psychiatric intervention was mainly composed of psychotherapy, pharmacotherapy, family support, and recommendation of physical symptom management from the standpoint of depression management. Each component is described in detail below.

Psychotherapy

Psychotherapy was individualized and modified for each patient. Supportive psychotherapy consisted of active listening with supportive verbal inter-

vention and the occasional interpretation is the fundamental element. Psychiatrists maintained ongoing contact and allowed patients to talk about anything they wanted, for example, their life, experience, death, and so on. Cognitive-behavioral interventions, such as relaxation and distraction with pleasant imagery, were also used. A psychoeducational approach with realistic assurance was used for patients who felt anxiety or hopelessness because of any misunderstandings (Wilson et al., 2000; Pessin et al., 2003).

Pharmacotherapy

We had previously developed a pharmacological treatment algorithm (Nakano et al., 1999), and the second version of the algorithm was used during the study period. One of two TCA antidepressants, clomipramine or amitriptyline, was chosen for patients unable to take drugs by mouth because these were the only antidepressants available in parenteral formula in Japan. Alprazolam or methylphenidate was chosen because of their rapid onset of action for patients with mild depression. Drugs were chosen because of their side effect profile for the other patients. For example, SSRI was avoided because it exacerbates nausea in patients with nausea. All drugs were started at the lowest possible dose, and the dose was escalated over the following 3–6 days till the optimal dose.

Family Support

Depression in cancer patients is closely associated with psychological distress in family members (Cassileth et al., 1985), and psychological distress in the family may cause low social support, which is associated with patient's depression (Wilson et al., 2000). We also evaluated family distress and gave family members some advice. When a family member's distress was severe, we sometimes recommended consultation in our psycho-oncology clinic.

Recommendation of Physical Treatment

Physical symptoms, such as pain and fatigue, are closely associated with depression. If we concluded that patients' physical symptoms affected the patients' depression, we recommend that the attending oncologist treat the symptom or sometime to consult with a specialist in physical symptom management.

Judgment of Improvement

A structured clinical interview based on the DSM-IV criteria (employing an inclusive approach) was used to diagnose major depressive disorder, and nine symptoms for major depressive episodes were routinely evaluated and recorded on the medical charts. Final determination of the psychiatric diagnoses and the follow-up evaluation of the patients were discussed at a weekly meeting of the psychiatric division. Treatment outcome in the present study was retrospectively rated by two independent psychiatrists (K.S., M.S.) according to the Clinical Global Impression-Improvement (CGI-I) Scale (Guy, 1976), and we assessed the change from baseline to the point when the greatest improvement was achieved. We used an anchor point that had been used in another study of terminal major depression (Table 1; Macleod, 1998). A "response" was defined when a patient's rating on the CGI-I was "very much improved" or "much improved," even in a short period. The reliability (kappa coefficient) of the rating for whether response had been achieved was 0.66. Whenever the raters disagreed, disagreements were discussed and a final rating was made.

Duration and Dose of Psychotropic Drugs Prescribed

We assumed that conventional evidence-based treatments for depression in noncancer patients were applicable (Berney et al., 2000), while accepting that further research is required to establish this. All pharmacological treatment to alleviate depressive symptoms was extracted from the medical charts. We evaluated "prescribed duration," which is the number of days the antidepressant was prescribed, and "% optimal dose," which is the dose administered as a percentage of the minimal optimal dose defined by the Japanese Ministry of Health, Labor and Welfare, based on results of clinical trials. If the dose prescribed was above the minimal optimal dose but within the defined range of the

Table 1. *Anchor points of the Clinical Global Impression–Improvement Scale*

Very much improved: a complete or nearly complete remission of all depressive symptoms.
Much improved: improvement in several symptoms but without complete remission.
Minimally improved: minor improvement in mood without improvement in other symptoms.
No change or worse: other than those above.

optimal dose, the "% optimal dosage" was evaluated as 100%. However, because of recent evidence suggesting that the TCAs prescribed may be effective at a dose of 75 mg (Furukawa et al., 2002), that dose was defined as the optimal dose for these agents. If pharmacotherapy was discontinued, the reason was also extracted.

Statistical Analysis

All patients who were prescribed psychotropic drugs were dichotomized into TCAs group and non-TCAs group, and "% optimal dose" was compared by the Mann–Whitney *U* test. All analyses were performed using SPSS 12.0 J for Windows statistical software (SPSS Japan Institute).

RESULTS

During the study period, 65 patients were referred to the psychiatry division and diagnosed with major depressive episodes. Nine patients were excluded from the analysis because follow-up was impossible due to transfer. Of the remaining 56 patients, 20 died within 90 days of the psychiatric referral and were included in this study. Their demographic characteristics, tumor sites, length of survival, pain intensity, and performance status as defined by Eastern Cooperating Oncology Group are listed in Table 2.

Table 3 shows the detailed course of treatment of all 20 patients. "Very much improved" was not achieved in any of the patients, but "much improved" was achieved in 7 (35%), and they were recorded as "response." Minimal improvement was achieved in three of the other 13 patients, and 10 showed no improvement at all. A "response" was not achieved in any of the eight patients who died within 3 weeks of the beginning of psychiatric treatment.

As shown in Table 3, one patient was treated by psychotherapy alone, and 19 patients received pharmacotherapy from start to the end of their psychiatric treatment for depression. The "prescribed duration" was shorter than survival time in most patients, and in four patients, it was shorter than 10 days, even when the survival time was more than 1 month. One patient received terminal sedation, but treatment for depression was stopped in the other 18 patients because of the development of terminal delirium.

Only five of the 19 patients were treated with the optimal dose of the psychotropic agent, and 11 of the 19 patients were treated with less than half that of the minimal optimal dose. All seven patients who were treated with antidepressant intravenously were chosen amitriptyline or clomipramine because oral intake was impossible. The median "percent of optimal dose" in the nine patients who were prescribed TCAs (amitriptyline, clomipramine, and nortriptyline) was 16.7%, and significantly lower than that of the other drugs (median 83.9%; $p = .007$).

Table 2. *Characteristics of patients*

Patient number	20
Age (mean ± *SD*, median)	59 ± 11, 60.5
Gender	10 men, 10 women
Primary tumor site	Lung (4), stomach (4), esophagus (4), colon (3), others (5)
Survival length (mean ± *SD*)	41 ± 29 days
Current pain intensity	
0 (none)	7
1 (a little)	6
2 (tolerable)	5
3 (intolerable)	2
Performance status (ECOG)	
0	0
1	1
2	5
3	11
4	3

DISCUSSION

This is a preliminary study whose results provide information on whether major depression in terminally ill cancer patients is treatable by psychiatric intervention or not. The results suggest the therapeutic potential of psychiatric intervention, because one third showed considerable improvement of their depressive symptoms, even though no patient could achieve complete remission. Another important finding was that no responses were achieved in the patients whose survival time was less than 3 weeks.

The closer end-of-life cancer patients approach death, the more untreatable their depression may become. Macleod et al. assessed the efficacy of methylphenidate for major depression in the terminally ill and observed a response in 50% of those who survived more than 6 weeks as opposed in only 7% of those who survived less than 6 weeks (Macleod, 1998). In our study, also dividing patients by 6 weeks of survival time, 54.5% (6/11) of those who survived more than 6 weeks showed a response, as opposed to only 11.1% of those who survived less than 6 weeks. Our colleagues previously reported successful antidepressant treatment of major depression in six end-of-life patients whose median survival was 4 weeks (Kugaya et al., 1999), but

Table 3. *Improvement after Psychiatric Intervention*

Case	Age	Sex	PS	Pain	Cancer site	Survival length (days)	CGI-I	Drug	Prescribed duration (days)	Administrated dose (mg)	% Optimal dose (%)
1	57	M	2	0	Bile duct	6	No change or worse	Methylphenidate	6	10	50
2	47	F	4	3	Colon	7	Minimally improved	Clomipramine i.v.[b]	6	6	8
3	67	F	4	1	Primary unknown	8	No change or worse	None	—	—	—
4	68	F	4	1	Stomach	8	No change or worse	Amitriptyline i.v.[b]	8	10	13.3
5	72	M	3	0	Lung	11	No change or worse	Milnacipran	7	15	30
6	58	F	3	1	Colon	13	No change or worse	Amoxapine	10	50	100
7	32	F	3	0	Breast	14	No change or worse	Trazodone	13[c]	150	100
8	45	F	3	0	Stomach	16	Minimally improved	Milnacipran	5	30	60
9	61	F	3	3	Colon	26	Much improved[a]	Amitriptyline i.v.[b]	25	10	13.3
10	36	M	3	2	Liposarcoma	48	No change or worse	Amitriptyline i.v.[b]	6	10	13.3
11	50	M	2	2	Esophagus	53	Much improved[a]	Clomipramine i.v.[b]	50	12.5	16.7
12	72	F	3	2	Stomach	55	Much improved[a]	Amitriptyline i.v.[b]	44	15	20
13	64	F	3	2	Lung	58	Much improved[a]	Nortriptyline[b]	26	25	33.3
14	63	M	3	2	Esophagus	63	No change or worse	Mianserin	7	10	33.3
15	71	M	1	0	Lung	64	Much improved[a]	Paroxetine	41	30	100
16	66	F	2	0	Lung	66	Much improved[a]	Amoxapine	43	25	100
17	60	M	3	1	Stomach	67	No change or worse	Nortriptyline[b]	67	35	46.7
18	57	M	3	1	Esophagus	73	No change or worse	Trazodone	9	50	67.7
19	59	M	2	0	Esophagus	82	Much improved[a]	Amitriptyline i.v.[b]	80	20	26.7
20	65	M	3	1	Pancreas	86	Minimally improved	Alprazoram	58	1.2	100

PS: Performance status as defined by Eastern Cooperative Oncology Group; CGI-I: Clinicl Grobal Impression-Improvement Scale; % Optimal Dosage: the administrated dose/the minimal optimal dose.
[a]Recorded as "response"
[b]Tricyclic Antidepressants
[c]Stopping pharmacotherapy due to continuous sedation

these cases may be a minority in whole treated very near end-of-life depression. Although both our result and Macleod's are preliminary, they suggest that patients' survival time largely determines treatability, and about 1 month may be the turning point. Aggressive pharmacotherapy often induces adverse effects in cancer patients (Popkin et al., 1985), so setting impossible goals of treatment may cause them unnecessary suffering. Treatment by the usual strategy for depression may be harmful to patients whose life expectancy is estimated to be less than 1 month. For those patients, alternative approaches should be considered, including withholding administration of antidepressants.

As a proactive approach, early detection and treatment may be the key to overcoming end-of-life depression. There exists the condition of the underrecognition and the introduction of treatment too late in end-of-life depression, and this may lead to missing the chance to treat (Lloyd-Williams et al., 1999). Screening end-of-life patients for depression can be an important approach (Hotopf et al., 2002). In addition, development of novel methods of preventiving major depression among end-of-life cancer patients is needed.

The results of our study suggested that pharmacotherapy for end-of-life depression is difficult. The short survival time restricts the duration of treatment, and the development of delirium prevents continuation of pharmacotherapy. The psychotropic agents, especially the TCAs, were prescribed in fairly low doses, and a previous study showed results similar to ours in a British palliative care setting (Lloyd-Williams et al., 1999). Even with specialized knowledge of psychopharmacology, it was hard to achieve the optimal dose, which was defined based on physically healthy subjects. Delirium in the terminally ill occurs in most patients (Lawlor et al., 2000), and psychiatrists must be very cautious about treating with drugs such as TCAs that sometimes induce delirium (Degner et al., 2004). TCAs may be a difficult choice for depression in the terminally ill, but about half the patients in our study were prescribed TCAs in very low doses. Terminally ill cancer patients often lack a functioning gastrointestinal tract, and psychiatrists chose intravenous TCAs in such a case. A variety of antidepressants that can be administered by alternate routes are needed when oral intake is impossible (Koelle & Dimsdale, 1998).

There were several limitations in this study. First, it was based on a retrospective chart review of clinical practice at a single teaching cancer center hospital. Because there were biases due to patient selection and physician's influence, caution is required in terms of generalizing the results. Second, a problem of assessment existed concerning diagnosis and treatment course. Although we made the diagnoses and evaluation according to structured diagnostic interview based on the DSM-IV criteria, there exists difficulty in evaluating major depression in the terminally ill (Wilson et al., 2000; Pessin et al., 2003). Third, some important information that may be associated with depression, such as physical distress, other treatment in parallel, past history of psychiatric disorders, social support, and coping style, was not included.

Although our study was not based on a rigorous design, some highly suggestive results emerged as a clue to the next step. Further research is needed to elucidate proper treatment strategies for major depression at the end of life according to the patient's prognosis. Also, it is hard to prescribe TCAs in conventional doses for end-of-life patients, and alternative, nonoral formulations of antidepressants are needed.

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SC route intermittently, without the problems of skin irritation, by flushing the solution through with hypodermoclysis. Prospective trials are needed to further investigate these observations. Thus far, we have had experience with 18 patients given SC methadone using this method, all achieving adequate pain control, without additional morbidity arising from the infusion site. This allows physicians more flexibility with regard to the use of methadone. It will provide patients with more options for effective pain management, even in the terminal phase of their lives. This is of particular importance in patients who, by virtue of decreased level of consciousness in the terminal phase of illness, can no longer continue on oral methadone, and in whom the rectal route of administration proves difficult or invasive.

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First Panic Attack Episodes in Head and Neck Cancer Patients Who Have Undergone Radical Neck Surgery

To the Editor:

Panic disorders or panic attacks in cancer patients are not well understood. Derogatis et al. found that only 2% of randomly surveyed cancer patients had anxiety disorders and that none of these disorders were related to panic.[1] However, physicians must often treat patients who have experienced clinically significant panic attacks in clinical oncology settings; such patients must receive immediate treatment, as marked fear could lead to a discontinuation of cancer treatment.[2] Panic attacks can occur in the context of several medical conditions (e.g., cardiac, respiratory, vestibular, or gastrointestinal disorders),[3] and certain types of cancer patients may be at risk for panic attacks.

We treated two cases who experienced first panic attack episodes after undergoing radical head and neck surgery. In both cases, the occurrence of panic attack symptoms were notable, and pain, which sometimes occurs after radical neck surgery,[4–6] seemed to contribute to the panic attacks. As the panic attacks were recognized immediately, the attacks were successfully treated using both psychological and pharmacological interventions. To the best of our knowledge, this is the first report

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concerning panic attacks in patients who have undergone radical neck surgery, and who might have an increased risk of panic attacks.

Case 1

Ms. A. was a 44-year-old woman who was hospitalized in the Head and Neck Surgery unit to undergo surgery for hypopharyngeal cancer (T4a N2b M0, Stage IVA). On admission, she had normal concerns about the surgery, and her case was not remarkable in any way. She was a homemaker and had three children. She had no past history of psychiatric disorder, including panic attack, and no family history of major psychiatric illness.

She underwent a total pharyngolaryngoesophagectomy, bilateral neck dissection, and a free jejunum transfer for a pharyngoesophageal reconstruction. Two days after her operation, she felt a gradually increasing stiffness in her neck and expressed great concern about this symptom. Three days after her operation, she began screaming, "I am being strangled!! I am dying!!" and had a terrified facial expression. Her attending physician performed a physical examination but observed no unusual findings, including the postoperative wound. The patient's degree of oxygen saturation was normal. Laboratory tests revealed anemia, hypoalbuminemia, liver dysfunction, and an inflammatory reaction, but these findings were consistent with the usual postoperative state. A psychiatric problem was suspected, and the patient was referred to the psychiatric division.

A psychiatric evaluation revealed that her consciousness was clear and that her major complaint was neck stiffness. She complained that the degree of stiffness would suddenly increase and that she felt an intense fear of death from strangulation. She had concomitant symptoms of palpitation, sweating, sensations of shortness of breath, feeling of choking, and simultaneous fear of losing control, and her episodes met the DSM-IV-TR criteria for a panic attack. Such episodes would cease after a few minutes but occurred repetitively. She never felt at ease and was afraid of her next attack.

We informed the patient that her vital signs were normal and that there was no threat to her life. We explained that an autonomic imbalance arising from anxiety was the cause of her attacks, promised relief from her symptoms, and showed her how to perform diaphragmatic breathing. We also administered a bolus injection of diazepam (5 mg) and a continuous intravenous injection of diazepam (10 mg/day) and clomipramine (12.5 mg/day). Her symptoms improved immediately after the diazepam injection, and the intensity and frequency of her attacks decreased gradually. Seven days after surgery, her attacks had completely disappeared, and her anticipatory fear of attacks had also disappeared, although the administration of psychotropic agents was stopped 10 days after her surgery. A tolerable degree of mild neck stiffness continued after the cessation of the panic attacks. She was discharged from hospital 25 days after surgery.

Case 2

Mr. B. was a 53-year-old man who was hospitalized in the Head and Neck Surgery unit to undergo surgery for oropharyngeal cancer (T3 N2b M0, Stage IVA). On admission, he was extremely worried about the surgery and appeared agitated and uncomfortable; consequently, he was referred to the psychiatric division and was diagnosed as having an adjustment disorder with anxiety. He was treated with alprazolam (0.8 mg/day) until the day before his surgery, and his symptoms disappeared. He had no other history of psychiatric disorder, including panic attack, and he had no family history of major psychiatric illness.

The patient underwent a total glossectomy with a total laryngectomy, bilateral neck dissection, and a rectus abdominis free flap transfer for pharyngeal reconstruction. After the operation, he felt a gradually increasing stiffness in his neck. Seven days after his operation, he became extremely agitated and could not stay in bed. He stood up and began to walk around with a very upset appearance. As a peripheral venous line and a surgical drain had been inserted, the patient was in danger of pulling out the line and drain. Consequently, the nurse made an emergency call to the attending physician and psychiatrist. No unusual findings were found, including the postoperative wound, the degree of oxygen saturation, and laboratory tests.

A psychiatric evaluation revealed that his consciousness was clear and that his major complaint was very severe neck stiffness of a degree that varied widely and immediately from